Saturated fats and health

sacn

Scientific Advisory Committee on Nutrition

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Executive summary

Background

S.1 In June 2014, the Scientific Advisory Committee on Nutrition (SACN) considered undertaking a review of the evidence of the role of fats in health, including monounsaturated fats (MUFA), polyunsaturated fats (PUFA) and saturated fats. The topic had been suggested as part of the horizon scanning process and specific advice on saturated fats was requested by the Food Standards Agency (Scotland) (now Food Standards Scotland). A scoping exercise highlighted a large evidence base. It was agreed that a review of the evidence on saturated fats was most pressing.

S.2 This report considers the relationship between saturated fats, health outcomes and risk factors for non-communicable diseases in the general UK population. This report does not consider total fat in the diet, individual saturated fatty acids, or the role of unsaturated fats other than as a replacement for saturated fats. This report also does not consider specific foods or food groups. The risk assessment of other fatty acids will be considered by SACN in the future.

S.3 The role of saturated fats in health was last considered by the Committee on the Medical Aspects of Food Policy (COMA) in their reports: Dietary Reference Values for Food Energy and Nutrients for the United Kingdom in 1991 and Nutritional Aspects of Cardiovascular Disease in 1994. In 1994, COMA recommended that the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than about 10%[1]. This recommendation applies to adults and children aged 5 years and older[2]. This recommendation does not apply before 2 years of age and applies in full from 5 years of age. A flexible approach was recommended to the timing and extent of dietary change for individual children between 2 and 5 years (COMA, 1994). The COMA recommendation was based on evidence that "increasing or decreasing the contribution of saturated fats to dietary energy is followed by a rise or fall in serum low density lipoprotein (LDL) cholesterol and in the commensurate risk of coronary heart disease". Since the publication of the 1994 COMA report, a considerable body of research has been published and many

[1] This value was based on total dietary energy (which includes any intake from alcohol). The COMA Dietary reference values report 1991 noted that the corresponding recommendation for food energy (which excludes any intake from alcohol) would be 11%. The 1994 report stated that "the precision of our recommendations does not warrant such a distinction. These do not therefore take account of the small, variable differences between fat as a proportion of total or of food (i.e. excluding alcohol) energy".

[2] COMA also recommended no further increase in the average intakes of n-6 PUFA; an increase in the population average consumption of n-3 PUFA from about 0.1g per day to about 0.2g per day; trans fatty acids should provide no more than the 'current' (as 1994) average of about 2% of dietary energy. COMA made no specific recommendation on MUFA.

organisations, including those from the United States of America, France, the Netherlands and Australia, have reviewed the evidence on the relationship between saturated fats and a range of health outcomes, including cardiovascular disease (CVD) risk, type 2 diabetes risk, cognitive outcomes and various cancers, with most setting similar recommendations to COMA.

Terms of reference

S.4 In October 2015, SACN convened a working group to review the evidence in this area and to ensure that the dietary reference value (DRV) reflects the current evidence base. The terms of reference were to:

- review the evidence for the relationship between saturated fats and health and make recommendations
- review evidence on the association between saturated fats and key risk factors and health outcomes at different life stages for the general UK population.

Methods

S.5 This report considers evidence from systematic reviews, meta-analyses and pooled analyses of randomised controlled trials (RCTs) and prospective cohort studies (PCS). The report examines the relationship between saturated fats and the following health outcomes, intermediate markers and risk factors:

Health outcomes:

- cardiovascular mortality
- cardiovascular events (coronary heart disease (CHD), stroke and peripheral vascular disease)
- type 2 diabetes
- selected common cancers (colorectal, pancreatic, lung, breast and prostate)
- cognitive impairment and dementias (including Alzheimer's disease)

Intermediate markers and risk factors:

- blood lipids (total cholesterol, serum low density lipoprotein (LDL) cholesterol, serum high density lipoprotein (HDL) cholesterol, serum total cholesterol:HDL cholesterol ratio, triacylglycerol)
- blood pressure (systolic and diastolic)
- markers of glycaemic control (fasting blood glucose, fasting insulin, glycated haemoglobin, glucose tolerance, insulin resistance)

- anthropometric measures (weight change, body mass index, waist circumference and gestational weight gain)
- cognitive function (cognitive decline, mild cognitive impairment)

S.6 Systematic reviews, meta-analyses and pooled analyses that met the inclusion criteria were evaluated in line with the SACN Framework for the Evaluation of Evidence (SACN, 2012). Methods used in the SACN Carbohydrates and Health report (SACN, 2015) were also adapted to evaluate the evidence. When evaluating consistency and agreement of findings between reviews, consideration was given to the degree of overlap in the included primary studies. All included evidence was considered when grading the strength of the evidence on a specific outcome. Evidence was graded as adequate, moderate, limited, inconsistent or insufficient. The Committee agreed that only outcomes where the evidence base was graded as adequate or moderate would be used to inform recommendations.

S.7 A number of limitations were identified in some of the available evidence and these were considered as part of the assessment. These included:

- lack of information on statistical power
- limited number of cases and length of follow-up time of RCTs and PCS assessing disease as an outcome
- lack of information on the type of carbohydrates substituted for saturated fats
- lack of information on the type of unsaturated fats substituted for saturated fats
- lack of information distinguishing between PUFA and/or MUFA substitution or different classes of PUFA (for example, n-3 PUFA or n-6 PUFA) in studies substituting with unsaturated fats
- potential confounding by trans fat intakes, particularly in older data
- lack of sufficient data on the range of intakes of saturated fats
- complexity of dietary and other changes made during interventions
- poorly described interventions
- potential confounding (by changes in weight), especially in studies that did not use isoenergetic diets
- quality of methods for measuring dietary intake
- lack of standardisation of some biomarker assays which reduces the comparability of study outcomes
- potential confounding by pharmaceutical treatments (e.g. statins) in blood lipid profile studies
- potential confounding in PCS

- variation in the way 'secondary outcomes', are defined. For example, they may have been part of the search criteria and reported as secondary in terms of objectives and statistical testing or they may have been reported in studies selected for other outcomes. In the latter case, the evidence identified may be incomplete.

Classification, biochemistry and metabolism

S.8 Fats are one of the three macronutrients in our food, a major source of dietary energy and, for most people, the largest store of energy in the body. Fats consist of a glycerol backbone and fatty acids that form bonds with the glycerol. The most common fats in food are triacylglycerols (also called triglycerides) where three fatty acids are bonded to glycerol. The characteristics of fats are determined by the fatty acids they contain. Saturated fatty acids have no double bonds within the fatty acid chain. Monounsaturated fatty acids have a single double bond, while polyunsaturated fatty acids contain two or more double bonds.

S.9 Cholesterol is not a fat but is commonly found in foods containing animal fats. Cholesterol is also synthesised in the body and is an important component of membranes in cells. Only around 15% of cholesterol in the blood comes directly from dietary sources, and the intake of dietary cholesterol generally has a limited impact on cholesterol concentration in the blood.

S.10 One gram of dietary fat has a physiological fuel value of approximately 37 kJ (9 kcal) of energy compared with 17 kJ (4 kcal) per gram for carbohydrates and 17 kJ (4 kcal) per gram for proteins. Fats are largely stored in adipose tissue, often referred to as 'body fat' or simply 'fat'.

Dietary intakes and trends

S.11 The UK population average intake of saturated fats as a percentage of total dietary energy in adults aged 19 to 64 years has fallen since the mid-1980s (when it was around 16% of total dietary energy intake) but there was no change between 2008/09 and 2016/17. National Diet and Nutrition Survey data collected over 8 years between 2008 and 2016 indicated that mean intakes of saturated fats remained above UK Government recommendations. In 2014/15 to 2015/16 mean intakes as a percentage of total dietary energy were 12.4 to 13.0% in children (age 4 to 18 years), and 11.9% (19 to 64 years), 12.5% (65 to 74 years) and 14.3% (75years and over) in adults (Roberts et al, 2018). Saturated fat intake as a percentage of food energy increased on average by 0.1 to 0.2 percentage points for every £10,000 increase in equivalised income, for all age groups except children aged 1½ to3 years, although the differences did not reach statistical significance in all age/sex groups(Bates et al, 2019b).

S.12 Cereals and cereal products (mainly biscuits, buns, cakes, pastries and fruit pies), milk and milk products (mainly cheese and milk), and meat and meat products were the main contributors to saturated fat intake in all age groups. Milk and milk products (especially whole milk) made a larger contribution for children aged 4 to 10 years compared to other age groups (Roberts et al, 2018).

S.13 The main sources of saturated fats have changed little between 1986/87 and 2008/16. The overall percentage contribution of milk and milk products to daily saturated fat intake remained unchanged at around 21%. A notable decline in whole milk consumption led to a reduction in the contribution of whole milk to saturated fats from approximately 11% to 2% of the average daily saturated fat intake in adults. The contribution of fat spreads and butter to saturated fat intake has declined (from approximately 17% to 9% of the average daily saturated fat intake) mainly due to a decreased intake of butter, especially among adults aged 19 to 64 years (Roberts et al, 2018).

S.14 The National Diet and Nutrition Survey data indicated that between 2008 and 2016 there has been virtually no change in mean serum total cholesterol, LDL cholesterol and total cholesterol:HDL cholesterol ratio in adults and older adults. Comparison cannot be made with findings from earlier surveys (for example, 1986/87, 1994/5 and 2000/01) due to methodological differences.

Overall conclusions

S.15 Since 1994, the evidence base on saturated fats and health has grown considerably. In addition to further research on the blood lipid profile, a significant body of evidence on other intermediate factors, risk markers and health outcomes is now available. This evidence has been considered in a number of published meta-analyses and systematic reviews. This report is based on a further assessment of this evidence, with precedence given to evidence from RCTs and evidence graded as adequate or moderate. SACN considered the saturated fats recommendations in the context of existing UK Government dietary recommendations on macronutrients and energy. The SACN recommendations presented here are based on the totality of the evidence considered, including null findings, where the evidence was graded as *moderate* or *adequate*.

S.16 New evidence published since 1994 supports and strengthens the COMA conclusion that a reduction in intake of saturated fats from current population average levels would be beneficial.

S.17 Table S1 provides a summary of SACN's review of the evidence. Findings which did not inform the development of recommendations – because the quality of the evidence was not considered to be adequate or moderate – are shaded grey.

S.18 SACN noted a lack of evidence for a range of outcomes but considered the totality of evidence, which included significant effects or associations in relation to outcomes of major public health concern. The evidence indicates that reducing saturated fats reduces the risk of CVD and CHD events, lowers total, LDL and HDL cholesterol and improves indicators of glycaemic control. The evidence also indicates that reducing saturated fats is unlikely to increase health risks for the general UK population. SACN concluded that reducing population average saturated fat intakes from current levels of intake to no more than about 10% of [total] dietary energy would result in health benefits to the population.

S.19 There were significant relationships between intake of saturated fats and CVD and CHD events, but not CVD and CHD mortality. SACN noted that, irrespective of the lack of evidence for an effect on mortality, non-fatal CVD and CHD events have a serious adverse impact on health and quality of life.

S.20 In relation to what should take the place of saturated fats in the diet, more evidence is available from RCTs for substitution with PUFA than for substitution with MUFA, carbohydrates or proteins, in relation to CVD and CHD outcomes. Furthermore, there was evidence, though from PCS rather than RCTs, that substituting saturated fats with carbohydrates was associated with increased CHD events. Substituting saturated fats with PUFA and/or MUFA lowered serum LDL cholesterol, but had no effect on serum HDL cholesterol. Substituting saturated fats with carbohydrates lowered serum LDL and HDL cholesterol. For markers of glycaemic control, substitution of saturated fats with PUFA was more beneficial than substitution with MUFA and there was evidence of no benefit for substitution with carbohydrates.

S.21 There were gaps in the evidence considered. In particular, there was less evidence available for substituting saturated fats with MUFA compared to substitution with PUFA. There was also less evidence available for substitution with carbohydrates or proteins compared to substitution with PUFA. The available evidence on carbohydrates was further complicated by the fact that studies often did not describe the type of carbohydrates.

S.22 SACN was mindful that if all substitution of saturated fats was with PUFA alone this could increase the proportion of the population consuming in excess of about 10% energy from PUFA; at odds with current UK Government dietary recommendations.

S.23 There was limited evidence in children and older age groups. SACN concluded that the available evidence did not provide a basis for changing the existing recommendation for these age groups.

Recommendations

S.24 It is recommended that:

- the dietary reference value for saturated fats remains unchanged: the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than about 10%. This recommendation applies to adults and children aged 5 years and older.
- saturated fats are substituted with unsaturated fats. More evidence is available supporting substitution with PUFA than substitution with MUFA.

S.25 This recommendation is made in the context of existing UK Government recommendations for macronutrients and energy.

S.26 It is recommended that the government gives consideration to strategies to reduce the [population] average contribution of saturated fatty acids to [total] dietary energy to no more than about 10%. Risk managers should be mindful of the available evidence in relation to substitution of saturated fats with different types of unsaturated fats and ensure that strategies are consistent with wider dietary recommendations, including trans fats.

Research recommendations

S.27 While discussing the evidence considered for this report, SACN noted gaps in the evidence base relating saturated fats to health; the Committee has therefore made a number of recommendations for research which are set out in Chapter 17.

Table S1: Summary table of the evidence on the relationship between saturated fats and health outcomes, intermediate markers and risk factors

	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
Outcome	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Cardiovascular diseases (RCTs)										
CVD mortality	-	Adequate	-	Adequate	n/a	Insufficient	-	Limited	-	Limited
CVD events	↓	Adequate	↓	Adequate	n/a	Insufficient	-	Limited	-	Limited
CHD mortality	-	Adequate	-	Adequate	n/a	Insufficient	-	Limited	-	Limited
CHD events	↓	Moderate	↓	Moderate	n/a	Insufficient	-	Moderate	-	Moderate
Strokes	-	Adequate	n/a	Insufficient	n/a	No evidence	-	Limited	-	Limited
Peripheral vascular disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Cardiovascular diseases (PCS)										
CVD mortality	-	Adequate	↓	Limited[1]	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CVD events	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CHD mortality	↓	Moderate[2]	↓	Moderate	-	Limited	-	Adequate	n/a	No evidence
CHD events	↓	Moderate[2]	↓	Moderate	↑	Limited	↑	Adequate	n/a	No evidence
Strokes	-	Adequate[3,4]	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Peripheral vascular disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Blood lipids (RCTs)										
Total cholesterol	↓	Adequate	↓	Adequate[5]	↓	Adequate[5]	↓	Adequate	n/a	No evidence
LDL cholesterol	↓	Adequate	↓	Adequate	↓	Adequate	↓	Adequate	n/a	No evidence
HDL cholesterol	↓	Moderate[6]	-	Moderate	-	Moderate	↓	Moderate	n/a	No evidence
Total:HDL cholesterol	↓	Limited	-	Limited	-	Limited	-	Adequate	n/a	No evidence
Triacylglycerol	-	Adequate	-	Adequate	-	Adequate	↑	Moderate	n/a	No evidence
Blood lipids (PCS)										
Total cholesterol	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	No evidence
LDL cholesterol	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	No evidence
HDL cholesterol	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Total:HDL cholesterol	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Triacylglycerol	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Blood pressure (RCTs)										
Blood pressure	-	Limited	-	Limited	-	Limited	-	Limited	n/a	No evidence
Blood pressure (PCS)										
Blood pressure	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence	n/a	No evidence

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Type 2 diabetes and markers of glycaemic control (RCTs)										
Type 2 diabetes	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence
Fasting glucose	n/a	No evidence	↓	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Fasting insulin	n/a	No evidence	-	Adequate	↑	Adequate	↑	Adequate	n/a	No evidence
HbA1c	n/a	No evidence	↓	Adequate	↓	Adequate	-	Adequate	n/a	No evidence
Glucose tolerance	n/a	Insufficient	-	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Insulin resistance by homeostasis model assessment (HOMA)	n/a	Insufficient	↓	Adequate	↓	Adequate	-	Adequate	n/a	No evidence
Insulin resistance by infusion	n/a	No evidence	-	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Type 2 diabetes and markers of glycaemic control (PCS)										
Type 2 diabetes	-	Adequate	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence
Fasting glucose	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Fasting insulin	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
HbA1c	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Glucose tolerance	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Insulin resistance by homeostasis model assessment (HOMA)	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Insulin resistance by infusion	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Anthropometry (RCTs)										
Anthropometric measurements	n/a	Inconsistent	-	Adequate[7]	-	Adequate[7]	n/a	No evidence	n/a	No evidence
Gestational weight gain	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Anthropometry (PCS)										
Anthropometric measurements	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Gestational weight gain	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Cancers (RCTs)										
Colorectal cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Pancreatic cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Lung cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Breast cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Prostate cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Cancers (PCS)										
Colorectal cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Pancreatic cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Lung cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Breast cancer	-	Adequate	-	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Prostate cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Dementias and cognitive function (RCTs)										
Cognitive decline	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Mild cognitive impairment	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Alzheimer's disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Dementias	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Dementias and cognitive function (PCS)										
Cognitive decline	n/a	Inconsistent	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Mild cognitive impairment	-	Limited	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Alzheimer's disease	n/a	Inconsistent	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Dementias	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

n/a- not enough evidence to draw conclusions

Direction of effect for reported outcomes: ↑increased; ↓decreased; - no effect/association

[1] Limited evidence indicated that the substitution of saturated fats with a mixture of PUFA and MUFA decreased the risk of CVD mortality

[2] Reviews considered 'CHD outcomes' which included CHD mortality and/or events.

[3] Adequate evidence indicated that there was no association between lower intake of saturated fats and ischaemic strokes

[4] Limited evidence indicated that lower intake of saturated fats was associated with a higher risk of haemorrhagic strokes in Japanese populations living in Japan and total strokes in East-Asian populations living in East Asia

[5] Adequate evidence indicated that the substitution of saturated fats with a mixture of PUFA and MUFA decreased serum total cholesterol

[6] Moderate evidence indicated that lower saturated fat intake reduced HDL cholesterol in adults, however there was adequate evidence of no effect in children

[7] Adequate evidence indicated that the substitution of saturated fats with a mixture of PUFA and MUFA had no effect on body weight, body fat %, fat mass and waist circumference. There was insufficient evidence to draw a conclusion on the effect of the substitution of saturated fats with a mixture of PUFA and MUFA on fat mass

1 Introduction

Background

1.1 In June 2014, the Scientific Advisory Committee on Nutrition (SACN) considered undertaking a review of the evidence of the role of fats in health, including monounsaturated fats (MUFA), polyunsaturated fats (PUFA) and saturated fats. The topic had been suggested as part of the horizon scanning process and specific advice on saturated fats was requested by the Food Standards Agency (Scotland) (now Food Standards Scotland). A scoping exercise highlighted a large evidence base. It was agreed that a review of the evidence on saturated fats was most pressing.

1.2 This report considers the relationship between saturated fats, health outcomes and risk factors for non-communicable diseases in the general UK population. This report does not consider total fat in the diet, individual saturated fatty acids, or the role of unsaturated fats other than as a replacement for saturated fats. This report also does not consider specific foods or food groups. A potential risk assessment of other fatty acids will be considered by SACN in the future.

1.3 The role of saturated fats in health was last considered by the Committee on Medical Aspects of Food Policy (COMA, the predecessor of SACN) in the following reports: Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (COMA, 1991) and Nutritional Aspects of Cardiovascular Disease (COMA, 1994).

1.4 COMA recommended in 1994 that the [population] average contribution of saturated fatty acids to [total][3] dietary energy be reduced to no more than about 10%. This recommendation applies to adults and children aged 5 years and older[4]. This recommendation is set at a population level, does not apply before 2 years of age, and applies in full from the age of 5 years. A flexible approach was recommended to the timing and extent of dietary change for individual children between 2 and 5 years (COMA, 1994). This advice was based on evidence that "increasing or decreasing the contribution of saturated fats to dietary energy is followed by a rise or fall in low density lipoprotein (LDL)

[3] This value was based on total dietary energy (which includes any intake from alcohol). The COMA Dietary reference value report 1991 noted that the corresponding recommendation for food energy (which excludes any intake from alcohol) would be 11%. The 1994 report stated that "the precision of our recommendations does not warrant such a distinction. These do not therefore take account of the small, variable differences between fat as a proportion of total or of food (i.e. excluding alcohol) energy".

[4] COMA also recommended no further increase in the average intakes of n-6 PUFA and the proportion of the population consuming in excess of about 10% of energy should not increase; an increase in the population average consumption of n-3 PUFA from about 0.1g per day to about 0.2g per day; trans fatty acids should provide no more than the 'current' (as 1994) average of about 2% of dietary energy. COMA made no specific recommendation on MUFA. Also see Table 16.1 in Chapter 16.

cholesterol and in the commensurate risk of coronary heart disease". Since then many public health and research organisations have reviewed the evidence on saturated fats and a range of additional health outcomes including the risk of type 2 diabetes, dementias and various cancers (including colorectal, pancreatic, lung, breast and prostate) (see Table 4.1).

Terms of reference

1.5 In October 2015, SACN convened a working group to review the evidence in this area and to ensure that the dietary reference value reflects the current evidence base. The terms of reference were to:

- review the evidence for the relationship between saturated fats and health and make recommendations.
- review evidence on the association between saturated fats and key risk factors and health outcomes at different life stages for the general UK population.

2 Methods

Eligibility criteria and literature search

2.1 Public Health England's (PHE) Knowledge and Library Services team conducted an online database search for systematic reviews, meta-analyses and pooled analyses of randomised controlled trials (RCTs) and prospective cohort studies (PCS), examining the relationship between saturated fats and the following health outcomes, intermediate markers and risk factors.

Health outcomes:

- cardiovascular mortality
- cardiovascular morbidity (coronary heart disease (CHD), stroke (including ischaemic and haemorrhagic) and peripheral vascular disease)
- type 2 diabetes
- selected common cancers (colorectal, pancreatic, lung, breast and prostate)
- cognitive impairment and dementias (including Alzheimer's disease)

Intermediate markers and risk factors:

- blood lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, total cholesterol:HDL cholesterol ratio, triacylglycerols)
- blood pressure (systolic and diastolic)
- markers of glycaemic control (fasting blood glucose, fasting insulin, glycated haemoglobin (HbA1c), glucose tolerance, insulin resistance (assessed by homeostasis model assessment (HOMA) or infusion))
- anthropometric measurements (body weight, body mass index (BMI), waist circumference and gestational weight gain)
- cognitive function (cognitive decline, mild cognitive impairment)

2.2 In keeping with SACN's Framework for the Evaluation of Evidence, this report is based primarily on evidence provided by systematic reviews and meta-analyses of RCTs and PCS (SACN, 2012). Systematic reviews and meta-analyses provide a comprehensive and quantitative analysis of the research in a particular field thereby reducing the potential for bias.

2.3 Additional eligibility criteria included: English language publications, published in peer-reviewed scientific or medical journals between 1991 and March 2016. No geographical restriction was applied. The search started from 1991 when the COMA dietary reference values (DRVs) report was published, as the 1994 COMA Nutritional Aspects of Cardiovascular Disease report only considered the health outcome cardiovascular disease

(CVD). The following were excluded: primary research studies, systematic reviews and meta-analyses of case-control or cross-sectional studies, non-systematic reviews, published abstracts, grey literature such as dissertations, conference proceedings, magazine articles, books/book chapters, opinion pieces, information from websites, reports and other non-peer reviewed articles. Analyses that focused solely on diseased populations were also excluded because SACN provides advice for the general population and does not make recommendations related to clinical management.

2.4 EMBASE, MEDLINE, the Cochrane Library and Scopus were searched, using the search terms outlined in Annex 1, for relevant publications meeting the inclusion criteria, between 1991 and March 2016. SACN also invited interested parties to highlight relevant evidence which satisfied the inclusion criteria for the report. The call for evidence, which was placed on the SACN website, opened on 25 May 2016 and closed on 15 June 2016. Reference lists of all included publications (identified through the online database search or highlighted by members of the Saturated Fats Working Group and interested parties, up to March 2017) were hand searched. Reference lists of relevant reviews by international organisations were also considered. In addition, the draft report was made available for public consultation (8 May to 3 July 2018) and interested parties were invited to alert the committee to any evidence that it may have missed. Evidence highlighted through the consultation process or that had been published after March 2017 was considered by the committee. The report was amended if newly available evidence added substantial nuance or update to existing work or changed existing conclusions.

Selection of studies

2.5 After removing duplicates, titles and abstracts of the identified publications were screened by 2 reviewers for eligibility. Publications were rejected on initial screen if the reviewers could determine from the title and abstract that it did not meet the inclusion criteria. Differences were resolved by discussion. The full texts of potentially eligible publications were obtained and again screened by 2 reviewers with differences resolved by discussion. Where uncertainty remained, advice from the Saturated Fats Working Group was sought.

2.6 After the duplicates were removed, 996 abstracts, identified through the online database search, were screened for eligibility. Of these, full texts of 68 potentially relevant publications were retrieved and screened, 29 of which met the inclusion criteria. Forty additional publications were highlighted by interested parties through the call for evidence. After consideration by the Saturated Fats Working Group it was agreed that 5 of these publications met the inclusion criteria. Three additional publications were identified through hand searching of reference lists. Four additional publications were identified from other sources; 2 by members of the Saturated Fats Working Group during drafting; 2 which were published after the closing date for the call for evidence and submitted by an

interested party. Six publications were added after public consultation. In total, 47 systematic reviews, meta-analyses and pooled analyses were included. Figure 2.1 displays the flow diagram for inclusion of studies.

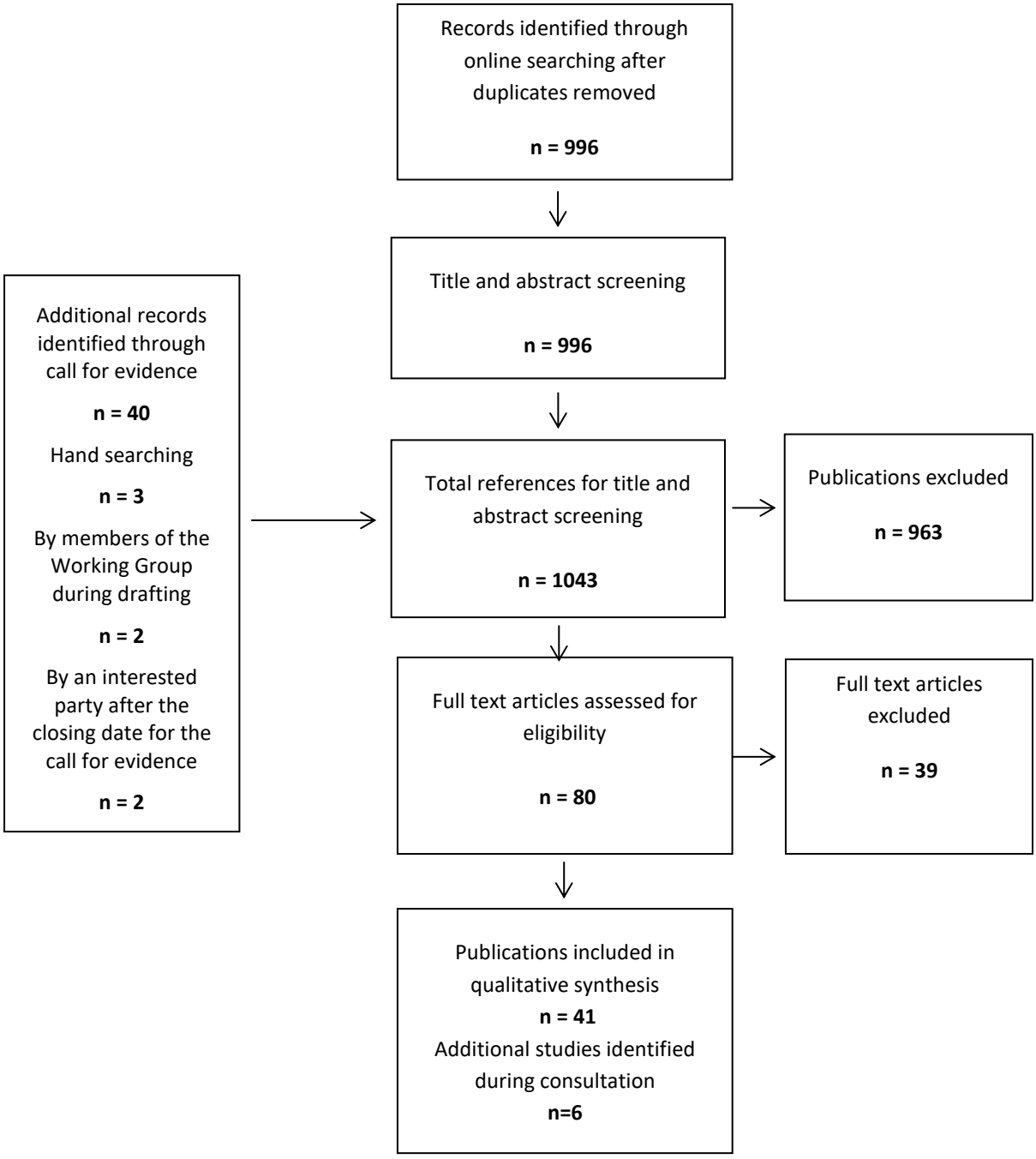

Figure 2.1. Flow diagram showing the number of publications assessed for eligibility and included in the report.

Data extraction

2.7 Relevant data from each of the included systematic reviews, meta-analyses and pooled analyses were extracted into tables (see Annex 2). Extracted data included the name of the first author, year of publication, research question, selection criteria, statistical analysis,

assessment of study quality, total number of participants, mean duration of study, demographics and results. Data on location, dietary assessment methods used and the study design of the primary evidence, as reported in the systematic reviews, meta-analyses and pooled analyses, were also extracted into the table. Percent energy from saturated fats (total or change) was reported where available (either in the text or associated annexes). The units in which the values for serum total cholesterol, serum LDL cholesterol, serum HDL cholesterol, serum triacylglycerol and HbA1c were expressed differed across studies. To convert serum total cholesterol, serum LDL cholesterol and serum HDL cholesterol from mg/dL to mmol/L, values were divided by 38.67; for serum triacylglycerol values were divided by 88.57[5]. The conversion tool for HbA1c can be found on the Diabetes UK website[6].

2.8 To help identify the individual primary studies included in each of the eligible systematic reviews, meta-analyses and pooled analyses, the first author and year of publication of the primary studies were tabulated (see Annex 2).

AMSTAR assessment

2.9 For each eligible publication, the methodological quality was assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR)[7]. The quality assessment tool for systematic reviews and meta-analyses was selected by applying potential assessment tools (AMSTAR and The Joanna Briggs Institute Critical Appraisal tool[8]) to 5 example publications identified through a literature search and comparing the findings. Limitations were identified across both tools, but AMSTAR was selected because it is more widely recognised and used by other organisations (for example, the United States of America (USA) Dietary Guidelines Advisory Committee and Nordic Council of Ministers) than other tools and the working group agreed that the AMSTAR questions provided a more useful assessment of quality. AMSTAR consists of 11 questions.

2.10 The methodological quality of each eligible publication was assessed by 2 reviewers and any differences were resolved by discussion between assessors. If the reviewers were unable to resolve differences, advice was sought from the Saturated Fats Working Group.

[5] https://www.heartuk.org.uk/downloads/health-professionals/factsheets/cholesterol---triglyceride-levels-conversion.pdf
[6] https://www.diabetes.org.uk/guide-to-diabetes/managing-your-diabetes/hba1c
[7] https://amstar.ca/Amstar_Checklist.php
[8] https://joannabriggs.org/critical_appraisal_tools

Methods for reviewing evidence

2.11 SACN considered systematic reviews, meta-analyses and pooled analyses that met the inclusion criteria. Chapters on saturated fats and health outcomes, intermediate markers and risk factors were initially drafted by members of the Saturated Fats Working Group. These chapters provided the basis for the working group's discussions with the final text, conclusions and recommendations, discussed and agreed with the SACN main Committee.

2.12 This draft report was made available for public consultation and the comments received from interested parties were taken into consideration before the report was finalised.

Grouping of evidence by research question

2.13 While some systematic reviews, meta-analyses and pooled analyses reported on the same health outcome, intermediate marker or risk factor, publications may have addressed different research questions. For example, some of the identified publications considered highest versus lowest intakes of saturated fats while others looked at the substitution of saturated fats with other fat classes or macronutrients. It is not appropriate to directly compare the findings of such evidence together (see paragraph 2.20); therefore, publications providing evidence for each of the health outcomes, intermediate markers or risk factors were subdivided according to the research questions (for example, reduction of saturated fats per se vs specified substitutions) considered in the publication.

Evaluation of the quality of identified evidence

2.14 The quality of included systematic reviews, meta-analyses and pooled analyses was assessed using:

- the SACN Framework for the Evaluation of Evidence (SACN, 2012)
- the AMSTAR tool
- the methods outlined in SACN's report on Carbohydrates and Health (which was based on primary studies) (SACN, 2015), which were modified for use in this report

The criteria considered were:

Systematic reviews, meta-analyses and pooled analyses

- scope and aims
- search dates (publication dates of studies included in the reviews or meta-analyses)
- inclusion and exclusion criteria
- number of primary studies and total number of participants and number of events

- conduct and reporting of pre-specified outcomes consistent with a registered protocol

Primary studies considered within systematic reviews/meta-analyses

- whether the primary studies were RCTs or PCS
- exposure/intervention duration and follow-up
- components of the diet that were considered or manipulated in the case of trials
- populations considered and relevant characteristics (for example, dietary fat intakes, presence of disease, relevant medication usage, smoking habits, physical activity levels, ethnicity or changes in relevant risk factors)
- quality of the dietary assessment methods and outcome assessment methods
- quality and appropriateness of the laboratory methods used

Interpretation of results and their analysis

- appropriateness of statistical methods used
- whether and which confounding factors were taken into account (where relevant)
- consistency of the effect/association (taking account of overlap in the primary studies considered)
- heterogeneity – an I^2 statistic of 0-25% was considered to represent low heterogeneity, 26-75% was considered to represent medium heterogeneity and >75% was considered to represent high heterogeneity. While a high I^2 statistic reflects uncertainty regarding the value of the pooled estimate, it does not necessarily reflect uncertainty regarding the direction of the effect/association (which may be consistent across studies)
- direction and size of effect and statistical significance
- results of sub-group and sensitivity analyses

2.15 In keeping with the SACN Framework for the Evaluation of Evidence (SACN, 2012), the word '*effect*' was used to describe the evidence from RCTs and the word '*association*' was used when referring to evidence from PCS. An effect/association was deemed to be statistically significant using the $p<0.05$ criterion.

Approach to considering statistical models

2.16 The results of 2 statistical models of meta-analysis, fixed-effect and random-effects, are increasingly being reported in systematic reviews. There are differences in the underlying assumptions and statistical considerations of the models. Random-effects models generally give proportionally more weight to small studies than to large studies, whereas fixed-effect models give weight in direct proportion to the size of the primary studies.

However, it should be noted that the choice of models and their interpretation remains an area of debate among statisticians.

2.17 More detailed information on differences between the 2 models can be found in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook).

2.18 SACN used the following approach when considering the results of the meta-analyses:

a) Where the results of only 1 model (that is, fixed-effect or random-effects) were stated in a publication, the results of this meta-analysis were reported by SACN and used to draw conclusions.

b) Where the results of both models were stated in a publication, these were reported by SACN. The Committee considered the appropriateness of the model assumptions, the direction and magnitude of the effect, statistical significance, and the level of agreement between the models. Where the results of the models differed, the totality of the evidence and expert judgement were used to draw conclusions and this was considered in the final grading of the evidence (see Grading of evidence below).

Grading of evidence

2.19 SACN used expert judgement, based on the criteria below, to grade the evidence. When evaluating consistency and agreement between reviews, consideration is given to the degree of overlap in the primary studies considered. The Committee agreed that only outcomes where the evidence base was graded as *adequate* or *moderate* would be used to inform recommendations.

Strength of evidence	**Explanatory notes**
Adequate	There is *adequate* evidence to make a decision about the effect/association of a factor(s)/intervention(s) in relation to a specific outcome. Taking into account overlap of primary studies included in the identified publications, the evidence from meta-analyses goes in the same direction. The results of meta-analyses are statistically significant or, in the case of systematic reviews without meta-analysis, there is convincing evidence of

Strength of evidence	Explanatory notes
	a consistent significant effect/association in the primary studies considered. Effects/associations are also consistent when major population sub-groups or other relevant factors are considered in additional analyses. The identified publications are considered to be of good quality based on the key factors listed above. The inclusion and exclusion criteria of the identified publications are well defined and appropriate. A judgement of *adequate* evidence is also made based on the number, size, quality and durations/follow-ups of randomised controlled trials and/or prospective cohort studies included in the identified systematic reviews, meta-analyses and pooled analyses. Where only 1 systematic review, meta-analysis or pooled analysis is identified on a specific outcome, evidence is considered *adequate* if the publication reports primary data from ≥ 3 randomised controlled trials or ≥ 5 cohort studies, of *adequate* size, considered to be of good quality and which were included in a meta-analysis or pooled analysis. Alternatively, for a single systematic review when a meta-analysis or pooled analysis is not conducted, evidence may be considered *adequate* if a total of ≥ 4 randomised controlled trials or ≥ 5 cohort studies, of *adequate* size and considered to be of good quality, consistently went in the same direction.
Moderate	There is *moderate* evidence (therefore less conclusive) to make a decision about the effect/association of a factor(s)/intervention(s) in relation to a specific outcome. Taking into account overlap of primary studies included in the identified publications, the majority of the evidence from meta-analyses goes in the same direction. The results of meta-analyses are statistically significant or, in the case of systematic reviews without meta-analysis, there is *moderate* evidence of a consistent significant effect/association in the primary studies considered.

Strength of evidence	Explanatory notes
	Effects/associations may be less consistent when major population sub-groups or other relevant factors are considered in additional analyses. The identified publications are considered to be of *moderate* to good quality based on the key factors listed above. The inclusion and exclusion criteria of the identified publications are reasonably well defined and generally appropriate. Compared to evidence considered *adequate*, there may be fewer and smaller randomised controlled trials and/or prospective cohort studies, of *moderate* quality with sufficient durations/follow-ups, included in the identified systematic reviews, meta-analyses and pooled analyses. Where only 1 systematic review, meta-analysis or pooled analysis is identified on a specific outcome, evidence is considered *moderate* if the publication reports primary data from ≥3 randomised controlled trials or 3-4 cohort studies of *moderate* size, considered to be of *moderate* quality and which were included in a meta-analysis or pooled analysis. Alternatively, for a single systematic review when a meta-analysis or pooled analysis was not conducted, evidence may be considered *moderate* if a total of ≥ 3 randomised controlled trials or ≥ 5 cohort studies, of *moderate* size and considered to be of *moderate* quality, consistently went in the same direction.
Limited	There is *limited* evidence (therefore, even less conclusive) to make a decision about the effect/association of a factor(s)/intervention(s) in relation to a specific outcome. Taking into account overlap of primary studies included in the identified publications, the majority of the evidence from meta-analyses goes in the same direction. The results of meta-analyses are statistically significant or, in the case of systematic reviews without meta-analysis, there is *limited evidence* of a consistent significant effect/association in the primary studies considered. Effects/associations may be inconsistent when major population sub-groups or other relevant factors are considered in additional analyses.

Strength of evidence	Explanatory notes
	The identified publications are considered to be of poor to moderate quality based on the key factors listed above. The inclusion and exclusion criteria of the identified publications are not well defined and may not be appropriate. Compared to evidence considered *adequate* or *moderate*, there may be fewer and smaller randomised controlled trials and/or prospective cohort studies, of low quality with inadequate durations/follow-ups, included in the identified systematic reviews, meta-analyses and pooled. Where only 1 systematic review, which did not include a meta-analysis, is identified on a specific outcome, evidence was considered *limited* if primary data from 3 to 4 randomised controlled trials or prospective cohort studies of *limited* size and considered to be of low quality were identified but there was some evidence that the results were in the same direction.
Inconsistent	There is *inconsistent* evidence after taking into account the above quality criteria and overlap of primary studies included in the identified systematic reviews, meta-analyses and pooled analyses, the results in relation to a specific outcome are conflicting and it is not possible to draw a conclusion.
Insufficient	There is *insufficient* evidence as a result of no systematic reviews, meta-analyses or pooled analyses of appropriate quality identified in relation to a specific outcome or, in a single review or analysis, <3 to 4 eligible randomised controlled trials or cohort studies were identified. Therefore, it is not possible to draw conclusions.

Limitations of evidence

2.20 A number of limitations were identified in some of the available evidence and considered as part of the assessment of the evidence. These are briefly summarised below.

- Studies with low statistical power have a lower chance of detecting a true effect. A common problem for the systematic reviews and meta-analyses considered, particularly with the included RCTs, was the statistical power of the original or combined studies. This was rarely reported in the reviews and no attempt was made

here to do this retrospectively but, where sample sizes were clearly small, this was noted.

- RCTs or PCS are typically only conducted for a small number of months or years and participants in cohort studies often followed for limited numbers of years, whilst the chronic diseases considered here typically develop over decades. For disease outcomes, the number of cases and duration may be a consideration when interpreting analyses which report no effect or association.
- Studies that substituted saturated fats with carbohydrates generally did not specify or undertake analyses which considered the type of carbohydrates. Different types of carbohydrates could have different effects/associations (for example, those with differing free sugars content; whole grains compared to refined starch)[9].
- Studies that substituted saturated fats with polyunsaturated fats (PUFA) generally did not consider the possible effects of different classes of PUFA (for example n-3 and n-6 PUFAs).
- Studies that substitute saturated fats with unsaturated fatty acids do not always distinguish between PUFA and/or MUFA substitution or different classes of PUFA (for example, n-3 PUFA or n-6 PUFA), therefore it is assumed to be a mixture of PUFA and MUFA used in the substitution.
- The results of older studies (pre-1990s) which substituted saturated fats with unsaturated fats may have been confounded by the presence of trans fats, which are known to have a detrimental impact on health (see paragraph 7.8). Trans fats were not consistently measured, monitored or reported in studies before the 1990s.
- The majority of systematic reviews and meta-analyses either compared the 'highest' with 'lowest' intakes of saturated fats or assessed the impact of a percentage change in (energy from) saturated fats without indicating the numerical values of intakes (for example, mean intake/range of intakes).
- In many cases, analyses of the effect of saturated fats included trials where there were reductions in the intakes of both saturated and total fats, which limit the ability to attribute the observed effects solely to a change in intakes of saturated fats.
- The dietary interventions in the trials considered were often complex, resulting in changes in more than just intake of saturated fats. Interventions which were not isoenergetic can also result in changes in body weight and BMI which themselves may influence disease risk and markers such as HDL and LDL cholesterol. Differences in body weight and/or total energy between categories of intake of saturated fats may also be relevant to PCS and other epidemiological evidence.

[9] More detailed information is available at: https://www.gov.uk/government/publications/sacn-carbohydrates-and-health-report

- Measurement errors associated with different dietary assessment methods contribute to a lack of precision around some estimates of effect, which may be a significant factor in some studies.
- HOMA assays are not standardised and HbA1c assays only became standardised in 2000. Therefore, the comparison of the data across different studies including these outcomes must be interpreted with caution.
- The results of the impact of dietary interventions on blood lipids may have been confounded by pharmaceutical treatments (for example, statins) in the studies published after 1990 due to a sharp increase in prescriptions of statins in the 1990s.
- Prospective cohort studies are potentially subject to bias, confounding and reverse causality.[10]
- There is variation in the way 'secondary outcomes' are defined. For example, they may have been part of the search criteria and reported as secondary in terms of objectives and statistical testing or they may have been reported in studies selected for other outcomes. In the latter case, the evidence identified may be incomplete.

2.21 A number of limitations of the remit of this report were also identified. These are briefly summarised below.

- Saturated fats is a collective term for a number of different saturated fatty acids (see Chapter 3). There is evidence showing that individual saturated fatty acids may exert distinct effects on lipid metabolism and therefore have a differential impact on health. Consideration of the impact of individual saturated fatty acids was outside the scope of this report.
- Consideration of specific foods/food groups rich in saturated fats was outside the scope of the report.

[10] More information available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/480493/SACN_Framework_for_the_Evaluation_of_Evidence.pdf

3 Classification, biochemistry and metabolism

3.1 Fats (and oils) are one of the three major macronutrients in our food, a major source of energy and the largest store of energy in the body. The Oxford English Dictionary defines fats as “Any of a group of natural esters of glycerol and various fatty acids, which are solid at room temperature and are the main constituents of animal and vegetable fat.”

3.2 In addition to fats, other common related terms used for this class of macronutrients are oils and lipids. The term oil is used to describe fats that are liquid at room temperature. Lipids “are fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds” (Christie, 1987). Thus, fats can be seen to be a sub-group of the larger chemical classification of lipids.

Chemical classification

3.3 Fats consist of a glycerol backbone and fatty acids that form ester bonds with the glycerol (Figure 3.1). Each fatty acid consists of a carboxylic acid group which forms the ester bond, and an aliphatic, hydrophobic chain consisting of carbon and hydrogen. Fats in food are predominantly in the form of triacylglycerols (also called triglycerides), where 3 fatty acids are esterified to glycerol, though smaller amounts of diacylglycerols (diglycerides; 2 fatty acids) and monoacylglycerols (monoglycerides; 1 fatty acid) may also be present.

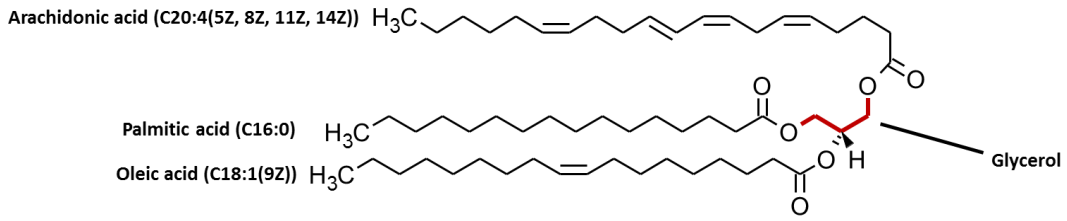

Figure 3.1. Chemical structure of a typical triacylglycerol. Triacylglycerols consist of 3 fatty acids each forming an ester bond with glycerol (shown in red). The example above shows a triacylglycerol formed by esterification with the 3 different fatty acids palmitic acid, oleic acid and arachidonic acid, though a variety of fatty acids are found in triacylglycerols.

3.4 The characteristics of fats are determined by the fatty acids they contain (Berg et al, 2012a). Saturated fatty acids have no double bonds. Monounsaturated fatty acids (MUFA) have a single double bond, while polyunsaturated fatty acids (PUFA) contain two or more double bonds (Figure 3.2). Naturally occurring fatty acids predominantly have *cis* double bonds, where the alkyl chain of the fatty acid is on the same side for the double bond. In addition, the industrial process of hydrogenation of unsaturated fats can produce trans fatty acids where the alkyl groups are on opposite side of the double bond. Increasing the number of double bonds lowers the melting point of fatty acids while increasing chain length increases the melting point. The fatty acid chains give fats their hydrophobic nature.

The biologically important n-3 (or omega-3) and n-6 (or omega-6) polyunsaturated fatty acids are so called because they have a double bond either 3 or 6 carbons from the n-terminus of the fatty acid chain.

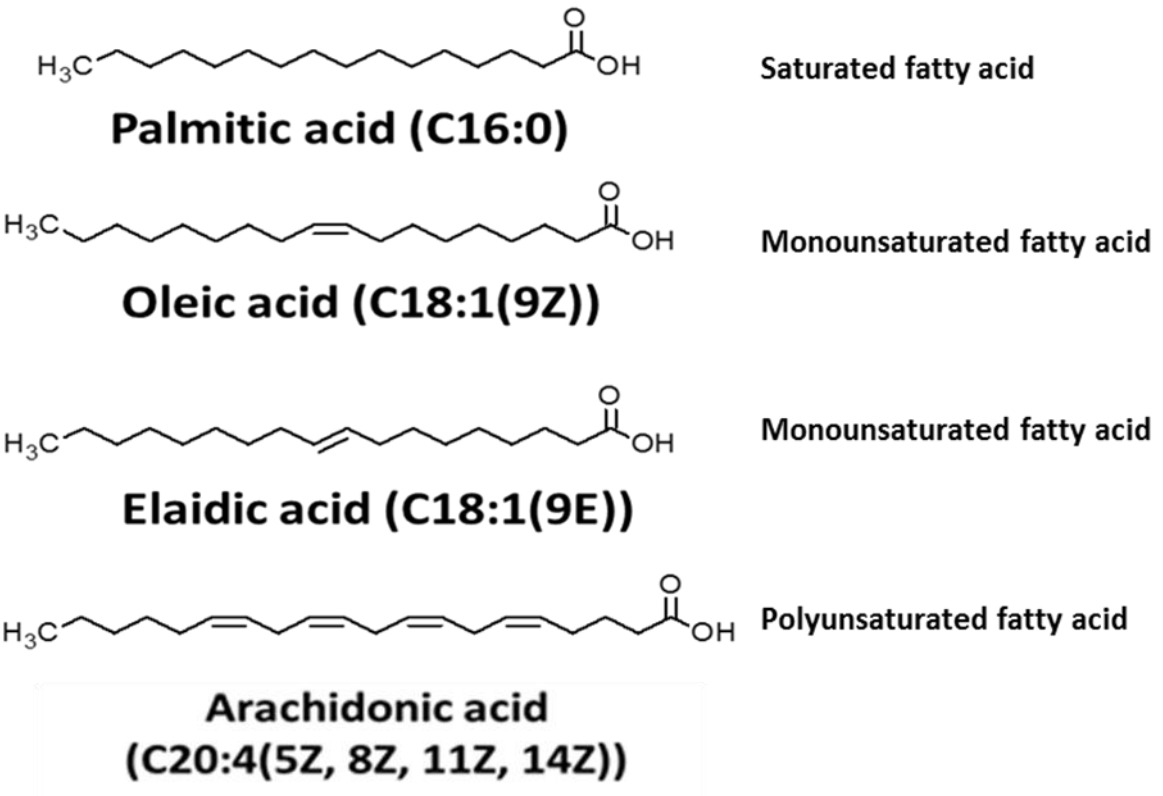

Figure 3.2. The structure of some different types of fatty acids. Double bonds influence the geometry of fatty acids, *cis* double bonds have the carbon chain on the same side of the double bond, while trans fatty acids are on opposite sides of the double bond. The double bonds have profound effects on the physicochemical properties of fats such as membrane fluidity.

3.5 Humans cannot synthesise the n-3 or n-6 double bond structure, therefore essential fats with this structure have to be ingested. Only 2 fatty acids are considered to be essential in the diet: linoleic (18:2 n-6) and *α*-linolenic (18:3 n-3). Once ingested, humans have the enzymes necessary to generate a range of more complex fatty acids, including the long chain polyunsaturated fatty acids (LCPUFAs), from these precursors. The majority of fatty acids consumed in the diet consist of an even number of carbons as part of their structure. However, dairy sources of fats contain small quantities of fatty acids with an odd number of carbons that are derived from microbial metabolism in ruminants. These fatty acids have been proposed as potential markers of dairy consumption (Jenkins et al, 2015).

3.6 Cholesterol is not a fat, but this compound and its derivatives are commonly found in foods containing animal fats. Cholesterol is a sterol with a ring structure containing an alcohol unit at one end (Berg et al, 2012b). As well as being found in the diet, cholesterol is synthesised in humans and other mammals, and is an important component of membranes in cells. It has a key role as the precursor of other important molecules such as steroids,

certain vitamins such as vitamin D, and bile acids, as well as maintaining membrane fluidity and normal cell function.

3.7 Cholesterol is synthesised within the cells of the body and only around 15% of cholesterol in the blood comes from dietary sources (Ginsberg et al, 1995; Ginsberg et al, 1994). As a consequence, dietary cholesterol has a limited impact on cholesterol levels in the blood or risk of disease unless intakes exceed around 300 mg per day (Ginsberg et al, 1995; Ginsberg et al, 1994). In randomised controlled trials (RCTs), the administration of 500 to 900 mg per day increased total cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol (Berger et al, 2015).

Nomenclature conventions of fatty acids

3.8 There are a number of naming conventions for fatty acids. The commonest form is the trivial name, often referring to the food substances where these fatty acids were originally derived from; for example, palmitic acid is found in high concentrations in palm oil and stearic acid is named after the Greek for tallow (στέαρ or *stéar*) where it is found in high concentrations (Berg et al, 2012b).

3.9 Systematic names are determined using conventions described by the International Union of Pure and Applied Chemistry (IUPAC) (IUPAC-IUB Commission on Biochemical Nomenclature, 1977) and are derived by counting the number of carbons present in the fatty acid. Double bonds are numbered from the carboxylic acid end using either Z to denote a *cis* bond or E to denote a trans bond. For example, (9Z)-octadecenoic acid signifies a fatty acid of 18-carbons length with one double bond between the 9^{th} and 10^{th} carbon atoms from the carboxylic end of the fatty acid. The trivial name for this fatty acid is oleic acid.

3.10 The “n” or “omega” nomenclature numbers the double bond position by counting the number of bonds from the methyl end of the fatty acid. Fatty acids with the same description, for example n-3, often share a common synthetic pathway (Berg et al, 2012b).

3.11 The delta (Δ) nomenclature identifies a fatty acid by counting the position of a double bond from the carboxylic side of the fatty acid, with each double bond preceded by a *cis* or trans to specify the nature of the bond (Berg et al, 2012b).

3.12 Fatty acids can also be described by 2 numbers specifying the number of carbons and double bonds in the fatty acid. For example, 18:2 signifies a fatty acid with 18 carbons and 2 double bonds. The position of these double bonds can be defined using Δ , n or omega nomenclature (for example, 18:2 n-6).

3.13 The trivial (common) names for the major saturated fatty acids found in nature are listed in Table 3.1.

Table 3.1: Saturated fatty acids commonly found in nature

Trivial name	IUPAC name	Chemical structure	C:D*
Butyric acid	butanoic acid	$CH_3(CH_2)_2COOH$	4:0
Caproic acid	hexanoic acid	$CH_3(CH_2)_4COOH$	6:0
Caprylic acid	octanoic acid	$CH_3(CH_2)_6COOH$	8:0
Capric acid	decanoic acid	$CH_3(CH_2)_8COOH$	10:0
Lauric acid	dodecanoic acid	$CH_3(CH_2)_{10}COOH$	12:0
Myristic acid	tetradecanoic acid	$CH_3(CH_2)_{12}COOH$	14:0
Pentadecylic acid	pentadecanoic acid	$CH_3(CH_2)_{13}COOH$	15:0
Palmitic acid	hexadecanoic acid	$CH_3(CH_2)_{14}COOH$	16:0
Margaric acid	heptadecanoic acid	$CH_3(CH_2)_{15}COOH$	17:0
Stearic acid	octadecanoic acid	$CH_3(CH_2)_{16}COOH$	18:0
Arachidic acid	eicosanoic acid	$CH_3(CH_2)_{18}COOH$	20:0
Behenic acid	docosanoic acid	$CH_3(CH_2)_{20}COOH$	22:0
Lignoceric acid	tetracosanoic acid	$CH_3(CH_2)_{22}COOH$	24:0
Cerotic acid	hexacosanoic acid	$CH_3(CH_2)_{24}COOH$	26:0

* C number of carbon atoms; D number of double bonds.

Digestion and absorption

3.14 Dietary fats must first be degraded into non-esterified fatty acids (NEFAs) (also known as free fatty acids) and monoacylglycerols before they can be absorbed by the gut. Digestion mainly occurs in the small intestine. Fats are hydrolysed by lipase released from the pancreas and the resulting NEFAs and monoacylglycerols are solubilised by bile produced by the liver (Newsholme & Leech, 2010).

3.15 Lipases are found on the surface of a number of cells in the body. These enzymes hydrolyse triacylglycerols to produce fatty acids and monoacylglycerols which can be taken up by the cell (Newsholme & Leech, 2010).

3.16 NEFAs and monoacylglycerols are absorbed by enterocytes in the small intestine, re-esterified, and incorporated into fat particles called chylomicrons containing triacylglycerols and cholesterol. They are surrounded by phospholipids and specialised proteins called apolipoproteins which enable the transport of the triacylglycerols throughout the body (Figure 3.3) (Newsholme & Leech, 2010). Chylomicrons are transported through the lymphatic system to the blood circulation. The action of various lipases in the tissues results in the release of NEFAs from chylomicrons and their uptake by

peripheral tissue such as skeletal muscle, the heart and adipose tissue. Unlike other food components, fats initially do not pass through the liver.

3.17 Hydrophobic fats are transported around the body in particles, characterised by their density with hydrophilic proteins and phospholipids on the outside. One such particle is termed very low density lipoprotein (VLDL), and contains fats (largely triacylglycerols) and cholesterol which are exported by the liver into the blood to supply other tissues with these molecules (Elliott & Elliott, 2005). As the VLDL fats are taken up by the peripheral tissues, VLDL is converted into intermediate density lipoprotein (IDL) and LDL, which are subsequently taken up by the liver for further metabolism.

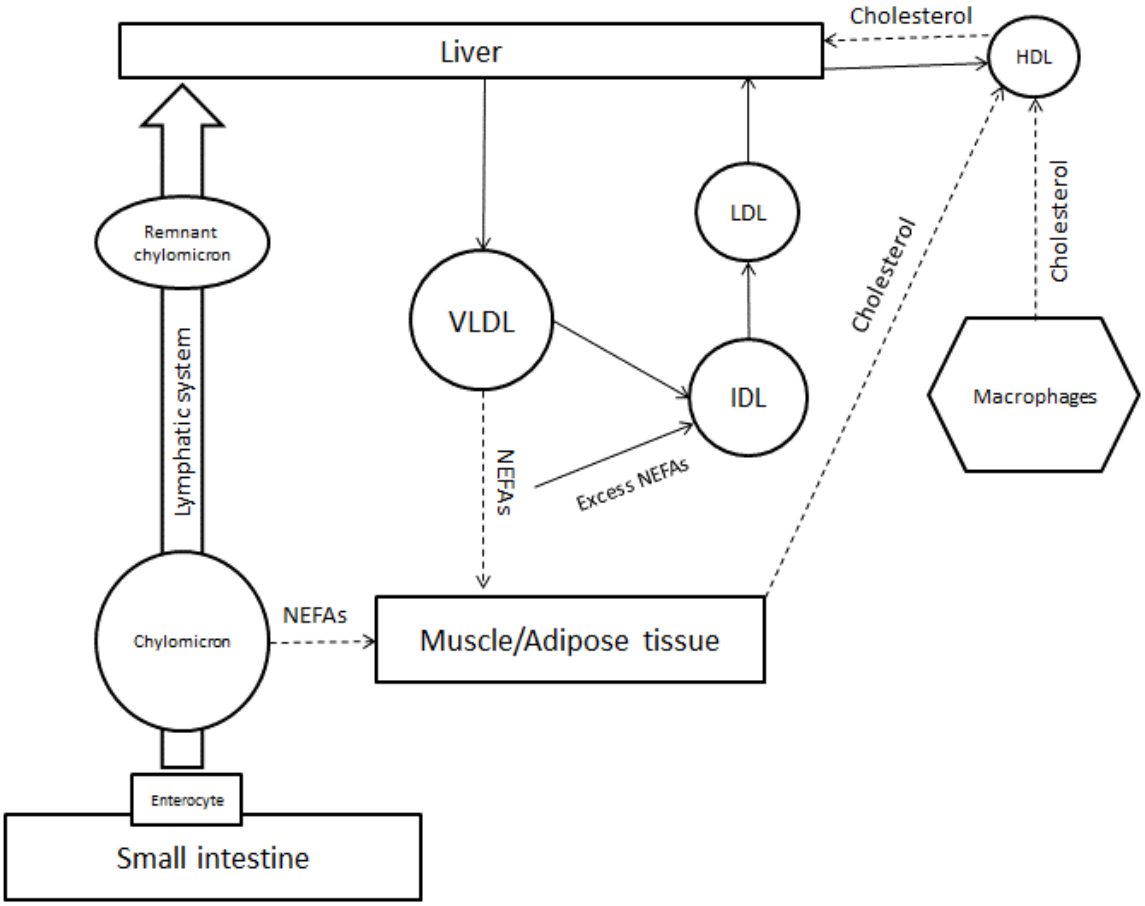

Figure 3.3 Schematic of some of the processes involved in the transport of cholesterol, NEFAs and lipoprotein particles in the body. Fats are absorbed from the intestine and form chylomicron particles. These are transported through the lymph system before emptying into the circulation. Chylomicron particles release NEFAs to the body and are degraded to form remnant chylomicrons. The liver packages fatty acids and cholesterol into very low density lipoprotein (VLDL) particles. These are metabolised to release NEFAs for uptake by the cells. Adipose tissue is a major source of triacylglycerols and will release NEFAs during fasting. High density lipoprotein (HDL) particles take up cholesterol from peripheral tissue like macrophages, muscle and adipose tissue and transport this cholesterol to the liver.

3.18 HDL is also released from the liver and it takes up cholesterol and fatty acids from other cells around the body. HDL can accumulate cholesterol and fatty acids from macrophages and artery-wall atheromas before transporting the cholesterol to the liver for excretion. High proportions of HDL cholesterol are generally associated with positive health outcomes. This has led to the term 'good cholesterol' which refers to cholesterol contained within HDL particles (Elliott & Elliott, 2005).

Metabolism

3.19 One gram of dietary fats provides approximately 37kJ (9 kcal) of energy compared with 17kJ (4 kcal) per gram for carbohydrates and proteins (Berg et al, 2012a). Fatty acids, stored as triacylglycerols in the body, form anhydrous droplets, while carbohydrates, stored as glycogen, bind water.

3.20 Fats are largely stored in adipose tissue, often referred to as 'body fat' or simply 'fat'. These fats can be classified into different depots including subcutaneous (beneath the skin), visceral (around internal organs), intermuscular (including epicardial fat around the heart), in bone marrow and in breast tissue. Adipocytes, the cells of adipose tissue, mainly consist of a large fat droplet in the centre surrounded by sub cellular organelles. During periods of fasting or exercise adipocytes activate lipase which breaks down triacylglycerols to monoacylglycerols and free fatty acids. Free fatty acids are released from the cell into the bloodstream and used in the body (Berg et al, 2012b).

3.21 The human body oxidises fats in a series of metabolic reactions, resulting in the generation of adenosine triphosphate, the main energy currency of the body, which in turn is used to maintain the body and do work (Berg et al, 2012b).

3.22 Fatty acids are metabolised in the mitochondria of cells and require oxygen to be present for this process to occur. In order to transport fatty acids into mitochondria, fatty acids are first converted into fatty acyl coenzyme A (CoA) and then transported via the carnitine shuttle (Berg et al, 2012b).

3.23 Fatty acids (in the form of fatty acyl CoA) are metabolised by the metabolic pathways: β-oxidation, the citric acid cycle and oxidative phosphorylation. Fatty acids are broken down, 2 carbons at a time, to produce the substrate acetyl CoA which is metabolised by the citric acid cycle. These processes only occur in the presence of oxygen as part of aerobic respiration (Berg et al, 2012b).

3.24 NEFAs enter the cell by diffusion across the cell membrane and also through dedicated transporters particularly for long chain and very-long chain fatty acids (Berg et al, 2012b). These transporters are collectively referred to as fatty acid transport proteins (FATPs).

3.25 Not all organs use fats as energy sources (Frayn, 2009). Slow twitch (red) muscle is highly oxidative in terms of metabolism and uses fats to produce energy during long periods of

exercise (for example long distance running and cycling). The heart also uses large amounts of fat relative to other tissues. However, some tissues favour the metabolism of glucose, such as the brain and fast twitch muscle (used for sprinting). Red blood cells are also unable to metabolise fats to produce energy.

3.26 The liver has a central role in fat metabolism. It both imports and exports fats contained in different lipoprotein particles, and it regulates the fatty acid composition of the blood plasma (Frayn, 2009). The liver can metabolise fats during periods of fasting or intense exercise to produce a set of compounds referred to as ketone bodies. Ketone bodies can be an energy source for the body and, in particular, are used in organs which do not metabolise fatty acids directly, such as the brain.

3.27 The liver can also convert carbohydrates into fat for long term storage by de novo lipogenesis (Berg et al, 2012b). During de novo lipogenesis, glucose and other carbohydrates are taken up by the liver and converted to the saturated fatty acids, myristic acid (C14:0), palmitic acid (C16:0) and stearic acid (C18:0). This pathway requires energy but also allows the body to efficiently store energy in adipose tissue.

3.28 Ectopic fat deposition occurs when fat accumulates in organs at higher concentrations than in healthy tissues. Ectopic fat deposition can occur in a variety of organs including the liver, skeletal muscle and the pancreas.

3.29 Once the two essential fatty acids have been ingested, humans have the enzymes necessary to generate a range of more complex fatty acids, including dihomo-γlinolenic (DGLA) [20:3 n-6], arachidonic acid (AA) [20:4 n-6], eicosapentaenoic acid (EPA) [20:5 n-3] and docosahexaenoic acid (DHA) [22:6 n-3] (Sprecher, 2002).

Metabolism in pregnancy

3.30 The LCPUFAs such as AA, EPA and DHA are not strictly essential in the diet. However, an important practical issue in pregnancy is whether the dietary supply is sufficient to support fetal development or whether the demand is such that AA, EPA and DHA should be considered as conditionally essential for the mother at this time (Haggarty, 2010). There is relatively little accumulation of lipid before 25 weeks of gestation but it increases rapidly after that, reaching a maximal rate of accretion of around 7 g/day just before term. In terms of individual fatty acids, the DHA 'requirement' rises from around 100 mg/day at 25 weeks to over 300 mg/day close to term. The rate of DHA deposition close to term is likely to exceed maternal dietary intakes of DHA in a significant proportion of women, particularly those who consume little or no fish (the dietary source of DHA). However, a number of adaptive mechanisms occur in pregnancy to optimise delivery of LCPUFAs to the fetus. These include de novo synthesis, mobilisation from maternal fat stores, and selective delivery to the fetus (Haggarty, 2014).

Other roles of fats and lipids in the body

3.31 Lipids have a variety of other roles in the body in addition to their use as important fuel sources. Fatty acids are the precursors of the metabolically active compounds such as the prostacyclins, prostaglandins, thromboxanes and leukotrienes. They perform many other functional and structural roles within the body, particularly in relation to membranes, and changes in their composition can have a profound effect on normal cellular function (Haggarty, 2010). Cholesterol is the precursor for a number of important metabolites which include the steroids and vitamin D.

Individual saturated fatty acids and health

3.32 Individual saturated fatty acids have different effects on blood lipids and health according to the length of the fatty acid. For example, Clarke et al (1997) reported that when lauric acid (C12:0), myristic acid (C14:0) and palmitic acid (C16:0) were replaced with carbohydrates there was a greater reduction in total cholesterol and LDL cholesterol compared with the longer chain fatty acids such as stearic acid (C18:0) (Clarke et al, 1997). Similarly, Mensink (2016) reported that, compared to a mixture of carbohydrates, a higher intake of lauric acid (C12:0), myristic acid (C14:0) or palmitic acid (C16:0) raised total cholesterol, LDL cholesterol and HDL cholesterol, but lowered triacylglycerol, whereas stearic acid (C18:0) had no significant effect on any of the blood lipids. However, consideration of the evidence on the impact of individual saturated fatty acids on health outcomes was outside the scope of this report.

4 UK and international recommendations

4.1 In the UK, the dietary reference value (DRV) for saturated fats was set by the Committee on Medical Aspects of Food Policy (COMA) in 1991 and reviewed in 1994 (COMA, 1994; COMA, 1991). COMA recommended in 1994 that the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than about 10%. This recommendation applies to adults and children aged 5 years and older[11]. This advice was based on evidence that "increasing or decreasing the contribution of saturated fatty acids to dietary energy is followed by a rise or fall in low density lipoprotein (LDL) cholesterol and in the commensurate risk of coronary heart disease". Since then many international organisations have reviewed the evidence on saturated fats and a range of health outcomes, with many setting similar recommendations.

4.2 The United States of America (USA) Dietary Guidelines Advisory Committee (DGAC, 2015), the Australian Government Department of Health and the New Zealand Ministry of Health (2013), the Nordic Council of Ministers (2012), the European Food Safety Authority (EFSA, 2010) and the Food and Agriculture Organization/World Health Organization (FAO/WHO, 2010) have all advised on maximum levels of saturated fat intake (see Table 4.1 for recommendations). The Australian Government Department of Health and New Zealand Ministry of Health recommend a range of 8 to 10% energy for saturated fat intake, the DGAC, the Nordic Council of Ministers and the FAO/WHO recommend consuming no more than 10% of energy as saturated fats and the EFSA advise consuming as little saturated fats as possible. The recommendations set by these organisations were all based on evidence from randomised controlled trials (RCTs) and prospective cohort studies (PCS), which indicate that reducing the intake of saturated fats and substituting them with polyunsaturated fatty acids, reduces total cholesterol and LDL cholesterol levels and the risk of cardiovascular disease (CVD).

4.3 The French Food Safety Agency (AFSSA) reviewed the evidence on dietary fats in 2010 (AFSSA, 2010). It concluded that recommendations should distinguish between different saturated fatty acids because they differ in "structure, metabolism, cell functions and deleterious effects in the case of excess". Based on evidence from observational studies that lauric, myristic, and palmitic acids are atherogenic, AFSSA recommended a maximum intake of 8% of energy intake for these saturated fatty acids. AFSSA found no evidence to suggest harmful effects for other saturated fatty acids, particularly short chain fatty acids. AFSSA was unable to set recommendations for these fatty acids but advised consuming no more than 12% of energy intake in the form of saturated fats.

[11] This recommendation does not apply before two years of age, and applies in full from the age of 5 years. A flexible approach is recommended to the timing and extent of dietary change for individual children between 2 and 5 years (COMA, 1994). Also see Table 16.1 in Chapter 16.

Table 4.1 Dietary recommendations for saturated fats set by national and international organisations

Organisation and country	Recommendations for saturated fats	Level of recommendation (population/ unstated)
(COMA, 1994); COMA (1991) (UK)	That the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than about 10% for adults and children aged ≥ 5 years	Population
DGAC (2015) (US)	<10% energy* for those aged ≥ 2 years Also recommended replacing saturated fats with unsaturated fatty acids, especially polyunsaturated fatty acids	Population
Australian Government Department of Health and the New Zealand Ministry of Health (2013) (Australia and New Zealand)	8 to 10% energy* (saturated and trans fatty acids combined) (age group not specified)	Unstated
Nordic Council of Ministers (2012) (Nordic countries)	<10% energy* for those aged ≥ 6 months	Population
EFSA (2010) (Europe)	As low as possible	Population
AFSSA (2010) (France)	≤12% food energy (of which lauric acid (C12:0) + myristic acid (C14:0) + palmitic acid (C16:0) should be ≤8% food energy) for adults	Population
FAO/WHO (2010)	≤10% energy* for adults aged >18 years 8% energy* for children aged 2 to 18 years	Population

* It is not clear whether the recommendation refers to total or food energy.

4.4 The 2015 recommendations of the Health Council of the Netherlands (HCN)[12] differ from other bodies in that advice on foods and dietary patterns are provided rather than saturated fat intakes (Health Council of the Netherlands, 2015). The HCN made 3 recommendations related to foods high in saturated fats. The first was to "replace butter, hard margarines, and cooking fats by soft margarines, liquid cooking fats, and vegetable oils" as evidence from RCTs showed that this reduced the risk of coronary heart disease. The second was to "limit the consumption of red meat, particularly processed meat". This was based on evidence from PCS which showed consumption of red and processed meat was associated with higher risks of stroke, type 2 diabetes, colorectal cancer and lung

[12] Please note HCN provides only food-based recommendations.

cancer. The third recommendation was to have “a few portions of dairy produce daily, including milk or yogurt”. This recommendation was based on evidence from PCS which suggested an association between consumption of dairy products and yogurt and reduced risk of colorectal cancer and type 2 diabetes, respectively.

5 Dietary intakes and sources of saturated fats

5.1 Nationally representative data on saturated fat intakes of the general UK population were drawn from the National Diet and Nutrition Survey (NDNS) rolling programme, a continuous survey of food consumption, nutrient intake and nutritional status in adults and children aged 18 months upwards. Intakes presented in this chapter are based on a UK representative sample of 6155 adults aged 19 years and over, and 5942 children aged 1.5 to 18 years, collected over 8 years between 2008 and 2016 (Bates et al, 2016; Bates et al, 2014b). A time trend analysis based on 9 years (2008 to 2017) and an equivalised income analysis based on 2012 to 2017 was published in 2019 (Bates et al, 2019b). Data are also available for Scotland (Bates et al, 2014a), Northern Ireland (Bates et al, 2015a) covering the 2008 to 2012 period, and Bates et al, 2019a, covering the 2013 to 2017 period, including time trend and income analyses. Data are also available for Wales (Bates et al, 2015b) covering 2009 to 2013.

5.2 Intakes for the UK low income/materially deprived populations (aged 2 years and over), collected in 2003 to 2005, are available from the Low Income Diet and Nutrition Survey (LIDNS) (Nelson et al, 2007).

5.3 The dietary data collection method used in the NDNS was a 4-day diary. Participants (or a parent/carer for children) were asked to keep a detailed diary of all foods and drinks consumed for 4 consecutive days. Quantities consumed were estimated using a combination of household measures and photographs with portion sizes. The survey was designed to represent all days of the week equally. The LIDNS used an interviewer-led 24-hour recall repeated on 4 non-consecutive days (Nelson et al, 2007).

5.4 Dietary surveys are reliant on self-reported measures of intake. Misreporting of food consumption, generally underreporting, is known to be a problem in the NDNS, as it is in dietary surveys worldwide. A doubly labelled water sub-study carried out as part of the NDNS rolling programme (Bates et al, 2014b) found that reported energy intake in adults aged 16 to 64 years was on average 34% lower than total energy expenditure (TEE) measured by doubly labelled water. The difference for other age groups was similar, except for children aged 4 to 10 years where reported energy intake was 12% lower than TEE. This discrepancy is likely to be due to a combination of underreporting actual dietary consumption (by failing to report foods or drinks consumed and/or under estimating quantities) and changing the diet during the recording period. A further doubly labelled water sub-study carried out in 2013/14-14/15 gave similar results (Bates et al, 2019b). In addition to underreporting of actual dietary consumption, there are also technical difficulties in the assessment process that can affect the accuracy of consumption estimates, such as assumptions that have to be made on food composition, recipes and portion sizes etc. It is not possible to extrapolate these estimates of underreporting energy intake to individual foods or nutrients, nor is it possible to correct or adjust the intake

estimates to take account of misreporting. For macronutrients, such as saturated fats, which are considered as a percent of energy, the absolute underestimate observed in NDNS is less critical if all macronutrients are underreported to the same degree. The key issue is whether the underestimate of intakes applies equally to different food sources of saturated fats, such as meat and meat products; milk and milk products; cereal and cereal products.

5.5 The saturated fat intakes of the general UK population have been tabulated and are included in Annex 3. Dietary intakes reported in this chapter are compared with the current dietary reference value (DRV) for saturated fats set by COMA in 1991 and 1994. Saturated fat intakes are presented as grams/day, as a percentage of total dietary energy intake (that is, including energy from alcohol), and as a percentage of food and drink energy intake (that is, excluding energy from alcohol).

Saturated fat intakes in the UK

5.6 Mean intake of saturated fats among different age groups in the UK are shown in Annex 3, Table A3.1. Mean intakes exceed the DRV (that is, that the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than about 10% for those aged 5 years and over). Based on the NDNS Years 7 and 8 data (collected 2014/15 to 2015/16), mean intake of saturated fats as a percentage of total dietary energy were 13.0% and 12.4% in children aged 4 to 10 years and 11 to 18 years, respectively. Mean intakes of saturated fats among adults aged 19 to 64 years were 11.9%; 12.5% among older adults aged 65 to 74 years and 14.3% among older adults aged 75 years and over. Additional analysis of the NDNS Years 5 and 6 data (collected 2012/13 to 2013/14) showed that the dietary recommendation for saturated fats was exceeded by 89.3% and 84.7% of children aged 4 to 10 years and 11 to 18 years, respectively. In addition, this recommendation was exceeded by 74.5% and 83.3% of adults aged 19 to 64 years and 65 years and over, respectively. The actual distribution of intake of saturated fats among adults (19 to 64 years) is shown in Figure 5.1.

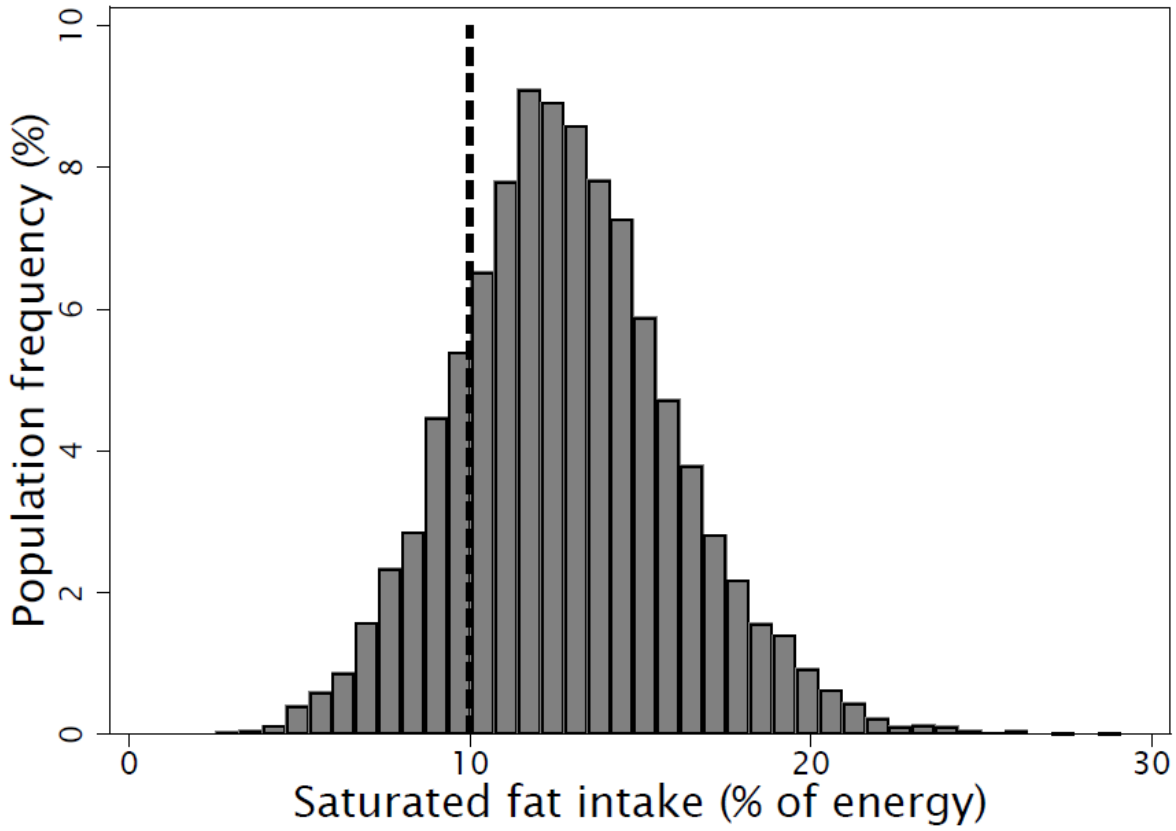

Figure 5.1 The distribution of intake of saturated fats (% of total energy) among adults (19-64 years). Data obtained from the NDNS (2008/09 to 2013/14).
The vertical dashed line (--) is the recommended [population] average contribution of saturated fatty acids to dietary energy of no more than about 10% (COMA, 1994)).

Contributors to saturated fat intake

5.7 The main contributors to saturated fat intake among different age groups in the UK are shown in Annex 3, Table A3.2.

5.8 For adults aged 19 to 64 years, the main contributors to saturated fat intake were meat and meat products, milk and milk products (about half from cheese) and cereals and cereal products (half from pizza, biscuits, buns, cakes, pastries, fruit pies and puddings), with each food group providing 21 to 24% of total saturated fat intake. Fat spreads, including butter, provided a further 9% of total saturated fat intake. The main contributors in Scotland, Northern Ireland and Wales were very similar to those in the UK as a whole.

5.9 For adults aged 65 years and over, the main contributors to saturated fat intake were meat and meat products (21% in older adults aged 65 to 74 years and 18% in those aged 75 years and over), milk and milk products (24% in older adults aged 65 to 74 years and 27% in those aged 75 years and over) and cereals and cereal products (21% in older adults aged 65 to74 years and 20% in those aged 75 years and over). Fat spreads provided a further

contribution to total saturated fat intake (13% in older adults aged 65 to 74 years and 16% in those aged 75 years and over).

5.10 In children aged 4 to 10 years, milk and milk products (30%) (about half from whole milk and cheese) and cereals and cereal products (27%) (mainly pizza, biscuits, buns, cakes, pastries, fruit pies and puddings) were the largest contributors to saturated fat intake. Meat and meat products (17%) was the other main contributor. For those aged 11 to 18 years, the main contributors to saturated fat intake were cereals and cereal products (28%), milk and milk products (22%) (about half from whole milk and cheese) and meat and meat products (22%). The main contributors in Scotland, Northern Ireland and Wales were very similar to those in the UK as a whole.

Socio-economic differences in saturated fat intakes

5.11 Analysis of the NDNS data (collected from years 5 to 9 (2012/13 to 2016/17)) showed that saturated fat intake as a percentage of food energy increased on average by 0.1 to 0.2 percentage points for every £10,000 increase in equivalised income, for all age groups except children aged 1.5 to 3 years, although the differences did not reach statistical significance in all age/sex groups (Annex 3, Figure A3.1). Intakes exceeded the DRV across the range of income for all age groups (Bates et al, 2019b).

5.12 For Northern Ireland there was no consistent pattern across the age groups with respect to income in saturated fat intake as a percentage of food energy. For every £10,000 increase in equivalised income, saturated fat intake as a percentage of food energy decreased, by 0.5 percentage points (CI 0.1, 0.9) for girls aged 11 to 18 years. This was significantly different from the same group in the UK as a whole (Bates et al, 2019a).

5.13 In the UK LIDNS (2003 to 2005), mean intakes of saturated fats as a percentage of energy were similar to or slightly lower than the general population based on the NDNS carried out in the 1990s/2000, but slightly higher than the 2008 to 2012 NDNS reported intakes in the general population. It is possible that these differences may be more related to temporal changes in saturated fat intake than socio-economic status (Nelson et al, 2007).

5.14 Analysis of intakes by equivalised household income quintile and by index of multiple deprivation in Scotland, Northern Ireland and Wales, shows no consistent pattern (Bates et al, 2014a).

Intakes of other fats in the UK

5.15 Based on the NDNS years 1 to 4 data (collected 2008/09 to 2011/12) (Bates et al, 2014b), mean intakes of *cis* n-3 polyunsaturated fats (PUFA) as a percentage of total energy, increased with age from 0.8% for children aged 4 to 10 years to 1% for adults aged 19 to

64 years. Mean intakes of *cis* n-6 PUFA as a percent of total energy showed a similar trend with age, ranging from 4.4% for children aged 4 to 10 years to 4.8 % for adults aged 19 to 64 years (Annex 3, Table A3.3). COMA recommended in 1994 that there be no further increase in average intake of n-6 PUFA and that the proportion of the population consuming in excess of about 10% energy should not increase (COMA, 1994).

5.16 Based on the NDNS years 1 to 4 data (collected 2008/09 to 2011/12) (Bates et al, 2016), mean intakes of *cis* monounsaturated fats (MUFA) provided 12% of total energy for children aged 4 to 10 years and adults aged 19 to 64 years and 12.7% of total energy for children aged 11 to 18 years (Annex 3, Table A3.4). The DRV for MUFA is 12% of total dietary energy as a population average (COMA, 1991).

Summary

5.17 Available survey data indicates that mean intakes of saturated fats in the UK exceed recommendations in all age, sex and income groups. Cereals and cereal products, milk and milk products, and meat and meat products were the main contributors to saturated fat intakes in adults. In children aged 4 to 10 years, milk and milk products (about half from cheese and whole milk) and cereals and cereal products were the leading contributors. Intakes tended to increase with income although the differences were small and not statistically significant in all age groups (Bates et al, 2019b; Roberts et al, 2018; Bates et al, 2016; Bates et al, 2014b).

6 Temporal trends from UK diet and nutrition surveys

Average daily intake of saturated fats among adults

6.1 The long-term trends in saturated fat intake among adults are shown in Annex 3, Tables A3.5 to A3.8. Between 1986/87 and 2008/09 to 2009/10, mean daily saturated fat intake among adults aged 19 to 64 years decreased from 16.0% to 12.2% of total energy. Regression analysis of time trends between years 1 to 9 of the NDNS rolling programme (2008/09-2016/17) shows that there were no changes over this time period in saturated fat intake as a percentage of energy in any age/sex group.

Percentage contribution of food groups to average daily saturated fat intake of adults

6.2 There has been little change between 1986/87[13] and 2008/09 to 2016/17 in the main sources of saturated fats. Cereal and cereal products (half from pizza, biscuits, buns, cakes, pastries, fruit pies and puddings), milk and milk products (about half from cheese) and meat and meat products were the main contributors across all survey years, each providing around 21 to 24% of total intake of saturated fats (Annex 3, Tables A3.9 to A3.13). Although there was a marked decline in the contribution of whole milk (from approximately 11% to 2% of average daily saturated fat intake), the overall percentage contribution of milk and milk products to daily saturated fat intake remained unchanged for adults (aged 19 to 64 years) and older adults (aged 65 years and over). The contribution of fat spreads to saturated fat intake has declined (from approximately 17% to 9% of average daily saturated fat intake) mainly due to decreased consumption of butter, especially among adults aged 19 to 64 years.

Long and short term trends in the percentage of energy derived from saturated fats from household food and drink purchases

6.3 Long term trend data on the content of saturated fats in food purchases at household level is available from the Family Food module of the Department of Environment, Food and Rural Affairs (DEFRA) Living Costs and Food Survey. This survey collects data on quantities of foods and drinks purchased at household level (including eating out purchases) and reports population average figures for food and drink categories as purchased and their

[13] This report included adults aged 16 to 64 years

nutrient content as a proxy for nutrient intake. Although less detailed than the NDNS, and with different methodology, the reported estimates and trends are broadly consistent.

6.4 Data from household purchases and purchases for eating out of the home confirm a long term decline in saturated fats as percentage of energy intake, from 18.6% in 1974 to 14.4% in 2015, however still remains above the DRV (Defra, 2017; Defra, 2014) (Annex 3, Figures A3.2 and A3.3).

Temporal trends in trans fats

6.5 There has been a substantial decline in trans fats as a percentage of total dietary energy intake among all age groups from 2.1% in 1986/87 to 0.5% in 2015/16 in adults aged 19 to 64 years (in line with the dietary reference value (DRV) that intakes should not exceed 2% of food energy) (Annex 3, Tables A3.14 to A3.17). Regression analysis of time trends between years 1 to 9 of the NDNS rolling programme (2008/09-2016/17) also shows a statistically significant reduction per year in trans fat intake as a percentage of food energy in all age sex groups.

6.6 The main sources of trans fats changed from fat spreads and cereals and cereal products in 1986/87 to milk and milk products and meat and meat products in 2014/16. This reflects the reduction in the content of manufactured trans fats in the food supply over this period (Annex 3, Table A3.18 and A3.19).

6.7 In the early to mid-1990s, the analysis of composite samples of fat spreads, including products based on unsaturated fats, found that samples typically contained 2 to 8g trans fats per 100g product. More recent data (2009/10) indicate that reduced and low fat spreads had much lower trans fats levels (0.05 to 0.15g) (Annex 3, Table A3.20).

Blood lipids analysis among adults by sex and age

6.8 Trends in blood lipids between 1986/87 and 2015/16 among adults are shown in Annex 3, Tables A3.21 and A3.22. Mean serum low density lipoprotein (LDL) cholesterol values cannot be directly compared across surveys because different methodologies were used for blood sample collection and estimation of mean serum LDL cholesterol in 1986/87, 1994/95, 2000/01 and 2008/16 surveys. In earlier surveys, non-fasting blood samples were used and values for serum LDL cholesterol were not corrected for serum triacylglycerol.

6.9 There has been virtually no change in mean serum total cholesterol (4.7mmol/L for adults 19 to 64 years and 4.8mmol/L for older adults 65 years and over), LDL cholesterol (2.8mmol/L for all adults), and total cholesterol:high density lipoprotein (HDL) cholesterol ratio (3.9 for adults 19 to 64 years and 3.6 for older adults 65 years and over) between 2008 and 2016. The NDNS data between 2008 and 2016 showed that recommendations

for mean serum total cholesterol (5mmol/L or less for healthy adults)[14] and mean serum LDL cholesterol (3mmol/L or less for healthy adults)[14] were almost met among adults (19 to 64 years) and men aged 65 years and over. Women aged 65 years and over exceeded the recommendation for serum total cholesterol (mean 5.3mmol/L) and serum LDL cholesterol (mean 3.1mmol/L). The recommendations for total cholesterol:HDL cholesterol ratio (4 or less)[14] were met by all age groups, except men aged 19-64 years (mean 4.2). Regression analysis of time trends between years 1 to 9 of the NDNS rolling programme (2008/09 - 2016/17) shows slight increases in the total cholesterol:HDL cholesterol ratio over this period in all age/sex groups, although not all of these were statistically significant.

Summary

6.10 Saturated fat intake as a percentage of energy decreased between 1986/87 and 2008/09 to 2009/10 but there was no change between 2008/09 and 2016/17. Intakes remain above the DRV in all age groups. . The main sources of saturated fats showed little change over time. Cereal and cereal products (about half from pizza, biscuits, buns, cakes, pastries, fruit pies and puddings), milk and milk products (about half from cheese) and meat and meat products have remained the top contributors to total saturated fat intakes across all survey years. There was a notable decline in whole milk consumption in adults and older adults but the overall contribution of milk and milk products to saturated fat intakes remained unchanged.

[14] NHS UK. High cholesterol. Available at https://www.nhs.uk/conditions/high-cholesterol/#what-should-my-cholesterol-levels-be

7 Background on health outcomes, intermediate markers and risk factors

Background

7.1 Outcomes were considered where there was an adequate evidence base and a significant disease burden. The relationships between intake of saturated fats and cardiometabolic outcomes, body weight change, selected cancers (including colorectal, pancreatic, lung, breast and prostate) and cognitive outcomes, are considered in this report.

7.2 Evidence from systematic reviews with/without meta-analyses and pooled analyses has been evaluated to assess whether intakes of saturated fats are a risk factor for these outcomes. All health outcomes, intermediate markers and risk factors (see Table 7.1) considered in this report were relevant to health and effect sizes were deemed to be meaningful, unless stated otherwise. In the subsequent chapters, the evidence on health outcomes, intermediate markers and risk factors is reviewed.

Dietary fats and blood lipids

7.3 Serum (or plasma) cholesterol is measured in millimoles per litre (mmol/L). As a general guide[15]:

- total serum cholesterol concentration should be 5mmol/L or less for healthy adults and 4mmol/L or less for those at high risk of CVD
- low density lipoprotein (LDL) concentration should be 3mmol/L or less for healthy adults and 2mmol/L or less for those at high risk of cardiovascular disease (CVD)
- high density lipoprotein (HDL) should be above 1mmol/L

7.4 The National Institute for Health and Care Excellence (NICE) recommend the QRISK®2 assessment tool which uses cholesterol and other factors to assess the 10 year risk of developing CVD in healthy individuals. The lipid parameter used in this tool is the ratio of total cholesterol:HDL cholesterol from a non-fasting blood sample[16].

7.5 Dyslipidaemia is an abnormal amount of lipids (triacylglycerols, cholesterol or phospholipids) in the blood. Hyperlipidaemia is increased concentrations of lipids in the

[15] NHS UK. High cholesterol. Available at https://www.nhs.uk/conditions/high-cholesterol/#what-should-my-cholesterol-levels-be

[16] NICE Cardiovascular disease: risk assessment and reduction, including lipid modification [CG181]; publication date: July 2014. Available at https://www.nice.org.uk/guidance/cg181

blood. Hyperlipidaemia is associated with a number of metabolic diseases including CVD and incident type 2 diabetes, and is a component of the metabolic syndrome (WHO Expert Panel on Detection, 2001).

7.6 Higher concentrations of cholesterol in LDL particles are associated with increased risk of developing CVD including atherosclerosis, myocardial infarction (MI) and stroke. In 2017, the European Atherosclerosis Society Consensus Panel concluded that evidence from genetic, epidemiologic and clinical studies demonstrated a consistent dose-dependent association between absolute exposure of the arterial endothelium to LDL cholesterol and risk of atherosclerotic CVD, which increased with longer exposure. The panel concluded that lowering LDL cholesterol reduces CVD (Ference et al, 2017). Dietary treatments and pharmaceutical intervention (for example, statins) which reduce the LDL cholesterol have been consistently shown to reduce CVD (Ference et al, 2017; Koizumi et al, 2002; McPherson et al, 2001). NICE recommends that people with a 10% chance of developing CVD in the next 10 years should be offered lipid-lowering drugs (for example, statins)[16]. In 2015/16, 14% of adults living in England were taking lipid-lowering drugs, one of the most commonly prescribed classes of medication (HSE, 2017b).

7.7 Increased concentration of serum HDL cholesterol has been associated with reduced risk of CVD, although the benefits of interventions to raise serum HDL cholesterol remain controversial (Tariq et al, 2014).

7.8 Trans fats are associated with an increased risk of developing CVD. This association is believed to be in part mediated by increased consumption of trans fats being associated with increased concentrations of LDL and reduced concentrations of HDL cholesterol in the blood (de Souza et al, 2015).

7.9 The Committee on Medical Aspects of Food Policy (COMA) based their recommendations for saturated fat intakes on the effect on LDL cholesterol concentrations and the link with morbidity and mortality. SACN endorsed the COMA conclusions that there is strong evidence that LDL cholesterol and other blood lipids are causally related to morbidity and mortality (Ference et al, 2017). The use of the serum total cholesterol:HDL cholesterol ratio has been proposed as a more sensitive and specific coronary heart disease (CHD) risk predictor than other individual cholesterol measures (Assmann et al, 1996; Kinosian et al, 1995; Stampfer et al, 1991). It has been found to be a predictor of CHD at all ages in women and the only lipid predictor independently related to CHD in men 65 to 80 years old (Castelli et al, 1992). This ratio is currently routinely used as the most discriminatory lipid risk marker to predict long-term CVD risk (QRISK 2 assessment)[17] in the clinical setting (Hippisley-Cox et al, 2017). SACN considered the evidence on all lipid markers.

[17] QRISK2 https://qrisk.org/

Cardiovascular diseases

7.10 Cardiovascular diseases are generally categorised into 3 types: CHD, cerebrovascular disease and peripheral vascular disease (for more detail see paragraph 8.1). CVD is the UK's single biggest cause of premature death and is responsible for approximately 158,000 deaths each year (BHF, 2015). Between 1961 and 2009, the mortality rate for CVD decreased from 322,917 to 180,626 deaths per year in the UK. The number of people dying from CHD has decreased from approximately 180,000 deaths per year in 1981 to approximately 70,000 in 2015. Between 1981 and 2015, the number of deaths from stroke has declined from approximately 80,000 to 40,000 deaths per year. There has been a dramatic reduction in mortality from cardiac events (including total CVD, CHD and stroke) since the 1980s (BHF, 2017; BHF, 2011) in line with better availability of coronary care and increased hospital admissions for CVD (Bhatnagar et al, 2016).

7.11 The underlying pathology of CVD is atherosclerosis, which may develop over many years and is usually advanced by the time symptoms occur, generally in middle age (WHO, 2007a). The rate of progression of atherosclerosis is influenced by diet, physical activity, obesity, tobacco use, elevated blood pressure (hypertension), abnormal blood lipids (dyslipidaemia) and elevated blood glucose (diabetes). Continuing exposure to these risk factors leads to progression of atherosclerosis, resulting in unstable atherosclerotic plaques, narrowing of blood vessels and obstruction of blood flow to vital organs, such as the heart and the brain.

Blood pressure

7.12 Blood is pumped around the body by the left ventricle of the heart imparting a pressure that is opposed by the resistance of the blood vessels through which it flows. The balance of these two opposing forces produces blood pressure. The blood pressure in the major arteries rises and falls as the heart contracts and relaxes. The peak, when the heart contracts, is known as the systolic pressure and the minimum, when the heart relaxes, as diastolic pressure. Blood pressure is measured in terms of the height (millimetres) of a column of mercury (Hg) and is conventionally recorded as systolic pressure over diastolic pressure (SACN, 2003). A blood pressure between 90/60 mmHg and 120/80 mmHg is considered 'ideal'; high blood pressure is considered to be 140/90 mmHg or higher[18] .

7.13 The prevalence of high blood pressure in 2016 was 30% among men and 26% among women (HSE, 2017a). The Health Survey for England indicates that there has been little change in the prevalence of high blood pressure between 2003 and 2016 (HSE, 2017a).

[18]NHS UK. Blood pressure. Available at https://www.nhs.uk/common-health-questions/lifestyle/what-is-blood-pressure/

7.14 High blood pressure is both a certified cause of death and a contributory factor in over 170,000 deaths per year in England alone (HSE, 2017a). High blood pressure is one of the most important modifiable risk factors for cardiovascular, cerebrovascular and renal disease (WHO, 2016). High intakes of salt, obesity, lack of physical activity, excess consumption of alcohol and smoking can increase the risk of high blood pressure (BHF, 2011).

Type 2 diabetes and markers of glycaemic control

7.15 In 2015, 6% of the UK population, almost 3.5 million people, were identified as having diabetes and, of these, 90% had type 2 diabetes (Diabetes UK, 2016). Between 1994 and 2016, the prevalence of diabetes increased from 2.9% to 7.6% among men and from 1.9% to 6.2% among women (HSE, 2017a).

7.16 Plasma glucose concentration or measurement of glycated haemoglobin (HbA1c) are used to diagnose diabetes (WHO, 2011; WHO, 2006). A considerable body of research has indicated that diabetes is a strong independent risk factor for CVD (Sarwar et al, 2010). Often, CVD and type 2 diabetes co-exist as they share common modifiable risk factors, such as obesity, and in particular elevated central adiposity. Type 2 diabetes has a strong association with obesity, and body weight control is a key factor in the prevention of progression from impaired glycaemic control to incident type 2 diabetes (Pi-Sunyer et al, 2007; American Diabetes Association and National Institute of Diabetes Digestive and Kidney Diseases, 2002).

7.17 Diet and lifestyle management are effective in reducing the incidence of type 2 diabetes (Diabetes UK, 2016). A range of measures are used in intervention or observational studies as indicators of glycaemic control and risk of developing diabetes. These include fasting blood glucose, glucose tolerance (response to a glucose challenge), fasting insulin, HbA1c and insulin resistance (insulin sensitivity) (Abbasi et al, 2016; Abbasi et al, 2012; WHO, 2006). Insulin resistance (insulin sensitivity) is determined by a range of indirect and direct methods (Patarrão et al, 2014). The Homeostasis Model Assessment (HOMA) is a widely applied surrogate index of insulin resistance, using fasting insulin and glucose values. More direct measures make use of infusions of glucose with or without insulin, including frequently sampled intravenous glucose tolerance test (FSIGTT) and the 'gold standard' hyperinsulinaemic euglycaemic glucose clamp method which quantifies the capacity for glucose disposal at a fixed insulin level.

Anthropometry

7.18 The prevalence of obesity (body mass index (BMI) of 30 kg/m^2 or over) in the UK is high; in England in 2014, 58% of women and 65% of men were overweight or obese and there was

an increase in the prevalence of obesity from 15% in 1993 to 26% in 2016 (Health and Social Care Information Centre, 2016). Obesity is associated with a range of health problems including type 2 diabetes, CVD and various cancers.

7.19 Obesity results from a long-term positive energy imbalance. The increasing prevalence of obesity must reflect temporal lifestyle changes, since genetic susceptibility remains stable over many generations, although inter-individual differences in susceptibility to obesity may have genetic determinants (SACN, 2015).

7.20 Around 5% of all pregnant women in the UK have a BMI ≥35 (Class II and Class III obesity). The prevalence of women with a BMI ≥40 (Class III obesity) during pregnancy in the UK is around 2%, while super-morbid obesity (BMI ≥50) affects around 0.2% of all women giving birth (CMACE, 2010).

7.21 BMI, both underweight and obesity, is an independent predictor of many adverse perinatal outcomes including pre-eclampsia, gestational diabetes and caesarean delivery and women should aim to enter pregnancy with a BMI in the normal range (NICE, 2010; Institute of Medicine, 2009). Excess gestational weight gain is linked to a greater risk of abnormal labour and emergency caesarean section (NICE, 2010) and has also been associated with subsequent overweight in children (Hillier et al, 2007). Maternal obesity is also associated with failure to initiate and sustain breastfeeding (Hilson et al, 1997) .

Cancers

7.22 Selected cancers, including colorectal, pancreatic, lung, breast and prostate, are a leading cause of death in many populations. In the UK, 359,960 cases of cancer were diagnosed in 2015, equating to 605 people per 100,000 of the population. Breast, prostate, lung and colorectal cancers together accounted for over half (53%) of all new cancer cases. In 2016, there were around 163,444 cancer deaths in the UK, of which lung, colorectal, breast and prostate cancers together accounted for almost half (46%) (Cancer Research UK, 2016). In the UK, 169 people per 100,000 of the population died from cancer in 2012 (European age-standardised mortality rate) (Cancer Research UK, 2016).

7.23 The aetiology of cancer is complex, with different factors being important for different cancers. However, in general cancer arises as a result of both genetic and environmental factors. The risk of most cancers increases with age, though some tumour types occur predominantly in younger people.

7.24 It has been estimated that nearly 40% of cancers in the UK would be preventable through risk factor modification, with the most important modifiable risk factors being smoking and overweight and obesity (Brown et al, 2018).

Cognitive impairment and dementias

7.25 In 2013, there were 815,827 people with dementia in the UK (Alzheimer's Society, 2014) and 773,502 of those were aged 65 years or over. In 2015, dementia (including Alzheimer's disease) accounted for 11.6% of all registered deaths in England and Wales, making it the leading cause of death using the World Health Organisation (WHO) disease groupings, ahead of ischaemic heart disease (11.5%) (ONS, 2016).

7.26 Dementia describes a group of symptoms, including memory loss, confusion, mood changes and difficulty with day-to-day tasks. Although the overwhelming majority of people with dementia are elderly and age is the biggest risk factor, dementia is not an inevitable part of ageing. Dementia is caused by a variety of diseases and injuries that primarily or secondarily affect the brain. The most common types of dementia are Alzheimer's disease (including early-onset Alzheimer's disease); vascular dementia; dementia with Lewy bodies[19]; frontotemporal dementia and mixed dementia. Alzheimer's disease accounts for an estimated 60% of cases (Qiu et al, 2007).

7.27 Assessing cognitive function is essential in detecting and diagnosing dementia and there are a wide range of different assessments used. These range from relatively simple short assessments which can be carried out by non-specialist staff to longer, more involved assessments which, while being more sensitive, require specially trained staff and more time to complete. In addition to tests of cognitive function, blood tests and brain imaging (computed tomography (CT), magnetic resonance image (MRI) or polyethylene terephthalate (PET) CT) are commonly used in clinical assessment for potential causes of dementia.

7.28 The diagnostic criteria for cognitive impairment and dementias have evolved with time. As a consequence of this, published research studies have used different definitions. It is important to take this into account when considering the evidence relating nutrient intake to cognitive function and dementia risk.

[19] This type of dementia is caused by abnormal deposits of the protein alpha-synuclein forming structures called Lewy bodies within brain cells. Symptoms differ from Alzheimer's disease in that fluctuating alertness, visual hallucinations and difficulty judging distances tend to occur before memory loss. Symptoms of tremor and rigidity (Parkinsonism) are also present. In the early course of the condition it may be difficult to distinguish dementia with Lewy bodies from Alzheimer's disease.

Table 7.1 Health outcomes associated with one or more risks factors or intermediate markers

Risk factors and intermediate markers	Health outcomes
Fasting blood lipid concentrations: Higher serum total cholesterol Higher serum LDL cholesterol Lower HDL cholesterol Higher total cholesterol:HDL cholesterol Higher serum triacylglycerol	Cardiovascular diseases, cognitive impairment and dementias
Blood pressure: Higher blood pressure Higher systolic blood pressure Higher diastolic blood pressure	Cardiovascular diseases
Glycaemic control: Higher fasting glucose Higher fasting insulin Higher HbA1c Impaired glucose tolerance Higher insulin resistance	Type 2 diabetes and cardiovascular diseases
Anthropometry: Higher body weight Higher BMI Higher waist circumference Excess gestational weight gain	Hypertension, cardiovascular diseases, type 2 diabetes, various cancers and dyslipidaemias

8 Cardiovascular diseases

8.1 Atherosclerotic cardiovascular diseases (CVD) include diseases that affect the heart or blood vessels and are generally categorised into 3 types:

- coronary heart disease (CHD), which includes myocardial infarction (MI) and other manifestations of coronary atherosclerosis, occurs when there is a complete or partial narrowing of the coronary arteries which supply the heart muscle
- cerebrovascular disease includes ischaemic and haemorrhagic stroke, which occurs when the arterial supply to parts of the brain is blocked, or cerebral haemorrhage
- peripheral vascular disease which results from narrowing or blockage in the arteries to the limbs (usually the legs) and aortic disease, which includes conditions that affect the aorta, including aortic aneurysm and carotid arterial narrowing

In this chapter evidence on the relationship between saturated fats and CVD is presented for total CVD followed by CHD and strokes separately. No evidence was found for peripheral vascular disease.

8.2 Nineteen systematic reviews, 14 with meta-analyses and 5 without meta-analyses, examined the relationship between saturated fats and CVD (Muto & Ezaki, 2018b; Harcombe et al, 2017; Hamley, 2017b; Harcombe et al, 2016b; Harcombe et al, 2016a; Cheng et al, 2016; Ramsden et al, 2016; Hooper et al, 2015; de Souza et al, 2015; Schwab et al, 2014; Farvid et al, 2014; Chowdhury et al, 2014; Ramsden et al, 2013; Siri-Tarino et al, 2010; Micha & Mozaffarian, 2010; Mozaffarian et al, 2010; Skeaff & Miller, 2009; Jakobsen et al, 2009; Mente et al, 2009). The Hooper et al (2015) review included virtually all randomised controlled trials (RCTs) included in the other reviews. The characteristics of these publications are summarised in Annex 2, Table A2.1. The quality of meta-analyses and systematic reviews is summarised in Annex 4.

8.3 One comprehensive Cochrane systematic review with meta-analysis of RCTs (Hooper et al, 2015) assessed the effect of saturated fat intake on CVD mortality and CVD events. In this review CVD mortality was the primary outcome in statistical models, whereas CVD events was a secondary statistical outcome. However, both cardiovascular outcomes were included in the search and therefore the evidence can be considered complete. In this review CVD events included cardiovascular deaths, cardiovascular morbidity (non-fatal myocardial infarction, angina, stroke, heart failure, peripheral vascular events, atrial fibrillation) and unplanned cardiovascular interventions (coronary artery bypass surgery or angioplasty). CHD events included fatal or non-fatal myocardial infarction, angina or sudden death. Hooper et al (2015) also separately analysed myocardial infarction, total (fatal and non-fatal) and non-fatal.

Total cardiovascular diseases (CVD)

Reduced intake of saturated fats and CVD outcomes

8.4 Four systematic reviews, 3 with meta-analyses (de Souza et al, 2015; Hooper et al, 2015; Siri-Tarino et al, 2010) and 1 without meta-analyses (Schwab et al, 2014) examined the relationship between reduced intake of saturated fats and CVD. One systematic review analysed the results from RCTs (Hooper et al, 2015), 2 evaluated the results from prospective cohort studies (PCS) (de Souza et al, 2015; Siri-Tarino et al, 2010) and 1 assessed the results from both RCTs and PCS (Schwab et al, 2014).

Randomised controlled trials

8.5 A Cochrane systematic review with meta-analysis by Hooper et al (2015) examined 15 RCTs covering 17 comparisons involving approximately 59,000 participants. The studies either aimed to assess the impact on total mortality and cardiovascular mortality of reducing intake of saturated fats or altering saturated fats. Interventions were at least 24-months in duration. On CVD mortality, Hooper et al (2015) analysed 10 RCTs and found no effect of saturated fats reduction compared with usual diet after a mean follow-up of 53 months using a random-effects model (10 RCTs, 53,421 participants, 1096 CVD deaths). This was also the case for fixed-effect models: Mantel-Haenszel model (10 RCTs, 53,421 participants, 1096 CVD deaths) and Peto model (10 RCTs, 53,421 participants, 1096 CVD deaths). Other sensitivity analyses[20] were performed that also found no effect on CVD mortality. Mean intakes of saturated fats reported in each RCT are summarised in Annex 2, Figure A2.1.

8.6 On CVD events, Hooper et al (2015) analysed 11 RCTs and found a 17% reduction in CVD events after a mean follow-up of 52 months in participants who had reduced their intake of saturated fats compared with usual diet, using a random-effects model (RR[21] 0.83, 95% CI 0.72 to 0.96, p=0.01; I^2 =65%; 11 RCTs, 53,300 participants, 4377 CVD events). They also observed a 7% reduction in CVD events with Mantel-Haenszel fixed-effect model (RR 0.93, 95% CI 0.88 to 0.98, p<0.05; I^2 =65%; 11 RCTs, 53,300 participants, 4377 CVD events) and an 8% reduction in CVD events with a Peto fixed-effect model (RR 0.92, 95% CI 0.86 to 0.98, p<0.05; I^2 =72%; 11 RCTs, 53,300 participants, 4377 CVD events). The direction of the effect size of other sensitivity analyses[20] were in agreement with the findings from random-

[20] Excluding studies which did not state an aim to reduce saturated fats; excluding studies which did not report saturated fat intake during the trial, or did not find a statistically significant reduction in saturated fats in the intervention compared to the control; excluding studies where total cholesterol (TC) or LDL (where TC was not reported) was not reduced; excluding the largest study (Women's Health Initiative (WHI) with CVD 2006; WHI without CVD 2006).

[21] Relative risk

effects and fixed-effect models. Mean intakes of saturated fats reported in each RCT are summarised in Annex 2, Figure A2.2.

Prospective cohort studies

8.7 Three systematic reviews, 2 with meta-analyses, assessed data from PCS (de Souza et al, 2015; Schwab et al, 2014; Siri-Tarino et al, 2010).

8.8 A systematic review with meta-analysis of 3 PCS by de Souza et al (2015) compared lower intake of saturated fats (<14% of energy) with higher intake of saturated fats (≥14% of energy). They reported no association between intake of saturated fats and CVD mortality using a random-effects model (3 PCS, 90,501 participants, 3792 CVD deaths). This analysis included 1 study (Wakai et al, 2014) which was not included in the analysis by Siri-Tarino et al (2010). The Wakai et al (2014) paper reported on a large study, the Japan Collaborative Cohort (JACC), which included 58,672 men and women, living in Japan who consumed relatively low intakes of saturated fats (7.3% of energy in the highest quintile compared to 3.0% of energy in the lowest quintile).

8.9 Siri-Tarino et al (2010) in a systematic review with meta-analysis of 21 PCS (24 publications) reported no association between saturated fats and CVD events (including data on CHD and strokes) when comparing the highest with the lowest quartiles of intake of saturated fats, using a random-effects model (21/24 PCS/publications, 347,747 participants, 11,006 CVD events). Fifteen of the 21 included PCS adjusted for energy intake. The findings were similar between sexes and ages (under and over 60 years of age) (Siri-Tarino et al, 2010).

8.10 Similar conclusions of no association between saturated fats and CVD mortality were given in a systematic review without meta-analysis of 5 PCS (Schwab et al, 2014).

8.11 In summary, the most comprehensive systematic review with meta-analysis by Hooper et al (2015) concluded that there was no effect of saturated fats on CVD mortality using both random-effects and fixed-effect models and this was confirmed by other sensitivity analyses. This evidence was considered as *adequate* due to the high number of studies and reported CVD cases. However, there was *adequate* evidence from 11 RCTs for a significant reduction in CVD events and the effect was observed using both random-effects (17%) and fixed-effect models (7% and 8% for Mantel-Haenszel and Peto respectively) (Hooper et al, 2015). This evidence was considered as *adequate* due to the high number of studies and reported CVD events. No association on CVD mortality was reported in the most up to date analysis of PCS (de Souza et al, 2015), which was limited in the number of included studies (n=3), but analysed the largest total cohort of participants (n=90,501). In addition, no association between intake of saturated fats and CVD events was reported in the most comprehensive meta-analysis of PCS, which included 21 studies and 53,300 participants (Siri-Tarino et al, 2010).The evidence was considered as *adequate* for both CVD mortality and CVD events.

Reduced intake of saturated fats and CVD outcomes
Randomised controlled trials CVD mortality • No effect • *Adequate* evidence CVD events • Effect • *Adequate* evidence • The direction of the effect indicates that reduced intake of saturated fats lowers the number of CVD events *Prospective cohort studies* CVD mortality • No association • *Adequate* evidence CVD events • No association • *Adequate* evidence

Substitution of saturated fats with PUFA or a combination of PUFA and MUFA and CVD outcomes

8.12 Three systematic reviews, 2 with meta-analyses (Hooper et al, 2015; Ramsden et al, 2013) and 1 without meta-analyses (Schwab et al, 2014) examined the relationship between substitution of saturated fats with polyunsaturated fats (PUFA) or unsaturated fats (mixture of PUFA and monounsaturated fats (MUFA)) and CVD. Two systematic reviews analysed the results from RCTs (Hooper et al, 2015; Ramsden et al, 2013), and 1 assessed the results from both RCTs and PCS (Schwab et al, 2014).

Randomised controlled trials

8.13 The comprehensive Cochrane systematic review with meta-analysis of 7 RCTs (Hooper et al, 2015) reported no effect of substitution of saturated fats with PUFA on CVD mortality using a random-effects model (7 RCTs, 4251 participants, 553 CVD deaths) after a mean follow-up of 55-months. However, there was a 27% lower risk of CVD events after a mean follow-up of 55-months using a random-effects model (RR 0.73, 95% CI 0.58 to 0.92, $p<0.05$; I^2 =69%; 7 RCTs, >3000 participants, 884 CVD events) (Hooper et al, 2015). These analyses did not separate the effects of different types of PUFA (that is, n-3 and n-6 PUFA).

8.14 Ramsden et al (2013) in a systematic review with meta-analysis of 7 RCTs published between 1965 and 1994 reported that substitution of saturated fats with PUFA had no effect on CVD mortality (7 RCTs, 11,275 participants). Of the 7 included RCTs, 3 investigated substitution with n-6 PUFA; a meta-analysis of these found no effect on CVD mortality (3 RCTs, 9569 participants; statistical model used was unclear). Four of the 7 RCTs investigated substitution with n-6 and/or n-3 PUFA. These found a significant 21% reduction in risk of CVD mortality when saturated fats were substituted with n-6 and n-3 PUFA (combined) or n-3 PUFA alone (hazard ratio (HR) 0.79, 95% CI 0.63 to 0.99, p=0.04; I^2 =0%; 4 RCTs, 1706 participants). It was reported that there was no effect from substituting saturated fats with n-6 PUFA alone (Ramsden et al, 2013). These analyses include recovered data from the Sydney Diet Heart Study which had not been published previously (Ramsden et al, 2013).

8.15 Schwab et al (2014) in their systematic review without meta-analysis, reported on the results from the Hooper et al (2012) meta-analysis which focused on evidence published after 2000. This reported that substitution of saturated fats with unsaturated fats (PUFA or MUFA) reduced the risk of CVD events by 14% (no statistics were provided in the paper).

Prospective cohort studies

8.16 Evidence from systematic reviews of PCS indicate a reduction in CVD mortality when saturated fats were substituted with PUFA (Schwab et al, 2014) or a mixture of MUFA and PUFA (Schwab et al, 2014), however, there was no formal meta-analysis of these data, which limits their quality.

8.17 No systematic reviews, meta-analyses or pooled analyses of PCS were identified that reported on the association between substitution of saturated fats with PUFA and CVD events.

8.18 In summary, the comprehensive Cochrane systematic review with meta-analysis (Hooper et al, 2015) reported a 27% lower risk of CVD events following substitution of saturated fats with PUFA. The evidence was classed as *adequate.* There was *adequate* evidence for no effect on CVD mortality. For PCS the evidence was considered to be *limited* due to the possible differential effect of different classes of PUFA and because there had been no meta-analysis.

Saturated fats substitution with PUFA or a combination of PUFA and MUFA and CVD outcomes
Randomised controlled trials CVD mortality • No effect • *Adequate* evidence CVD events • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with PUFA lowers CVD events *Prospective cohort studies* CVD mortality • Association for saturated fats substitution with PUFA or a combination PUFA and MUFA on CVD mortality • *Limited* evidence • The direction of the association indicates that substitution of saturated fats with PUFA or a combination of PUFA and MUFA lowers CVD mortality CVD events • No evidence

Substitution of saturated fats with MUFA and CVD outcomes

8.19 One systematic review with meta-analysis of RCTs (Hooper et al, 2015) examined the effect of substitution of saturated fats with MUFA on CVD. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

8.20 A Cochrane systematic review with meta-analysis by Hooper et al (2015) reported 1 RCT that investigated the effect of saturated fats substitution with MUFA on CVD outcomes. This RCT reported no effect on CVD mortality but this was based on 4 CVD deaths (1 RCT, 52 participants, 4 CVD deaths). This RCT also reported no effect on CVD events (1 RCT, 52 participants, 22 CVD events).

8.21 In summary, data were i*nsufficient* to draw any conclusions.

Saturated fats substitution with MUFA and CVD outcomes
Randomised controlled trials CVD mortality • *Insufficient* evidence CVD events • *Insufficient* evidence *Prospective cohort studies* CVD mortality • No evidence CVD events • No evidence

Substitution of saturated fats with carbohydrates and CVD outcomes

8.22 Two systematic reviews, 1 with meta-analysis (Hooper et al, 2015) and 1 without meta-analysis (Schwab et al, 2014) examined the relationship between substitution of saturated fats with carbohydrates and CVD. One systematic review analysed the results from RCTs (Hooper et al, 2015) and 1 evaluated the results from both RCTs and PCS (Schwab et al, 2014).

Randomised controlled trials

8.23 A Cochrane systematic review with meta-analysis of 6 RCTs by Hooper et al (2015) reported no effect on CVD mortality following substitution of saturated fats with carbohydrates at a mean follow-up of 46 months using a random-effects model (6 RCTs, 51,232 participants, 745 CVD deaths). They also reported no effect on CVD events using a random-effects model (6 RCTs, >51,000 participants, 3785 CVD events) (Hooper et al, 2015). The meta-analysis did not stratify by carbohydrates type and the analysis was dominated by data from the Women's Health Initiative (48,835 participants), which aimed to reduce total fat intake and increase the intake of fruits, vegetables and grains. The Women's Health Initiative resulted in some decrease in intake of saturated fats but did not explicitly test the effect of substitution of saturated fats with carbohydrates.

Prospective cohort studies

8.24 Schwab et al (2014) reported on the findings of a systematic review of PCS that included 3 studies. It was stated that substituting saturated fats with carbohydrates was associated with an increased risk of CVD outcomes. It was also reported that there was an increased risk of CVD outcomes following substitution of saturated fats with simple carbohydrates

(defined in the paper as high glycaemic index), but not complex carbohydrates (low glycaemic index) (1 PCS).

8.25 In summary, data from RCTs included in a systematic review with meta-analysis by Hooper et al (2015) indicated no effect of saturated fats substitution with carbohydrates on CVD mortality or CVD events. The evidence was classed as *limited* as it was dominated by data from the Women's Health Initiative, which did not explicitly test the effect of substitution of saturated fats with carbohydrates. There was also no information on carbohydrates type. Data from PCS were *insufficient* to draw any clear conclusions, as there were only a small number of studies included with no meta-analysis.

Saturated fats substitution with carbohydrates and CVD outcomes
Randomised controlled trials CVD mortality • No effect • *Limited* evidence CVD events • No effect • *Limited* evidence *Prospective cohort studies* CVD mortality • *Insufficient* evidence CVD events • *Insufficient* evidence

Substitution of saturated fats with proteins and CVD outcomes

8.26 One systematic review with meta-analysis of RCTs (Hooper et al, 2015) examined the effect of substitution of saturated fats with proteins on CVD. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

8.27 Hooper et al (2015) considered the effect of substituting saturated fats with proteins, based on 5 RCTs with a mean 48 month follow-up. They found no effect on CVD mortality using a random-effects model (5 RCTs, 51,177 participants, 741 CVD deaths). They also found no effect on CVD events using a random-effects model (5 RCTs, 51,177 participants, 3757 CVD events). The results were dominated by data from the Women's Health Initiative (48,835 participants), which aimed to reduce total fat intake and increase the intake of

fruits, vegetables and grains. The Women's Health Initiative resulted in some decrease in intake of saturated fats but did not explicitly test the effect of substitution of saturated fats with proteins.

8.28 In summary, the data from RCTs showed no effect of saturated fats substitution with proteins on CVD mortality or CVD events. The evidence was classed as *limited* due to the low number of CVD events and the reliance on the Women's Health Initiative, which did not explicitly test the effect of saturated fats substitution with proteins.

Saturated fats substitution with proteins and CVD outcomes
Randomised controlled trials CVD mortality • No effect • *Limited* evidence CVD events • No effect • *Limited* evidence *Prospective cohort studies* CVD mortality • No evidence CVD events • No evidence

Coronary heart disease (CHD)

Reduced intake of saturated fats and CHD outcomes

8.29 Nine systematic reviews, 7 with meta-analyses (Harcombe et al, 2017; Harcombe et al, 2016b; Hooper et al, 2015; de Souza et al, 2015; Chowdhury et al, 2014; Siri-Tarino et al, 2010; Skeaff & Miller, 2009) and 2 without meta-analyses (Harcombe et al, 2016a; Mente et al, 2009) examined the relationship between reduced intake of saturated fats and CHD. Two systematic reviews analysed the results from RCTs (Harcombe et al, 2016b; Hooper et al, 2015) and 7 evaluated the results from PCS (Harcombe et al, 2017; Harcombe et al, 2016a; de Souza et al, 2015; Chowdhury et al, 2014; Siri-Tarino et al, 2010; Mente et al, 2009; Skeaff & Miller, 2009).

Randomised controlled trials

8.30 Of the identified reviews, 2 included data on CHD outcomes from 6 to 12 RCTs (Harcombe et al, 2016b; Hooper et al, 2015).

8.31 In a systematic review with meta-analysis, Harcombe et al (2016b) analysed 10 RCTs; 7 secondary prevention studies, 1 primary prevention and 2 combined, with between 2 and 11 years follow-up (mean duration 4.7 ±3.3 years) published between 1965 and 2006. There was no effect of saturated fats on CHD mortality using a random-effects model (10 RCTs, 62,421 participants, 1218 CHD deaths).

8.32 In the Cochrane systematic review with meta-analysis, Hooper et al (2015) analysed 11 RCTs published between 1965 and 2006. It was reported that there was no effect of reduced intakes of saturated fats compared with usual intakes on myocardial infarction (MI) (fatal and non-fatal) after a mean 52-month follow-up using a random-effects model (11 RCTs, 53,167 participants, 1714 events). Similar results were reported when using a Mantel-Haenszel fixed-effect model and Peto fixed-effect model. Other sensitivity analyses were performed that found no effect on MI (fatal and non-fatal).

8.33 Hooper et al (2015) reported no effect of reduced intake of saturated fats compared with usual intakes on non-fatal MI after a mean 55-month follow-up using a random-effects model (9 RCTs, 52,834 participants, 1348 events). Similar results were reported when using a Mantel-Haenszel fixed-effect model and a Peto fixed-effect model. Other sensitivity analyses were performed that found no effect on non-fatal MI.

8.34 Hooper et al (2015) reported no effect of reduced intake of saturated fats compared with usual intakes on CHD mortality after a mean 65-month follow-up using a random-effects model (10 RCTs, 53,159 participants, 886 deaths). Similar results were reported when using a Mantel-Haenszel fixed-effect model and a Peto fixed-effect model. Other sensitivity analyses were performed that found no effect on CHD mortality. Mean intakes of saturated fats from individual RCTs are summarised in Annex 2, Figure A2.3.

8.35 Hooper et al (2015) reported no effect of reduced intakes of saturated fats compared with usual intakes on CHD events after a mean 59-month follow-up using a random-effects model (RR 0.87, 95% CI 0.74 to 1.03; p=0.07; I^2=66%; 12 RCTs, 53,199 participants, 3307 with at least 1 CHD event). This finding was not changed by other sensitivity analyses[22]. Hooper et al (2015) performed sensitivity analysis using two fixed-effect models (Mantel-Haenszel and Peto), which indicated a statistically significant effect on CHD events. Analysis using fixed-effect models indicated that reducing saturated fats compared with usual intake resulted in a 7 to 8% reduction in CHD events. This was the case for both a Mantel-Haenszel fixed-effect model (RR 0.93, 95% CI 0.87 to 0.99, p<0.05; I^2 =66%; 12 RCTs, 53,199 participants, 3307 with at least 1 CHD event) and Peto fixed-effect model (RR 0.92, 95% CI 0.86 to 0.99, p<0.05; I^2 =72%; 12 RCTs, 53,199 participants, 3307 with at least 1 CHD event).

[22] Excluding studies which did not state an aim to reduce saturated fats; excluding studies which did not report saturated fat intake during the trial, or did not find a statistically significant reduction in saturated fats in the intervention compared to the control; excluding studies where total cholesterol (TC) or LDL (where TC was not reported) was not reduced; excluding the largest study (Women's Health Initiative (WHI) with CVD 2006; WHI without CVD 2006).

The upper confidence level was 0.99 indicating a p value equivalent to p<0.05, illustrating a significant effect; this compares with a p value of 0.07 for a mean 13% reduction in the random-effects model. Mean intakes of saturated fats from individual RCTs are summarised in Annex 2, Figure A2.4.

Prospective cohort studies

8.36 There were 7 systematic reviews that included data on CHD outcomes (mortality and/or events) from 3 to 20 PCS (Harcombe et al, 2017; Harcombe et al, 2016a; de Souza et al, 2015; Chowdhury et al, 2014; Siri-Tarino et al, 2010; Mente et al, 2009; Skeaff & Miller, 2009).

8.37 Harcombe et al (2017) performed a systematic review with meta-analysis of 7 PCS, with mean follow-up of 11.9± 5.6 years. There was no association with CHD mortality and intake of saturated fats using the random-effects model (7 PCS, 89,801 participants, 2024 CHD deaths).

8.38 de Souza et al (2015) performed a systematic review with meta-analysis of 11 PCS with 15 comparisons and reported no association between the highest and lowest intakes of saturated fats and CHD mortality for the most adjusted multivariable ratio[23] using a random-effects model (11/15 PCS/comparisons), 101,712 participants, 2970 CHD deaths). Furthermore, no association was reported between the intake of saturated fats and total CHD (not defined) for the most adjusted risk ratio using a random-effects model (12/17 PCS/comparisons), 267,416 participants, 6383 CHD deaths).

8.39 Chowdhury et al (2014) performed the most comprehensive systematic review with meta-analysis on 20 PCS, comparing tertiles of intake of saturated fats with a follow-up of 5 to 20 years. No association was found with CHD outcomes when comparing the top tertile of intake of saturated fats with the bottom tertile using a random-effects model (RR 1.02, 95% CI 0.97 to 1.07; 20 PCS, 283,963 participants, 10,518 cases). Analysis using fixed-effect model found a significantly increased risk of CHD outcomes with higher intake of saturated fats (RR 1.04, 95% CI 1.01 to 1.07, p<0.05; 20 PCS, 283,963 participants, 10,518 CHD events).

8.40 Siri-Tarino et al (2010) performed a systematic review with meta-analysis on 16 PCS with follow-ups of 6 to 23 years. No association was found between upper and lower quartiles of intake of saturated fats and CHD outcomes using a random-effects model (16 PCS, 214,182 participants). There was also no association when intake of saturated fats were adjusted for total energy intake, energy from proteins, energy from carbohydrates, and energy from fats.

[23] The multivariable association measure with the highest number of covariates (smoking, age, LDL cholesterol and blood pressure)

8.41 Skeaff & Miller (2009) performed a systematic review with meta-analysis on associations with low (7 to 11 % total energy) versus high (14 to 18 % total energy) intakes of saturated fats, using random-effects models. There was no association with CHD mortality at 5 to 16 years follow-up (6 PCS, 80,655 participants, 1313 CHD deaths) or CHD events at 5 to 20 years follow-up (5 PCS, 147,818 participants, 2202 CHD events). Analysis of 5% total energy increments in saturated fats also showed no association for either CHD mortality (2 PCS, 46,695 participants, 367 CHD deaths) or CHD events (3 PCS, 126,221 participants, 2826 CHD events).

8.42 Harcombe et al (2016a) performed a systematic review which included data from 6 PCS (5 primary prevention trials, 1 combined (98% of participants CHD-free)), all published before 1982, involving 31,445 male participants and 360 CHD deaths with a mean follow-up of 7.5 ± 6.2 years. No meta-analysis was performed and it was reported that 1 of the 6 PCS found a significant association between CHD mortality and intakes of saturated fats.

8.43 Mente et al (2009) performed a systematic review of 11 PCS and reported that when the highest intakes of saturated fats were compared with the lowest, no association between saturated fats and coronary outcomes were identified (11 sub-cohorts, 160,673 participants). No meta-analysis was performed and the definitions for evidence and scoring systems could be considered arbitrary (although these had been validated previously).

8.44 In summary, evidence from the most recent systematic review with meta-analysis of RCTs (Harcombe et al, 2016b) reported no effect of saturated fats on CHD mortality using a random-effects model, but did not report on CHD events. In the most comprehensive and rigorous systematic review with meta-analysis performed according to the Cochrane protocol, Hooper et al (2015) reported on both CHD mortality and events. The Committee considered the evidence on CHD mortality *adequate* for no effect. Hooper et al (2015) also found no effect on CHD events when using a random-effects model. However, sensitivity analysis using two fixed-effect models (Mantel-Haenszel and Peto) indicated a statistically significant effect on CHD events. The Committee noted that the random-effects and fixed-effect models were consistent in the direction of the effect but gave different effect sizes and p values (random RR 0.87, 95% CI 0.74 to 1.03; p=0.07; fixed (Mantel-Haenszel) RR 0.93, 95% CI 0.87 to 0.99, p<0.05; fixed (Peto) RR 0.92, 95% CI 0.86 to 0.99, p<0.05). The Committee, therefore considered these data on reduced intake of saturated fats and lower RR for CHD events to be *moderate* evidence.

8.45 Regarding observational data, the most comprehensive systematic review with meta-analysis by Chowdhury et al (2014) of PCS, reported no association between CHD outcomes (as described in the individual studies) and intake of saturated fats using random-effects models. However, when Chowdhury et al (2014) used a fixed-effect model they found a significantly increased risk of CHD outcomes at the highest compared with lowest tertiles of intake of saturated fats (Chowdhury et al, 2014). The Committee noted that the random-

effects and fixed-effect model results were in the same direction and of similar size, it was only their significance that differed (random RR 1.02, 95% CI 0.97 to 1.07, p>0.05; fixed RR 1.04, 95% CI 1.01 to 1.07, p<0.05).Despite the adequate study numbers, large numbers of events and relative risks in the same direction, the Committee did not consider the evidence adequate due to differing p values after random and fixed-effect modelling and other less comprehensive reviews reporting no effect (on mortality and/or events) for a range of CHD outcomes. The Committee, therefore considered these data to be *moderate* evidence.

Reduced intake of saturated fats and CHD outcomes
Randomised controlled trials CHD mortality • No effect • *Adequate* evidence CHD events • Effect • *Moderate* evidence • The direction of the effect indicates that reduced intake of saturated fats lowers CHD events *Prospective cohort studies* CHD mortality/events • Association • *Moderate* evidence • The direction of the association indicates that lower intake of saturated fats lowers CHD mortality/events

Substitution of saturated fats with PUFA and CHD outcomes

8.46 Six systematic reviews, 4 with meta-analyses (Ramsden et al, 2016; Hooper et al, 2015; Farvid et al, 2014; Skeaff & Miller, 2009) and 2 with pooled analyses (Mozaffarian et al, 2010; Jakobsen et al, 2009) examined the relationship between substitution of saturated fats with PUFA and CHD. Four systematic reviews analysed the results from RCTs (Ramsden et al, 2016; Hooper et al, 2015; Mozaffarian et al, 2010; Skeaff & Miller, 2009) and 2 evaluated the results from PCS (Farvid et al, 2014; Jakobsen et al, 2009).

Randomised controlled trials

8.47 Four systematic reviews included data from 5 to 12 RCTs on the substitution of saturated fats with PUFA and the effect on CHD outcomes (Ramsden et al, 2016; Hooper et al, 2015; Mozaffarian et al, 2010; Skeaff & Miller, 2009).

8.48 Ramsden et al (2016) reported a systematic review with meta-analysis on 5 RCTs reporting substitution of saturated fats with linoleic acid or linoleic acid-rich vegetable oil. No effect on CHD mortality was observed in either case (10,808 participants; 324 CHD deaths).

8.49 Hooper et al (2015) performed the most comprehensive systematic review with meta-analysis of 10 RCTs that substitution of saturated fats with PUFA had no effect on fatal or non-fatal MI using a random-effects model (>3000 participants, 591 fatal or non-fatal MI events). There was no effect on non-fatal MI using random-effects model (>3000 participants, 233 non-fatal MI events). There was also no effect on CHD mortality (4000 participants, 491 CHD deaths). However, there was a 24% reduction in CHD events (RR 0.76, 95% CI 0.57 to 1.00, no p value reported; I^2=71% >3000 participants, 737 CHD events).

8.50 Skeaff & Miller (2009) reported on a systematic review with meta-analysis. There was no effect of high PUFA and lower saturated fats on CHD deaths (5 RCTs, 4528 participants, 284 CHD deaths) using a random-effects model. However, there was a reduction in CHD events (RR 0.83, 95% CI 0.69 to 1.00, p=0.05; I^2=44.2%; 8 RCTs, 4528 participants, 284 CHD events) using a random-effects model. In addition, in the 3 trials where there was a significant reduction in mean serum cholesterol concentration in the intervention group, there was a significant decrease in CHD mortality using a random-effects model (RR 0.52, 95% CI 0.30 to 0.87, p=0.014; I^2 =0.0%; 3 RCTs, 2102 participants, 61 CHD deaths). This was also the case for CHD events using a random-effects model (RR 0.68, 95% CI 0.49 to 0.94, p=0.02; I^2 =40.3%; 5 RCTs, 3002 participants; 288 CHD events).

8.51 Mozaffarian et al (2010) reported on a pooled analysis of 7 RCTs and 1 cross-over trial (of which 5 were conducted in populations with established CHD or a recent MI) with 13,614 participants and 1042 CHD events. Pooled effects were calculated using random-effects meta-analysis. Average weighted PUFA intake was 14.9% energy (range 8.0% to 20.7%) in intervention groups versus 5.0% energy (range 4.0% to 6.4%) in controls. The overall pooled risk reduction was 19% (RR 0.81, 95% CI 0.70 to 0.95, p =0.008), corresponding to 10% reduced risk of CHD events (RR 0.90, 95% CI 0.83 to 0.97) for each 5% energy of increased PUFA in place of saturated fats. Meta-regression identified study duration as an independent determinant of risk reduction (p=0.017), with studies of longer duration showing greater benefits.

Prospective cohort studies

8.52 Three systematic reviews (Farvid et al, 2014; Schwab et al, 2014; Jakobsen et al, 2009), 1 with meta-analysis (Farvid et al, 2014), 1 without meta-analysis (Schwab et al, 2014) and 1

with pooled analysis (Jakobsen et al, 2009) comprising 5 to 13 PCS included data on the substitution of saturated fats with PUFA in relation to CHD outcomes

8.53 Farvid et al (2014), in a systematic review with meta-analysis of 13 PCS with 310,602 participants, reported on the modelled substitution of saturated fats with dietary linoleic acid (n-6 PUFA). Substituting 5% of energy from saturated fats with linoleic acid was associated with a 13% lower risk of CHD deaths using a fixed-effect (Mantel-Haenszel) model (RR 0.87, 95% CI 0.82 to 0.94, $p<0.05$; $I^2=0.0$, 10 PCS). This finding was found to be non-significant using a random-effects model (RR 0.90, 95% CI 0.80 to 1.01). There was a 9% lower risk of CHD events using a fixed-effect model (RR 0.91, 95% CI 0.87 to 0.96, $p=0.012$; $I^2=55.9\%$; 8 PCS), which was not significant using a random-effects model (RR 0.90, 95% CI 0.80 to 1.01).

8.54 Jakobsen et al (2009) reported on 11 PCS (344,696 participants, 4 to 10 years duration, age 47 to 61 years; 71% women; healthy at baseline). They used evidence from PCS analyses which modelled the substitution of saturated fats with PUFA, MUFA or carbohydrates to investigate associations with CHD. The models used are described in detail in their paper. Overall, a 5% lower energy intake from saturated fats and a concomitant higher energy intake from PUFA was significantly associated with a decrease in CHD deaths (HR 0.74, 95% CI 0.61 to 0.89, p value not reported) and CHD events (HR 0.87, 95% CI 0.77 to 0.97, p value not reported).

8.55 Schwab et al (2014) limited their analysis to a summary of the findings of Jakobsen et al (2009), which are discussed above.

8.56 In summary, the evidence from the most comprehensive meta-analysis of RCTs (Hooper et al, 2015) reported no effect of saturated fats substitution with PUFA on CHD mortality, but did find a significant effect on CHD events. The evidence was graded as *adequate* for CHD mortality and *moderate* for CHD events, based on an adequate number of studies and events, consistency with the outcome of Mozaffarian et al (2010), and an upper confidence interval from Hooper et al (2015) and Skeaff & Miller (2009) of 1.00. In addition to the systematic reviews with meta-analyses in paragraph 8.29, 1 meta-analysis by Hamley (2017b) was identified during the consultation. Hamley (2017b) concluded that when all RCTs were pooled together, substitution of saturated fats with PUFA reduced the risk of CHD events and had no effect on CHD mortality, in line with the Committee's conclusions. Hamley (2017b) also performed a sensitivity analysis for 'adequately' and 'inadequately' controlled trials and reported that there was no effect of substitution of saturated fats with mainly n-6 PUFA on CHD events from 'adequately' controlled trials. However, SACN agreed that although it was a novel sensitivity analysis, the criteria for 'adequately' or 'inadequately' controlled trials were not clear and prone to bias as they were developed after the literature search. Due to lack of detailed description of criteria for 'adequately' controlled trials, SACN agreed that Hamley (2017b) could not be considered in drawing the conclusions.

8.57 Based on the most recent systematic review with meta-analysis Farvid et al (2014) there was evidence from PCS data indicating reduced CHD outcomes when models substituting saturated fats with PUFA were analysed, with reported differences in statistical significance between random versus fixed effects models. The modelling by Jakobsen et al (2009) in particular showed a significant decrease in CHD events and mortality. The evidence was graded as *moderate.*

Saturated fats substitution with PUFA and CHD outcomes
Randomised controlled trials CHD mortality • No effect • *Adequate* evidence CHD events • Effect • *Moderate* evidence • The direction of the effect indicates that substitution of saturated fats with PUFA lowers CHD events *Prospective cohort studies* CHD mortality • Association • *Moderate* evidence • The direction of the association indicates that substitution of saturated fats with PUFA lowers CHD mortality CHD events • Association • *Moderate* evidence • The direction of the association indicates that substitution of saturated fats with PUFA lowers CHD events

Substitution of saturated fats with MUFA and CHD outcomes

8.58 Three systematic reviews, 1 with meta-analysis (Hooper et al, 2015), 1 without meta-analysis (Micha & Mozaffarian, 2010) and 1 with pooled analysis (Jakobsen et al, 2009) examined the relationship between the substitution of saturated fats with MUFA and CHD. Two systematic reviews analysed the results from RCTs (Hooper et al, 2015; Micha & Mozaffarian, 2010) and 1 evaluated the results from PCS (Jakobsen et al, 2009).

Randomised controlled trials

8.59 Of the identified reviews, 2 included data on substitution of saturated fats with MUFA on CHD outcomes (Hooper et al, 2015; Micha & Mozaffarian, 2010).

8.60 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported that in 1 RCT, there was no effect of substitution of saturated fats with MUFA on fatal or non-fatal MI (1 RCT, 52 participants, 12 fatal and non-fatal MI events). There was also no effect on non-fatal MI alone (1 RCT, 52 participants, 11 non-fatal MI events) or CHD mortality (1 RCT, 52 participants, 11 CHD deaths). There was no reduction in CHD events (1 RCT, 52 participants, 15 CHD events).

8.61 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) concluded that the effects of substitution of saturated fats with MUFA on CHD events were uncertain.

Prospective cohort studies

8.62 One pooled analysis that included data on the substitution of saturated fats with MUFA in relation to CHD outcomes from 11 PCS (Jakobsen et al, 2009) was identified.

8.63 Jakobsen et al (2009) reported on 11 PCS (344,696 participants, 4 to 10 years duration, age: 47 to 61 years (median at baseline); 71% women; healthy at baseline). They used a modelling approach to investigate associations with CHD following substitution of saturated fats with PUFA, MUFA or carbohydrates. The models used are described in detail in their paper. A 5% lower energy intake from saturated fats and a concomitant higher energy intake from MUFA was associated with an increase in CHD events (HR 1.19, 95% CI 1.00 to 1.42) but not CHD deaths. Jakobsen et al (2009) noted that there may have been confounding by trans fat intakes, as the major sources of MUFA in the studies considered were dairy, meat, and partially hydrogenated oils.

8.64 In summary, *insufficient* evidence was available from RCTs on substitution of saturated fats with MUFA to reach any conclusion. For PCS, evidence was graded as *limited* due to potential confounding by intake of trans fats.

Saturated fats substitution with MUFA and CHD outcomes
Randomised controlled trials CHD mortality • *Insufficient* evidence CHD events • *Insufficient* evidence *Prospective cohort studies* CHD mortality • No association • *Limited* evidence CHD events • Association • *Limited* evidence • The direction of the association indicates that substitution of saturated fats with MUFA increases CHD events

Substitution of saturated fats with carbohydrates and CHD outcomes

8.65 Three systematic reviews, 1 with meta-analysis (Hooper et al, 2015), 1 without meta-analysis (Micha & Mozaffarian, 2010) and 1 with pooled analysis (Jakobsen et al, 2009) examined the relationship between the substitution of saturated fats with carbohydrates and CHD. Two systematic reviews analysed the results from RCTs (Hooper et al, 2015; Micha & Mozaffarian, 2010) and 1 evaluated the results from PCS (Jakobsen et al, 2009).

Randomised controlled trials

8.66 Of the identified reviews, 2 included data on the substitution of saturated fats with carbohydrates and CHD outcomes (Hooper et al, 2015; Micha & Mozaffarian, 2010).

8.67 In a Cochrane systematic review with meta-analysis of 10 RCTs, Hooper et al (2015) reported no effect of substitution of saturated fats with carbohydrates on fatal and non-fatal MI combined (10 RCTs, >51,000 participants, 1392 fatal and non-fatal MI events). There was also no effect on non-fatal MI alone (5 RCTs, >51,000 participants, 1188 non-fatal MI events) or CHD mortality (3 RCTs, >51,000 participants, 586 CHD deaths). There was no reduction in CHD events (5 RCTs, >51,000 participants, 2846 CHD events). The analysis did not stratify by carbohydrates type and the analysis was dominated by data from the Women's Health Initiative (48,835 participants), which aimed to reduce total fat intake and increase the intake of fruits, vegetables and grains. The Women's Health

Initiative resulted in some decrease in intake of saturated fats but did not explicitly test the effect of substitution of saturated fats with carbohydrates.

8.68 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) concluded that there was no effect of saturated fats substitution with carbohydrates on CHD events.

Prospective cohort studies

8.69 One pooled analysis, including data on the substitution of saturated fats with carbohydrates and CHD outcomes from 11 PCS (Jakobsen et al, 2009), was identified.

8.70 Jakobsen et al (2009) reported on 11 PCS (344,696 participants, 4 to 10 years duration, age: 47 to 61 years; 71% women; healthy at baseline). They used a modelling approach to investigate associations with CHD following substitution of saturated fats with PUFA, MUFA or carbohydrates. The models used are described in detail in their paper. A 5% lower energy intake from saturated fats and concomitant higher energy intake from carbohydrates was associated with an increase in CHD events (HR 1.07, 95% CI 1.01 to 1.14) but not CHD deaths.

8.71 In summary, evidence from RCTs suggests that there was no effect from substituting saturated fats with carbohydrates on CHD outcomes (Hooper et al, 2015). However, substitution with different types of carbohydrates may have differential effects. The evidence for CHD mortality was classed as *limited,* as 3 RCTs were included, with a low number of deaths (50,868 participants; 586 deaths) and 1 of the RCTs was the Women's Health Initiative, which did not explicitly test the effect of substitution of saturated fats with carbohydrates. The evidence for CHD events was graded as *moderate,* as 5 RCTs were included in the meta-analysis, with a high number of events (51,104 participants; 2846 events). The evidence was graded *moderate* rather than *adequate* as 1 of the 5 included RCTs was the Women's Health Initiative, which did not explicitly test the effect of substitution of saturated fats with carbohydrates.

8.72 For PCS, conclusions rely on the modelling of Jakobsen et al (2009), which demonstrates that substitution of saturated fats with carbohydrates is associated with an increase in CHD events but not CHD deaths. Due to the number of studies included in the review the evidence was deemed *adequate.*

Saturated fats substitution with carbohydrates and CHD outcomes
Randomised controlled trials CHD mortality • No effect • *Limited* evidence CHD events • No effect • *Moderate* evidence *Prospective cohort studies* CHD mortality • No association • *Adequate* evidence CHD events • Association • *Adequate* evidence • The direction of the association indicates that substitution of saturated fats with carbohydrates increases CHD events

Substitution of saturated fats with proteins and CHD outcomes

8.73 One systematic review with meta-analysis of RCTs (Hooper et al, 2015) examined the effect of substitution of saturated fats with proteins on CHD outcomes. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

8.74 In a Cochrane systematic review with meta-analysis of 3 RCTs, Hooper et al (2015) reported no effect of substitution of saturated fats with proteins on fatal and non-fatal MI using a random-effects model (3 RCTs, >51 000 participants, 1389 fatal and non-fatal MI events). There was also no effect on non-fatal MI alone using a random-effects model (3 RCTs, >51,000 participants, 1188 non-fatal MI events) or CHD mortality using a random-effects model (3 RCTs, >51,000 participants, 586 CHD deaths). There was no reduction in CHD events using a random-effects model (4 RCTs, >51,000 participants, 2833 CHD events). The results were dominated by data from the Women's Health Initiative (48,835 participants), which aimed to reduce total fat intake and increase the intake of fruits, vegetables and grains. The Women's Health Initiative resulted in some decrease in intake of saturated fats but did not explicitly test the effect of saturated fats substitution with proteins.

8.75 In summary, the evidence from the most recent meta-analysis of RCTs (Hooper et al, 2015) found no effect of saturated fats substitution with proteins on CHD mortality and CHD events. The evidence was deemed as *limited* for CHD mortality as 3 RCTs were included, with a low number of deaths (49,011 participants, 586 deaths) and 1 of the RCTs included was the Women's Health Initiative (48,835 participants), which did not explicitly test the effect of substitution of saturated fats with proteins. The evidence for CHD events was graded *moderate,* as 4 RCTs were included in the meta-analysis, with a high number of events (51,044 participants, 2833 events). The evidence was graded *moderate* rather than *adequate* as 1 of the 4 included RCTs, was the Women's Health Initiative, which did not explicitly test the effect of saturated fats substitution with proteins.

Saturated fats substitution with proteins and CHD outcomes
Randomised controlled trials CHD mortality • No effect • *Limited* evidence CHD events • No effect • *Moderate* evidence *Prospective cohort studies* CHD mortality/events • No evidence

Strokes

Reduced intake of saturated fats and strokes (all types, fatal and non-fatal)

8.76 Six systematic reviews, 5 with meta-analyses (Muto & Ezaki, 2018b; Cheng et al, 2016; de Souza et al, 2015; Hooper et al, 2015; Siri-Tarino et al, 2010) and 1 without meta-analysis (Micha & Mozaffarian, 2010) examined the relationship between reduced intake of saturated fats and strokes. One systematic review analysed the results from RCTs (Hooper et al, 2015) and 5 evaluated the results from PCS (Muto & Ezaki, 2018b; Cheng et al, 2016; de Souza et al, 2015; Micha & Mozaffarian, 2010; Siri-Tarino et al, 2010).

8.77 It is possible that the relationship between the intake of saturated fats and stroke may differ by type of stroke. However, the majority of the evidence presented for the outcomes of strokes did not differentiate between the type of stroke (for example haemorrhagic or ischaemic), although 1 systematic review with meta-analysis of PCS reported on ischaemic stroke only (de Souza et al, 2015) and 1 systematic review with meta-analysis of PCS

reported on both ischaemic stroke and haemorrhagic stroke separately (Muto & Ezaki, 2018b).

Randomised controlled trials

8.78 Only 1 systematic review with meta-analysis was identified evaluating the effect of saturated fats on strokes in RCTs (Hooper et al, 2015).

8.79 A Cochrane systematic review with meta-analysis of 7 RCTs (Hooper et al, 2015) reported no effect of reduction of saturated fats on all fatal or non-fatal strokes using a random-effects model (7 RCTs, 50,952 participants, 1125 fatal or non-fatal strokes). This was also the case for fixed-effect analysis (Mantel-Haenszel and Peto 50,952 participants, 1125 fatal or non-fatal strokes). Other sensitivity analyses were performed that also found no effect on fatal or non-fatal strokes (Hooper et al, 2015). Mean intakes of saturated fats from individual RCTs are summarised in Annex 2, Figure A2.5.

Prospective cohort studies

8.80 Muto & Ezaki (2018b) conducted a meta-analysis of 5 PCS of intracerebral haemorrhage and 11 PCS of ischaemic stroke. Overall, a higher intake of saturated fats was significantly associated with a reduction in the risk of both intracerebral haemorrhage (HR 0.69; 95% CI 0.48 to 1.00, p=0.0048; I^2=58.1%; 5 PCS) and ischaemic stroke (HR 0.89; 95% CI 0.82 to 0.96, p=0.004; I^2= 38.8%; 11 RCTs). In a pre-specified secondary analysis, for intracerebral haemorrhage excluding subarachnoid haemorrhage, there was a strong inverse association between intake of saturated fats and risk in Japanese individuals living in Japan (HR 0.55, 95% CI 0.32 to 0.94, p value not reported; 3 PCS). A meta-analysis of ischaemic stroke showed a milder inverse association in Japanese individuals (HR 0.82, 95% CI 0.71 to 0.93, p=0.003; I^2=19.0%; 4 PCS) but no association in non-Japanese individuals (7 PCS).

8.81 Cheng et al (2016) conducted a systematic review with meta-analysis of 15 PCS. They did not differentiate between ischaemic and haemorrhagic stroke. Higher intake of saturated fats was associated with reduced overall stroke risk (RR 0.89, 95% CI 0.82 to 0.96; 15 PCS, 476,569 participants, 11,074 strokes) and fatal stroke risk (RR 0.75, 95 % CI 0.59 to 0.94; 4 PCS). Subgroup analyses indicated that higher intake of saturated fats was associated with reduced stroke risk for East-Asians living in East Asia (RR 0.79, 95% CI 0.69 to 0.90; 6 PCS), for intake <25 g/day (RR 0.81, 95% CI 0.71 to 0.92; 6 PCS), for men (RR 0.85, 95 % CI 0.75 to 0.96; 6 PCS), and for individuals with body mass index (BMI) <24 kg/m^2 (RR 0.75, 95% CI 0.65 to 0.87; 5 PCS), but not for non East-Asians (9 PCS), women (4 PCS), individuals with intake ≥25 g/day (5 PCS) and BMI ≥24 kg/m^2 (5 PCS).

8.82 de Souza et al (2015) performed the most comprehensive systematic review on ischaemic stroke mortality with meta-analysis on 12 PCS with 15 comparisons. They reported no association between intake of saturated fats and ischaemic stroke mortality for the most adjusted random-effects model (12/15 (PCS/comparisons), 339,090 participants, 6226

ischaemic stroke deaths) and least adjusted models (12/15 (PCS/comparisons), 339,090 participants, 6226 ischaemic stroke deaths). No study was an influential outlier (de Souza et al, 2015).

8.83 Siri-Tarino et al (2010) reported on 8 PCS with between 8 and 23 years follow-up. After a meta-analysis, no association between saturated fats and total strokes was observed using a random-effects model (8 PCS, 179,436 participants, 2362 strokes). This was the case when extreme quartiles of intake of saturated fats were compared or when saturated fats adjusted for total energy intake, energy from proteins, carbohydrates and fats, but not PUFA, were compared.

8.84 In a systematic review without meta-analysis of 5 PCS, Micha & Mozaffarian (2010) concluded that there was no association between intake of saturated fats and risk of strokes.

8.85 In summary, no effect was identified between the intake of saturated fats and total strokes in RCTs. The evidence was considered *adequate* as sufficient studies were assessed in the most comprehensive meta-analyses of RCTs (n=7) (Hooper et al, 2015).

8.86 For PCS lower intake of saturated fats was associated with higher total and fatal strokes with significant associations found only in East Asian populations after sub-group analysis (Cheng et al, 2016). The evidence was therefore considered *limited* as these relationships were only found in East Asian populations living in East Asia, where intake of saturated fats are lower than in the UK and there are other differences in overall dietary patterns, lifestyle, genetic background, and stroke aetiology. There was *adequate* evidence for no association between saturated fats and ischaemic stroke from the most comprehensive systematic review with meta-analysis (de Souza et al, 2015). An association was identified between lower intake of saturated fats and higher intracerebral haemorrhagic strokes (excluding subarachnoid haemorrhage) in Japanese populations only in PCS (Muto & Ezaki, 2018b). The evidence was considered *limited* as significant associations were found in Japanese populations living in Japan only, these associations may be apparent only in populations with very low intake of saturated fats and there are important differences in dietary patterns and stroke aetiology in Japanese, compared with the general UK population.

Reduced intake of saturated fats and strokes (all types, fatal and non-fatal)
Randomised controlled trials Total strokes • No effect • *Adequate* evidence *Prospective cohort studies* Total strokes • Association • *Limited* evidence • The direction of association indicates that lower intake of saturated fats was associated with a higher risk of total and fatal strokes in East Asian populations living in East Asia Ischaemic Strokes • No association • *Adequate* evidence Haemorrhagic strokes • Association • *Limited* evidence • The direction of the association indicates that lower intake of saturated fats was associated with higher risk of haemorrhagic strokes in Japanese Asian populations living in Japan

Substitution of saturated fats with PUFA and strokes (all types, fatal and non-fatal)

8.87 One systematic review with meta-analysis of RCTs (Hooper et al, 2015) examined the effect of substitution of saturated fats with PUFA on strokes. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

8.88 In a Cochrane systematic review with meta-analysis by Hooper et al (2015) of 4 RCTs no effect of substitution of saturated fats with PUFA on strokes (any type, fatal or non-fatal) was reported after a mean follow-up of 63 months using a random-effects model (4 RCTs, 1706 participants, 41 stroke deaths).

8.89 In summary, the meta-analysis of 4 RCTs found no effect of saturated fats substitution with PUFA on strokes (Hooper et al, 2015). This Cochrane analysis was comprehensive, but the evidence was classed as *insufficient* as only 41 cases of strokes were identified.

Saturated fats substitution with PUFA and strokes (all types, fatal and non-fatal)
Randomised controlled trials • *Insufficient* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and strokes (all types, fatal and non-fatal)

8.90 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on the relationship between saturated fats substitution with MUFA and strokes.

Substitution of saturated fats with carbohydrates and strokes (all types, fatal and non-fatal)

8.91 One systematic review with meta-analysis of RCTs (Hooper et al, 2015) examined the effect of substitution of saturated fats with carbohydrates on strokes. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

8.92 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) identified 4 RCTs, with a mean 60 months follow-up, and found no effects of substitution of saturated fats with carbohydrates on strokes using a random-effects model (any type, fatal or non-fatal) (4 RCTs, 49,066 participants, 1083 strokes). The results were dominated by data from the Women's Health Initiative (48,835 participants), which aimed to reduce total fat intake and increase the intake of fruits, vegetables and grains. The Women's Health Initiative resulted in some decrease in intake of saturated fats but did not explicitly test the effect of saturated fats substitution with carbohydrates.

8.93 In summary, a meta-analysis of 4 RCTs found no effect of saturated fats substitution with carbohydrates on strokes (Hooper et al, 2015). This Cochrane analysis was comprehensive but was dominated by data from the Women's Health Initiative, which did not explicitly test the effect of substitution of saturated fats with carbohydrates, therefore the evidence was classed as *limited*.

Saturated fats substitution with carbohydrates and strokes (all types, fatal and non-fatal)
Randomised controlled trials • No effect • *Limited* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with proteins and strokes (all types, fatal and non-fatal)

8.94 One systematic review with meta-analysis of RCTs (Hooper et al, 2015) examined the effect of substitution of saturated fats with proteins on strokes. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

8.95 Hooper et al (2015) identified 3 RCTs with a mean follow-up of 72 months and reported no effect of saturated fats substitution with proteins on strokes using a random-effects model (any type, fatal or non-fatal) (3 RCTs, 49,011 participants, 1082 strokes). The results were dominated by data from the Women's Health Initiative (48,835 participants), which aimed to reduce total fat intake and increase the intake of fruits, vegetables and grains. The Women's Health Initiative resulted in some decrease in intake of saturated fats but did not explicitly test the effect of saturated fats substation with proteins.

8.96 In summary, a meta-analysis of 3 RCTs found no effect of saturated fats substitution with proteins on strokes (Hooper et al, 2015). This Cochrane analysis was comprehensive but was dominated by data from the Women's Health Initiative which did not explicitly test the effect of substitution of saturated fats with proteins. Therefore, the evidence was classed as *limited*.

Saturated fats substitution with proteins and strokes (all types, fatal and non-fatal)
Randomised controlled trials • No effect • *Limited* evidence *Prospective cohort studies* • No evidence

Summary

8.97 There was *adequate* evidence from RCTs for a reduction in CVD events with lower intake of saturated fats compared with usual intake. This effect was observed using both fixed-effect and random-effects models. There was *adequate* evidence of no effect from PCS.

8.98 There was *moderate* evidence from RCTs for lower risk for CHD events with lower intake of saturated fats compared with usual intake. The size and direction of effects were generally consistent for both random-effects and fixed-effect models. However, despite the large numbers of included studies and recorded CHD events for RCTs, the evidence was not considered *adequate* due to the statistical differences observed when using random-effects and fixed-effect models. There was also *moderate* evidence from PCS for an increased risk of CHD outcomes with higher compared with lower intake of saturated fats. This was the case using both fixed-effect and random-effects models.

8.99 There was *adequate* evidence from RCTs for no effect of reducing saturated fats on CHD and CVD mortality. There was *adequate* evidence from PCS for no association between lower intake of saturated fats and CVD mortality and the evidence for CHD mortality was *moderate*. There was *adequate* evidence from RCTs that reducing saturated fats had no effect on total strokes and no evidence was available for different types of strokes (ischaemic and haemorrhagic strokes). There was *limited* evidence from PCS that reduction in saturated fats increased the risk of total strokes and haemorrhagic strokes. *Adequate* evidence from PCS indicated that there was no association between reduction in saturated fats and the risk of ischaemic strokes.

8.100 There was evidence for a differential impact on risk when the macronutrient that substitutes saturated fats is considered. Evidence from RCTs indicated no effect of saturated fats substitution with PUFA on mortality for CVD (*adequate*) or CHD (*adequate*). *Adequate* evidence from RCTs was identified for an effect of saturated fats substitution with PUFA on the reduction in risk for CVD events and *moderate* evidence for CHD events. There was evidence from PCS for a reduction in risk of CVD mortality (*limited*) and CHD mortality (*moderate*) with substitution of saturated fats with PUFA. There was no evidence from PCS for the association between substitution of saturated fats with PUFA and CVD events. *Insufficient* evidence was available for the effect of saturated fats substitution with PUFA on strokes.

8.101 *Insufficient* evidence from RCTs was available to determine the effect of saturated fats substitution with MUFA on CVD and CHD events or mortality. Although prospective data that examined saturated fats substitution with both PUFA and MUFA reported a beneficial reduction in risk for CHD mortality, the evidence was *limited* and it was uncertain whether benefit was due to MUFA and/or PUFA.

8.102 No effect was observed from RCTs for effects of saturated fats substitution with carbohydrates on CVD or strokes. However, *adequate* evidence for higher CHD events when saturated fats were substituted with carbohydrates was identified from modelling of PCS. The effect may depend on the type of carbohydrates consumed, but it was not possible to comment further on this due to lack of evidence. Substitution of saturated fats with carbohydrates had no effect on CHD mortality or events according to data from RCTs.

8.103 There was no evidence for an association between saturated fats substitution with proteins and risk of CVD, CHD or stroke.

8.104 The evidence on the differential effects or associations of individual saturated fatty acids and the different types of foods that contain these saturated fatty acids on health outcomes requires evaluation.

8.105 Figure 8.1 shows box plots of intakes of saturated fats in control and intervention arms for individual outcomes. Data from the Hooper et al (2015) systematic review with meta-analysis was used to create the box plot. Data from other systematic reviews or meta-analyses could not be used for the box plot due to either insufficient data or difficulty of extracting information. Mean intakes of saturated fats from individual RCTs that assessed the effect on cardiovascular outcomes are summarised in Annex 2, Figures A2.1 to A2.5.

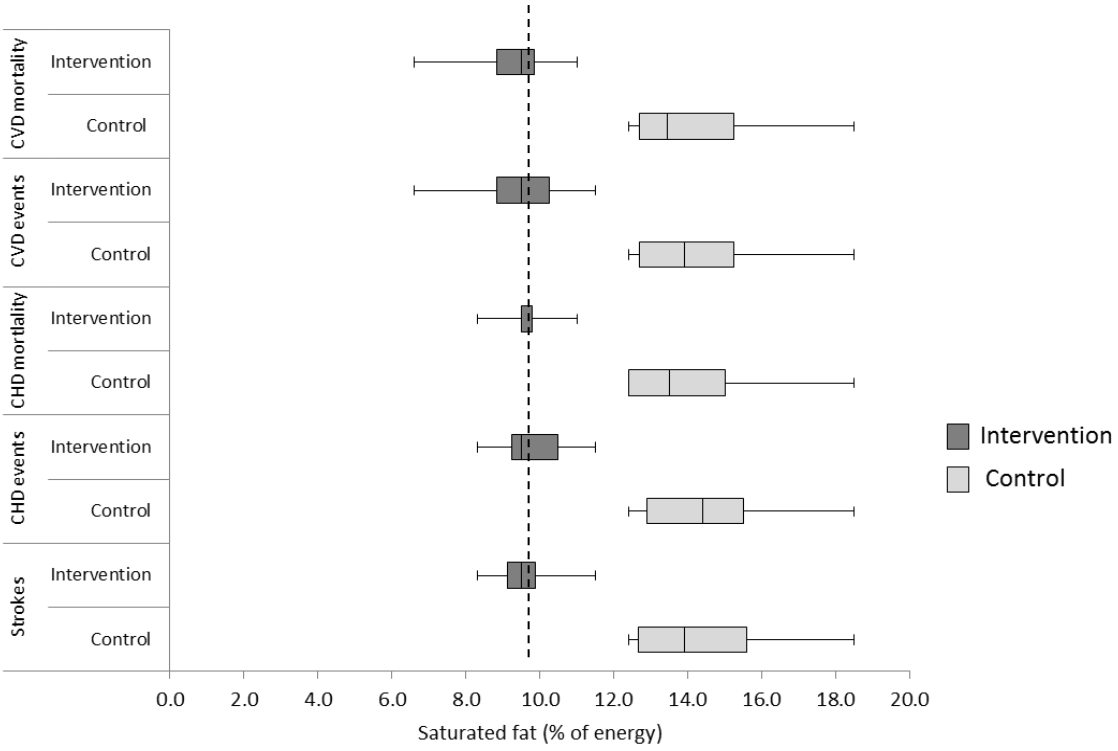

Figure 8.1 Box plots of intakes of saturated fats as percentage of total energy intake in control and intervention arms for individual outcomes (Hooper et al, 2015).
The vertical dashed line (---) represents the dietary reference value for saturated fats (that the [population] average contribution of saturated fatty acids to [tota] dietary energy be reduced to no more than about 10% (COMA, 1994)).

8.106 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and cardiovascular outcomes is summarised below in Table 8.1.

Table 8.1 Summary table of the evidence on the relationship between saturated fats and cardiovascular outcomes

Outcome	Reduced intake of saturated fats*		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
RCTs										
CVD mortality	-	Adequate	-	Adequate	n/a	Insufficient	-	Limited	-	Limited
CVD events	↓	Adequate	↓	Adequate	n/a	Insufficient	-	Limited	-	Limited
CHD mortality	-	Adequate	-	Adequate	n/a	Insufficient	-	Limited	-	Limited
CHD events	↓	Moderate	↓	Moderate	n/a	Insufficient	-	Moderate	-	Moderate
Strokes	-	Adequate	n/a	Insufficient	n/a	No evidence	-	Limited	-	Limited
Peripheral vascular disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
PCS										
CVD mortality	-	Adequate	↓	Limited[1]	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CVD events	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CHD mortality	↓	Moderate[2]	↓	Moderate	-	Limited	-	Adequate	n/a	No evidence
CHD events	↓	Moderate[2]	↓	Moderate	↑	Limited	↑	Adequate	n/a	No evidence
Strokes	-	Adequate[3,4]	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Peripheral vascular disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

n/a – not enough evidence to draw conclusions

Direction of effect/association for reported outcomes: ↑increased; ↓decreased; - no effect/association

*Range of mean intakes of saturated fats (% of total dietary energy) for reported outcomes: CVD mortality (control 12.4- 18.5%; intervention 6.6-11.0%); CVD events (control 12.4-18.5%; intervention 6.6-11.5%); CHD mortality (control 12.4-18.5%; intervention 8.3-11.0%); CHD events (intervention 12.4-18.5%; control 8.3-11.5%); strokes (intervention 12.4-18.5%; control 8.3-11.5%).

[1] Limited evidence indicated that the substitution of saturated fats with a mixture of PUFA and MUFA was associated with a lower risk of CVD.

[2] Reviews considered 'CHD outcomes' which included CHD mortality and/or events.

[3]Adequate evidence indicated that there was no association between lower intake of saturated fats and ischaemic strokes.

[4] Limited evidence indicated that lower intake of saturated fats was associated with a higher risk of haemorrhagic strokes in Japanese populations living in Japan and total strokes in East-Asian populations living in East Asia.

9 Blood lipids

9.1 Eleven systematic reviews, 8 with meta-analyses and 3 without meta-analyses examined the relationship between saturated fats and blood lipids (Hannon et al, 2017a; Te Morenga & Montez, 2017a; Hooper et al, 2015; Schwab et al, 2014; Micha & Mozaffarian, 2010; Van Horn et al, 2008; Mensink et al, 2003; Yu-Poth et al, 1999; Tang et al, 1998; Clarke et al, 1997; Howell et al, 1997). These reviews considered diets where saturated fats were decreased in an isoenergetic manner (with polyunsaturated fats (PUFA), monounsaturated fats (MUFA) or carbohydrates) and/or diets where the total calorie intake was decreased. The characteristics of these publications are summarised in Annex 2, Table A2.4. The quality of the meta-analyses and systematic reviews is summarised in Annex 4.

9.2 The reviews varied considerably in their inclusion criteria. For example, focusing on different subject populations, or focusing on longer-term RCTs of free-living participants (such as Hooper et al (2015)) or shorter-term, highly-controlled RCTs (such as Clarke et al (1997). Therefore, the identified reviews tend to provide additional rather than overlapping evidence. The reviews also varied depending on whether blood lipids were considered as primary or secondary outcomes (see Chapter 2 Methods). In particular, the Cochrane systematic review with meta-analysis of RCTs (Hooper et al, 2015) did not include blood lipids in the search and the evidence is identified from studies selected for other outcomes.

9.3 No systematic reviews, meta-analyses or pooled analyses of randomised controlled trials (RCTs) and prospective cohort studies (PCS) were identified that reported on the relationship between saturated fats substituted with proteins.

Serum total cholesterol

Reduced intake of saturated fats and serum total cholesterol

9.4 Six systematic reviews, 5 with meta-analyses (Te Morenga & Montez, 2017a; Hooper et al, 2015; Yu-Poth et al, 1999; Tang et al, 1998; Howell et al, 1997) and 1 without meta-analysis (Van Horn et al, 2008) examined the relationship between reduced intake of saturated fats and serum total cholesterol. Five systematic reviews analysed the results from randomised controlled trials (RCTs) (Te Morenga & Montez, 2017a; Hooper et al, 2015; Yu-Poth et al, 1999; Tang et al, 1998; Howell et al, 1997) and 1 evaluated the results from both RCTs and prospective cohort studies (PCS) (Van Horn et al, 2008).

Randomised controlled trials

9.5 The most recent systematic review with meta-analysis by Te Morenga & Montez (2017a) examined 8 RCTs, studying young people aged 2 to 16 years (2430 participants, 5 weeks – 19 years follow-up). Five out of the 8 RCTs included children under 5 years, of which 1 RCT

was of children who were pre-specified as hyperlipidemic and 2 included a mixture of hyperlipidemic and normolipidemic children. These involved a range of dietary interventions (through advice and/or the provision of foods) to reduce the intake of saturated fats. Based on dietary intake data, intakes of PUFA, MUFA, proteins and/or carbohydrates changed with a reduction in saturated fats. They found that reduced intake of saturated fats lowers serum total cholesterol using a random-effects model (mean difference -0.16 mmol/L, 95% CI -0.25 to -0.07, p=0.0004; I^2=64%; 7RCTs, 2372 participants).

9.6 A Cochrane systematic review with meta-analysis by Hooper et al (2015) examined 15 RCTs covering 17 comparisons involving approximately 59,000 free-living participants. The studies aimed to assess the impact on total mortality and cardiovascular mortality of either reducing intake of saturated fats or altering saturated fats. Interventions were at least 24-months in duration. As a secondary outcome, serum total cholesterol was not included in the original search. Hooper et al (2015) concluded that serum total cholesterol was lowered by a reduction in intake of saturated fats using a random-effects model (mean difference -0.24 mmol/L, 95% CI -0.36 to -0.13, p<0.001; I^2 =60%; 13/14 (RCTs/comparisons), 7115 participants). The authors reported that there was no differential effect on serum total cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture.

9.7 Yu-Poth et al (1999) conducted a systematic review with meta-analysis of 37 RCTs published between 1981 and 1997, to investigate the effects of the American Heart Association National Cholesterol Education Programme (NCEP) Step 1 and Step 2 diet. The study involved 9276 participants in the intervention group and 2310 in the control group. Using bivariate regression analysis, both diets significantly lowered serum total cholesterol (mean difference -0.63 ± 0.06 mmol/L (10%), p<0.01 for Step 1 diet (where intake of saturated fats is 8 to 10% of dietary energy); mean difference 0.81 ± 0.12 mmol/L (13%), p<0.01 for Step 2 diet (where intake of saturated fats is <7% of dietary energy)). Results were the same for men and women. There was also evidence that those with highly elevated serum total cholesterol were less responsive to dietary interventions than those with mild to moderate hypercholesterolemia. Regression analysis indicated that every 1% reduction in energy from saturated fats resulted in a decrease in serum total cholesterol by 0.056 mmol/L (r^2 =0.59[24], p=0.001). However, these were complex dietary interventions where both dietary cholesterol and fatty acid composition were altered and in many of the studies weight loss also occurred.

9.8 Tang et al (1998) examined the effect of dietary advice on lowering serum total cholesterol in a systematic review with meta-analysis of 19 RCTs published before 1996. Interventions

[24] Regression coefficient

were classified according to the American Heart Association NCEP Step 1 diet[25] (where intake of saturated fats is 8 to 10% of dietary energy) and Step 2 diet[26] (where intake of saturated fats is ≤7% of dietary energy). The overall weighted mean reduction in serum total cholesterol across all studies was 5.3% (mean difference -5.3%, 95% CI -4.7 to -5.9, p<0.001; 19 RCTs, 8430 participants, fixed-effect model) for interventions where participants consumed the NCEP Step 1 or 2 diets for at least 6-months. The Step 2 diet was more effective in reducing serum total cholesterol compared with the Step 1 diet (mean difference - 3.0%, 95% CI -4.1 to -1.8, p<0.001; 8 RCTs, 3069 participants for Step 1 diets; mean difference - 5.6%, 95% CI -4.7 to -6.5, p<0.001; 9 RCTs, 2252 participants for Step 2 diets, fixed-effect model). However, these were complex dietary interventions where both dietary cholesterol and fatty acid composition were altered and in many of the studies weight loss also occurred.

9.9 Howell et al (1997) conducted a systematic review with meta-analysis on 224 RCTs including 8143 participants to examine primarily how changes in dietary cholesterol and fat intakes affect serum total cholesterol, lipoprotein cholesterol concentrations and triacylglycerol. Univariate analysis was used to explore the relationship between saturated fats and serum total cholesterol. The correlation coefficient between saturated fats and serum total cholesterol was 0.803 (r^2=0.803, p<0.0005; 224 study groups). A multivariate analysis predicted that a 1 % change in total energy from saturated fats will result in a 0.0491 mmol/L change in serum total cholesterol.

9.10 Van Horn et al (2008) examined the effect of a number of dietary factors on cardiovascular disease (CVD) risk in a systematic review without meta-analysis of 83 RCTs and 19 review articles from 1991 to 2004. RCTs provided evidence that diets high in saturated fats increased serum total cholesterol. They reported that both American Heart Association NCEP Step 1 and Step 2 diets reduced serum total cholesterol. However, these were complex dietary interventions where both dietary cholesterol and fatty acid composition were altered and in many of the studies weight loss also occurred (no statistics were provided in the paper).

Prospective cohort studies

9.11 Evidence from PCS was reported in 1 systematic review without meta-analysis considering evidence from PCS alongside results from RCTs (Van Horn et al, 2008). However, the details of the PCS were not provided and the main conclusions from the systematic review by Van Horn et al (2008) focused on RCTs. Thus, the evidence was classed as *insufficient*.

[25] <30% of total energy intake as fat, with 8-10% as saturated fats; ratio of PUFA to saturated fats >1.0; cholesterol intake<300 mg/day; and energy intake to achieve desirable body weight

[26] <30% of total energy intake as fat, with 7% or less as saturated fats; ratio of PUFA to saturated fats >1.4; cholesterol intake <200 mg/ day; and energy intake to achieve desirable body weight

9.12 In summary, the evidence from the largest systematic review with meta-analysis in free-living participants (Hooper et al, 2015) indicated that reducing intake of saturated fats reduces serum total cholesterol. Hooper et al (2015) included 13 RCTs (with 7115 participants), however, in this review serum total cholesterol was not part of the original search. Similar reductions were reported in the meta-analysis by Yu-Poth et al (1999). The reductions in serum total cholesterol were greater for diets with greater reductions in saturated fats. For example, the American Heart Association NCEP Step 2 diet (where intake of saturated fats is ≤7% of dietary energy) reduced serum total cholesterol by 6.1% compared with 3% for the Step 1 diet (where intake of saturated fats is 8 to 10% of dietary energy) (Tang et al, 1998). The evidence was graded *adequate.* There was *insufficient* evidence from PCS.

Reduced intake of saturated fats and serum total cholesterol
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that reduced intake of saturated fats lowers serum total cholesterol *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with PUFA (or unsaturated fats)[27] and serum total cholesterol

9.13 Five systematic reviews, 4 with meta-analyses (Hannon et al, 2017a; Hooper et al, 2015; Micha & Mozaffarian, 2010; Clarke et al, 1997) and 1 without meta-analyses (Schwab et al, 2014) examined the relationship between substitution of saturated fats with PUFA and serum total cholesterol. Three systematic reviews analysed the results from RCTs (Hannon et al, 2017a; Hooper et al, 2015; Micha & Mozaffarian, 2010), 1 analysed the results from clinically controlled metabolic ward experiments (Clarke et al, 1997) and 1 analysed the results from both RCTs and PCS (Schwab et al, 2014).

Randomised controlled trials

9.14 In a systematic review with meta-analysis of 8 RCTs (663 participants), Hannon et al (2017a) reported no effect on serum total cholesterol when saturated fats were substituted with unsaturated fats (a mixture of PUFA and MUFA) using a random-effects

[27] Unsaturated fatty acids assumed to be a mixture of PUFA and MUFA.

model. As the authors noted this meta-analysis was performed on a very small number of individuals in a specific population and the meta-analysis showed a high degree of heterogeneity (I^2=97%) making it difficult to draw a conclusion.

9.15 In a Cochrane systematic review with meta-analysis Hooper et al (2015) reported that serum total cholesterol was lowered by a reduction in intake of saturated fats using a random-effects model (mean difference -0.24 mmol/L, 95% CI -0.36 to -0.13, p<0.0001; I^2 =60%; 13 RCTs, 7115 participants). The authors reported that there was no differential effect on serum total cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, serum total cholesterol was not included in the original search.

9.16 The systematic review with meta-analysis of RCTs (number of RCTs not reported) by Micha & Mozaffarian (2010) reported that increased intake of PUFA in the diet as a substitution for saturated fats reduced serum total cholesterol (no statistics were provided in the paper for this comparison).

9.17 In a systematic review with meta-analysis Clarke et al (1997) considered the quantitative importance of dietary fatty acids and dietary cholesterol to blood concentrations of serum total cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol across 395 'metabolic ward' experiments (using highly controlled dietary interventions) representing 5901 participants/diet measurements. In the paper, Clarke et al (1997) did not provide statistics but stated that "isocaloric replacement of saturated fats by unsaturated fats produced about three times the reduction in blood cholesterol than produced by the replacement of total fat by complex carbohydrate". Separate results were not provided for PUFA and MUFA.

9.18 Schwab et al (2014) undertook a systematic review without meta-analysis of 44 RCTs and 1 PCS (published between January 2000 and October 2010) on the effects of saturated fats on serum lipid profile. Diets rich in PUFA and/or MUFA lowered serum total cholesterol (9 out of 9 RCTs demonstrated this effect, 476 participants, no statistics were provided in the paper).

Prospective cohort studies

9.19 Evidence from PCS was reported in 2 systematic reviews without meta-analyses. Micha & Mozaffarian (2010) focused their results on RCTs rather than the PCS, and Schwab et al (2014) included only 1 PCS. Both reviews reported that substitution of saturated fats with PUFA was associated with a reduction in serum total cholesterol.

9.20 In summary, the evidence from the largest systematic review with meta-analysis in free-living populations (Hooper et al, 2015) indicated that substitution of saturated fats with PUFA lowered serum total cholesterol. Hooper et al (2015) included 13 longer-term RCTs (with 7115 participants), however, in this review serum total cholesterol was not included in the original search. The findings of Hooper et al (2015) were supported by a review of

metabolic ward experiments where blood lipids were a primary outcome and the effects of saturated fats substitution with PUFA were examined under highly controlled conditions (Clarke et al, 1997). The results of meta-analyses across the publications were statistically significant and systematic reviews without meta-analyses agreed with this outcome. The evidence from RCTs was graded as *adequate*. There was *insufficient* evidence from PCS.

Saturated fats substitution with PUFA (or unsaturated fats)[28] and serum total cholesterol
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substituting saturated fats with PUFA (or unsaturated fats) lowers serum total cholesterol *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with MUFA (or unsaturated fats)[28] and serum total cholesterol

9.21 Four systematic reviews, 3 with meta-analyses (Hooper et al, 2015; Micha & Mozaffarian, 2010; Clarke et al, 1997) and 1 without meta-analyses (Schwab et al, 2014) examined the relationship between substitution of saturated fats with MUFA and serum total cholesterol. Two systematic reviews analysed the results from RCTs, 1 of longer-term trials with free-living subjects (Hooper et al, 2015; Micha & Mozaffarian, 2010) and 1 of metabolic ward experiments (Clarke et al, 1997). Two evaluated the results from both RCTs and PCS (Schwab et al, 2014; Micha & Mozaffarian, 2010).

Randomised controlled trials

9.22 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported that serum total cholesterol was lowered by reduced intake of saturated fats using a random-effects model (mean difference -0.24 mmol/L, 95% CI -0.36 to -0.13, $p<0.001$; I^2 =60%; 13 RCTs, 7115 participants). The authors reported that there was no differential effect on serum total cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum total cholesterol was not included in the original search.

[28] Unsaturated fatty acids assumed to be a mixture of PUFA and MUFA.

9.23 Micha & Mozaffarian (2010) performed a systematic review with meta-analysis of RCTs (number of RCTs not reported) that considered the effect of diet on blood lipid outcomes. Substituting saturated fats with MUFA were reported to reduce serum total cholesterol (no statistics were provided in the paper for this comparison).

9.24 In a systematic review with meta-analysis Clarke et al (1997) considered the quantitative importance of dietary fatty acids and dietary cholesterol to blood concentrations of serum total cholesterol, LDL cholesterol and HDL cholesterol across 395 'metabolic ward' experiments (using highly controlled dietary interventions) representing 5901 participants/diet measurements. In the paper Clarke et al (1997) did not provide statistics, but stated that "isocaloric replacement of saturated fats by unsaturated fats produced about three times the reduction in blood cholesterol than produced by the replacement of total fat by complex carbohydrate". Separate results were not provided for MUFA and PUFA.

9.25 Schwab et al (2014), in a systematic review without meta-analysis of 44 RCTs and 1 PCS, published between January 2000 and October 2010, reporting on the effects of saturated fats on serum lipid profiles, concluded that diets rich in MUFA and/or PUFA lowered serum total cholesterol (9 out of 9 RCTs demonstrated this effect, 476 participants, no statistics were provided in the paper).

Prospective cohort studies

9.26 Evidence from PCS was reported by 2 systematic reviews without meta-analyses. Micha & Mozaffarian (2010) focused their results on RCTs rather than PCS, and Schwab et al (2014) included only 1 PCS. Both reviews reported that substitution of saturated fats with MUFA was associated with a reduction in serum total cholesterol.

9.27 In summary, the largest systematic review of RCTs with meta-analysis by Hooper et al (2015) indicates that substitution of saturated fats with MUFA lowered serum total cholesterol. Hooper et al (2015) included 13 RCTs (with 7115 participants), however, in this review serum total cholesterol was not included in the original search. The results of meta-analyses across the publications were statistically significant and systematic reviews without meta-analyses agreed with this outcome (Schwab et al, 2014; Micha & Mozaffarian, 2010; Clarke et al, 1997). The evidence from RCTs was graded as *adequate*. There was *insufficient* evidence from PCS.

Saturated fats substitution with MUFA (or unsaturated fats)[29] and serum total cholesterol
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substituting saturated fats with MUFA (or unsaturated fats) lowers serum total cholesterol *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with carbohydrates and serum total cholesterol

9.28 Three systematic reviews with meta-analyses (Hooper et al, 2015; Micha & Mozaffarian, 2010; Clarke et al, 1997) examined the relationship between substitution of saturated fats with carbohydrates and serum total cholesterol. Two systematic reviews analysed the results from RCTs, 1 of longer-term trials with free-living subjects (Hooper et al, 2015) and 1 of metabolic ward experiments (Clarke et al, 1997) and 1 evaluated the results from RCTs and PCS (Micha & Mozaffarian, 2010).

Randomised controlled trials

9.29 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported that serum total cholesterol was lowered by reduced intake of saturated fats using a random-effects model (mean difference -0.24 mmol/L, 95% CI -0.36 to -0.13, $p<0.001$; I^2 =60%; 13 RCTs, 7115 participants). The authors reported that there was no differential effect on serum total cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum total cholesterol was not included in the original search.

9.30 Micha & Mozaffarian (2010) performed a systematic review with meta-analysis of RCTs (number of RCTs not reported) that considered the effect of diet on blood lipid outcomes. Substituting saturated fats with carbohydrates was reported to lower serum total cholesterol but to a lesser extent than substitution with PUFA or MUFA (no statistics were provided in the paper for this comparison).

9.31 The systematic review with meta-analysis of 395 'metabolic ward' experiments (using highly controlled dietary interventions) by Clarke et al (1997) reported that isoenergetic substitution of saturated fats with complex carbohydrates equivalent to 10% of total

[29] Unsaturated fatty acids assumed to be a mixture of PUFA and MUFA.

calories resulted in a decrease in serum total cholesterol (mean difference 0.52 mmol/L, 95% CI 0.58 to 0.43, p<0.001; 395 RCTs, 5740 participants).

Prospective cohort studies

9.32 Evidence from PCS was reported in 1 systematic review without meta-analysis considering evidence from PCS alongside results from RCTs, however their results focused on RCTs rather than PCS (Micha & Mozaffarian, 2010).

9.33 In summary, the evidence from the largest systematic review of RCTs with meta-analysis by Hooper et al (2015) indicates that substitution of saturated fats with carbohydrates lowered serum total cholesterol. Hooper et al (2015) included 13 RCTs (with 7115 participants), however in this review serum total cholesterol was not included in the original search. The findings of Hooper et al (2015) were supported by a review of metabolic ward experiments reported by Clarke et al (1997) where blood lipids were a primary outcome and the effects of saturated fats substitution with carbohydrates were examined under highly controlled conditions. The evidence from RCTs was graded as *adequate*. There was *insufficient* evidence from PCS.

Saturated fats substitution with carbohydrates and serum total cholesterol
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substituting saturated fats with carbohydrates lowers serum total cholesterol *Prospective cohort studies* • *Insufficient* evidence

Serum LDL cholesterol

Reduced intake of saturated fats and serum LDL cholesterol

9.34 Five systematic reviews, 4 with meta-analyses (Te Morenga & Montez, 2017a; Hooper et al, 2015; Yu-Poth et al, 1999; Howell et al, 1997) and 1 without meta-analysis (Van Horn et al, 2008) reported on the relationship between reduced intake of saturated fats and serum LDL cholesterol. Four systematic reviews analysed the results from RCTs (Te Morenga & Montez, 2017a; Hooper et al, 2015; Yu-Poth et al, 1999; Howell et al, 1997) and 1 examined the results from both RCTs and PCS (Van Horn et al, 2008).

Randomised controlled trials

9.35 Te Morenga & Montez (2017a) performed a systematic review with meta-analysis on 8 RCTs, studying young people aged 2 to 16 years (2430 participants, 5 weeks – 19 years follow-up). Five out of the 8 RCTs included children under 5 years, of which 1 RCT was of children who were pre-specified as hyperlipidemic and 2 included a mixture of hyperlipidemic and normolipidemic children. These involved a range of dietary interventions (through advice and/or the provision of foods) to reduce the intake of saturated fats. Based on dietary intake data, intakes of PUFA, MUFA, proteins and/or carbohydrates changed with a reduction in saturated fats. They found that reduced intake of saturated fats lowered serum LDL cholesterol using random-effects model (7 RCTs; 2004 participants). The heterogeneity is above the pre-specified cut-off of 75% (I^2= 77%) and therefore, the pooled estimate is not reported.

9.36 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported that reduced intake of saturated fats lowered serum LDL cholesterol using a random-effects model (mean difference -0.19 mmol/L, 95% CI -0.33 to -0.05, p<0.05; I^2 =37%; 5 RCTs, 3291 participants). The authors reported that there was no differential effect on serum LDL cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum LDL cholesterol was not included in the original search.

9.37 Yu-Poth et al (1999) conducted a systematic review with meta-analysis of 37 RCTs published between 1981 and 1997, focusing on the American Heart Association NCEP Step 1 diet (where intake of saturated fats is 8 to 10% of dietary energy) and Step 2 diet (where intake of saturated fats is ≤7% of dietary energy) (9276 participants in the intervention group, 2310 in the control group). Using bivariate regression analysis, they calculated both diets significantly lowered serum LDL cholesterol (mean difference -0.49±0.05 mmol/L (12%), p<0.05 for Step 1 diet and mean difference -0.65±0.09 mmol/L (16%), p<0.01 for Step 2 diet). Regression analysis indicated that every 1% reduction in energy from saturated fats resulted in a decrease in serum LDL cholesterol of 0.056 mmol/L. However, these were complex dietary interventions where both dietary cholesterol and fatty acid composition were altered and in many of the studies weight loss also occurred.

9.38 Howell et al (1997) performed a systematic review with meta-analysis of 224 RCTs including 8143 participants to examine primarily how changes in dietary cholesterol and fat intakes affect serum total cholesterol, triacylglycerol, and lipoprotein cholesterol concentrations. Univariate analysis was used to explore the relationship between saturated fats and serum LDL cholesterol. The correlation coefficient between saturated fats and serum LDL cholesterol was 0.79 (r^2=0.79, p<0.0005; 129 study groups). A multivariate analysis predicted that a 1 % change in total energy from saturated fats will result in a 0.0465 mmol/L change in serum LDL cholesterol.

9.39 Van Horn et al (2008) performed a systematic review without meta-analysis of the effect of intake of saturated fats on serum LDL cholesterol and risk of CVD across 83 RCTs and 19 review articles. They reported that both American Heart Association NCEP Step 1 and Step 2 diets lowered serum LDL cholesterol. However, these were complex dietary interventions where both dietary cholesterol and fatty acid composition were altered and in many of the studies weight loss also occurred (no statistics were provided in the paper).

Prospective cohort studies

9.40 Evidence from PCS was reported in 1 systematic review without meta-analysis considering the evidence from PCS alongside results from RCTs (Van Horn et al, 2008).

9.41 In summary, based on the systematic reviews with the largest number of subjects (Yu-Poth et al, 1999) and largest number of RCTs (Howell et al, 1997) reducing intake of saturated fats lowers serum LDL cholesterol. Yu-Poth et al (1999) included complex dietary interventions where both dietary cholesterol and fatty acid composition were altered and in many of the studies weight loss also occurred. These findings were supported by the next largest systematic review in a free-living population (Hooper et al, 2015) where blood lipids were not included in the original search. The evidence was graded as *adequate.* There was *insufficient* evidence from PCS.

Reduced intake of saturated fats and serum LDL cholesterol
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that reduced intake of saturated fats lowers serum LDL cholesterol *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with PUFA and serum LDL cholesterol

9.42 Four systematic reviews, 3 with meta-analyses (Hannon et al, 2017a; Hooper et al, 2015; Micha & Mozaffarian, 2010) and 1 without meta-analyses (Schwab et al, 2014) examined the relationship between substitution of saturated fats with PUFA and serum LDL cholesterol. Two systematic reviews analysed the results from RCTs (Hannon et al, 2017a; Hooper et al, 2015), and 2 analysed the results from both RCTs and PCS (Schwab et al, 2014; Micha & Mozaffarian, 2010).

Randomised controlled trials

9.43 In a systematic review with meta-analysis of 8 RCTs (663 participants) Hannon et al (2017a) reported that when saturated fats were substituted with unsaturated fats (a mixture of PUFA and MUFA) there was no effect on serum LDL cholesterol using a random-effects model. As the authors noted, this meta-analysis was performed on a very small number of individuals in a specific population and the meta-analysis showed a high degree of heterogeneity (I^2=96%), making it difficult to draw a conclusion from this meta-analysis.

9.44 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported that reduced intake of saturated fats lowered serum LDL cholesterol using a random-effects model (mean difference -0.19 mmol/L, 95% CI -0.33 to -0.05, p<0.05; I^2 =37%; 5 RCTs, 3291 participants). The authors reported that there was no differential effect on serum LDL cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum LDL serum cholesterol was not included in the original search.

9.45 Micha & Mozaffarian (2010) described in their systematic review with meta-analysis of RCTs (number of RCTs not reported) that where saturated fats were substituted with PUFA there was a reported decrease in serum LDL cholesterol (further characteristics of studies not summarised, no statistics were provided in the paper for this comparison).

9.46 Schwab et al (2014) conducted a systematic review without meta-analysis considering 44 RCTs and 1 PCS and reported that diets rich in PUFA and/or MUFA lowered serum LDL cholesterol compared with diets higher in saturated fats (8 out of 9 RCTs demonstrated this effect, no statistics were provided in the paper).

Prospective cohort studies

9.47 Evidence from PCS was reported in 2 systematic reviews without meta-analyses. Micha & Mozaffarian (2010) focused their results on RCTs rather than PCS, and Schwab et al (2014) included only 1 PCS. Both reviews reported that substitution of saturated fats with PUFA was associated with a reduction in serum LDL cholesterol.

9.48 In summary, the evidence from the largest systematic review with meta-analysis by Hooper et al (2015) indicated that reducing intake of saturated fats by substitution with PUFA lowers serum LDL cholesterol in RCTs. Hooper et al (2015) included 5 RCTs (with 3291 participants) however in this review, serum LDL cholesterol was not included in the original search. The findings of Hooper et al (2015) were supported by the systematic review by Micha & Mozaffarian (2010). The evidence from RCTs was graded as *adequate*. There was *insufficient* evidence from PCS.

Saturated fats substitution with PUFA and serum LDL cholesterol
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substituting saturated fats with PUFA lowers serum LDL cholesterol *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with MUFA and serum LDL cholesterol

9.49 Three systematic reviews, 2 with meta-analyses (Hooper et al, 2015; Micha & Mozaffarian, 2010) and 1 without meta-analyses (Schwab et al, 2014) examined the relationship between substitution of saturated fats with MUFA and serum LDL cholesterol. One systematic review analysed the results from RCTs (Hooper et al, 2015), and 2 examined the results from both RCTs and PCS (Schwab et al, 2014; Micha & Mozaffarian, 2010).

Randomised controlled trials

9.50 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported that reduced intake of saturated fats lowered serum LDL cholesterol using a random-effects model (mean difference -0.19 mmol/L, 95% CI -0.33 to -0.05, $p<0.05$; I^2 =37%; 5 RCTs, 3291 participants). The authors reported that there was no differential effect on serum LDL cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum total cholesterol was not included in the original search.

9.51 Micha & Mozaffarian (2010) described in their systematic review with meta-analysis of RCTs (number of RCTs and participants not reported) that where saturated fats were substituted with MUFA this led to a reported decrease in serum LDL cholesterol (further characteristics of studies not summarised, no statistics were provided in the paper for this comparison).

9.52 Schwab et al (2014) conducted a systematic review without meta-analysis considering 44 RCTs and 1 PCS and reported that diets rich in PUFA and/or MUFA produced a decrease in serum LDL cholesterol compared with diets rich in saturated fats (8 out of 9 RCTs demonstrated this effect, no statistics were provided in the paper).

Prospective cohort studies

9.53 Evidence from PCS was reported in 2 systematic reviews without meta-analyses. Micha & Mozaffarian (2010) focused their results on RCTs rather than the PCS, and Schwab et al (2014) included only 1 PCS. Both reviews reported that substitution of saturated fats with MUFA was associated with a reduction in serum LDL cholesterol.

9.54 In summary, the evidence from the largest systematic review with meta-analysis by Hooper et al (2015) indicated that reducing intake of saturated fats by substitution with MUFA lowers serum LDL cholesterol in RCTs. Hooper et al (2015) included 5 RCTs (with 3291 participants), however in this review serum LDL cholesterol was not included in the original search. The findings of Hooper et al (2015) were supported by a systematic review by Micha & Mozaffarian (2010). The evidence from RCTs was graded as *adequate.* There was *insufficient* evidence from PCS.

Saturated fats substitution with MUFA and serum LDL cholesterol
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substituting saturated fats with MUFA lowers serum LDL cholesterol *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with carbohydrates and serum LDL cholesterol

9.55 Three systematic reviews with meta-analyses (Hooper et al, 2015; Micha & Mozaffarian, 2010; Clarke et al, 1997) examined the relationship between substitution of saturated fats with carbohydrates and serum LDL cholesterol. Two systematic reviews analysed the results from RCTs, 1 of longer-term trials with free-living subjects (Hooper et al, 2015) and 1 of metabolic ward experiments (Clarke et al, 1997) and 1 examined the results from both RCTs and PCS (Micha & Mozaffarian, 2010).

Randomised controlled trials

9.56 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported that reduced intake of saturated fats lowered serum LDL cholesterol using a random-effect model (mean difference -0.19 mmol/L, 95% CI -0.33 to -0.05, $p<0.05$; I^2 =37%; 5 RCTs, 3291 participants). The authors reported that there was no differential effect on serum LDL cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or

carbohydrates or a mixture. However, in the Hooper et al (2015) review serum LDL cholesterol was not included in the original search.

9.57 Micha & Mozaffarian (2010) described in their systematic review with meta-analysis of RCTs (number of RCTs and participants not reported) that substitution of saturated fats with carbohydrates lowered serum LDL cholesterol (β=-0.032 mmol/L, $p<0.05$; 0.032 mmol/L decrease in serum LDL cholesterol for 1% isoenergetic substitution of saturated fats with carbohydrates).

9.58 In a systematic review with meta-analysis Clarke et al (1997) described 227 'metabolic ward' experiments (using highly controlled dietary interventions) that examined the effects of intake of saturated fats on serum LDL cholesterol. Isoenergetic substitution of saturated fats with complex carbohydrates lowered serum LDL cholesterol (mean difference -0.036 mmol/L per percentage decrease in total calories from saturated fats; 95% CI -0.046 to -0.026, $p<0.001$; 227 RCTs; number of participants not provided); based on multivariate and univariate regression analysis).

Prospective cohort studies

9.59 Evidence from PCS was reported in 1 systematic review without meta-analyses (Micha & Mozaffarian, 2010). Furthermore, evidence was considered alongside RCTs in this review, making it difficult to interpret results from PCS alone.

9.60 In summary, the evidence from the largest systematic review with meta-analysis by Hooper et al (2015) indicated that reducing intake of saturated fats by substitution with carbohydrates lowers serum LDL cholesterol in RCTs. Hooper et al (2015) included 5 RCTs (with 3291 participants), however, in this review serum LDL cholesterol was not included in the original search. The findings of Hooper et al (2015) were supported by a review of metabolic ward experiments reported by Clarke et al (1997) where the effects of saturated fats substitution with carbohydrates were examined under highly controlled conditions. The evidence was graded as *adequate.* There was *insufficient* evidence from PCS.

Saturated fats substitution with carbohydrates and serum LDL cholesterol
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with carbohydrates lowers serum LDL cholesterol *Prospective cohort studies* • *Insufficient* evidence

Serum HDL cholesterol

Reduced intake of saturated fats and serum HDL cholesterol

9.61 Four systematic reviews with meta-analyses of RCTs (Te Morenga & Montez, 2017a; Hooper et al, 2015; Yu-Poth et al, 1999; Howell et al, 1997) analysed the effect of reduced intake of saturated fats on serum HDL cholesterol. No systematic reviews, meta-analyses, pooled analyses that evaluated PCS were identified.

Randomised controlled trials

9.62 Te Morenga & Montez (2017a) performed a systematic review with meta-analysis on 8 RCTs, studying young people aged 2 to 16 years (2430 participants, 5 weeks to 19 years follow-up). Five out of the 8 RCTs included children under 5 years, of which 1 RCT was of children who were pre-specified as hyperlipidemic and 2 included a mixture of hyperlipidemic and normolipidemic children. These involved a range of dietary interventions (through advice and/or the provision of foods) to reduce the intake of saturated fats. Based on dietary intake data, intakes of PUFA, MUFA, proteins and/or carbohydrates changed with a reduction in saturated fats. They found that there was no effect of reduced intake of saturated fats on serum HDL cholesterol using random-effects model (6 RCTs, 1565 participants).

9.63 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum HDL cholesterol using a random-effects model (7 RCTs, 5147 participants). The authors reported that there was no differential effect on serum HDL cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum HDL cholesterol was not included in the original search.

9.64 Yu-Poth et al (1999) conducted a systematic review with meta-analysis of 37 RCTs in 9276 participants from 1981 to 1997 to investigate the effects of the American Heart Association NCEP Step 1 diet (where intake of saturated fats is 8 to 10% of dietary energy) and Step 2 diet (where intake of saturated fats is ≤7% of dietary energy) (9276 participants in the intervention group, 2310 in the control group). The correlation between change in saturated fats and serum HDL cholesterol was 0.55, $p<0.001$ (bivariate regression analysis). From multiple regression analyses with body weight as a co-variable, every 1% reduction in energy from saturated fats resulted in a decrease in serum HDL cholesterol by 0.012 mmol/L. However, these were complex dietary interventions where both dietary cholesterol and fatty acid composition were altered and in many studies weight loss also occurred.

9.65 Howell et al (1997) conducted a systematic review with regression meta-analysis of 224 RCTs on 8143 participants to investigate how changes in intake of saturated fats influenced concentrations of serum HDL cholesterol. Univariate analysis was used to explore the

relationship between saturated fats and serum HDL cholesterol. The correlation coefficient between saturated fats and serum HDL cholesterol was 0.604 (r=0.604, p<0.0005; 169 study groups). A multivariate analysis predicted that a 1 % change in total energy from saturated fats will result in a 0.007 mmol/L change in serum HDL cholesterol.

9.66 In summary, based on the systematic reviews with meta-analysis with the largest number of participants (Yu-Poth et al, 1999) and largest number of individual trials (Howell et al, 1997), reduction in intake of saturated fats was associated with a reduction in serum HDL cholesterol. Yu-Poth et al (1999) included complex dietary interventions where both dietary cholesterol and fatty acid composition were altered and, in many studies, weight loss occurred. In contrast, Hooper et al (2015) found no effect, but serum HDL cholesterol was not included in the original search. Also a smaller systematic review with meta-analysis in children by Te Morenga & Montez (2017a) found no effect. Therefore, the evidence of an effect is limited to adults and has been downgraded to *moderate.*

Reduced intake of saturated fats and serum HDL cholesterol
Randomised controlled trials Adults • Effect • *Moderate* evidence • The direction of the effect indicates that a reduced intake of saturated fats lowers serum HDL cholesterol in adults Children • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with PUFA and serum HDL cholesterol

9.67 Four systematic reviews with meta-analyses (Hannon et al, 2017a; Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003) analysed the relationship between substitution of saturated fats with PUFA and serum HDL cholesterol. Four systematic reviews analysed the results from RCTs (Hannon et al, 2017a; Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003). No systematic reviews, meta-analyses or pooled analyses were identified that included data from PCS.

Randomised controlled trials

9.68 A systematic review with meta-analysis of 8 RCTs (Hannon et al, 2017a) reported that when saturated fats were substituted with unsaturated fats (a mixture of PUFA and MUFA) there was no effect on serum HDL cholesterol using a random-effects model (8 RCTs, 663 participants). The authors noted this meta-analysis was performed on a very small number of individuals in a specific population and the meta-analysis showed a high degree of heterogeneity (I^2=98%) making it difficult to draw a conclusion.

9.69 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum HDL cholesterol using a random-effects model (7 RCTs, 5147 participants). The authors reported that there was no differential effect on serum HDL cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum HDL cholesterol was not included in the original search.

9.70 Micha & Mozaffarian (2010) reported in their systematic review with meta-analysis (number of RCTs and participants not reported) that substitution of saturated fats with PUFA resulted in a "slight lowering of HDL cholesterol" (further characteristics of studies not summarised, no statistics were provided in the paper for this comparison).

9.71 Mensink et al (2003) performed a systematic review with meta-analysis across 60 RCTs and estimated using a regression analysis that the substitution of 1% of energy from saturated fats with an equal percentage of PUFA had a small lowering effect on serum HDL cholesterol concentrations (no variance or test of significance reported), suggesting that saturated fats substitution with PUFA had a marginal impact on serum HDL cholesterol (60 RCTs, 1672 participants).

9.72 In summary, based on the largest systematic review with meta-analysis by Hooper et al (2015) there was no effect of substituting saturated fats with PUFA on serum HDL cholesterol. Hooper et al (2015) included 7 RCTs (with 5147 participants) however, in this review, serum HDL cholesterol was not included in the original search. While Micha & Mozaffarian (2010) described an effect it was described as "slight" and Mensink et al (2003) reported a "small lowering effect". The committee considered this evidence to be *moderate*.

Saturated fats substitution with PUFA and serum HDL cholesterol
Randomised controlled trials • No effect • *Moderate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and serum HDL cholesterol

9.73 Two systematic reviews with meta-analyses (Hooper et al, 2015; Mensink et al, 2003) examined the relationship between substitution of saturated fats with MUFA and serum HDL cholesterol, both of which analysed only the results from RCTs. No systematic reviews, meta-analyses or pooled analyses were identified that included data from PCS.

Randomised controlled trials

9.74 In a systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum HDL cholesterol using a random-effects model (7 RCTs, 5147 participants). The authors reported that there was no differential effect on serum HDL cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review, serum total cholesterol was not included in the original search.

9.75 Mensink et al (2003) performed a systematic review with meta-analysis across 60 RCTs (1672 participants) and estimated using a regression analysis that the substitution of 1% of energy from saturated fats with an equal percentage of MUFA had a small lowering effect on serum HDL cholesterol concentrations by 0.002 mmol/L (no statistics were provided in the paper), suggesting that substituting saturated fats with MUFA had a marginal impact on serum HDL cholesterol.

9.76 In summary, based on the largest systematic review with meta-analysis by Hooper et al (2015) there was no effect of substituting saturated fats with MUFA on serum HDL cholesterol. Hooper et al (2015) included 7 RCTs (with 5147 participants) however, in this review, serum HDL cholesterol was not included in the original search. Mensink et al (2003) estimated any lowering of HDL cholesterol to be 0.002 mmol/L, suggesting that if there is any effect it would be small. The committee considered this evidence to be *moderate.*

Saturated fats substitution with MUFA and serum HDL cholesterol
Randomised controlled trials • No effect • *Moderate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with carbohydrates and serum HDL cholesterol

9.77 Four systematic reviews with meta-analyses (Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003; Clarke et al, 1997) examined the relationship between substitution of saturated fats with carbohydrates and serum HDL cholesterol. Four systematic reviews analysed the results from RCTs, 3 of longer-term trials with free-living subjects (Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003) and 1 of metabolic ward experiments (Clarke et al, 1997). No systematic reviews, meta-analyses or pooled analyses were identified that included data from PCS.

Randomised controlled trials

9.78 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum HDL cholesterol using a random-effects model (7 RCTs; 5147 participants). The authors reported that there was no differential effect on serum HDL cholesterol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum HDL cholesterol was not included in the original search.

9.79 Micha & Mozaffarian (2010) reported in their systematic review with meta-analysis (number of RCTs and participants not reported) that substitution of saturated fats with carbohydrates lowered serum HDL cholesterol (β=-0.01 mmol/L, $p<0.05$; 0.01 mmol/L decrease in serum HDL cholesterol for 1% isoenergetic substitution of saturated fats with carbohydrates).

9.80 Mensink et al (2003) performed a systematic review with meta-analysis across 60 RCTs (1672 participants) where fatty acid composition was varied while maintaining other components of the diet constant including dietary cholesterol. Regression analysis across the RCTs indicated that serum HDL cholesterol increased with higher intake of saturated fats (β=0.010 mmol/L, 95% CI 0.007 to 0.013, $p<0.001$).

9.81 In a systematic review with meta-analysis Clarke et al (1997) described 227 'metabolic ward' experiments (using highly controlled dietary interventions) to examine the impact of the substitution of saturated fats with carbohydrates on serum HDL cholesterol concentrations. Substitution of saturated fats with carbohydrates lowered serum HDL cholesterol (β=-0.013 mmol/L, 95% CI -0.017 to -0.009, $p<0.001$; 227 RCTs; number of participants not provided; change in blood serum HDL cholesterol per unit of isoenergetic change in carbohydrates adjusted for age, weight, and all other dietary factors).

9.82 In summary, Clarke et al (1997), Mensink et al (2003) and Micha & Mozaffarian (2010) all reported that serum HDL cholesterol lowered when saturated fats were substituted with carbohydrates. Statistics were available for all these systematics with meta-analysis. This was not supported by Hooper et al (2015); although this represented the largest systematic review with meta-analysis of 7 RCTs (with 5147 participants), serum HDL cholesterol was

not included in the original search. The Committee, considered this evidence to be *moderate.*

Saturated fats substitution with carbohydrates and serum HDL cholesterol
Randomised controlled trials • Effect • *Moderate* evidence • The direction of the effect indicates that substituting saturated fats with carbohydrates lowers serum HDL cholesterol *Prospective cohort studies* • No evidence

Serum total cholesterol:HDL cholesterol ratio

Reduced intake of saturated fats and serum total cholesterol:HDL cholesterol ratio

9.83 Two systematic reviews with meta-analyses from RCTs (Hooper et al, 2015; Yu-Poth et al, 1999) examined the relationship between reduction in saturated fats and the serum total cholesterol:HDL cholesterol ratio. No systematic reviews, meta-analyses or pooled analyses were identified that included data from PCS.

Randomised controlled trials

9.84 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum total cholesterol:HDL cholesterol ratio using a random-effects model (3 RCTs, 2985 participants). The authors reported that there was no differential effect on serum total cholesterol: HDL cholesterol ratio depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum total cholesterol:HDL cholesterol ratio was not included in the original search.

9.85 Yu-Poth et al (1999) conducted a systematic review with meta-analysis of 37 RCTs in 9276 participants from 1981 to 1997 to investigate the effects of the American Heart Association NCEP Step 1 (where intake of saturated fats is 8 to 10% of dietary energy) and Step 2 (where intake of saturated fats is ≤7% of dietary energy) diets. Serum total cholesterol:HDL ratio cholesterol decreased after both Step I and Step II diets (0.50 ± 0.11 (10%), 0.34 ± 0.12 (7%) ($p<0.01$)). However, these were complex dietary interventions, where both dietary cholesterol and fatty acid composition were altered and in many of the studies weight loss also occurred.

9.86 In summary, the largest meta-analysis by Yu-Poth et al (1999) (37 RCTs, 9276 participants) reported that a reduction in intake of saturated fats lowered the serum total

cholesterol:HDL cholesterol ratio, although many of these interventions were associated with weight loss and/or reduced dietary cholesterol and total fat intake. This effect was not observed by Hooper et al (2015), although serum total cholesterol:HDL cholesterol was not included in the original search. The Committee considered this evidence to be *limited.*

Reduced intake of saturated fats and serum total cholesterol:HDL cholesterol ratio
Randomised controlled trials • Effect • *Limited* evidence • The direction of the effect indicates that reducing saturated fats lowers the total cholesterol:HDL cholesterol ratio *Prospective cohort studies* • No evidence

Substitution of saturated fats with PUFA and serum total cholesterol:HDL cholesterol ratio

9.87 Three systematic reviews with meta-analyses (Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003) examined the relationship between substitution of saturated fats with PUFA and serum total cholesterol:HDL cholesterol ratio. All 3 systematic reviews analysed the results from RCTs (Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003). No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

9.88 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum total cholesterol:HDL cholesterol ratio using a random-effects model (3 RCTs, 2985 participants). The authors reported that there was no differential effect on serum total cholesterol: HDL cholesterol ratio depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum total cholesterol:HDL cholesterol ratio was not included in the original search.

9.89 Micha & Mozaffarian (2010) performed a systematic review with meta-analysis of RCTs (number of RCTs not reported) of the evidence of saturated fats contributing to CVD risk. Diets where saturated fats were substituted with PUFA were reported to “lower” the ratio of serum total cholesterol:HDL cholesterol (further characteristics of studies not summarised, no statistics were provided in the paper for this comparison).

9.90 Mensink et al (2003) performed a systematic review with meta-analysis of 60 RCTs (1672 participants) and estimated using a regression analysis that the substitution of 1% of energy from saturated fats with an equal percentage of PUFA lowered the serum total cholesterol:HDL cholesterol ratio (no statistics were provided in the paper).

9.91 In summary, based on the largest systematic review with meta-analysis in free-living populations by Hooper et al (2015) there was no effect of substituting saturated fats with PUFA on the ratio of serum total cholesterol:HDL cholesterol. Hooper et al (2015) included 3 RCTs (with 2985 participants), although the ratio of serum total cholesterol:HDL cholesterol was not included in the original search. The other meta-analysis identified reported that replacing saturated fats with PUFA (or MUFA and PUFA) resulted in a lowering of the ratio of serum total cholesterol:HDL cholesterol but did not report other statistics (Micha & Mozaffarian, 2010; Mensink et al, 2003). The Committee considered this evidence to be *limited*.

Saturated fats substitution with PUFA and serum total cholesterol:HDL cholesterol ratio
Randomised controlled trials • No effect • *Limited* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and serum total cholesterol:HDL cholesterol ratio

9.92 Three systematic reviews with meta-analyses (Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003) examined the relationship between substitution of saturated fats with MUFA and serum total cholesterol:HDL cholesterol ratio. All 3 systematic reviews analysed the results from RCTs (Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003). No systematic reviews, meta-analyses or pooled analyses were identified that included data from PCS.

Randomised controlled trials

9.93 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum total cholesterol:HDL cholesterol ratio using a random-effects model (3 RCTs, 2985 participants). The authors reported that there was no differential effect on serum total cholesterol: HDL cholesterol ratio depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a

mixture. However, in the Hooper et al (2015) review serum total cholesterol:HDL cholesterol ratio was not included in the original search.

9.94 Micha & Mozaffarian (2010) performed a systematic review with meta-analysis of RCTs (number of RCTs not reported) of the evidence of saturated fats contributing to CVD risk. Diets where saturated fats were substituted with MUFA "lowered" the ratio of serum total cholesterol:HDL cholesterol (further characteristics of studies not summarised, no statistics were provided in the paper for this comparison).

9.95 Mensink et al (2003) performed a systematic review with meta-analysis of 60 RCTs and estimated using a regression analysis that the substitution of 1% of energy from saturated fats with an equal percentage of MUFA lowered the serum total cholesterol:HDL cholesterol ratio (60 RCTs, 1672 participants; no statistics were provided in the paper for this comparison).

9.96 In summary, based on the largest systematic review with meta-analysis by Hooper et al (2015) there was no effect of substituting saturated fats with MUFA on the ratio of serum total cholesterol:HDL cholesterol. Hooper et al (2015) included 3 RCTs (with 2985 participants), however the ratio of serum cholesterol:HDL cholesterol was not included in the original search. The other meta-analyses identified (Micha & Mozaffarian, 2010; Mensink et al, 2003) stated that diets where saturated fats were substituted with MUFA lowered the ratio of serum total cholesterol:HDL cholesterol but no statistics were provided in the paper. The Committee considered this evidence to be *limited.*

Saturated fats substitution with MUFA and serum total cholesterol:HDL cholesterol ratio
Randomised controlled trials • No effect • *Limited* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with carbohydrates and serum total cholesterol:HDL cholesterol ratio

9.97 Three systematic reviews with meta-analyses (Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003) examined the relationship between substitution of saturated fats with carbohydrates and serum total cholesterol:HDL cholesterol ratio. All 3 systematic reviews analysed the results from RCTs (Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003).

Randomised controlled trials

9.98 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum total cholesterol:HDL cholesterol ratio using a random-effects model (3 RCTs, 2985 participants). The authors reported that there was no differential effect on serum total cholesterol: HDL cholesterol ratio depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum total cholesterol: HDL cholesterol ratio was not included in the original search.

9.99 Micha & Mozaffarian (2010) performed a systematic review with meta-analysis of RCTs (number of RCTs not reported) of the evidence of saturated fats contributing to CVD risk. They reported that there was no effect of substitution of saturated fats with carbohydrates on the ratio of serum total cholesterol:HDL cholesterol.

9.100 Mensink et al (2003) performed a systematic review and meta-analysis of 60 RCTs (1672 participants) where fatty acid composition was varied while maintaining other components of the diet constant including dietary cholesterol. Regression analysis across the studies demonstrated that serum total cholesterol:HDL cholesterol ratio did not change when saturated fats were substituted with carbohydrates, as serum total cholesterol and HDL cholesterol lowered to a similar extent.

9.101 In summary, based on the largest systematic review with meta-analysis by Hooper et al (2015) there was no effect of substituting saturated fats with carbohydrates on the ratio of serum total cholesterol:HDL cholesterol. Hooper et al (2015) included 3 RCTs (with 2985 participants), the ratio of total serum cholesterol:HDL cholesterol was not included in the original search. The findings of Hooper et al (2015) were supported by Mensink et al (2003) and Micha & Mozaffarian (2010). The evidence was graded *adequate.*

Saturated fats substitution with carbohydrates and serum total cholesterol:HDL cholesterol ratio
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Serum triacylglycerol

Reduced intake of saturated fats and serum triacylglycerol

Randomised controlled trials

9.102 Four systematic reviews with meta-analysis of RCTs (Te Morenga & Montez, 2017a; Hooper et al, 2015; Yu-Poth et al, 1999; Howell et al, 1997) analysed the effect of reduced intake of saturated fats on serum triacylglycerol.

9.103 Te Morenga & Montez (2017a) performed a systematic review with meta-analysis on 6 RCTs, studying young people aged 2 to 16 years (2430 participants, 5 weeks to 19 years follow-up). Five out of the 8 RCTs included children under 5 years, of which 1 RCT was of children who were pre-specified as hyperlipidemic and 2 included a mixture of hyperlipidemic and normolipidemic children. These involved a range of dietary interventions (through advice and/or the provision of foods) to reduce the intake of saturated fats. Based on dietary intake data, intakes of PUFA, MUFA, proteins and/or carbohydrates changed with a reduction in saturated fats. In a meta-analysis of 6 trials, they found that there was no effect of reduced intake of saturated fats on triacylglycerol using random-effects model (6 RCTs, 1565 participants).

9.104 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum triacylglycerol using a random-effects model (7 RCTs, 3845 participants). The authors reported that there was no differential effect on serum triacylglycerol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review triacylglycerol was not included in the original search.

9.105 Yu-Poth et al (1999) conducted a systematic review with meta-analysis of 37 RCTs including 9276 free-living subjects from 1981 to 1997 to investigate the effects of the American Heart Association NCEP Step 1 and Step 2 diets. Both diets significantly lowered plasma triacylglycerols (mean difference 0.17 mmol/L (8%), 95% CI 0.25 to 0.09, (8%) for Step 1 diet, $p<0.01$, and mean difference 0.19 mmol/L (8%), 95% CI 0.27 to 0.11 for Step 2 diet, $p<0.01$). However, when adjusting for weight loss in multiple regression, there was no effect of intake of saturated fats on serum triacylglycerol. This questions whether the effects associated with intake of saturated fats were direct or mediated through weight loss.

9.106 Howell et al (1997) performed a systematic review with meta-analysis on 224 RCTs including 8143 participants to examine primarily how changes in dietary cholesterol and fat intakes affect serum total cholesterol, triacylglycerol, and lipoprotein cholesterol concentrations. Univariate analysis was used to explore the relationship between saturated fats and serum triacylglycerol. The results indicated that intake of saturated fats had no effect on serum triacylglycerol (r^2= -0.20, p=0.807; 155 study groups).

9.107 In summary, based on the largest systematic review with meta-analysis by Hooper et al (2015) there was no effect of reduced intake of saturated fats on serum triacylglycerol. Hooper et al (2015) included 7 RCTs (with 3845 participants), however, serum triacylglycerol was not included in the original search. However, the findings of Hooper et al (2015) were supported by an analysis of 155 study groups by Howell et al (1997) and in Te Morenga & Montez (2017a) which considered a wide range of dietary interventions to decrease saturated fats. The Committee considered this evidence to be *adequate.*

Reduced intake of saturated fats and serum triacylglycerol
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with PUFA and serum triacylglycerol

9.108 Five systematic reviews, 3 with meta-analyses (Hannon et al, 2017a; Hooper et al, 2015; Micha & Mozaffarian, 2010) and 2 without meta-analyses (Schwab et al, 2014; Van Horn et al, 2008) examined the relationship between substitution of saturated fats with PUFA and serum triacylglycerol from RCTs. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

9.109 In a systematic review with meta-analysis of 8 RCTs, Hannon et al (2017a) reported that when saturated fats were substituted with unsaturated fats (a mixture of PUFA and MUFA) there was no effect on serum triacylglycerol using a random-effects model (8 RCTs, 663 participants). The authors noted this meta-analysis was performed on a very small number of individuals in a specific population and the meta-analysis showed a high degree of heterogeneity (I^2=96%) making it difficult to draw a conclusion from this meta-analysis.

9.110 In a Cochrane systematic review with meta-analysis of 7 RCTs, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum triacylglycerol using a random-effects model (7 RCTs, 3845 participants). The authors reported that there was no differential effect on serum triacylglycerol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum triacylglycerol was not included in the original search.

9.111 Micha & Mozaffarian (2010) performed a systematic review with meta-analysis of RCTs (number of RCTs not reported) of the evidence of saturated fats contributing to CVD risk. Diets where saturated fats were substituted with PUFA were reported to have a slight lowering effect on blood triacylglycerol level (further characteristics of studies not summarised, no statistics were provided in the paper for this comparison).

9.112 Schwab et al (2014), in their systematic review of 8 RCTs (648 participants) published between 2000 and 2010 without meta-analysis, investigated the effect of diets rich in MUFA and PUFA compared with diets rich in saturated fats on serum fasting triacylglycerol concentrations. No differences in fasting plasma/serum triacylglycerol were found in 6 out of 8 studies which reported this as an end-point and thus, the authors reported that an effect was 'unlikely' (no statistics were provided in the paper for this comparison).

9.113 Van Horn et al (2008), in the systematic review of RCTs without meta-analysis, reported that substitution of saturated fats with a mixture of PUFA and MUFA produced a small decrease in serum triacylglycerol (0.19 mmol/L) but this was based on a single RCT (the OminiHeart Randomised trial (Appel et al, 2005); 164 individuals randomised to three diets, no statistics were provided in the paper for this comparison).

9.114 In summary, based on the largest systematic review with meta-analysis by Hooper et al (2015) there was no effect of substituting saturated fats with PUFA on serum triacylglycerol. Hooper et al (2015) included 7 RCTs (with 3845 participants), however serum triacylglycerol was not included in the original search. Similar findings were reported in the other systematic reviews with meta-analysis (Hannon et al, 2017a; Micha & Mozaffarian, 2010). The evidence was graded as *adequate.*

Saturated fats substitution with PUFA and serum triacylglycerol
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and serum triacylglycerol

9.115 Four systematic reviews, 2 with meta-analysis (Hooper et al, 2015; Micha & Mozaffarian, 2010) and 2 without meta-analyses (Schwab et al, 2014; Van Horn et al, 2008) examined the relationship between substitution of saturated fats with MUFA and serum

triacylglycerol from RCTs. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

9.116 In a Cochrane systematic review with meta-analysis, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum triacylglycerol using a random-effects model (7 RCTs, 3845 participants). The authors reported that there was no differential effect on serum triacylglycerol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum triacylglycerol was not included in the original search.

9.117 Micha & Mozaffarian (2010) performed a systematic review with meta-analysis of RCTs (number of RCTs not reported) of the evidence of saturated fats contributing to CVD risk. Substitution of saturated fats with PUFA or MUFA was reported to have a slight lowering effect on blood triacylglycerol level (further characteristics of studies not summarised, no statistics were provided in the paper for this comparison).

9.118 Schwab et al (2014) performed a systematic review without meta-analysis of 8 RCTs (456 individuals), published between January 2000 and October 2010, investigating the effect of diets rich in PUFA and/or MUFA compared with diets rich in saturated fats on serum fasting triacylglycerol concentrations. No differences in fasting plasma/serum triacylglycerol were found in 5 out of 8 RCTs which reported this as an end-point and thus they reported that an effect was 'unlikely' (no statistics were provided in the paper).

9.119 Van Horn et al (2008), in their systematic review of 1 RCT without meta-analysis, reported that substitution of saturated fats with a mixture of PUFA and MUFA produced a small decrease in serum triacylglycerol (0.19 mmol/L[30]) but this was based on a single RCT (the OmniHeart Randomised trial (Appel et al, 2005), 164 individuals randomised to 3 diets, no statistics were provided in the systematic review).

9.120 In summary, based on the largest systematic review with meta-analysis by Hooper et al (2015) there was no effect of substituting saturated fats with MUFA on serum triacylglycerol. Hooper et al (2015) included 7 RCTs (with 3845 participants), however serum triacylglycerol was not included in the original search. The findings of Hooper et al (2015) were supported by the other systematic review with meta-analysis (Micha & Mozaffarian, 2010). The evidence was graded as *adequate.*

[30] 1mmol/L=88.57mg/dL

Saturated fats substitution with MUFA and serum triacylglycerol
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with carbohydrates and serum triacylglycerol

9.121 Four systematic reviews, 3 with meta-analyses (Hooper et al, 2015; Micha & Mozaffarian, 2010; Mensink et al, 2003) and 1 without meta-analysis (Van Horn et al, 2008) of RCTs examined the relationship between substitution of saturated fats with carbohydrates and serum triacylglycerol. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

9.122 In a Cochrane systematic review with meta-analysis of 7 RCTs, Hooper et al (2015) reported no effect of reduced intake of saturated fats on serum triacylglycerol using a random-effects model (7 RCTs, 3845 participants). The authors reported that there was no differential effect on serum triacylglycerol depending on whether saturated fats were substituted with PUFA or MUFA or carbohydrates or a mixture. However, in the Hooper et al (2015) review serum triacylglycerol was not included in the original search.

9.123 Micha & Mozaffarian (2010) performed a systematic review with meta-analysis of RCTs (number of RCTs not reported) of the evidence of saturated fats contributing to CVD risk. Diets where saturated fats were substituted with carbohydrates were reported to increase serum triacylglycerol (further characteristics of studies not summarised, no statistics were provided in the paper for this comparison).

9.124 Mensink et al (2003) performed a systematic review and meta-analysis of 60 RCTs (1672 participants) where fatty acid composition was varied while maintaining other components of the diet constant including dietary cholesterol. Regression analysis across the RCTs indicated that serum triacylglycerol increased when saturated fats were substituted with carbohydrates (β=0.021 mmol/L; 95% CI 0.015 to 0.027, p<0.001).

9.125 Van Horn et al (2008) reported that substitution of saturated fats with carbohydrates produced a small increase in serum triacylglycerol (0.001mmol/L) but this was based on a single RCT (the OmniHeart Randomised trial (Appel et al, 2005), 164 individuals randomised to 3 diets, no statistics were provided in the systematic review).

9.126 In summary, Mensink et al (2003) and Micha & Mozaffarian (2010) reported that serum triacylglycerol increased when saturated fats were substituted with carbohydrate. Statistics were available for both of these systematic reviews with meta-analyses. This was not supported by Hooper et al (2015); although this represented the largest total subject population in a systematic review with meta-analysis (7 RCTs, 3845 participants) serum triacylglycerol was not included in the original search. The Committee considered this evidence to be *moderate.*

Saturated fats substitution with carbohydrates and serum triacylglycerol
Randomised controlled trials • Effect • *Moderate* evidence • The direction of the effect indicates that replacement of saturated fats with carbohydrates increases serum triacylglycerol *Prospective cohort studies* • No evidence

Summary

9.127 Eleven systematic reviews examining the relationship between saturated fats and blood lipids. There was good agreement across systematic reviews. The reviews varied considerably in their inclusion criteria, for example, focusing on different subject populations, or focusing on longer-term RCTs of free-living participants (such as Hooper et al (2015)) or shorter-term highly controlled RCTs (such as Clarke et al (1997)). Therefore, the identified reviews tend to provide additional rather than overlapping evidence. The reviews also varied depending on whether blood lipids were considered primary or secondary outcomes. In particular, the Cochrane systematic review with meta-analysis of RCTs (Hooper et al, 2015) did not include blood lipids in the search and the evidence is identified from studies selected for other outcomes.

9.128 Overall, reducing intake of saturated fats lowered serum total cholesterol and LDL cholesterol, regardless of dietary intervention (reduction in saturated fats and substitution with PUFA, MUFA or carbohydrates).

9.129 Reducing intake of saturated fats lowered serum HDL cholesterol in adults, but not in children. Substitution of saturated fats with PUFA or MUFA had no effect on HDL cholesterol, whereas substitution of saturated fats with carbohydrates lowered serum HDL cholesterol.

9.130 Reducing saturated fats lowered the total cholesterol:HDL cholesterol ratio; however, this was based on limited evidence. Substitution of saturated fats with PUFA, MUFA or carbohydrates had no effect on the ratio.

9.131 Reducing saturated fats had no effect on serum triacylglycerol concentrations. Substitution of saturated fats with carbohydrates increased serum triacylglycerol, while substitution with PUFA or MUFA had no effect on serum triacylglycerol concentrations.

9.132 There were fewer systematic reviews that considered evidence from PCS. Therefore, there was either no or *insufficient* evidence from PCS.

9.133 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and blood lipids is summarised below in Table 9.1

Table 9.1 Summary table of the evidence on the effect/association between saturated fats and blood lipids

	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
Outcome	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
RCTs										
Total cholesterol	↓	Adequate	↓	Adequate[1]	↓	Adequate[1]	↓	Adequate	n/a	No evidence
LDL cholesterol	↓	Adequate	↓	Adequate	↓	Adequate	↓	Adequate	n/a	No evidence
HDL cholesterol	↓	Moderate[2]	-	Moderate	-	Moderate	↓	Moderate	n/a	No evidence
Total/HDL cholesterol ratio	↓	Limited	-	Limited	-	Limited	-	Adequate	n/a	No evidence
Triacylglycerol	-	Adequate	-	Adequate	-	Adequate	↑	Moderate	n/a	No evidence
PCS										
Total cholesterol	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	No evidence
LDL cholesterol	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	No evidence
HDL cholesterol	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Total/HDL cholesterol ratio	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Triacylglycerol	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

[1] Adequate evidence indicated that the substitution of saturated fats with a mixture of PUFA and MUFA decreased serum total cholesterol

2 In adults – effect, moderate evidence and in children – no effect, adequate evidence

n/a – not enough evidence to draw conclusions

Direction of effect/association for reported outcomes: ↑increased; ↓decreased; - no effect/association

10 Blood pressure

10.1 Four systematic reviews, 2 with meta-analyses (Te Morenga & Montez, 2017a; Hooper et al, 2015) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) were identified that evaluated the relationship between saturated fats and blood pressure. The characteristics of these publications are summarised in Annex 2, Table A2.5. The quality of meta-analyses and systematic reviews is summarised in Annex 4.

10.2 No meta-analyses, systematic reviews or pooled analyses of randomised controlled trials (RCTs) or prospective cohort studies (PCS) were identified that reported on the relationship between substitution of saturated fats with proteins and blood pressure. No meta-analyses, systematic reviews or pooled analyses of PCS were identified that reported on the association of saturated fats substitution with polyunsaturated fats (PUFA) or carbohydrates and blood pressure.

10.3 The reviews also varied depending on whether blood pressure was considered a primary or secondary outcome. In particular, the Cochrane systematic review with meta-analysis of RCTs (Hooper et al, 2015) did not include blood pressure in the search and the evidence is identified from studies selected for other outcomes.

Blood pressure

Reduced intake of saturated fats and blood pressure

10.4 Two systematic reviews with meta-analyses of RCTs (Te Morenga & Montez, 2017a; Hooper et al, 2015) assessed the effect of reduced intake of saturated fats on blood pressure. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

10.5 Te Morenga & Montez (2017a) performed a systematic review with meta-analysis of 2 RCTs studying young people aged 2 to 16 years. There was no effect of reducing saturated fats on systolic blood pressure (2 RCTs; 1106 participants). For diastolic blood pressure there was a significant decrease with reduced saturated fats (mean difference -1.45, 95% CI -2.34 to -0.56, p=0.001; I^2 = 0%; 2 RCTs, 1106 participants).

10.6 A Cochrane systematic review with meta-analysis by Hooper et al (2015) examined 15 RCTs covering 17 comparisons involving approximately 59,000 participants. The studies either aimed to assess the impact on total mortality and cardiovascular mortality of reducing intake of saturated fats or altering saturated fats. Interventions were at least 24-months in duration. As a secondary outcome, blood pressure was not included in the original search. Hooper et al (2015) found no effect of reducing intakes of saturated fats on systolic

blood pressure (5 RCTs, 3812 participants) or diastolic blood pressure (5 RCTs, 3812 participants).

10.7 In summary, the evidence from 2 systematic reviews with meta-analyses of RCTs (Hooper et al, 2015) indicated that reduced intake of saturated fats had no effect on blood pressure. The evidence was graded as *limited* because Te Morenga & Montez (2017a) included only 2 RCTs and blood pressure was not included in the original search by Hooper et al (2015).

Reduced intake of saturated fats and blood pressure
Randomised controlled trials • No effect • *Limited* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with PUFA and blood pressure

10.8 Two systematic reviews without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) reported the results of RCTs evaluating the effect of substituting saturated fats with PUFA on blood pressure. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

10.9 A systematic review without meta-analysis of 5 RCTs (360 participants, with follow-up of 6-months) (Micha & Mozaffarian, 2010) reported that substituting saturated fats with PUFA had no effect on blood pressure in 4 of the 5 RCTs. The only RCT (42 participants, intervention duration of 5 weeks; p value not reported) to report a reduction in blood pressure was the non-randomised trial, which also involved a monounsaturated fats (MUFA) comparison where diets were administered consecutively.

10.10 Schwab et al (2014) in a systematic review without meta-analysis reported the results of a single RCT where substitution of saturated fats with fish oil in 79 subjects over 12 weeks (Dyerberg et al, 2004) resulted in a reduction in blood pressure. However, the use of fish oil represents a complex substitution of mostly n-3 long chain PUFA.

10.11 In summary, the evidence from systematic reviews of RCTs (Schwab et al, 2014; Micha & Mozaffarian, 2010) indicated that substituting saturated fats with PUFA had no effect on blood pressure. The evidence was graded as *limited* because there was a limited number

of systematic reviews which included a low number of RCTs and with no formal meta-analysis of the data.

Saturated fats substitution with PUFA and blood pressure
Randomised controlled trials • No effect • *Limited* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and blood pressure

10.12 Two systematic reviews without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) evaluated the effect of substituting saturated fats with MUFA on blood pressure. One systematic review assessed the results of RCTs (Micha & Mozaffarian, 2010) and 1 systematic review assessed the results of RCTs and PCS (Schwab et al, 2014). Only 1 of the 3 included RCTs (Rasmussen et al, 2006) was also considered in the systematic review by Micha & Mozaffarian (2010). None of the 13 RCTs considered by Micha & Mozaffarian (2010) and Schwab et al (2014) were included in the review by Hooper et al (2015).

Randomised controlled trials

10.13 Schwab et al (2014) reported on the effect of substituting saturated fats with MUFA on blood pressure in 3 RCTs. The 2 larger RCTs (involving 648 participants) reported that substitution of saturated fats with MUFA lowered blood pressure while the smaller study (60 participants) reported no significant effect of MUFA relative to saturated fats on blood pressure.

10.14 In a systematic review without meta-analysis Micha & Mozaffarian (2010) analysed 5 RCTs (481 participants) with follow-up of 6-months. Three of the 5 RCTs found that substituting saturated fats with MUFA had no effect on blood pressure. In the other 2 RCTs (204 participants) there was evidence of a reduction in blood pressure; however, only 1 of these was randomised.

Prospective cohort studies

10.15 In a systematic review without meta-analysis Schwab et al (2014) reported no association between substitution of saturated fats with MUFA and blood pressure in 1 PCS (1 PCS, 28,100 participants).

10.16 In summary, there was no effect of saturated fats substitution with MUFA on blood pressure. The evidence was graded as *limited* because there were a limited number of

systematic reviews with low number of RCTs included and with no formal meta-analysis of the data. For PCS the evidence was considered *insufficient* due to only 1 PCS being available.

Saturated fats substitution with MUFA and blood pressure
Randomised controlled trials • No effect • *Limited* evidence *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with carbohydrates and blood pressure

10.17 One systematic review without meta-analysis, (Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of substituting saturated fats with carbohydrates on blood pressure. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

10.18 In the systematic review without meta-analysis by Micha & Mozaffarian (2010) no effect on blood pressure in any of the 4 RCTs that evaluated substitution of saturated fats with carbohydrates was reported.

10.19 In summary, there was no effect of substituting saturated fats with carbohydrates on blood pressure. The evidence was graded as *limited* due to the availability of only 1 systematic review with a low number of RCTs included and with lack of formal meta-analysis of the data.

Saturated fats substitution with carbohydrates and blood pressure
Randomised controlled trials • No effect • *Limited* evidence *Prospective cohort studies* • No evidence

Summary

10.20 Evidence from systematic reviews with and without meta-analyses of RCTs was identified which reported on blood pressure and intake of saturated fats. There was *limited* evidence from RCTs that reduced intake of saturated fats or substituting saturated fats with PUFA, MUFA or carbohydrates had no effect on blood pressure. It should be noted that the value of the information on blood pressure in the largest, most recent meta-analysis (Hooper et al, 2015) was reduced because blood pressure was not a primary outcome and it was not included in the search terms used. Overall, there was no or *insufficient* evidence from systematic reviews of PCS on any association between reduced intake of saturated fats or PCS analyses substituting saturated fats with PUFA, MUFA, carbohydrates or proteins and blood pressure.

10.21 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and blood pressure is summarised below in Table 10.1.

Table 10.1 Summary table of the evidence on the effect/association between saturated fats and blood pressure

	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
Outcome	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
RCTs										
Blood pressure	-	Limited	-	Limited	-	Limited	-	Limited	n/a	No evidence
PCS										
Blood pressure	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence	n/a	No evidence

n/a – not enough evidence to draw conclusions

Direction of effect/association for reported outcomes: ↑increased; ↓decreased; - no effect/association

11 Type 2 diabetes and markers of glycaemic control

11.1 Seven systematic reviews, of which 4 included meta-analyses, were identified that examined the relationship between saturated fats or saturated fats substitution and risk of type 2 diabetes and markers of glycaemic control in RCTs (Te Morenga & Montez, 2017a; Imamura et al, 2016; de Souza et al, 2015; Hooper et al, 2015; Schwab et al, 2014; Alhazmi et al, 2012; Micha & Mozaffarian, 2010). The characteristics of these publications are summarised in Annex 2, Table A2.9. The quality of systematic reviews is summarised in Annex 4.

11.2 No systematic reviews, meta-analyses or pooled analyses of randomised controlled trials (RCTs) and prospective cohort studies (PCS) were identified that reported on the relationship between saturated fats and markers of glycaemic control. No systematic reviews, meta-analyses or pooled analyses of RCTs and PCS were identified that reported on the relationship between saturated fats substituted with proteins and risk of type 2 diabetes and markers of glycaemic control.

Type 2 diabetes

Reduced intake of saturated fats and type 2 diabetes

11.3 Four systematic reviews, 3 with meta-analyses (de Souza et al, 2015; Alhazmi et al, 2012; Micha & Mozaffarian, 2010) and 1 without meta-analysis (Schwab et al, 2014) considered the evidence on saturated fats and risk of type 2 diabetes. Four systematic reviews assessed the results of PCS (de Souza et al, 2015; Schwab et al, 2014; Alhazmi et al, 2012; Micha & Mozaffarian, 2010). No systematic reviews, meta-analyses or pooled analyses of RCTs were identified.

Prospective cohort studies

11.4 All 4 of the identified systematic reviews considered evidence from PCS (de Souza et al, 2015; Schwab et al, 2014; Alhazmi et al, 2012; Micha & Mozaffarian, 2010). Three of these reviews included a meta-analysis.

11.5 A systematic review with meta-analysis of 8 PCS by de Souza et al (2015) reported no association between the highest versus lowest intakes of saturated fats and risk of type 2 diabetes for the most adjusted multivariable ratio using a random-effects model (8 PCS, 237,454 participants, 8739 cases).

11.6 A systematic review with meta-analysis of 7 PCS by Alhazmi et al (2012) reported no association between saturated fats and risk of type 2 diabetes when the highest intakes were compared with the lowest using a random-effects model (7PCS, 352,262 participants,

5442 cases). Four of the PCS included in the meta-analysis by Alhazmi et al (2012) were also included in the meta-analysis by de Souza et al (2015).

11.7 A systematic review with meta-analysis of 4 PCS by Micha & Mozaffarian (2010) reported no association between saturated fats and risk of type 2 diabetes using a fixed-effect model (4 PCS). Three of the PCS considered by Micha & Mozaffarian (2010) were also included in the meta-analyses by de Souza et al (2015) and Alhazmi et al (2012).

11.8 A systematic review without meta-analysis by Schwab et al (2014) reported on 2 PCS that both found no associations between intake of saturated fats and risk of type 2 diabetes.

11.9 In summary, there was no evidence from RCTs on the effect of the reduced intake of saturated fats and risk of type 2 diabetes. Based on the most recent and largest systematic review with meta-analysis of 8 PCS by de Souza et al (2015) there was no association between intake of saturated fats and risk of type 2 diabetes. Based on the size and the number of studies included in this review the evidence was graded as *adequate*.

Reduced intake of saturated fats and type 2 diabetes
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Substitution of saturated fats with PUFA and type 2 diabetes

11.10 One systematic review without meta-analysis (Schwab et al, 2014) analysed the association between substitution of saturated fats with polyunsaturated fats (PUFA) and risk of type 2 diabetes in PCS. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

11.11 In a systematic review without meta-analysis, Schwab et al (2014) reported on 2 PCS that considered associations between substitution of saturated fats with PUFA and risk of type 2 diabetes. In 1 PCS, substitution of saturated fats with PUFA reduced the risk of type 2 diabetes (RR 0.84, 95% CI 0.71 to 0.98, p=0.02). The other reported no association of changing the PUFA: saturated fats ratio, although the association was significant when the model was not adjusted for body mass index (BMI) and waist hip ratio (OR 0.88, 95% CI 0.78 to 0.99).

11.12 In summary, the evidence from PCS was *insufficient* to draw any conclusions on substitution of saturated fats with PUFA and risk of type 2 diabetes.

Saturated fats substitution with PUFA and type 2 diabetes
Randomised controlled trials • No evidence *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with MUFA or proteins and type 2 diabetes

11.13 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on the relationship between substitution of saturated fats with monounsaturated fats (MUFA) or proteins and risk of type 2 diabetes.

Substitution of saturated fats with carbohydrates and type 2 diabetes

11.14 Two systematic reviews, 1 with meta-analysis (Hooper et al, 2015) and 1 without meta-analysis (Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of substituting saturated fats with carbohydrates and risk of type 2 diabetes. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.15 A Cochrane systematic review with meta-analysis by Hooper et al (2015) examined 15 RCTs covering 17 comparisons involving approximately 59,000 participants. The studies either aimed to assess the impact on total mortality and cardiovascular mortality of reducing intake of saturated fats or altering saturated fats. Interventions were at least 24-months in duration. As secondary outcomes they examined the effects of reduced intake of saturated fats on risk of type 2 diabetes, glucose tolerance (2-hour oral glucose tolerance tests (OGTT)) and insulin resistance; however, these outcomes were not included in the original search and not reported in all studies. Hooper et al (2015) identified 1 RCT, the Women's Health Initiative, which reported no effect of reduced intake of saturated fats on risk of type 2 diabetes (1 RCT, 48,835 participants). However, the main aim of the intervention was to reduce total fat intake and increase the intake of fruits, vegetables and grains.

11.16 A systematic review without meta-analysis (Micha & Mozaffarian, 2010) reported on the same RCT, the Woman's Health Initiative, which included data on 45,887 post-menopausal women. Reducing intake of saturated fats from 12.7 to 9.5% energy intake over 8 years was reported to have no effect on the risk of type 2 diabetes. However, the aim of the Women's Health Initiative was not to explicitly test the effect of substitution of saturated

fats with carbohydrates. Both reviews reported that saturated fats were substituted mainly with carbohydrates but did not differentiate between the different types of carbohydrates.

11.17 In summary, there was *insufficient* evidence from RCTs on the effect of saturated fats substitution with carbohydrates on risk of type 2 diabetes. Although the Women's Health Initiative trial (the only trial identified by Micha & Mozaffarian (2010) and Hooper et al (2015)) was a large RCT that included more than 45,000 people, the participants were all women . Another limitation of this RCT was that, as well as reducing intake of saturated fats, the main aim of the intervention was to reduce overall fat intake and increase the intake of fruits, vegetables and grains.

Saturated fat substitution with carbohydrates and type 2 diabetes
Randomised controlled trials • *Insufficient* evidence *Prospective cohort studies* • No evidence

Markers of glycaemic control

11.18 Five systematic reviews, 2 with meta-analyses (Imamura et al, 2016; Hooper et al, 2015) and 3 without meta-analyses (Te Morenga & Montez, 2017a; Schwab et al, 2014; Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of changes in intake of saturated fats on markers of glycaemic control, including fasting glucose, fasting insulin, glycated haemoglobin (HbA1c), glucose tolerance, and insulin resistance. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

11.19 Given the later date, higher quality, larger number of trials, more complete reporting and quantitative data analyses in Imamura et al (2016), this has been used as the primary basis for data synthesis and drawing conclusions. In the Hooper et al (2015) systematic review with meta-analysis, markers of glycaemia were not primary outcomes or used as search terms, so these data were only included if reported in papers selected for consideration in relation to other primary outcomes such as cardiovascular disease (CVD). Notably, Imamura et al (2016) also carried out multiple-treatment meta-regression to model the dose-response effects of isoenergetic substitutions among fat types and other macronutrients, based on actual reported dietary intakes. This generates an estimate of the effect of substitutions for saturated fats from a large pool of studies, regardless of the primary or intended intervention. In the narrative text that follows in paragraphs 11.20 to 11.102, all results from Imamura et al (2016) reflect these modified effect sizes, and are expressed in a way that is consistent with the original paper, although this may differ from

the direction and phrasing used to describe these effects in the standard summary box texts. Results from 2 other systematic reviews without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) are also described. Micha & Mozaffarian (2010) only included a meta-analysis for the outcome type 2 diabetes and not glycaemic control.

Fasting glucose

Reduced intake of saturated fats and fasting glucose

11.20 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on the relationship between intake of saturated fats or substitution of saturated fats with proteins and fasting glucose.

Substitution of saturated fats with PUFA and fasting glucose

11.21 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of substituting saturated fats with PUFA on measures of fasting glucose. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.22 Imamura et al (2016) carried out a meta-regression analysis of data from 99 RCTs. There was a significant beneficial effect (that is, lower fasting glucose) when 5% energy as saturated fats was isoenergetically substituted with PUFA (mean difference -0.04 mmol/L, 95% CI -0.07 to -0.01, $p<0.05$; 99 RCTs, 4144 participants). These results are largely reflected in sensitivity analyses of a subset of 30 RCTs aimed at reducing saturated fats, and 68 RCTs of participants without diabetes.

11.23 Schwab et al (2014) reported on 8 RCTs with varying specificity of saturated fats substitution in a systematic review without meta-analysis. One study included some participants with type 2 diabetes and the rest were healthy or at-risk (for example, overweight) populations. One RCT evaluated the effect of saturated fats compared with PUFA on fasting glucose and reported that no effect was identified.

11.24 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) reported on fasting glucose results from 10 RCTs with various saturated fats substitutions, 5 of which recruited participants with or predisposed to insulin resistance and the other 5 recruited healthy participants. Three RCTs (2 RCTs with participants with or predisposed to insulin resistance and 1 RCT with healthy participants) evaluated the effect of saturated fats compared with PUFA on fasting glucose and reported that no effect was identified.

11.25 In summary*, adequate* evidence from RCTs for a small beneficial decrease in fasting blood glucose when saturated fats are substituted with PUFA, is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016). However, for a relatively high saturated fats substitution with PUFA the observed effect size is small.

Saturated fats substitution with PUFA and fasting glucose
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with PUFA lowers fasting glucose *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and fasting glucose

11.26 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) reported the results of RCTs evaluating the effect of saturated fats substitution with MUFA on measures of fasting glucose. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.27 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data from 99 RCTs. There was no effect on fasting glucose when saturated fats were substituted with MUFA (99 RCTs, 4144 participants). These results are largely reflected in sensitivity analyses of a subset of 30 RCTs aimed at reducing saturated fats, and 68 RCTs of participants without diabetes.

11.28 Schwab et al (2014) reported on 8 RCTs with varying specificity of saturated fats substitution in a systematic review without meta-analysis. One study included some participants with type 2 diabetes and the rest were healthy or at-risk (for example, overweight) populations. Seven RCTs evaluated the effect of saturated fats compared with MUFA on fasting glucose, 6 reported no significant effect, whereas 1 RCT reported a decrease in fasting glucose.

11.29 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) reported on fasting glucose results from 10 RCTs with various saturated fats substitution, 5 of which recruited participants with or predisposed to insulin resistance and the other 5 recruited

healthy participants. Eight RCTs (3 RCTs with participants with or predisposed to insulin resistance and 5 RCTs with healthy participants) evaluated the effect of saturated fats compared with MUFA on fasting glucose, 7 reported no effect, whereas 1 RCT reported an increase in fasting blood glucose (11 participants, intervention duration of 28 days, $p<0.05$).

11.30 In summary, there was *adequate* evidence for no effect on fasting blood glucose when saturated fats were substituted with MUFA.

Saturated fats substitution with MUFA and fasting glucose
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with carbohydrates and fasting glucose

11.31 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of changes in substituting saturated fats with carbohydrates on measures of fasting glucose. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.32 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data from 99 RCTs. This showed no effect on fasting glucose when 5% energy as saturated fats was isoenergetically substituted with carbohydrates (99 RCTs, 4144 participants). However, the analysis did not stratify by carbohydrates type.

11.33 Schwab et al (2014) reported on the findings of a systematic review without meta-analysis of 8 RCTs with varying specificity of saturated fats substitution. One study included some participants with type 2 diabetes and the rest were healthy or at-risk (for example, overweight) populations. Four RCTs evaluated the effect of saturated fats compared to carbohydrates on fasting glucose and reported that no effect was identified.

11.34 In a systematic review without meta-analysis Micha & Mozaffarian (2010) reported on fasting glucose results from 10 RCTs, 5 of which recruited participants with or predisposed to insulin resistance and the other 5 RCTs were in healthy participants. Four RCTs (1 RCT with participants with or predisposed to insulin resistance and 3 RCTs with healthy

participants) evaluated the effect of saturated fats substitution with carbohydrates on fasting glucose. One RCT reported that saturated fats increased fasting blood glucose compared to carbohydrates (1 RCT, 11 participants, 28 days intervention duration $p<0.05$), whereas the 2 RCTs in healthy participants reported no significant difference.

11.35 In summary, there was *adequate* evidence for no effect on fasting glucose when saturated fats are substituted with carbohydrates.

Saturated fats substitution with carbohydrates and fasting glucose
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Fasting Insulin

Reduced intake of saturated fats and fasting insulin

11.36 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on the relationship between saturated fat intake or saturated fats substitution with proteins and fasting insulin.

Substitution of saturated fats with PUFA and fasting insulin

11.37 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of substitution of saturated fats with PUFA on measures of fasting insulin. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.38 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data from 90 RCTs. These show no statistically significant effect when saturated fats were substituted with PUFA (90 RCTs, 3774 participants). These results are also largely reflected in sensitivity analyses of a subset of 28 RCTs aimed at varying saturated fats and 65 RCTs of participants without type 2 diabetes.

11.39 Schwab et al (2014) reported on 8 RCTs with varying specificity of saturated fats substitution in a systematic review without meta-analysis. One RCT evaluated the effect of

saturated fats compared with PUFA on fasting insulin and reported that no statistically significant effect was identified (1 RCT, 17 participants).

11.40 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) reported on fasting insulin results from 10 RCTs, 5 of which recruited participants with or predisposed to insulin resistance and the other 5 RCTs were in healthy participants. Three RCTs (2 RCTs with participants with or predisposed to insulin resistance and 1 RCT with healthy participants) reported on the effects of saturated fats compared to PUFA on fasting insulin. No significant effect was reported.

11.41 In summary, *adequate* evidence for no effect on fasting insulin for substitution of saturated fats with PUFA is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016). However, SACN previously judged that variation in methodologies precluded use of fasting insulin data in meta-analyses (SACN, 2015). Furthermore, although elevated fasting insulin can be seen as an indicator of insulin resistance, the health benefits and relevance of the reported changes in fasting insulin are uncertain.

Saturated fats substitution with PUFA and fasting insulin
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and fasting insulin

11.42 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of changes in substitution of saturated fats with MUFA on measures of fasting insulin. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.43 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data from 90 RCTs. These showed a statistically significant higher fasting insulin when saturated fats were substituted with MUFA (mean difference 1.17 pmol/L[31], 95% CI 0.57 to 1.78,

[31] 1 pmol/L= 0.14 µIU/mL

p<0.001; 90 RCTs, 3774 participants). These results are largely also reflected in sensitivity analyses of a subset of 28 RCTs aimed at varying saturated fats, and 65 RCTs of participants without type 2 diabetes.

11.44 Schwab et al (2014) reported on 7 RCTs with varying specificity of saturated fats substitution in a systematic review without meta-analysis. In 5 RCTs fasting insulin was reported to be significantly higher with saturated fats compared with MUFA, with no significant effect of saturated fats in the other 2 RCTs.

11.45 In a systematic review without meta-analysis Micha & Mozaffarian (2010) reported on fasting insulin results from 10 RCTs, 5 of which recruited participants with or predisposed to insulin resistance and the other 5 RCTs were in healthy participants. Eight RCTs (4 RCTs with participants with or predisposed to insulin resistance and 4 RCTs with healthy participants) evaluated the effect of saturated fats compared to MUFA on fasting insulin, 7 reported no effect, whereas 1 RCT (59 participants, 28 days intervention duration, p<0.001) reported an increase in fasting insulin.

11.46 In summary*, adequate* evidence for an increase in fasting insulin when saturated fats are substituted with MUFA is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016). However, SACN previously judged that variation in methodologies precluded use of fasting insulin data in meta-analyses (SACN, 2015). Furthermore, although elevated fasting insulin can be seen as an indicator of insulin resistance, the health benefits and relevance of the reported changes in fasting insulin are uncertain.

Saturated fats substitution with MUFA and fasting insulin
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with MUFA increases fasting insulin *Prospective cohort studies* • No evidence

Substitution of saturated fats with carbohydrates and fasting insulin

11.47 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of changes in substituting saturated fats with carbohydrates on

measures of fasting insulin. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.48 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data from 90 RCTs. These show a statistically significantly lower fasting insulin when 5% energy as carbohydrates was isoenergetically substituted with saturated fats (mean difference -1.12 pmol/L[32], 95% CI -1.72 to -0.53, p<0.01; 90 RCTs, 3774 participants), therefore saturated fats substitution with carbohydrates significantly increased fasting insulin. These results are largely also reflected in sensitivity analyses of a subset of 28 RCTs aimed at varying saturated fats, and 65 RCTs of participants without type 2 diabetes.

11.49 Schwab et al (2014) reported on 7 RCTs with varying specificity of saturated fats substitution in a systematic review without meta-analysis. Two RCTs evaluated the effect of saturated fats substitution with carbohydrates on fasting insulin. Both RCTs reported fasting insulin to be higher with saturated fats compared with carbohydrates.

11.50 Micha & Mozaffarian (2010) reported on fasting insulin results from 10 RCTs, 5 of which recruited participants with or predisposed to insulin resistance and the other 5 RCTs were in healthy participants. Three RCTs (1 RCT with participants with or predisposed to insulin resistance and 2 RCTs with healthy participants) evaluated the effect of saturated fats compared to carbohydrates on fasting insulin. One RCT including healthy participants reported saturated fats significantly increased fasting insulin in comparison with carbohydrates (59 participants, intervention duration 28 days, p<0.001). There was no significant effect of saturated fats in the other 2 RCTs with carbohydrates.

11.51 In summary, *adequate* evidence for an increase in fasting insulin when saturated fats are substituted with carbohydrates is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016). However, SACN previously judged that variation in methodologies precluded use of fasting insulin data in meta-analyses (SACN, 2015). Furthermore, although elevated fasting insulin can be seen as an indicator of insulin resistance, the health benefits and relevance of the reported changes in fasting insulin are uncertain.

[32] 1 pmol/L= 0.14 µIU/mL

Saturated fats substitution with carbohydrates and fasting insulin
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with carbohydrates increases fasting insulin *Prospective cohort studies* • No evidence

Glycated haemoglobin (HbA1c)

Reduced intake of saturated fats and glycated haemoglobin (HbA1c)

11.52 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on the relationship between saturated fat intake or saturated fats substitution with proteins and glycated haemoglobin (HbA1c).

Substitution of saturated fats with PUFA and glycated haemoglobin (HbA1c)

11.53 One systematic review with meta-analysis (Imamura et al, 2016) reported results of RCTs evaluating the effect of substituting saturated fats with PUFA on measures of HbA1c. A further systematic review with meta-analysis (Hooper et al, 2015) noted that HbA1c was not measured in any of the included studies. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.54 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data from 23 RCTs. These show that HbA1c was significantly lower when saturated fats were substituted with PUFA (mean difference -0.15%, 95% CI -0.23 to -0.06; p<0.001; 23 RCTs, 618 participants). These results are generally also reflected in sensitivity analyses of a subset of 5 RCTs of participants without type 2 diabetes (though with much wider CI, and not statistically significant). No estimates could be derived from the subset of 4 RCTs aimed at varying intake of saturated fats.

11.55 In summary*, adequate* evidence for a beneficial decrease in HbA1c for saturated fats substitution with PUFA, is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016). The size of the effect is biologically relevant.

Saturated fats substitution with PUFA and HbA1c
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with PUFA lowers HbA1c *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and glycated haemoglobin (HbA1c)

11.56 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of substituting saturated fats with MUFA on measures of HbA1c. A further systematic review with meta-analysis (Hooper et al, 2015) noted that HbA1c was not measured in any of the included studies. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.57 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data from 23 RCTs. These show that HbA1c was significantly lower when saturated fats were substituted with MUFA (mean difference -0.12%, 95% CI -0.19 to -0.05, p<0.001; 23 RCTs, 618 participants). These results are generally also reflected in sensitivity analyses of a subset of 5 RCTs of participants without type 2 diabetes (though with much wider CI and not statistically significant). No estimates could be derived from the subset of 4 RCTs aimed at varying intake of saturated fats.

11.58 In a systematic review without meta-analysis, Schwab et al (2014) reported results from 1 RCT in overweight and obese participants, in which saturated fats led to an increased HbA1c in comparison to MUFA.

11.59 In a systematic review without meta-analysis Micha & Mozaffarian (2010) reported results from 1 RCT in participants with or predisposed to insulin resistance, in which saturated fats increased HbA1c in comparison to MUFA (11 participants, 28 days intervention duration, p<0.01).

11.60 In summary*, adequate* evidence for a beneficial decrease in HbA1c for saturated fats substitution with MUFA, is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016). The size of the effect is biologically relevant.

Saturated fats substitution with MUFA and HbA1c
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with MUFA lowers HbA1c *Prospective cohort studies* • No evidence

Substitution of saturated fats with carbohydrates and glycated haemoglobin (HbA1c)

11.61 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010) reported results of RCTs evaluating the effect of substituting saturated fats with carbohydrates on measures of HbA1c. A further systematic review with meta-analysis (Hooper et al, 2015) noted that HbA1c was not measured in any of the included studies. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.62 Imamura et al (2016) carried out a meta-regression analysis of data from 23 RCTs. These show that HbA1c was not significantly different when 5% energy as saturated fats was isoenergetically substituted with carbohydrates (23 RCTs, 618 participants). These results are generally also reflected in sensitivity analyses of a subset of 5 RCTs of participants without type 2 diabetes (though with much wider CI, and not statistically significant). No estimates could be derived from the subset of 4 RCTs aimed at varying intake of saturated fats.

11.63 In a systematic review without meta-analysis, Schwab et al (2014) reported results from 1 RCT in overweight and obese participants, in which saturated fats led to an increased HbA1c in comparison to carbohydrates.

11.64 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) reported results from 1 RCT in participants with or predisposed to insulin resistance, in which saturated fats increased HbA1c in comparison to carbohydrates (11 participants, 28 days intervention duration, $p<0.01$).

11.65 In summary*, adequate* evidence for no effect of substitution of saturated fats with carbohydrates and HbA1c is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016).

Saturated fats substitution with carbohydrates and HbA1c
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Glucose tolerance

Reduced intake of saturated fats and glucose tolerance

11.66 One systematic review with meta-analysis of RCTs reported on the effect of saturated fats on glucose tolerance (Hooper et al, 2015). No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.67 A Cochrane systematic review with meta-analysis of RCTs (Hooper et al, 2015) included data from 3 RCTs, reporting changes in 2-hour OGTT following reductions in intake of saturated fats. Interventions reducing intake of saturated fats significantly reduced 2-hour OGTT glucose values (that is, improved glucose tolerance) (mean difference -1.69 mmol/L, 95% CI -2.55 to -0.82, p =0.0001; I^2 =45%; 3 RCTs, 249 participants). The 2 largest RCTs included participants with diabetes or impaired glucose tolerance, and in 2 of the 3 RCTs the primary intervention was reduced total fat. However, in the Hooper et al (2015) review glucose tolerance was not included in the original search.

11.68 In summary, although Hooper et al (2015) reported a significant reduction in OGTT response from a meta-analysis of 3 studies of saturated fats reduction, this was not included in the original search, and the results were largely derived from reduced total fat interventions in populations with impaired glycaemic control. Therefore, these results were given less weight when grading the evidence for the effects of saturated fats reduction in the general population. Overall, the data were considered *insufficient* to draw conclusions on the effect of saturated fat intake on glucose tolerance.

Reduced intake of saturated fats and glucose tolerance
Randomised controlled trials • *Insufficient* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with PUFA and glucose tolerance

11.69 Two systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 1 without meta-analysis (Micha & Mozaffarian, 2010), reported results of RCTs evaluating the effect of substituting saturated fats with PUFA on measures of glucose tolerance (for example, OGTT). No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.70 Imamura et al (2016) carried out a systematic review with meta-regression analysis on data from 11 RCTs. These show that glucose tolerance derived from a 2-hour OGTT was not significantly different when saturated fats were substituted with PUFA (mean difference 0.26 mmol/L, 95% CI -0.34 to 0.85; 11 RCTs, 615 participants). These results are also reflected in sensitivity analyses of a subset of 5 RCTs of participants without type 2 diabetes, as well as 6 RCTs of subjects with type 2 diabetes.

11.71 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) reported on glucose tolerance (OGTT) results from 6 RCTs, 3 of which recruited participants with or predisposed to insulin resistance and the other 3 RCTs were in healthy participants. Two RCTs (1 RCT with participants with or predisposed to insulin resistance and 1 RCT with healthy participants) evaluated the effect of saturated fats substitution with PUFA on glucose tolerance (response to a standard glucose load) and reported no significant difference.

11.72 In summary, *adequate* evidence for no effect on glucose tolerance for saturated fats substitution with PUFA, is supported by results reported by Imamura et al (2016).

Saturated fats substitution with PUFA and glucose tolerance
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and glucose tolerance

11.73 Two systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 1 without meta-analysis (Micha & Mozaffarian, 2010), reported results of RCTs evaluating the effect of substituting saturated fats with MUFA on measures of glucose tolerance (for example 2-hour OGTT). No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.74 Imamura et al (2016) carried out a systematic review with meta-regression analysis on data from 11 RCTs. These show that glucose tolerance derived from a 2-hour OGTT was not significantly different when saturated fats were substituted with MUFA (11 RCTs, 615 participants). These results are also reflected in sensitivity analyses of a subset of 5 RCTs of participants without type 2 diabetes, as well as 6 RCTs of subjects with type 2 diabetes.

11.75 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) reported on glucose tolerance (OGTT) results from 6 RCTs, 3 of which recruited participants with or predisposed to insulin resistance and the other 3 RCTs were in healthy participants. There was no significant difference in glucose tolerance (response to a standard glucose load) reported when saturated fats were substituted with MUFA in the 6 RCTs.

11.76 In summary, *adequate* evidence for no effect on glucose tolerance for saturated fats substitution with MUFA, is supported by results reported by Imamura et al (2016).

Saturated fats substitution with MUFA and glucose tolerance
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with carbohydrates and glucose tolerance

11.77 Two systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 1 without meta-analysis (Micha & Mozaffarian, 2010), reported results of RCTs evaluating the effect of substituting saturated fats with carbohydrates on measures of glucose tolerance (for example, 2-hour OGTT). No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.78 Imamura et al (2016) carried out a systematic review with meta-regression analysis on data from 11 RCTs. These showed that glucose tolerance derived from a 2-hour OGTT was not significantly different when 5% energy as saturated fats were isoenergetically substituted with carbohydrates (11 RCTs, 615 participants). These results are also reflected in sensitivity analyses of a subset of 5 RCTs of participants without type 2 diabetes, as well as 6 RCTs of subjects with type 2 diabetes.

11.79 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) reported on glucose tolerance (OGTT) results from 6 RCTs, 3 of which recruited participants with or predisposed to insulin resistance and the other 3 RCTs were in healthy participants. Three RCTs (in healthy participants) reported on the effects of saturated fats substitution with carbohydrates on glucose tolerance. No significant effect was reported.

11.80 In summary, *adequate* evidence for no effect of saturated fats substitution with carbohydrates on glucose tolerance, is supported by results reported by Imamura et al (2016).

Saturated fats substitution with carbohydrates and glucose tolerance
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Insulin resistance

Reduced intake of saturated fats and insulin resistance

11.81 One systematic review with meta-analysis of RCTs (Te Morenga & Montez, 2017a) examined the effect of reduced saturated fats on measures of insulin resistance. No

systematic reviews, meta-analyses or pooled analyses of PCS were identified that reported on the relationship between intake of saturated fats and insulin resistance.

11.82 Te Morenga & Montez (2017a) performed a systematic review with meta-analysis of RCTs in young people aged 2 to 16 years. Data for insulin resistance measured by homeostatic model assessment (HOMA) were reported from only 1 long-term RCT, where reduced intake of saturated fats had no significant effect at age 19 years (1 RCT, 437 participants).

11.83 In summary, *insufficient* evidence was available from RCTs on saturated fat intake and insulin resistance to reach any conclusions.

Reduced intake of saturated fats and insulin resistance assessed by HOMA
Randomised controlled trials • *Insufficient* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with PUFA and insulin resistance

11.84 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010), reported results of RCTs evaluating the effect of substituting saturated fats with PUFA on measures of insulin resistance (or inversely, insulin sensitivity) derived from HOMA or infusion tests (for example, frequently sampled intravenous glucose tolerance test [FSIGTT] or euglycaemic clamp). Where data were identified as coming only from *in vitro* assessments of insulin sensitivity, these results were excluded. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.85 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data on HOMA insulin resistance from 30 RCTs. This showed significant beneficial effects (that is, less insulin resistance) in substitutions of saturated fats with PUFA (mean difference -4.1%, 95% CI -6.4 to -1.6, $p<0.05$; 30 RCTs, 1801 participants). These results are also reflected in sensitivity analyses of a subset of 24 RCTs of participants without type 2 diabetes.

11.86 Imamura et al (2016) also reported that the analyses of insulin sensitivity index data were available from 13 infusion studies (including hyperglycaemic or euglycaemic clamp and FSIGTT; it was unclear which infusion test was used), all without type 2 diabetes. This

showed no statistically significant differences when saturated fats were substituted with PUFA (13 RCTs, 1292 participants).

11.87 In a systematic review without meta-analysis, Schwab et al (2014) reported on 9 RCTs with varying specificity of saturated fats substitution (5 RCTs reported on substitution of saturated fats with MUFA or PUFA; 4 RCTs reported on substitution of saturated fats with MUFA and carbohydrates). Two RCTs tested HOMA insulin resistance and 7 RCTs used other methods to measure insulin resistance (including FSIGTT and clamp, but not all reported). One RCT examined the effect of saturated fats substitution with PUFA, reporting that saturated fats increased insulin resistance (euglycaemic clamp) relative to PUFA.

11.88 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) reported insulin resistance results from 7 RCTs either using HOMA or infusions (FSIGTT and the euglycaemic clamp) to measure insulin resistance. One RCT in participants with or predisposed to insulin resistance compared intake of saturated fats to PUFA on insulin resistance tested by HOMA and reported no effect. Two RCTs tested insulin resistance using infusions (FSIGTT and euglycaemic clamp). Saturated fats increased insulin resistance relative to PUFA in 1 RCT in participants with or predisposed to insulin resistance (17 participants, intervention duration 5 weeks, p=0.02), whereas there was no statistically significant effect in the RCT of healthy participants.

11.89 In summary, *adequate* evidence for a decrease in HOMA insulin resistance with saturated fats substitution by PUFA, is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016). The size of the effect is biologically relevant; however, because of the lack of standardisation in the methods used to measure insulin values for deriving HOMA insulin resistance, some caution must be applied to these data. For insulin resistance from infusion studies, the same analyses provide *adequate* evidence for a lack of effect from saturated fats substitution by PUFA.

Saturated fats substitution with PUFA and insulin resistance assessed by HOMA
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with PUFA lowers insulin resistance *Prospective cohort studies* • No evidence

Saturated fats substitution with PUFA and insulin resistance assessed by infusion
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with MUFA and insulin resistance

11.90 Three systematic reviews, 1 with meta-analysis (Imamura et al, 2016) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010), reported results of RCTs evaluating the effect of substituting saturated fats with MUFA on measures of insulin resistance (or inversely, insulin sensitivity) derived from HOMA or infusion tests (for example, FSIGTT or euglycaemic clamp). Where data were identified as coming only from *in vitro* assessments of insulin sensitivity, these results were excluded. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.91 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data on HOMA insulin resistance from 30 RCTs. This showed significant beneficial effects (less insulin resistance) in substitutions of saturated fats with MUFA (mean difference -3.1%, 95% CI -5.8 to -0.4, $p<0.01$; 30 RCTs, 1801 participants). These results are also reflected in sensitivity analyses of a subset of 24 trials of participants without type 2 diabetes.

11.92 Imamura et al (2016) also reported that the analyses of insulin sensitivity index data were available from 13 infusion studies (including hyperglycaemic or euglycaemic clamp and FSIGTT; it was unclear which infusion test was used), all without type 2 diabetes. This showed no statistically significant differences when saturated fats were substituted with MUFA (13 RCTs, 1292 participants).

11.93 In a systematic review without meta-analysis Schwab et al (2014) reported on 9 RCTs with varying specificity of saturated fats replacement. Two RCTs tested HOMA insulin resistance and 7 RCTs used other methods to measure insulin resistance (including FSIGTT and clamp, but not all reported). In the 2 RCTs testing HOMA insulin resistance, saturated fats increased insulin resistance relative to MUFA. In 4 RCTs using other methods (including FSIGTT and clamp, but not all reported), saturated fats increased insulin resistance relative to MUFA.

11.94 In a systematic review without meta-analysis Micha & Mozaffarian (2010) reported insulin resistance results from 7 RCTs either using HOMA or infusions (FSIGTT and the euglycaemic

clamp) to measure insulin resistance. Two RCTs (in participants with or predisposed to insulin resistance) compared saturated fats to MUFA on insulin resistance tested by HOMA and reported no effect. In 4 RCTs which tested insulin resistance using infusions (FSIGTT and euglycaemic clamp), saturated fats increased insulin resistance relative to MUFA in 1 RCT in participants with or predisposed to insulin resistance (162 participants, intervention duration 3-months, p=0.05), whereas in 3 RCTs of healthy participants there was no significant difference.

11.95 In summary, *adequate* evidence for a decrease in insulin resistance (assessed by HOMA) with saturated fats substitution by MUFA is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016). The size of the effect is biologically relevant; however, because of the lack of standardisation in the methods used to measure insulin values for deriving HOMA insulin resistance, some caution must be applied to these data. For insulin resistance from infusion studies, the same analyses provide *adequate* evidence for a lack of effect from saturated fats substitution by MUFA.

Saturated fats substitution with MUFA and insulin resistance assessed by HOMA
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with MUFA lowers insulin resistance *Prospective cohort studies* • No evidence

Saturated fats substitution with MUFA and insulin resistance assessed by infusion
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Substitution of saturated fats with carbohydrates and insulin resistance

11.96 Four systematic reviews, 2 with meta-analyses (Imamura et al, 2016; Hooper et al, 2015) and 2 without meta-analyses (Schwab et al, 2014; Micha & Mozaffarian, 2010), reported results of RCTs evaluating the effect of substituting saturated fats with carbohydrates on measures of insulin resistance (or inversely, insulin sensitivity) derived from HOMA or infusion tests (for example, FSIGTT or euglycaemic clamp). Where data were identified as coming only from *in vitro* assessments of insulin sensitivity, these results were excluded. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.97 Imamura et al (2016) carried out a systematic review with meta-regression analysis of data on HOMA insulin resistance from 30 RCTs. This showed no significant effect when 5% energy as saturated fats was isoenergetically substituted with carbohydrates (30 RCTs, 1801 participants). These results are also reflected in sensitivity analyses of a subset of 24 trials of participants without type 2 diabetes.

11.98 Imamura et al (2016) also reported that the analyses of insulin sensitivity index data were available from 13 infusion studies (including hyperglycaemic or euglycaemic clamp and FSIGTT; it was unclear which infusion test was used), all without type 2 diabetes. This showed no statistically significant differences when 5% energy as saturated fats was isoenergetically substituted with carbohydrates (13 RCTs, 1292 participants).

11.99 The Cochrane systematic review with meta-analysis of RCTs from Hooper et al (2015) excluded studies with exposure duration <24 months, and reported data on HOMA from only 1 RCT, the Women's Health Initiative. In that RCT there was no effect of substitution of saturated fats with carbohydrates on HOMA insulin sensitivity (1 RCT, 2832 participants). However, the Women's Health Initiative did not explicitly test the effect of substitution of saturated fats with carbohydrates. Also, in the Hooper et al (2015) systematic review insulin resistance was not include in the original search.

11.100 In a systematic review without meta-analysis Schwab et al (2014) reported on 9 RCTs with varying specificity of saturated fats substitution. Two RCTs tested HOMA insulin resistance and 7 RCTs used other methods to measure insulin resistance (including FSIGTT and clamp, but not all reported). One RCT using other methods (including FSIGTT and clamp, but not all reported) reported that saturated fats increased insulin resistance relative to carbohydrates.

11.101 In a systematic review without meta-analysis Micha & Mozaffarian (2010) reported insulin resistance results from 7 RCTs either using HOMA or infusions (FSIGTT and the euglycaemic clamp) to measure insulin resistance. One RCT in participants with or predisposed to insulin resistance compared saturated fats to carbohydrates on insulin resistance tested by HOMA and reported no effect. Two RCTs compared saturated fats with carbohydrates using

infusions (FSIGTT and euglycaemic clamp) to measure insulin resistance in healthy participants, reporting no significant differences.

11.102 In summary, *adequate* evidence for no effect of saturated fats substitution with carbohydrates is supported by the statistical significance and consistency of results from a large body of studies as reported by Imamura et al (2016). However, because of the lack of standardisation in the methods used to measure insulin values for deriving HOMA insulin resistance, some caution must be applied to these data. For insulin resistance from infusion studies, the same analyses provide *adequate* evidence for no effect from saturated fats substitution by carbohydrates.

Saturated fats substitution with carbohydrates and insulin resistance assessed by HOMA
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Saturated fats substitution with carbohydrates and insulin resistance assessed by infusion
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No evidence

Summary

11.103 Results from systematic reviews of RCTs provide no or *insufficient* evidence to draw a conclusion on the effect of saturated fats or the effect of specific substitutions for saturated fats on risk of type 2 diabetes.

11.104 Systematic reviews with meta-analyses of PCS provide *adequate* evidence of no association between saturated fats and risk of type 2 diabetes in adults, when the highest intakes were compared with the lowest.

11.105 Results were available from systematic reviews with meta-analyses of RCTs reporting evidence on fasting glucose, fasting insulin, HbA1c, glucose tolerance, and insulin resistance determined by HOMA or infusions. The comprehensive quantitative data analyses from Imamura et al (2016) have been used as the primary basis for data synthesis and drawing conclusions.

11.106 The results indicate small beneficial decreases in fasting glucose for saturated fats substitution with PUFA, while changes in fasting insulin for saturated fats substitution with MUFA or carbohydrates were of uncertain relevance. Beneficial and biologically relevant decreases in HbA1c and HOMA insulin resistance were observed for saturated fats substitution with PUFA or MUFA. However, there were no effects of saturated fats substitution with PUFA, MUFA or carbohydrates on glucose tolerance or for insulin resistance determined by infusion methods.

11.107 Overall, substitutions for saturated fats show a neutral or beneficial effect on markers of glycaemic control, with the exception of substituting saturated fats with MUFA or carbohydrates on fasting insulin, which were of uncertain health relevance.

11.108 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and risk of type 2 diabetes and glycaemic control is summarised below in Table 11.1.

Table 11.1 Summary table of the evidence on the effect/relationship between saturated fats and type 2 diabetes and markers of glycaemic control

	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
Outcome	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
RCTs										
Type 2 diabetes	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence
Fasting glucose	n/a	No evidence	↓	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Fasting insulin	n/a	No evidence	-	Adequate	↑	Adequate	↑	Adequate	n/a	No evidence
HbA1c	n/a	No evidence	↓	Adequate	↓	Adequate	-	Adequate	n/a	No evidence
Glucose tolerance	n/a	Insufficient	-	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Insulin resistance HOMA	n/a	Insufficient	↓	Adequate	↓	Adequate	-	Adequate	n/a	No evidence
Insulin resistance by infusion	n/a	No evidence	-	Adequate	-	Adequate	-	Adequate	n/a	No evidence
PCS										
Type 2 diabetes	-	Adequate	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence
Fasting glucose	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Fasting insulin	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
HbA1c	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Glucose tolerance	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Insulin resistance HOMA	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Insulin resistance by infusion	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

n/a – not enough evidence to draw conclusions

Direction of effect/association for reported outcomes: ↑increased; ↓decreased; - no effect/association

12 Anthropometry

12.1 Six systematic reviews, 3 with meta-analyses (Hannon et al, 2017a; Te Morenga & Montez, 2017a; Hooper et al, 2015) and 3 without meta-analyses (Tielemans et al, 2016; Fogelholm et al, 2012a; Micha & Mozaffarian, 2010) examined the relationship between saturated fats and anthropometric measurements (body weight, body mass index (BMI), waist circumference) or gestational weight gain. Three systematic reviews analysed the results from randomised controlled trials (RCTs) (Hannon et al, 2017a; Te Morenga & Montez, 2017a; Hooper et al, 2015) and 3 evaluated the results from prospective cohort studies (PCS) (Tielemans et al, 2016; Fogelholm et al, 2012a; Micha & Mozaffarian, 2010). The characteristics of these publications are summarised in Annex 2, Table A2.12. The quality of the meta-analyses and systematic reviews are summarised in Annex 4.

12.2 No systematic reviews, meta-analyses or pooled analyses of RCTs and PCS were identified that reported on the relationship between saturated fats substituted with carbohydrates or proteins and anthropometric measurements.

12.3 The reviews also varied depending on whether anthropometric measurements were considered primary or secondary outcomes. In particular, the Cochrane systematic review with meta-analysis of RCTs (Hooper et al, 2015) did not include anthropometric measurements in the search and the evidence is identified from studies selected for other outcomes.

Anthropometric measurements (body weight, BMI or waist circumference)

Reduced intake of saturated fats and anthropometric measurements (body weight, BMI or waist circumference)

Randomised controlled trials

12.4 Two systematic reviews with meta-analysis (Te Morenga & Montez, 2017a; Hooper et al, 2015) assessed the effect of intake of saturated fats on anthropometric measurements.

12.5 Te Morenga & Montez (2017a) performed a systematic review studying young people aged 2 to 16 years. There was no effect of reducing saturated fats on BMI (3 RCTs, 1189 participants), body weight (4 RCTs, 1419 participants) and waist circumference (2 RCTs, 576 participants).

12.6 A systematic review with meta-analysis by Hooper et al (2015) examined 15 RCTs covering 17 comparisons involving approximately 59,000 participants. The studies either aimed to assess the impact on total mortality and cardiovascular mortality of reducing intake of

saturated fats or altering saturated fats. Interventions were at least 24-months in duration. As secondary outcomes, body weight and BMI were not included in the original search, and not reported in all studies. Hooper et al (2015) reported that reducing the intake of saturated fats significantly reduced body weight using a random-effects model (mean difference -1.97 kg, 95% CI -3.67 to -0.27; I^2 =72%; 6 RCTs, 4541 participants), and BMI (mean difference -0.50 kg/m^2, 95% CI -0.82 to -0.19; I^2 =55%; 6 RCTs, 5553 participants). With the exception of 1 data set each for body weight (Oslo Diet-Heart (Leren, 1966)) and BMI (Sydney Diet-Heart (Woodhill et al, 1978)), the intervention arm in all studies involved reductions in total fat intake, with substitution of dietary fats including saturated fats mainly by carbohydrates; however, no data are presented on saturated fats substitution by specific macronutrients.

Prospective cohort studies

12.7 Two systematic reviews without meta-analyses reported results derived from PCS (Fogelholm et al, 2012a; Micha & Mozaffarian, 2010).

12.8 In a systematic review, Fogelholm et al (2012a) stated that 'no conclusion' could be drawn from 2 identified PCS. One PCS (also cited by Micha & Mozaffarian (2010)) reported a positive association of intake of saturated fats with body weight, while the other found no association of intake of saturated fats with body weight or waist circumference.

12.9 Micha & Mozaffarian (2010) identified 2 large cohort studies. After adjusting for other risk factors and lifestyle and dietary behaviours, intake of saturated fats was associated with small increases in abdominal circumference and body weight (1 study for each outcome) compared with carbohydrates.

12.10 In summary, significant effects of reduction in saturated fats were reported in a good quality meta-analysis with a sufficient number of studies (Hooper et al, 2015). However, in that analysis body weight and BMI were only reported where available in studies selected for other outcomes, and the bulk of evidence came from studies where reduction of saturated fats was part of an overall reduction in fat intake. In addition, the systematic review with meta-analysis by Te Morenga & Montez (2017a) in children and adolescents found no significant effects of saturated fats reduction on anthropometric outcomes. It was further noted that the SACN Carbohydrates and Health Report (SACN, 2015) found *limited* evidence that energy restricted, higher carbohydrates, lower fat diets may be beneficial in reducing BMI. Therefore, there is *inconsistent* evidence to attribute effects to a reduction in saturated fats specifically rather than reducing saturated fats as part of total dietary fat intake.

Reduced intake of saturated fats and anthropometric measurements (body weight, BMI or waist circumference)
Randomised controlled trials • *Inconsistent* evidence *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrates or proteins and anthropometric measurements (body weight, body fat %, fat mass or waist circumference)

12.11 One systematic review with meta-analysis of RCTs reported on the relationship between substituting saturated fats with unsaturated fats (a mixture of PUFA and MUFA) and anthropometric measurements (Hannon et al, 2017a). No systematic reviews, meta-analyses or pooled analyses of PCS were identified that reported on the relationship between substituting saturated fats with polyunsaturated fats (PUFA), monounsaturated fats (MUFA), carbohydrates or proteins on anthropometric measurements.

12.12 Hannon et al (2017a) performed a systematic review with meta-analysis of 8 RCTs in obese and overweight adults reporting changes in body weight, body fat %, fat mass and waist circumference. Using a fixed-effects model, saturated fats substitution with unsaturated fats had no effect on body weight (6 RCTs, 387 participants), body fat % (3 RCTs, 230 participants), fat mass (2 RCTs, 60 participants) or waist circumference (3 RCTs, 117 participants).

12.13 In summary, there was no effect of saturated fats substitution with unsaturated fats (a mixture of PUFA and MUFA) on anthropometric measurements, including body weight, body fat %, fat mass and waist circumference. The evidence was graded *adequate* for all outcomes except fat mass (which was graded *insufficient* evidence, as this was based on only 2 RCTs and had high heterogeneity).

Saturated fats substitution with unsaturated fats (mixture of PUFA and MUFA) and anthropometric measurements (body weight, body fat %, fat mass or waist
Randomised controlled trials Body weight, body fat %, waist circumference • No effect • *Adequate* evidence Fat mass • *Insufficient evidence* *Prospective cohort studies* • No evidence

Gestational weight gain

Reduced intake of saturated fats and gestational weight gain

12.14 One systematic review, without meta-analysis (Tielemans et al, 2016) of PCS evaluated the association between intake of saturated fats and excess gestational weight gain. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

12.15 Of the 56 articles included in a systematic review, without meta-analysis (Tielemans et al, 2016), 8 longitudinal observational studies of various sizes, ranging from 39 to 3360 participants, described intake of saturated fats in relation to the adequacy of gestational weight gain. In most cases, gestational weight gain was calculated using measured weight in the third trimester compared with self-reported pre-pregnancy weight.

12.16 The authors stated that 2 of the 8 studies were rated high quality using standard quality assessment methods; these were also the largest of the studies that examined saturated fats and gestational weight gain, comprising 80% of the total sample. Of these 2 high quality studies, 1 study (3360 participants) reported an association with saturated fat intake and marginally higher gestational weight gain (no effect size reported, $p<0.04$), assessed using measured weights in the first and third trimesters (Uusitalo et al, 2009). The other study (1388 participants) reported no increase in the odds ratio of excessive gestational weight gain of increased intake of saturated fats (per 5% of energy compared with carbohydrates); however the measured third trimester weight was compared with a self-reported pre-pregnancy weight (Stuebe et al, 2009).

12.17 Tielemans et al (2016) stated that the remaining 6 studies ranged from very poor to moderate quality; of these, 5 reported no association with intake of saturated fats and gestational weight gain, although all used self-reported pre-pregnancy weight. One study

reported a positive association of saturated fat intake and gestational weight retention, but this study used weight data collected in the post-partum period (≤15 days).

12.18 In summary, the evidence on intake of saturated fats and gestational weight gain was graded as *insufficient* due to 1 systematic review without meta-analysis of 8 PCS, with inconsistent results.

Reduced intake of saturated fats and gestational weight gain
Randomised controlled trials • No evidence *Prospective cohort studies* • *Insufficient* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrates or proteins and gestational weight gain

12.19 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on saturated fats substitution with PUFA, MUFA, carbohydrates or proteins on gestational weight gain.

Summary

12.20 Results were available from systematic reviews with meta-analyses of RCTs, which reported on anthropometric measurements (body weight, BMI, waist circumference) and intake of saturated fats. Reducing the intake of saturated fats was found to significantly reduce body weight and BMI in a systematic review with meta-analysis in adults. However, the majority of the data included in the analysis came from trials where there were reductions in the intakes of both saturated and total fats. This limits the ability to attribute the observed effects to a reduction in saturated fats. Also, body weight and BMI were not the primary outcomes considered in the review and data on these outcomes were only identified if they were reported in a paper that also reported on one of the primary outcomes of interest. Reducing saturated fats was found to have no effect on anthropometric measurements in children, therefore the evidence was graded *inconsistent.*

12.21 There was *insufficient* evidence from systematic reviews of PCS to draw a conclusion on the association between saturated fats and anthropometric measurements (body weight, BMI, waist circumference).

12.22 There was no effect of saturated fats substitution with unsaturated fats (a mixture of PUFA and MUFA) on anthropometric measurements, including body weight, % body fat and waist circumference. The evidence was graded *adequate.* There was *insufficient* evidence for fat mass.

12.23 No evidence from RCTs was identified that reported on the effect of saturated fats on gestational weight gain. There was *insufficient* evidence from PCS to draw a conclusion on the association between saturated fats and gestational weight gain.

12.24 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and anthropometry is summarised below in Table 12.1.

Table 12.1 Summary table of the evidence on the effect/association between saturated fats and anthropometric measurements/gestational weight gain

	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
Outcome	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
RCTs										
Anthropometric measurements	n/a	Inconsistent	-	Adequate[1]	-	Adequate[1]	n/a	No evidence	n/a	No evidence
Gestational weight gain	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
PCS										
Anthropometric measurements	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Gestational weight gain	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

n/a – not enough evidence to draw conclusions

Direction of effect/association for reported outcomes: ↑increased; ↓decreased; - no effect/association

[1] Adequate evidence indicated that the substitution of saturated fats with a mixture of PUFA and MUFA had no effect on body weight, body fat % and waist circumference. There was insufficient evidence to draw conclusions on the effect of the substitution of saturated fats with a mixture of PUFA and MUFA on fat mass.

13 Cancers

13.1 Thirteen systematic reviews of which 9 included meta-analyses were identified that considered the evidence on intake of saturated fats and various cancers (colorectal, pancreatic, lung, breast and prostate) (Cao et al, 2016; Brennan et al, 2015; Xia et al, 2015; Xu et al, 2015a; Yao & Tian, 2015; Schwab et al, 2014; Makarem et al, 2013; Liu et al, 2011; Turner, 2011; Dennis et al, 2004; Boyd et al, 2003; Smith-Warner et al, 2002; Smith-Warner et al, 2001). The characteristics of these publications are summarised in Annex 2, Table A2.15. The quality of the meta-analyses and systematic reviews is summarised in Annex 4.

13.2 No systematic reviews, meta-analyses or pooled analyses of randomised controlled trials (RCTs) were identified that reported on the effect of saturated fats on cancers. No systematic reviews, meta-analyses or pooled analyses of RCTs or prospective cohort studies (PCS) were identified that reported on the relationship between saturated fats substituted with polyunsaturated fats (PUFA), monounsaturated fats (MUFA) orcarbohydrates and cancers, with the exception of breast cancer. No PCS were identified that reported on the association of saturated fats substitution with proteins and cancers.

13.3 Although the Women's Health Initiative trial is a single RCT and therefore did not meet the inclusion criteria, the size of the study made it of interest. The Women's Health Initiative trial randomised 48,835 postmenopausal women to usual diet or a low fat diet with increased intake of fruit, vegetables and grains. After 8.1 years there were 480 incident cases of colorectal cancer (Beresford et al, 2006) and 1727 incident cases of breast cancer (Prentice et al, 2006) in the low fat group. However, the participants were all women and they did not explicitly test for the effect of low saturated fats.

Colorectal cancer

Reduced intake of saturated fats and colorectal cancer

13.4 Two systematic reviews, 1 with meta-analysis (Liu et al, 2011) and 1 without meta-analysis (Schwab et al, 2014) were identified that examined the association between saturated fats and colorectal cancer. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

13.5 Liu et al (2011) performed a systematic review with meta-analysis of 12 PCS. There was no association between the intake of saturated fats and risk of colorectal cancer using a random-effects model (12 PCS, 451,956 participants, 3182 cases) for the highest versus the lowest category of intake (adjusted for energy in 8 out of the 12 studies).

13.6 In a systematic review without meta-analysis of fat (saturated fats, PUFA, MUFA) and chronic diseases, Schwab et al (2014) described the results from 1 PCS, which reported no association between saturated fats and colorectal cancer among women. This PCS was also included in the meta-analysis by Liu et al (2011).

13.7 In summary, the evidence from the only comprehensive systematic review with meta-analysis of PCS (Liu et al, 2011) reported no association between lower intake of saturated fats and the risk for colorectal cancer. The evidence was graded as *adequate.*

Reduced intake of saturated fats and colorectal cancer
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Pancreatic cancer

Reduced intake of saturated fats and pancreatic cancer

13.8 One systematic review with meta-analysis of PCS (Yao & Tian, 2015) was identified that evaluated the association between saturated fats and pancreatic cancer. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

13.9 Yao & Tian (2015) performed a systematic review with meta-analysis of 6 PCS. They reported no association between intakes of saturated fats and risk of pancreatic cancer (6 PCS, 1,130,815 participants, 3072 cases) for the highest versus the lowest category of intake (using energy-adjusted results where available).

13.10 In summary, the evidence from the only comprehensive systematic review with meta-analysis of PCS (Yao & Tian, 2015) reported no association between the intake of saturated fats and the risk for pancreatic cancer. The evidence was graded as *adequate*.

Reduced intake of saturated fats and pancreatic cancer
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Lung cancer

Reduced intake of saturated fats and lung cancer

13.11 One pooled analysis of PCS (Smith-Warner et al, 2002) was identified that evaluated the association between saturated fats and lung cancer. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

13.12 Smith-Warner et al (2002) reported a pooled analysis of individual participant data from 8 PCS. There was no association between the intake of saturated fats and risk of lung cancer for the highest versus lowest quartile (adjusted for energy), and for a 5% increase in intake of energy from saturated fats (8 PCS, 430,281 participants, 3188 cases).

13.13 In summary, the evidence from the only comprehensive pooled analysis of PCS (Smith-Warner et al, 2002) reported no association between the intake of saturated fats and the risk for lung cancer. The evidence was graded as *adequate.*

Reduced intake of saturated fats and lung cancer
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Breast cancer

Reduced intake of saturated fats and breast cancer

13.14 Four systematic reviews with meta-analyses (Cao et al, 2016; Xia et al, 2015; Turner, 2011; Boyd et al, 2003), 1 pooled analysis (Smith-Warner et al, 2001) and 1 systematic review without meta-analyses (Schwab et al, 2014) of PCS were identified that evaluated the association between saturated fats and risk of breast cancer. One systematic review of PCS with meta-analysis (Brennan et al, 2015) and 1 without meta-analysis of PCS (Makarem et al, 2013) assessed the association between saturated fats and survival in women with breast cancer. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

13.15 Cao et al (2016) performed a systematic review with meta-analysis of 20 PCS. There was no association between the intake of saturated fats and risk of breast cancer using a random-effects model (20 PCS, 1,220,608 participants, 35,344 cases) for the highest versus lowest category of intake of energy from saturated fats (adjusted for energy in 17 out of the 20 studies). To note, Cao et al (2016) superseded Boyd et al (2003) that reported a meta-analysis of 14 PCS of the association between the intake of saturated fats and risk of breast cancer.

13.16 Brennan et al (2015) reported a meta-analysis of saturated fats and survival in women with breast cancer. Brennan et al (2015) considered 4 PCS, of which 2 included some adjustment for stage of the disease and none included details of treatment. Without detailed adjustment for stage, grade and treatment these observational results are difficult to interpret. Therefore the committee agreed not to report the results of the Brennan et al (2015) meta-analysis.

13.17 Xia et al (2015) reported a meta-analysis of 24 PCS of the association between the intake of saturated fats and risk of breast cancer. They found no association between saturated fats and risk of breast cancer. Although the Xia et al (2015) meta-analysis included the

largest number of studies and cases, more consideration was given to the results from Cao et al (2016) due to the apparent double counting of participants from sequential publications and misclassifications of PCS as case-control studies in Xia et al (2015). For this reason, the committee agreed not to report the results of the Xia et al (2015) meta-analysis.

13.18 Turner (2011) reported on a systematic review with meta-analysis of 19 PCS of the association between the intake of saturated fats and risk of breast cancer. They found no association using a random-effects model (based on the DerSimonian-Laird method) between saturated fats and risk of breast cancer (19 PCS, 1,379,666 participants, 24,257 cases) when comparing the highest to the lowest quartile of intake of saturated fats.

13.19 Makarem et al (2013) reported a systematic review without meta-analysis of 6 PCS of saturated fats and survival in women with breast cancer. Four PCS reported the hazard ratio (HR) or risk ratio (RR) for breast cancer mortality but in the other 2 PCS this information was not available. All 4 PCS showed that an increase in intake of saturated fats increased the risk of breast cancer mortality.

13.20 Smith-Warner et al (2001) reported a pooled analysis of individual participant data from 8 PCS of the association between the intake of saturated fats (ranging from 10% to 16% of total dietary energy) and risk of breast cancer. There was no association between intake of saturated fats and risk of breast cancer (8 PCS, 351,821 women, 7329 cases) for a 5% increase in intake of energy from saturated fats.

13.21 In a systematic review without meta-analysis of fat (saturated fats, PUFA, MUFA) and chronic diseases, Schwab et al (2014) described the results from 6 PCS of saturated fats and breast cancer, and these 6 PCS were also included in the meta-analysis by Cao et al (2016).

13.22 In summary, the evidence from the most comprehensive meta-analysis of PCS (Cao et al, 2016), reported no association between the intake of saturated fats and the risk of breast cancer. The evidence was graded as *adequate.*

Reduced intake of saturated fats and breast cancer
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Substitution of saturated fats with PUFA and breast cancer

13.23 One pooled analysis (Smith-Warner et al, 2001) evaluated the evidence from PCS analyses which modelled the association of substituting saturated fats with PUFA on breast cancer risk. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

13.24 Smith-Warner et al (2001) reported a pooled analysis of individual participant data from 8 PCS of the association between the intake of saturated fats and risk of breast cancer, using evidence from PCS analyses which modelled substituting saturated fats with PUFA. There was no association between saturated fats substitution with PUFA and the risk of breast cancer using a random-effects model, in PCS analyses substituting saturated fats with 5% of energy from PUFA.

13.25 In summary, based on the evidence from PCS analyses (Smith-Warner et al, 2001), substitution of saturated fats with PUFA was not associated with the risk of breast cancer. The evidence was graded as *adequate*.

Saturated fats substitution with PUFA and breast cancer
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Substitution of saturated fats with MUFA and breast cancer

13.26 One pooled analysis of PCS (Smith-Warner et al, 2001) evaluated the evidence from PCS analyses which modelled substituting saturated fats with MUFA in relation to breast cancer risk. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

13.27 Smith-Warner et al (2001) reported a pooled analysis of individual participant data from 8 PCS of the association between the intake of saturated fats and risk of breast cancer, using evidence from PCS analyses which modelled substituting saturated fats with MUFA. Using a random effect model, there was no association between saturated fats substitution with

MUFA and risk of breast cancer in PCS analyses substituting saturated fats with 5% of energy from MUFA.

13.28 In summary, based on the evidence from PCS analyses (Smith-Warner et al, 2001), substitution of saturated fats with MUFA was not associated with the risk of breast cancer. The evidence was graded as *adequate.*

Saturated fats substitution with MUFA and breast cancer
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Substitution of saturated fats with carbohydrates and breast cancer

13.29 One pooled analysis of PCS (Smith-Warner et al, 2001) evaluated the evidence from PCS analyses which modelled substituting saturated fats with carbohydrates in relation to breast cancer risk. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

13.30 Smith-Warner et al (2001) reported a pooled analysis of individual participant data from 8 PCS of the association between the intake of saturated fats and risk of breast cancer using evidence from PCS analyses substituting saturated fats with carbohydrates. Using random-effects models, there was no association between saturated fats substitution with carbohydrates and risk of breast cancer in PCS analyses substituting saturated fats with 5% of energy from carbohydrates.

13.31 In summary, based on the evidence from PCS analyses (Smith-Warner et al (2001), substitution of saturated fats with carbohydrates was not associated with the risk of breast cancer. The evidence was graded as *adequate.*

Saturated fats substitution with carbohydrates and breast cancer
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Prostate cancer

Reduced intake of saturated fats and prostate cancer

13.32 Two meta-analyses (Xu et al, 2015a; Dennis et al, 2004) and 1 systematic review without meta-analysis (Schwab et al, 2014) were identified that considered the evidence from PCS on saturated fats and prostate cancer risk. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

13.33 Xu et al (2015a) reported in a systematic review with meta-analysis of 9 PCS on the relationship between saturated fats and risk of prostate cancer (RR 1.00, 95% CI 1.00 to 1.00; 9 PCS, number of participants not reported, 33,983 cases) for a 28.35 g/day increment in intake of saturated fats (adjusted for energy intake in 6 of the 9 studies). However, it was unclear how this estimate of the RR was obtained, how confidence intervals of 1.00 to 1.00 could be obtained, or where the authors obtained the estimates for the individual studies; therefore, this estimate was not considered reliable.

13.34 Dennis et al (2004) reported in a systematic review with meta-analysis of 3 PCS. They reported no association between intake of saturated fats and risk of prostate cancer (3 PCS, 130,875 participants, 2,536 cases) for a 25 g/day increment in intake of saturated fats (adjusted for energy).

13.35 The World Cancer Research Fund (WCRF) (WCRF, 2014) reported the results from a systematic review with meta-analysis on intake of saturated fats and risk of prostate cancer using random-effects model (RR 0.99, 95% CI 0.96 to 1.03) per 10 g/day increase in intake of saturated fats (9 PCS, 4887 cases, and using energy-adjusted results where available), and (RR 0.97, 95% CI 0.92 to 1.03) per 5% increase in energy from saturated fats (4 PCS, 30,698 cases). This is not a peer-reviewed journal publication, but the project has a detailed published protocol and independent review by a panel of international scientists (Continuous Update project (CUP) Expert Panel).

13.36 Schwab et al (2014) summarised the results from Dennis et al (2004) and 3 subsequent PCS which were also included by Xu et al (2015a) and therefore the results of Schwab et al (2014) were not considered further.

13.37 In summary, based on the most comprehensive systematic review with meta-analysis of PCS (Dennis et al, 2004) and consideration of the WCRF report (WCRF, 2014), there was no association between the intake of saturated fats and the risk of prostate cancer. The evidence was graded as *adequate.*

Reduced intake of saturated fats and prostate cancer
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Summary

13.38 No systematic reviews, meta-analyses or pooled analyses of RCTs were identified that reported on saturated fats or their substitution with PUFA, MUFA, carbohydrates or proteins and incidental colorectal, pancreatic, lung, breast or prostate cancer.

13.39 There was *adequate* evidence from systematic reviews, meta-analyses or pooled analyses of PCS, comparing the highest intakes of saturated fats with the lowest. This evidence suggested there is no association between intake of saturated fats and risk of colorectal, pancreatic, lung, breast or prostate cancer.

13.40 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and cancers is summarised below in Table 13.1

Table 13.1 Summary table of the evidence on the effect/association between saturated fats and cancers

	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
Outcome	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
RCTs										
Colorectal cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Pancreatic cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Lung cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Breast cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Prostate cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
PCS										
Colorectal cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Pancreatic cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Lung cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Breast cancer	-	Adequate	-	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Prostate cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

n/a – not enough evidence to draw conclusions

Direction of effect/association for reported outcomes: ↑increased; ↓decreased; - no effect/association

14 Cognitive impairment and dementias

14.1 Five systematic reviews, 1 with meta-analysis (Xu et al, 2015b) and 4 without meta-analyses (Barnard et al, 2014; Lee et al, 2010; Patterson et al, 2007; Ernst, 1999) evaluated the evidence on the association between saturated fats and cognitive outcomes (cognitive decline, mild cognitive impairment, dementias, including Alzheimer's disease and other forms of dementias). The characteristics of these publications are summarised in Annex 2, Table A2.17. The quality of the meta-analysis and systematic reviews are summarised in Annex 4.

14.2 No systematic reviews, meta-analyses or pooled analyses of randomised controlled trials (RCTs) were identified that reported on the effect of saturated fats or their substitution with polyunsaturated fats (PUFA), monounsaturated fats (MUFA), carbohydrates or proteins on cognitive outcomes. No systematic reviews, meta-analyses or pooled analyses of prospective cohort studies (PCS) were identified that reported on the substitution of saturated fats with PUFA, MUFA, carbohydrates or proteins on cognitive outcomes.

14.3 The systematic review with meta-analysis by Xu et al (2015b) reported on 3 PCS, 2 of which were included in a meta-analysis which compared the lowest and highest quartiles of intake of saturated fats. Data from 9 PCS (reported in 12 publications) were considered in the systematic review by Barnard et al (2014). The reviewers stated that it was not possible to combine the data from the 9 PCS in a meta-analysis due to differences in reporting of the relationship between saturated fats and Alzheimer's disease. The systematic reviews by Ernst (1999), Lee et al (2010) and Patterson et al (2007) have not been considered further because the studies included in them were also reported in the meta-analysis by Xu et al (2015b) and the largest and most up-to-date systematic review by Barnard et al (2014).

14.4 Apolipoprotein E (APOE) is recognised as the main genetic risk factor, with semi-dominant inheritance, for late-onset Alzheimer's disease (Yu et al, 2014). Genetic variation within the APOE gene[33] (OMIM 107741) has been linked to cognitive decline and dementia (Davies et al, 2014), and the postulated links between diet and cognitive decline (Whalley et al, 2008). Although recent large genome-wide association studies have identified many other new loci for late-onset Alzheimer's disease, the associations of these genes with risk of Alzheimer's disease are much smaller than those of APOE. In general terms, 1 allele of APOE-ε4 shifts the risk curve for the disease to 5 years earlier, 2 copies of APOE-ε4 shift it 10 years earlier, and 1 copy of APOE-ε2 allele shifts it 5 years later. The magnitude of this

[33] The APOE gene is located on chromosome19q13.2 and it contains several single nucleotide polymorphisms (SNPs). Two in particular – rs7412 (C/T) and rs429358 (C/T) – are responsible for the 3 major alleles: epsilon-2 (ε2), epsilon-3 (ε3), and epsilon-4 (ε4); resulting in 3 major protein isoforms, APOE-ε2, APOE-ε3, and APOE-ε4, which differ from each other by 1 or 2 amino acids at positions 112 and 158 which alter APOE structure and function (Giau et al, 2015).

genetic association and its possible modulating role in the cognitive response to diet, have resulted in this genotype being reported in a number of the primary publications and reviews. Where relevant to the interpretation of nutritional evidence it has also been reported here.

Cognitive decline

Reduced intake of saturated fats and cognitive decline

14.5 One systematic review without meta-analysis of PCS evaluated the association between saturated fats and cognitive decline (Barnard et al, 2014). No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

14.6 Barnard et al (2014) performed a systematic review without meta-analysis of 12 PCS on the association between saturated fats and risk of cognitive impairment. They identified 4 PCS (278 to 6183 participants with a mean age at baseline of 71 to 74 years and a follow-up of 3 to 8.5 years). Cognitive decline was assessed using a variety of cognitive tests in the 4 studies. Two larger studies (2560 to 6138 participants) reported significant associations between lower intakes of saturated fats, less than 12.2g/day (7% of energy) compared to greater than 24.3g/day saturated fats (13% of energy) and a reduction in cognitive function (-0.023 standard unit/year, p= 0.04; global cognitive function: 1.64 (95% CI 1.04 to 2.58; p= 0.02), verbal memory: 1.65 (95% CI 1.04 to 2.61; p= 0.02)). Two smaller studies (278 to 482 participants) reported no association between saturated fats and cognitive function (9.1 g/day or less of saturated fats compared to 13.0g/day or more; mean intake of saturated fats 20.8g/day in another PCS), one of which also found no association after adjusting for APOE genotype.

14.7 In summary, a systematic review without meta-analysis (Barnard et al, 2014) provided *inconsistent* evidence on the association between saturated fats and cognitive decline. Conflicting results between studies may be explained by differences in intakes of saturated fats in the highest and lowest groups.

Reduced intake of saturated fats and cognitive decline
Randomised controlled trials • No evidence *Prospective cohort studies* • *Inconsistent* evidence

Mild cognitive impairment

Reduced intake of saturated fats and mild cognitive impairment

14.8 One systematic review without meta-analysis (Barnard et al, 2014) of PCS evaluated the association between saturated fats and mild cognitive impairment. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

14.9 Barnard et al (2014) reported on the association between saturated fats and mild cognitive impairment. The systematic review without meta-analysis included 4 PCS involving 278 to 1528 participants aged 50 to 80 years (mean at baseline). Ten to 192 cases of mild cognitive impairment were identified across 4 PCS with follow-up of 2.6 to 21.0 years. Mild cognitive impairment was diagnosed using the criteria developed by Petersen (2004)[34], or modifications of them, in all 4 studies. Three PCS, 2 of which controlled for APOE genotype, found no association between the intake of saturated fats and mild cognitive impairment. The fourth study found a significant association between higher intakes of saturated fats and an increased risk of mild cognitive impairment (OR 2.36, 95% CI 1.17 to 4.74; no p value reported). Subgroup analysis identified a stronger association in women (OR 3.20, 95% CI 1.13 to 9.06; no p value reported) than in men. In the same study, after stratification by APOE genotype, the association between saturated fats and the risk of mild cognitive impairment only remained among participants with the APOE-ε4 allele (OR 5.06, 95% CI 1.35 to 18.94; no p value reported). The finding that this effect was apparently specific to those with the APOE-ε4 allele is noteworthy and scientifically interesting but not relevant to the aims of this report and the provision of advice to populations.

14.10 In summary, 3 PCS included in the systematic review without meta-analysis by Barnard et al (2014) reported no association between the intake of saturated fats and mild cognitive impairment in the general population. In the fourth study an association between the intake of saturated fats and mild cognitive impairment was reported for the group as a whole. Overall, evidence of no significant association between the intake of saturated fats and the risk of mild cognitive impairment was graded as *limited*.

[34] Criteria includes: a) memory complaint usually corroborated by an informant; b) objective memory impairment for age; c) essentially preserved general cognitive function; d) largely intact functional activities; e) not demented.

Reduced intake of saturated fats and mild cognitive impairment
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Limited* evidence

Alzheimer's disease

Reduced intake of saturated fats and Alzheimer's disease

14.11 One meta-analysis (Xu et al, 2015b) and 1 systematic review without meta-analysis (Barnard et al, 2014) of PCS evaluated the association between saturated fats and Alzheimer's disease. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

14.12 The meta-analysis of 2 PCS (Xu et al, 2015b) reported no association between Alzheimer's disease and the intake of saturated fats using a fixed-effect meta-analysis (2 PCS, 6201 participants, 168 cases; 2.1 to 3.9 years of follow-up). Both studies adjusted for age, sex, and education, 1 also adjusted for total energy intake whilst the other adjusted for race, APOE genotype and the interaction between race, APOE genotype and other types of dietary fats.

14.13 Barnard et al (2014), in their systematic review without meta-analysis, reviewed 4 PCS (reported in 5 publications). Seventy six to 242 cases of Alzheimer's disease were diagnosed in 815 to 5395 participants, and in the study that reported genotype 28% to 35% of individuals carried an APOE-ε4 allele. Participants were aged 50.4 to 73.1 years (mean at baseline) with follow-ups of 2.1 to 21.0 years. One study reported a significant positive association (RR 2.2, 95% CI 1.1 to 4.7; 1 PCS, 815 participants, 131 cases; 3.9 years follow-up,) and 2 studies reported no association in a comparison of the highest and lowest quartile of intake of saturated fats (4 to 21 years follow-up). Another study reported that Alzheimer's disease risk was lower in those with higher intakes of saturated fats (RR 0.83 per standard deviation increase in intake, 95% CI 0.70 to 0.98; 1 PCS, 5395 participants, 146 cases; 6 years of follow-up). Barnard et al (2014) included both PCS considered by Xu et al (2015b). For 1 of the cohorts, Barnard et al (2014) reported on both the 2- and the 6-year follow-up while Xu et al (2015b) only reported on the 2-year follow-up.

14.14 One study included in the systematic review by Barnard et al (2014) stratified participants by APOE genotype. The results remained non-significant in groups with and without the APOE-ε4 allele. This study does not provide enough evidence to draw a conclusion on the relationship between saturated fats and the risk of Alzheimer's disease in APOE-ε4 allele carriers.

14.15 In summary, while the meta-analysis by Xu et al (2015b) reported no association between Alzheimer's disease risk and the intake of saturated fats, the PCS included in the larger systematic review by Barnard et al (2014) reported conflicting results. Due to the conflicting results the evidence has been graded as *inconsistent*.

Reduced intake of saturated fats and Alzheimer's disease
Randomised controlled trials • No evidence *Prospective cohort studies* • *Inconsistent* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrates or proteins and Alzheimer's disease

14.16 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on substitution of saturated fats with PUFA, MUFA, carbohydrates or proteins and Alzheimer's disease.

Dementias

Reduced intake of saturated fats and dementias

14.17 One systematic review without meta-analysis of PCS (Barnard et al, 2014) evaluated the association between saturated fats and dementias (Alzheimer's disease and other forms of dementia). No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

14.18 Barnard et al (2014) considered 2 PCS that evaluated the association between saturated fats and dementias (Alzheimer's disease and other forms of dementia). One of the studies reported on 1449 participants with 117 cases of dementia after 21 years and another reported on 5395 participants with 197 cases of dementia after 6 years. No association

was reported between the intake of saturated fats and the risk of dementia at both the 6-year and the 21-year follow-up. The longer PCS also stratified participants by APOE status (35% were APOE-ε4 allele carriers), but did not find a significant association in either group when comparing the highest and lowest intakes of saturated fats.

14.19 In summary, given that Barnard et al (2014) only reported on 2 PCS, there is *insufficient* evidence to draw a conclusion on the association between the intake of saturated fats and dementias (Alzheimer's disease and other forms of dementias).

Reduced intake of saturated fats and dementias
Randomised controlled trials • No evidence *Prospective cohort studies* • *Insufficient* evidence

Summary

14.20 No systematic reviews, meta-analyses or pooled analyses of RCTs were identified that reported on the effect of saturated fats and cognitive outcomes.

14.21 A systematic review of PCS was identified which reported on intake of saturated fats and cognitive outcomes. The PCS included in the systematic review reported *inconsistent* results for associations between saturated fats and both cognitive decline, measured using a range of tests, and the incidence of Alzheimer's disease. There was *limited* evidence for no association between mild cognitive impairment and saturated fats and there was *insufficient* evidence to draw a conclusion on the association with dementias.

14.22 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and cognitive outcomes is summarised below in Table 14.1

Table 14.1 Summary table of the evidence on the effect/association between saturated fats and cognitive outcomes

	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
Outcome	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
RCTs										
Cognitive decline	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Mild cognitive impairment	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Alzheimer's disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Dementias	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
PCS										
Cognitive decline	n/a	Inconsistent	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Mild cognitive impairment	-	Limited	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Alzheimer's disease	n/a	Inconsistent	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Dementias	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

n/a – not enough evidence to draw conclusions

Direction of effect/association for reported outcomes: ↑increased; ↓decreased; - no effect/association

15 Overall summary and conclusions

Overall summary

15.1 This report considers the relationship between saturated fats, health outcomes and risk factors for non-communicable diseases in the general UK population. This report does not consider total fat in the diet, individual saturated fatty acids, or the role of unsaturated fats other than as a replacement for saturated fats.

Cardiovascular diseases

15.2 Evidence on the relationship between intakes of saturated fats and their substitution with polyunsaturated fats (PUFA), monounsaturated fats (MUFA), carbohydrates or proteins, and cardiovascular outcomes is summarised below and in Table 15.1. Atherosclerotic cardiovascular diseases (CVD) include diseases that affect the heart or blood vessels and are generally categorised into 3 types: coronary heart disease (CHD), cerebrovascular disease (for example, stroke) and peripheral vascular disease.

Total cardiovascular diseases

15.3 There was *adequate* evidence from RCTs that reducing intake of saturated fats had no effect on CVD mortality.

15.4 There was *adequate* evidence from RCTs that reducing intake of saturated fats reduced the risk of CVD events.

15.5 There was *adequate* evidence from PCS that intake of saturated fats was not associated with CVD mortality or CVD events.

15.6 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA had no effect on CVD mortality.

15.7 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA reduced the risk of CVD events.

15.8 There was *limited* evidence from PCS that substituting saturated fats with unsaturated fats (a mixture of PUFA and MUFA) was associated with a lower risk of CVD mortality. The evidence was graded as *limited* due to the differential effect of different classes of PUFA and because there had been no formal meta-analysis. There was no evidence for CVD events.

15.9 *Insufficient* evidence was available from RCTs to determine any effect of substituting saturated fats with MUFA on CVD mortality and events. There was no evidence from PCS.

15.10 There was *limited* evidence from RCTs that substituting saturated fats with carbohydrates or proteins had no effect on CVD mortality and events. The evidence was graded as *limited* because the analyses underpinning the conclusion relied heavily on a study which did not explicitly test for the effect of substituting saturated fats with carbohydrates or proteins.

15.11 *Insufficient* evidence was available from PCS to determine any association between substituting saturated fats with carbohydrates and CVD mortality or events.

15.12 There was no evidence available from PCS to determine if there was an association between substituting saturated fats with proteins and CVD mortality or events.

Coronary heart disease

15.13 There was *adequate* evidence from RCTs that reducing intake of saturated fats had no effect on CHD mortality.

15.14 There was *moderate* evidence from RCTs that reducing intake of saturated fats reduced risk of CHD events. The evidence was graded as *moderate* because of the differences in statistical significance between reported statistical models, although these generated similar effect estimates and the differences between the p values were small.

15.15 There was *moderate* evidence from PCS that lower intake of saturated fats was associated with a lower risk of CHD mortality and events. The evidence was graded as *moderate* due to the differences in statistical significance between reported statistical models, although these generated similar effect estimates and the differences between p values were small and other less comprehensive reviews reporting no effect (on mortality and/or events for.

15.16 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA had no effect on CHD mortality.

15.17 There was *moderate* evidence from RCTs that substituting saturated fats with PUFA lowered the risk of CHD events. The evidence was graded as *moderate* based on an adequate number of studies and events, but the reported upper confidence interval of 1.00.

15.18 There was *moderate* evidence from PCS that substituting saturated fats with PUFA was associated with a lower risk of CHD mortality and CHD events. The evidence was graded as *moderate* due to some differences in statistical significance between reported statistical models, although these generated similar effect estimates and the differences between p values were small.

15.19 There was *insufficient* evidence from RCTs to determine any effect of substituting saturated fats with MUFA on CHD mortality and events.

15.20 There was *limited* evidence from PCS analyses that substituting saturated fats with MUFA was not associated with CHD mortality. The same substitution was associated with an

increased risk of CHD events. In both cases the evidence was graded as *limited* due to potential confounding by trans fats.

15.21 There was *limited* evidence from RCTs indicating that substituting saturated fats with carbohydrates had no effect on CHD mortality. The evidence was graded as *limited* because the analyses underpinning the conclusion included 3 RCTs, with a low number of deaths and was also dominated by 1 RCT which did not explicitly test for the effect of substituting saturated fats with carbohydrates.

15.22 There was *moderate* evidence from RCTs that substituting saturated fats with carbohydrates had no effect on CHD events. The evidence was graded as *moderate* because the analyses underpinning the conclusion included 5 RCTs with a high number of events, however the analysis was dominated by 1 RCT which did not explicitly test for the effect of substituting saturated fats with carbohydrates.

15.23 There was *adequate* evidence from PCS analyses that substituting saturated fats with carbohydrates was not associated with a change in risk of CHD mortality but was associated with an increased risk of CHD events.

15.24 There was *limited* evidence from RCTs that substituting saturated fats with proteins had no effect on CHD mortality. The evidence was graded as *limited,* because the analyses underpinning the conclusion included 3 RCTS with a low number of deaths and was dominated by 1 RCT which did not explicitly test for the effect of substituting saturated fats with proteins.

15.25 There was *moderate* evidence from RCTs that substituting saturated fats with proteins had no effect on CHD events. The evidence was graded as *moderate* because the analyses underpinning the conclusion included 4 RCTs with a high number of events, however the analysis was dominated by 1 RCT which did not explicitly test for the effect of substituting saturated fats with proteins.

Strokes

15.26 There was *adequate* evidence from RCTs of no effect between intake of saturated fats and total strokes. There was *limited* evidence from PCS that lower intake of saturated fats was associated with the increased risk of total stroke primarily in East Asian populations living in East Asia. There was *adequate* evidence from PCS for no association between lower intake of saturated fats and ischaemic strokes. However, there was *limited* evidence from PCS that lower intake of saturated fats increased the risk of haemorrhagic strokes in Japanese Asian populations living in Japan.

15.27 There was *insufficient* or no evidence from RCTs of any effect of substituting saturated fats with PUFA or MUFA on strokes. There was no evidence from PCS.

15.28 There was *limited* evidence from RCTs that substituting saturated fats with carbohydrates or proteins had no effect on strokes. The evidence was graded as *limited* because the

analyses underpinning the conclusion relied heavily on a study which did not explicitly test for the effect of substitution of saturated fats with carbohydrates or proteins. There was no evidence from PCS.

Blood lipids

15.29 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and blood lipids is summarised below and in Table 15.1.

Serum total cholesterol

15.30 There was *adequate* evidence from RCTs that reducing the intake of saturated fats lowered serum total cholesterol.

15.31 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA, MUFA, a mixture of PUFA and MUFA or carbohydrates lowered serum total cholesterol.

15.32 There was *insufficient* evidence from PCS on any association between lower intake of saturated fats and serum total cholesterol. There was also *insufficient* evidence from PCS analyses substituting saturated fats with PUFA, MUFA or carbohydrates to determine any association with serum total cholesterol.

15.33 There was no evidence available from RCTs or PCS to determine if there was an effect/association between substituting saturated fats with proteins and serum total cholesterol.

Serum LDL and HDL cholesterol

15.34 There was *adequate* evidence from RCTs that reducing the intake of saturated fats lowered serum LDL.

15.35 There was *moderate* evidence from RCTs that reducing the intake of saturated fats lowered serum HDL cholesterol in adults. The evidence was graded as *moderate* due to the nature of the evidence base. However, there was *adequate* evidence of no effect in children.

15.36 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrates lowered serum LDL cholesterol.

15.37 There was *moderate* evidence from RCTs that substituting saturated fats with PUFA or MUFA had no effect on serum HDL cholesterol. The evidence was graded as *moderate* due to the nature of the evidence base.

15.38 There was *moderate* evidence from RCTs that substituting saturated fats with carbohydrates reduced serum HDL cholesterol. The evidence was graded as *moderate* due to the nature of the evidence base.

15.39 There was *insufficient* evidence from PCS on any association between lower intake of saturated fats and serum LDL cholesterol. There was also *insufficient* evidence on substitution of saturated fats with PUFA, MUFA or carbohydrates and serum LDL cholesterol. No evidence from PCS was identified that reported on similar associations with serum HDL cholesterol.

15.40 There was no evidence available from RCTs or PCS to determine if there was an effect/association between substituting saturated fats with proteins and serum LDL and HDL cholesterol.

Serum total cholesterol:HDL cholesterol ratio

15.41 There was *limited* evidence from RCTs that reduced intake of saturated fats lowered the serum total cholesterol:HDL cholesterol ratio. The evidence was graded as *limited* as many of the RCTs included in the largest systematic review with meta-analysis were associated with weight loss and /or reduced dietary cholesterol and total fat intake.

15.42 There was *limited* evidence from RCTs that substituting saturated fats with PUFA or MUFA had no effect on the serum total cholesterol:HDL cholesterol ratio. The evidence was graded as *limited* as this finding was not consistent in all the systematic reviews and meta-analyses.

15.43 There was *adequate* evidence from RCTs that substituting saturated fats with carbohydrates had no effect on serum total cholesterol:HDL cholesterol ratio. There was no evidence for proteins.

15.44 No evidence from PCS was identified that reported on the association between a lower intake of saturated fats, or saturated fats substitution with PUFA, MUFA, carbohydrates or proteins and serum total cholesterol:HDL cholesterol ratio.

Serum triacylglycerol

15.45 There was *adequate* evidence from RCTs that reducing intake of saturated fats had no effect on serum triacylglycerol.

15.46 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA or MUFA had no effect on serum triacylglycerol.

15.47 There was *moderate* evidence from RCTs that substituting saturated fats with carbohydrates increased serum triacylglycerol. The evidence was graded as *moderate* due to the nature of the evidence base. There was no evidence for proteins.

15.48 No evidence from PCS was identified that reported on the association between lower intake or substitution of saturated fats with PUFA, MUFA, carbohydrates or proteins and serum triacylglycerol.

Blood pressure

15.49 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and blood pressure is summarised below and in Table 15.1.

15.50 There was *limited* evidence from RCTs that reducing intake of saturated fats had no effect on systolic or diastolic blood pressure. The evidence was graded *limited* as blood pressure was not included in the original search in the largest, most recent review.

15.51 There was *limited* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrates had no effect on blood pressure. The evidence base was small and heterogeneous. The evidence was graded as *limited* as blood pressure was not included in the original search in the largest, most recent review. There was no evidence for proteins.

15.52 There was *insufficient* evidence from PCS analyses substituting saturated fats with MUFA to determine any association with blood pressure. There was no evidence on the association between reduced intake of saturated fats or substituting saturated fats with PUFA, carbohydrates or proteins, and blood pressure from PCS.

Type 2 diabetes and markers of glycaemic control

15.53 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and risk of type 2 diabetes and glycaemic control is summarised below and in Table 15.1.

Type 2 diabetes

15.54 There was no or *insufficient* evidence from RCTs to determine any effect of reducing intake of saturated fats and risk of type 2 diabetes, or the effect of specific substitutions for saturated fats.

15.55 There was *adequate* evidence from PCS for no association between intake of saturated fats and risk of type 2 diabetes, when the highest intakes were compared with the lowest. There was no or *insufficient* evidence from PCS analyses substituting saturated fats to determine any association with risk of type 2 diabetes.

Fasting glucose

15.56 There was no evidence from RCTs to draw a conclusion on the relationship between reduced saturated fats and fasting glucose.

15.57 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA resulted in a small beneficial decrease in fasting blood glucose.

15.58 There was *adequate* evidence from RCTs that substituting saturated fats with MUFA or carbohydrates had no effect on fasting blood glucose.

15.59 There was no evidence from PCS to draw a conclusion on the association between lower intake of saturated fats and fasting glucose, or the association of specific substitutions for saturated fats.

Fasting insulin

15.60 There was no evidence from RCTs to draw a conclusion on the relationship between reduced saturated fats and fasting insulin.

15.61 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA had no effect on fasting insulin.

15.62 There was *adequate* evidence from RCTs that substituting saturated fats with MUFA or carbohydrates resulted in an increase in fasting insulin.

15.63 There was no evidence from PCS to draw a conclusion on the association between lower intake of saturated fats and fasting insulin, or the effect of specific substitutions for saturated fats.

HbA1c

15.64 There was no evidence from RCTs to draw a conclusion on the relationship between reduced saturated fats and HbA1c.

15.65 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA or MUFA resulted in a decrease in HbA1c.

15.66 There was *adequate* evidence from RCTs that substituting saturated fats with carbohydrates had no effect on HbA1c.

15.67 There was no evidence from PCS to draw a conclusion on the association between lower intake of saturated fats and HbA1c, or the association with PCS analyses substitutions for saturated fats.

Glucose tolerance

15.68 There was *insufficient* evidence from RCTs on the effect of intake of saturated fats on glucose tolerance.

15.69 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrates had no effect on glucose tolerance.

15.70 There was no evidence from PCS to draw a conclusion on the association between reducing intake of saturated fats and glucose tolerance, or the effect of specific substitutions for saturated fats.

Insulin resistance

15.71 There was *insufficient* evidence from RCTs on the effect of intake of saturated fats on insulin resistance (assessed by HOMA).

15.72 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA or MUFA resulted in a decrease in insulin resistance (assessed by HOMA).

15.73 There was *adequate* evidence from RCTs that substituting saturated fats with carbohydrates had no effect on insulin resistance (assessed by HOMA).

15.74 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrates had no effect on insulin resistance (assessed by infusion tests).

15.75 There was no evidence from PCS to draw a conclusion on the association between reducing intake of saturated fats and insulin resistance, or the effect of specific substitutions for saturated fats.

Anthropometry (body weight, BMI, waist circumference, gestational weight gain)

15.76 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and anthropometry is summarised below and in Table 15.1.

15.77 There was *inconsistent* evidence from RCTs that reduced intakes of saturated fats reduced body weight, BMI or waist circumference.

15.78 There was *adequate* evidence from RCTs of no effect of saturated fats substitution with unsaturated fats on body weight, body fat % and waist circumference and *insufficient* evidence for fat mass.

15.79 There was *insufficient* evidence from PCS to determine any association between intake of saturated fats and anthropometric measurements (body weight, BMI, waist circumference). There was no evidence from PCS on the effect of specific substitutions for saturated fats.

15.80 No RCTs were identified that reported the effect of saturated fats intake on gestational weight gain, or the effect of specific substitutions for saturated fats. There was no or *insufficient* evidence from PCS to determine any association.

Cancers

15.81 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and cancers is summarised below and in Table 15.1.

15.82 No RCTs were identified that reported the effect of reduced intake of saturated fats, or saturated fats substitution with PUFA, MUFA, carbohydrates or proteins, on the incidence of colorectal, pancreatic, lung, breast or prostate cancer.

15.83 There was *adequate* evidence from PCS for no association between reduced intake of saturated fats and colorectal, pancreatic, lung, breast or prostate cancer incidence. Also, there was *adequate* evidence from PCS analyses substituting saturated fats with PUFA, MUFA or carbohydrates for no association with breast cancer risk. There was no evidence for saturated fats substitutions and other cancers.

Cognitive impairment and dementias

15.84 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrates or proteins, and cognitive outcomes is summarised below and in Table 15.1.

15.85 No RCTs were identified that reported the effect of saturated fats on cognitive outcomes, or the effect of specific substitutions for saturated fats.

15.86 There was *limited* evidence from PCS indicating no association between intake of saturated fats and mild cognitive impairment.

15.87 The evidence from PCS on the association between intake of saturated fats and cognitive decline and Alzheimer's disease was *inconsistent* whilst the evidence for dementias (including Alzheimer's disease and other forms of dementias) was graded as *insufficient*. There was no evidence from PCS for saturated fats substitutions for any cognitive outcomes.

Overall conclusion

15.88 Since 1994, the evidence base on saturated fats and health has grown considerably. In addition to further research on the blood lipid profile, a significant body of evidence on other intermediate factors, risk markers and health outcomes is now available. This evidence has been considered in a number of published meta-analyses and systematic reviews. This report is based on a further assessment of this evidence, with precedence given to evidence from RCTs and evidence graded as adequate or moderate. SACN considered the saturated fats recommendations in the context of existing UK Government dietary recommendations on macronutrients and energy. The SACN recommendations presented here are based on the totality of the evidence considered, including null findings, where the evidence was graded as *moderate* or *adequate*.

15.89 New evidence published since 1994 supports and strengthens the COMA conclusion that a reduction in intake of saturated fats from current population average levels would be beneficial.

15.90 Table 15.1 provides a summary of SACN's review of the evidence. Findings which did not inform the development of recommendations – because the quality of the evidence was not considered to be adequate or moderate – are shaded grey.

15.91 SACN noted a lack of evidence for a range of outcomes but considered the totality of evidence, which included significant effects or associations in relation to outcomes of major public health concern. The evidence indicates that reducing saturated fats reduces the risk of CVD and CHD events, lowers total, LDL and HDL cholesterol and improves indicators of glycaemic control. The evidence also indicates that reducing saturated fats is unlikely to increase health risks for the general UK population. SACN concluded that reducing population average intake of saturated fats from current levels of intake to no more than about 10% of [total] dietary energy would result in health benefits to the population.

15.92 There were significant relationships between intake of saturated fats and CVD and CHD events, but not CVD and CHD mortality. SACN noted that, irrespective of the lack of evidence for an effect on mortality, non-fatal CVD and CHD events have a serious adverse impact on health and quality of life.

15.93 In relation to what should take the place of saturated fats in the diet, more evidence is available from RCTs for substitution with PUFA than for substitution with MUFA, carbohydrates or proteins, in relation to CVD and CHD outcomes. Furthermore, there was evidence, though from PCS rather than RCTs, that substituting saturated fats with carbohydrates was associated with increased CHD events. Substituting saturated fats with PUFA and/or MUFA lowered serum LDL cholesterol, but had no effect on serum HDL cholesterol. Substituting saturated fats with carbohydrates lowered serum LDL and HDL cholesterol. For markers of glycaemic control, substitution of saturated fats with PUFA was more beneficial than substitution with MUFA and there was evidence of no benefit for substitution with carbohydrates.

15.94 There were gaps in the evidence considered. In particular, there was less evidence available for substituting saturated fats with MUFA compared to substitution with PUFA. There was also less evidence available for substitution with carbohydrates or proteins compared to substitution with PUFA. The available evidence on carbohydrates was further complicated by the fact that studies often did not describe the type of carbohydrates.

15.95 SACN was mindful that if all substitution of saturated fats was with PUFA alone this could increase the proportion of the population consuming in excess of about 10% energy from PUFA; at odds with the current UK Government dietary recommendations.

15.96 There was limited evidence in children and older age groups. SACN concluded that the available evidence did not provide a basis for changing the existing recommendation for these age groups.

Table 15.1 Summary table of the evidence on the relationship between saturated fats and health outcomes, intermediate markers and risk factors

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Cardiovascular diseases (RCTs)										
CVD mortality	-	Adequate	-	Adequate	n/a	Insufficient	-	Limited	-	Limited
CVD events	↓	Adequate	↓	Adequate	n/a	Insufficient	-	Limited	-	Limited
CHD mortality	-	Adequate	-	Adequate	n/a	Insufficient	-	Limited	-	Limited
CHD events	↓	Moderate	↓	Moderate	n/a	Insufficient	-	Moderate	-	Moderate
Strokes	-	Adequate	n/a	Insufficient	n/a	No evidence	-	Limited	-	Limited
Peripheral vascular disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Cardiovascular diseases (PCS)										
CVD mortality	-	Adequate	↓	Limited[1]	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CVD events	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CHD mortality	↓	Moderate[2]	↓	Moderate	-	Limited	-	Adequate	n/a	No evidence
CHD events	↓	Moderate[2]	↓	Moderate	↑	Limited	↑	Adequate	n/a	No evidence
Strokes	-	Adequate[3,4]	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Peripheral vascular disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Blood lipids (RCTs)										
Total cholesterol	↓	Adequate	↓	Adequate[5]	↓	Adequate[5]	↓	Adequate	n/a	No evidence
LDL cholesterol	↓	Adequate	↓	Adequate	↓	Adequate	↓	Adequate	n/a	No evidence
HDL cholesterol	↓	Moderate[6]	-	Moderate	-	Moderate	↓	Moderate	n/a	No evidence
Total:HDL cholesterol	↓	Limited	-	Limited	-	Limited	-	Adequate	n/a	No evidence
Triacylglycerol	-	Adequate	-	Adequate	-	Adequate	↑	Moderate	n/a	No evidence
Blood lipids (PCS)										
Total cholesterol	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	No evidence
LDL cholesterol	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	No evidence
HDL cholesterol	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Total:HDL cholesterol	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Triacylglycerol	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Blood pressure (RCTs)										
Blood pressure	-	Limited	-	Limited	-	Limited	-	Limited	n/a	No evidence
Blood pressure (PCS)										
Blood pressure	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence	n/a	No evidence

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Type 2 diabetes and markers of glycaemic control (RCTs)										
Type 2 diabetes	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence
Fasting glucose	n/a	No evidence	↓	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Fasting insulin	n/a	No evidence	-	Adequate	↑	Adequate	↑	Adequate	n/a	No evidence
HbA1c	n/a	No evidence	↓	Adequate	↓	Adequate	-	Adequate	n/a	No evidence
Glucose tolerance	n/a	Insufficient	-	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Insulin resistance by homeostasis model assessment (HOMA)	n/a	Insufficient	↓	Adequate	↓	Adequate	-	Adequate	n/a	No evidence
Insulin resistance by infusion	n/a	No evidence	-	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Type 2 diabetes and markers of glycaemic control (PCS)										
Type 2 diabetes	-	Adequate	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence
Fasting glucose	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Fasting insulin	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
HbA1c	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Glucose tolerance	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Insulin resistance by homeostasis model assessment (HOMA)	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Insulin resistance by infusion	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Anthropometry (RCTs)										
Anthropometric measurements	n/a	Inconsistent	-	Adequate[7]	-	Adequate[7]	n/a	No evidence	n/a	No evidence
Gestational weight gain	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Anthropometry (PCS)										
Anthropometric measurements	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Gestational weight gain	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Cancers (RCTs)										
Colorectal cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Pancreatic cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Lung cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Breast cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Prostate cancer	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Cancers (PCS)										
Colorectal cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Pancreatic cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Lung cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Breast cancer	-	Adequate	-	Adequate	-	Adequate	-	Adequate	n/a	No evidence
Prostate cancer	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Dementias and cognitive function (RCTs)										
Cognitive decline	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Mild cognitive impairment	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Alzheimer's disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Dementias	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Dementias and cognitive function (PCS)										
Cognitive decline	n/a	Inconsistent	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Mild cognitive impairment	-	Limited	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Alzheimer's disease	n/a	Inconsistent	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Dementias	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

n/a- not enough evidence to draw conclusions

Direction of effect for reported outcomes: ↑increased; ↓decreased; - no effect/association

[1] Limited evidence indicated that the substitution of saturated fats with a mixture of PUFA and MUFA decreased the risk of CVD mortality

[2] Reviews considered 'CHD outcomes' which included CHD mortality and/or events

[3] Adequate evidence indicated that there was no association between lower intake of saturated fats and ischaemic strokes

[4]Limited evidence indicated that lower intake of saturated fats was associated with a higher risk of haemorrhagic strokes in Japanese populations living in Japan and total strokes in East-Asian populations living in East Asia

[5]Adequate evidence indicated that the substitution of saturated fats with a mixture of PUFA and MUFA decreased serum total cholesterol

[6] Moderate evidence indicated that lower intake of saturated fats reduced HDL cholesterol in adults, however adequate evidence of no effect in children[7]Adequate evidence indicated that the substitution of saturated fats with a mixture of PUFA and MUFA had no effect on body weight, body fat %, fat mass and waist circumference. There was insufficient evidence to draw a conclusion on the effect of the substitution of saturated fats with a mixture of PUFA and MUFA on fat mass

16 Recommendations

16.1 It is recommended that:

- the dietary reference value for saturated fats remains unchanged: the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than about 10%. This recommendation applies to adults and children aged 5 years and older.
- saturated fats are substituted with unsaturated fats. More evidence is available supporting substitution with PUFA than substitution with MUFA.

16.2 This recommendation is made in the context of existing UK Government recommendations for macronutrients and energy (see Table 16.1).

16.3 It is recommended that the government gives consideration to strategies to reduce [population] average contribution of saturated fatty acids to [total] dietary energy to no more than about 10%. Risk managers should be mindful of the available evidence in relation to substitution of saturated fats with different types of unsaturated fats and ensure that strategies are consistent with wider dietary recommendations, including trans fats (see Table 16.1).

Table 16.1 UK Government dietary recommendations[1] for energy and macronutrients and salt for men and women in the UK

Energy	2500 kcal/day for men; 2000 kcal/day for women[7]
Proteins[2]	0.75g of proteins per kilogram of bodyweight[8]
Total fats[3]	Reduce to about 35% of dietary energy[9]
Of which Saturated fats[3]	Reduce to no more than about 10% of dietary energy[10]
MUFA[3]	No specific recommendations for MUFA [11]
n-6 PUFA[3]	No further increase in the average intakes and the proportion of the population consuming in excess of about 10% of energy should not increase[12]
Linoleic acid[2]	Provide at least 1% of total energy
Long chain n-3 PUFA[4]	Increase from 0.2g/day to 0.45g/day[13]
Alpha linolenic acid[2]	Provide at least 0.2% of total energy
Trans fats[3]	Provide no more than about 2% of dietary energy
Carbohydrates[5]	Approximately 50% of total dietary energy
Of which Free sugars[5]	Should not exceed 5% of total dietary energy
Dietary fibre[5]	30g/day[14]
Salt[6]	6g/day

[1]Values are expressed as proportions of either total (dietary) energy or dietary energy, depending on the source report.
[2]From COMA Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (1991) recommendations.
[3] From COMA Nutritional Aspects of Cardiovascular disease (1994) recommendations.
[4] From SACN Advice on fish consumption benefits & risks (2004). SACN endorsed the population recommendation (including pregnant women) to eat at least two portions of fish per week, of which one should be oily. Two portions of fish per week, one white and only oily, contain approximately 0.45g/day long chain n-3 PUFA.
[5] From SACN Carbohydrates and Health (2015) recommendations for population aged 2 years and over.
[6] From SACN Salt and Health (2003) recommendations for the adult population.
[7]These figures are based on the UK government advice and they are not in line with SACN Dietary Reference Values for energy (2011). SACN recommended that DRVs for adult men and women should be 2605kcal/day and 2079 kcal/day respectively; these recommendations were not adopted by the government because of issues of overweight and obesity in the UK.
[8]Reference Nutrient Intake (RNI) for adults aged 19 to 50 years. RNI varies depending on age and gender and whether pregnant or breastfeeding.

[9] COMA Nutritional Aspects of Cardiovascular disease (1994) recommends a reduction in the average contribution of total fat to dietary energy in the population to about 35%.

[10] COMA Nutritional Aspects of Cardiovascular disease (1994) recommends that the [population] average contribution of saturated fatty acids to [total] dietary energy be reduced to no more than about 10%. This value was based on total dietary energy (which includes any intake from alcohol). The COMA DRV report 1991 noted that the corresponding recommendation for food energy (which excludes any intake from alcohol) would be 11%. The 1994 report stated that "the precision of our recommendations does not warrant such a distinction. These do not therefore take account of the small, variable differences between fat as a proportion of total or of food (i.e. excluding alcohol) energy".

[11]To note that COMA Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (1991) recommended that *cis*-MUFA (principally oleic acid) should continue to provide on average 12% of dietary energy for population.

[12] COMA Nutritional Aspects of Cardiovascular disease (1994) recommends no further increase in average intakes of n-6 PUFA and recommends that the proportion of the population consuming excess of about 10% energy should not increase.

[13] To note that COMA Nutritional Aspects of Cardiovascular disease (1994) recommended 'an increase in the population average consumption of long chain n-3 PUFA from about 0.1g/day to about 0.2g/day (1.5g/week)'.

[14]DRV for adults aged 19 years and over; DRVs vary depending on age.

17 Research recommendations

Approach

17.1 Throughout the development of this report, a number of limitations of the available evidence were identified (see chapter 2). It is therefore recommended that future research:

- ensures study designs are of sufficient power and duration, to examine the effect of reduced intake of saturated fats or specific substitutions on chronic disease outcomes
- specifies the type of carbohydrates and considers this in analyses and interpretation (for example, those with differing free sugars content; whole grains compared to refined starch)
- takes into consideration the widespread use of statins, which may affect the ability to gain evidence of nutritional benefit in future studies on saturated fats
- makes use of opportunities for sub-analysis or re-analysis of data from existing studies which substituted saturated fats with unsaturated fats, provided that the issues above and confounding by the presence of trans fats are adequately addressed.

Topics

17.2 A number of gaps in the evidence were identified during the development of this report. Therefore, further research is required to:

- examine the effects of substitution of saturated fats with
    - different types of PUFA (n-3, n-6 and chain length)
    - different types of MUFA
    - different types of carbohydrates
    - proteins

  and health outcomes, intermediate markers and/or risk factors
- undertake systematic reviews and meta-analyses (and possibly further primary research) investigating the potential effect of intake of saturated fats and health outcomes, intermediate markers and/or risk factors for longer term health in children under 5 years
- undertake systematic reviews and meta-analyses (and possibly further primary research) investigating the potential effect of saturated fat intakes on health outcomes, intermediate markers and/or risk factors in older adults

- undertake intervention studies, sufficiently powered and of longer duration, to test the effect of lower saturated fat intakes on chronic disease outcomes
- consider novel study designs, such as the use of genetic information in Mendelian randomisation
- examine the effects of saturated fat intakes lower than currently recommended (that is, below 10% of dietary energy intake) on health outcomes, intermediate markers and/or risk factors.

References

Abbasi A, Peelen L, Corpeleijn E, van der Schouw Y, Stolk R, Spijkerman A, et al (2012) Prediction models for risk of developing type 2 diabetes: systematic literature search and independent external validation study. BMJ : British Medical Journal. 345.

Abbasi A, Sahlqvist AS, Lotta L, Brosnan JM, Vollenweider P, Giabbanelli P, et al (2016) A Systematic Review of Biomarkers and Risk of Incident Type 2 Diabetes: An Overview of Epidemiological, Prediction and Aetiological Research Literature. PLoS ONE. 11(10):e0163721.

AFSSA (2010) Opinion of the French Food Safety Agency on the update of French population reference intakes (ANCs) for fatty acids. Available from: https://www.anses.fr/en/system/files/NUT2006sa0359EN.pdf

Alhazmi A, Stojanovski E, McEvoy M & Garg ML (2012) Macronutrient intakes and development of type 2 diabetes: a systematic review and meta-analysis of cohort studies. J Am Coll Nutr. 31(4):243-258.

Alzheimer's Society (2014) Dementia UK update. Available from: https://www.alzheimers.org.uk/download/downloads/id/2323/dementia_uk_update.pdf

American Diabetes Association and National Institute of Diabetes Digestive and Kidney Diseases (2002) The Prevention or Delay of Type 2 Diabetes. Diabetes Care. 25(4):742.

Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER, 3rd, et al (2005) Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. Jama. 294(19):2455-2464.

Assmann G, Schulte H, von Eckardstein A & Huang Y (1996) High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. Atherosclerosis. 124:S11-S20.

Australian Government Department of Health and the New Zealand Ministry of Health (2013) Macronutrient Balance Available from: https://www.nrv.gov.au/chronic-disease/macronutrient-balance

Barnard ND, Bunner AE & Agarwal U (2014) Saturated and trans fats and dementia: A systematic review. Neurobiology of Aging. 35:S65-S73.

Bates B, Clifford R, Collins D, Cox L, Davidson N, Gay C, et al (2019a) National Diet and Nutrition Survey (NDNS RP): Results for Years 5 to 9 (combined) of the Rolling Programme for Northern Ireland (2012/13 - 2016/17) and time trend and income analysis (Years 1 to 9; 2008/09 - 2016/17). A survey carried out on behalf of the Food Standards Agency in Northern Ireland and Public Health England.

Bates B, Collins D, Cox L, Nicholson S, Page P, Roberts C, et al (2019b) National Diet and Nutrition Survey, Years 1 to 9 of the Rolling Programme (2008/2009 – 2016/2017): Time trend and income analyses.

Bates B, Cox L, Nicholson P, Prentice A, Steer T & Swan G (2016) National Diet and Nutrition Survey Results from Years 5 and 6 (combined) of the Rolling Programme (2012/2013 – 2013/2014). Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/551352/NDNS_Y5_6_UK_Main_Text.pdf

Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson s, et al (2014a) National Diet and Nutrition Survey Rolling Programme (NDNS RP) Results from Years 1-4 (combined) for Scotland (2008/09-2011/12)

Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, et al (2014b) National Diet and Nutrition Survey Results from Years 1, 2, 3 and 4(combined) of the Rolling Programme (2008/2009 – 2011/2012).

Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, et al (2015a) National Diet and Nutrition Survey Rolling Programme (NDNS RP) Results from Years 1-4 (combined) for Northern Ireland (2008/09-2011/12).

Bates B, Lennox A, Prentice A, Bates C, Page P, Nicholson S, et al (2015b) National Diet and Nutrition Survey Rolling Programme (NDNS RP) Results from Years 2-5 (combined) for Wales (2009/10-2012/13).

Beresford SA, Johnson KC, Ritenbaugh C, Lasser NL, Snetselaar LG, Black HR, et al (2006) Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. Jama. 295(6):643-654.

Berg JM, Tymoczko JL & Stryer L (2012a) Biochemistry. Chapter 12: Lipids and Cell membranes. Seventh edition ed. New York: WH Freeman Palgrave Macmillan.

Berg JM, Tymoczko JL & Stryer L (2012b) Biochemistry. Chapter 22: Fatty Acid metabolism. Seventh edition ed. New York: WH Freeman Palgrave Macmillan

Berger S, Raman G, Vishwanathan R, Jacques PF & Johnson EJ (2015) Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr. 102(2):276-294.

Bhatnagar P, Wickramasinghe K, Wilkins E & Townsend N (2016) Trends in the epidemiology of cardiovascular disease in the UK. Heart. 102:1945-1952.

BHF (2011) Trends in Coronary Heart Disease 1961-2011.

BHF (2015) Cardiovascular disease statistics 2015 Available from: https://www.bhf.org.uk/-/media/files/publications/research/bhf-cvd-statistics-2015-final.pdf

BHF (2017) Cardiovascular Disease Statistics 2017.

Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ & Minkin S (2003) Dietary fat and breast cancer risk revisited: A meta-analysis of the published literature. British Journal of Cancer. 89(9):1672-1685.

Brennan SF, Woodside JV, Lunny PM, Cardwell CR & Cantwell MM (2015) Dietary fat and breast cancer mortality: A systematic review and meta-analysis. Crit Rev Food Sci Nutr.0.

Brown K, Rumgay H, Dunlop C, Ryan M, Quartly F, Cox A, et al (2018) The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer. 118:1130-1141.

Brunner E, White I, Thorogood M, Bristow A, Curle D & Marmot M (1997) Can dietary interventions change diet and cardiovascular risk factors? A meta-analysis of randomized controlled trials. American Journal of Public Health. 87(9):1415-1422.

Cancer Research UK (2016) Cancer Incidence Statistics. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence

Cao Y, Hou L & Wang W (2016) Dietary total fat and fatty acids intake, serum fatty acids and risk of breast cancer: A meta-analysis of prospective cohort studies. International Journal of Cancer. 138(8):1894-1904.

Castelli W, Anderson K, Wilson P & Levy D (1992) Lipids and risk of coronary heart disease. The Framingham Study. . Ann Epidemiol. 2:23-28.

Cheng P, Wang J, Shao W, Liu M & Zhang H (2016) Can dietary saturated fat be beneficial in prevention of stroke risk? A meta-analysis. Neurol Sci. 37:1089-1098.

Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, et al (2014) Association of dietary, circulating, and supplement fatty acids with coronary risk: A systematic review and meta-analysis. Annals of Internal Medicine. 160(6):398-406.

Christie (1987) High-performance liquid chromatography and Lipids: A Practical Guide Pergamon Press, Oxford.

Clarke R, Frost C, Collins R, Appleby P & Peto R (1997) Dietary lipids and blood cholesterol: Quantitative meta-analysis of metabolic ward studies. British Medical Journal. 314(7074):112-117.

CMACE (2010) Maternal obesity in the UK: findings from a national project. Available from: http://www.publichealth.hscni.net/sites/default/files/Maternal%20Obesity%20in%20the%20UK.pdf

COMA (1991) Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. London: HMSO.

COMA (1994) Nutritional aspects of cardiovascular disease, 46 ed. London: HMSO.

Davies G, Harris SE, Reynolds CA, Payton A, Knight HM, Liewald DC, et al (2014) A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. Mol Psychiatry. 19(1):76-87.

de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, et al (2015) Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: Systematic review and meta-analysis of observational studies. BMJ (Online). 351.

Defra (2014) UK-household and eating out nutrient intakes Available from: https://www.gov.uk/government/statistical-data-sets/family-food-datasets

Defra (2017) Family Food 2015. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/597667/Family_Food_2015-09mar17.pdf

Dennis LK, Snetselaar LG, Smith BJ, Stewart RE & Robbins MEC (2004) Problems with the assessment of dietary fat in prostate cancer studies. American Journal of Epidemiology. 160(5):436-444.

DGAC (2015) Scientific Report of the 2015 Dietary Guidelines Advisory Committee.

Diabetes UK (2016) Diabetes Prevalence 2015 (November 2015) Available from: https://www.diabetes.org.uk/Professionals/Position-statements-reports/Statistics/diabetes-prevalence-2015/

Dyerberg J, Eskesen DC, Andersen PW, Astrup A, Buemann B, Christensen JH, et al (2004) Effects of trans- and n-3 unsaturated fatty acids on cardiovascular risk markers in healthy males. An 8 weeks dietary intervention study. Eur J Clin Nutr. 58(7):1062-1070.

EFSA (2010) Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids,transfatty acids, and cholesterol. EFSA Journal. 8(3):1461.

Elliott W & Elliott D (2005) Biochemistry and Molecular Biology. Chapter 10: Biochemical mechanisms involved in transport, storage and mobilisation of dietary components. Third Edition ed. Oxford, UK: Oxford University Press.

Ernst E (1999) Diet and Dementia, is there a Link? A Systematic Review. Nutritional Neuroscience. 2(1):1-6.

FAO/WHO (2010) Fats and fatty acids in human nutrition.

Farvid MS, Ding M, Pan A, Sun Q, Chiuve SE, Steffen LM, et al (2014) Dietary linoleic acid and risk of coronary heart disease: A systematic review and meta-analysis of prospective cohort studies. Circulation. 130(18):1568-1578.

Ference B, Ginsberg H, Graham I, Ray K, Packard C, Bruckert E, et al (2017) Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic,

epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 38:2459-2472.

Fogelholm M, Anderssen S, Gunnarsdottir I & Lahti-Koski M (2012a) Dietary macronutrients and food consumption as determinants of long-term weight change in adult populations: a systematic literature review. Food & nutrition research. 56(1):19103.

Fogelholm M, Anderssen S, Gunnarsdottir I & Lahti-Koski M (2012b) Dietary macronutrients and food consumption as determinants of long-term weight change in adult populations: a systematic literature review. Food Nutr Res. 56.

Frayn KN (2009) Metabolic regulation: a human perspective: John Wiley & Sons.

Giau VV, Bagyinszky E, An SS & Kim SY (2015) Role of apolipoprotein E in neurodegenerative diseases. Neuropsychiatric Disease and Treatment. 11:1723-1737.

Ginsberg HN, Karmally W, Siddiqui M, Holleran S, Tall AR, Blaner WS, et al (1995) Increases in dietary cholesterol are associated with modest increases in both LDL and HDL cholesterol in healthy young women. Arterioscler Thromb Vasc Biol. 15(2):169-178.

Ginsberg HN, Karmally W, Siddiqui M, Holleran S, Tall AR, Rumsey SC, et al (1994) A dose-response study of the effects of dietary cholesterol on fasting and postprandial lipid and lipoprotein metabolism in healthy young men. Arterioscler Thromb. 14(4):576-586.

Haggarty P (2010) Fatty Acid Supply to the Human Fetus. Annual review of nutrition. 30(1):237-255.

Haggarty P (2014) Meeting the fetal requirement for polyunsaturated fatty acids in pregnancy. Curr Opin Clin Nutr Metab Care. 17(2):151-155.

Hamley S (2017a) The effect of replacing saturated fat with mostly n-6 polyunsaturated fat on coronary heart disease: a meta-analysis of randomised controlled trials. Nutr J. 16(1):30.

Hamley S (2017b) The effect of replacing saturated fat with mostly n-6 polyunsaturated fat on coronary heart disease: a meta-analysis of randomised controlled trials. Nutr J. 16.

Hannon B, Thompson S, An R & M. T-G (2017a) Clinical Outcomes of Dietary Replacement of Saturated Fatty Acids with Unsaturated Fat Sources in Adults with Overweight and Obesity: A Systematic Review and Meta-Analysis of Randomized Control Trials. Ann Nutr Metab. 71:107-117.

Hannon BA, Thompson SV, An R & Teran-Garcia M (2017b) Clinical Outcomes of Dietary Replacement of Saturated Fatty Acids with Unsaturated Fat Sources in Adults with Overweight and Obesity: A Systematic Review and Meta-Analysis of Randomized Control Trials. Ann Nutr Metab. 71(1-2):107-117.

Harcombe Z, Baker J & Davies B (2017) Evidence from prospective cohort studies does not support current dietary fat guidelines: a systematic review and meta-analysis. Br J Sports Med. 51:1743-1749.

Harcombe Z, Baker JS & Davies B (2016a) Evidence from prospective cohort studies did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review. Br J Sports Med.

Harcombe Z, Baker JS & Davies B (2016a) Evidence from prospective cohort studies does not support current dietary fat guidelines: a systematic review and meta-analysis. British Journal of Sports Medicine.

Harcombe Z, Baker JS, DiNicolantonio JJ, Grace F & Davies B (2016b) Evidence from randomised controlled trials does not support current dietary fat guidelines: a systematic review and meta-analysis. Open Heart. 3(2):e000409.

Harcombe Z, Baker JS, DiNicolantonio JJ, Grace F & Davies B (2016b) Evidence from randomised controlled trials does not support current dietary fat guidelines: a systematic review and meta-analysis. Open Heart. 3(2).

Health and Social Care Information Centre (2016) Statistics on Obesity, Physical Activity and Diet. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/statistics-on-obesity-physical-activity-and-diet-england-2016

Health Council of the Netherlands (2015) Dutch dietary guidelines 2015

Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA & Pettitt DJ (2007) Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. Diabetes Care. 30(9):2287-2292.

Hilson JA, Rasmussen KM & Kjolhede CL (1997) Maternal obesity and breast-feeding success in a rural population of white women. The American journal of clinical nutrition. 66(6):1371-1378.

Hippisley-Cox J, Coupland C & Brindle P (2017) Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 357.

Hooper L, Martin N, Abdelhamid A & Davey Smith G (2015) Reduction in saturated fat intake for cardiovascular disease. The Cochrane database of systematic reviews. 6.

Hooper L, Summerbell CD, Thompson R, Sills D, Roberts FG, Moore HJ, et al (2012) Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane database of systematic reviews (Online). 5.

Howell WH, McNamara DJ, Tosca MA, Smith BT & Gaines JA (1997) Plasma lipid and lipoprotein responses to dietary fat and cholesterol: A meta-analysis. American Journal of Clinical Nutrition. 65(6):1747-1764.

HSE (2017a) Health Survey for England 2016 Adult health trends. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/health-survey-for-england-2016

HSE (2017b) Health Survey for England 2016 Prescribed medicines. Available from: https://files.digital.nhs.uk/pdf/3/c/hse2016-pres-med.pdf

Imamura F, Micha R, Wu JH, de Oliveira Otto MC, Otite FO, Abioye AI, et al (2016) Effects of Saturated Fat, Polyunsaturated Fat, Monounsaturated Fat, and Carbohydrate on Glucose-Insulin Homeostasis: A Systematic Review and Meta-analysis of Randomised Controlled Feeding Trials. PLoS Med. 13(7):e1002087.

Institute of Medicine (2009) National Research Council Committee to Reexamine, I. O. M. Pregnancy Weight Guidelines. In: Rasmussen KM & Yaktine AL, editors. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington (DC): National Academies Press (US). National Academy of Sciences.

IUPAC-IUB Commission on Biochemical Nomenclature (1977) The Nomenclature of Lipids. Recommendations. European Journal of Biochemistry p. 11-21.

Jakobsen U, O'Reilly J, Heitmann L, Pereira A, Bälter K, Fraser E, et al (2009) Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. The American journal of clinical nutrition. 89(5):1425.

Jenkins B, West JA & Koulman A (2015) A review of odd-chain fatty acid metabolism and the role of pentadecanoic Acid (c15:0) and heptadecanoic Acid (c17:0) in health and disease. Molecules. 20(2):2425-2444.

Kinosian B, Glick H, Preiss L & Puder K (1995) Cholesterol and coronary heart disease: predicting risks in men by changes in levels and ratios. J Investig Med. 43:443-450.

Koizumi J, Shimizu M, Miyamoto S, Origasa H & Mabuchi H (2002) Effect of pravastatin-induced LDL-cholesterol reduction on coronary heart disease and cerebrovascular disease in Japanese: Hokuriku lipid coronary heart disease study-pravastatin atherosclerosis trial (Holicos-PAT). J Atheroscler Thromb. 9:251-259.

Lee Y, Back JH, Kim J, Kim SH, Na DL, Cheong HK, et al (2010) Systematic review of health behavioral risks and cognitive health in older adults. International Psychogeriatrics. 22(2):174-187.

Leren P (1966) The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. A controlled clinical trial. . Acta Medica Scandinavia. 466:1-92.

Liu L, Zhuang W, Wang RQ, Mukherjee R, Xiao SM, Chen Z, et al (2011) Is dietary fat associated with the risk of colorectal cancer? A meta-analysis of 13 prospective cohort studies. European Journal of Nutrition. 50(3):173-184.

Makarem N, Chandran U, Bandera V & Parekh N (2013) Dietary fat in breast cancer survival. Annual review of nutrition. 33:319.

McPherson R, Angus C, Murray P, Genest JJ & Investigators. W (2001) Efficacy of atorvastatin in achieving National Cholesterol Education Program low-density lipoprotein targets in women with severe dyslipidemia and cardiovascular disease or risk factors for

cardiovascular disease: The Women's Atorvastatin Trial on Cholesterol (WATCH). Am Heart J. 141:949-956.

Mensink R (2016) Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. .

Mensink RP, Zock PL, Kester AD & Katan MB (2003) Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. The American journal of clinical nutrition. 77(5):1146-1155.

Mente A, de Koning L, Shannon S & Anand S (2009) A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Archives of internal medicine. 169(7):659.

Micha R & Mozaffarian D (2010) Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. Lipids. 45(10):893-905.

Mozaffarian D, Micha R & Wallace S (2010) Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: A systematic review and meta-analysis of randomized controlled trials. PLoS Medicine. 7(3).

Muto M & Ezaki O (2018a) High Dietary Saturated Fat is Associated with a Low Risk of Intracerebral Hemorrhage and Ischemic Stroke in Japanese but not in Non-Japanese: A Review and Meta-Analysis of Prospective Cohort Studies. J Atheroscler Thromb. 25(5):375-392.

Muto M & Ezaki O (2018b) High Dietary Saturated Fat is Associated with a Low Risk of Intracerebral Hemorrhage and Ischemic Stroke in Japanese but not in Non-Japanese: A Review and Meta-Analysis of Prospective Cohort Studies. J Atheroscler Thromb. 25:375-392.

Nelson M, Erens B, Bates B, Church S & Boshier T (2007) Low income diet and nutrition survey.

Newsholme E & Leech T (2010) Functional Biochemistry in Health and Disease. Chapter 4: Transport into the Body: The Gastrointestinal tract, digestion and absorption. Chichester, UK: Wiley-Blackwell.

NICE (2010) Weight management before, during and after pregnancy. [Cited 23 April]. Available from: https://www.nice.org.uk/guidance/ph27/chapter/2-public-health-need-and-practice

Nordic Council of Ministers (2012) Nordic Nutrition Recommendations 2012: Nordic Council of Ministers.

ONS (2016) Deaths registered in England and Wales (Series DR): 2015.

Patarrão RS, Wayne Lautt W & Paula Macedo M (2014) Assessment of methods and indexes of insulin sensitivity. Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo. 9(1):65-73.

Patterson C, Feightner J, Garcia A & MacKnight C (2007) General risk factors for dementia: a systematic evidence review. Alzheimers Dement. 3(4):341-347.

Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. J Intern Med. 256(3):183-194.

Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al (2007) Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 30(6):1374-1383.

Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al (2006) Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. Jama. 295(6):629-642.

Qiu C, De Ronchi D & Fratiglioni L (2007) The epidemiology of the dementias: an update. Curr Opin Psychiatry. 20(4):380-385.

Ramsden CE, Zamora D, Leelarthaepin B, Majchrzak-Hong SF, Faurot KR, Suchindran CM, et al (2013) Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ. 346:e8707.

Ramsden CE, Zamora D, Majchrzak-Hong S, Faurot KR, Broste SK, Frantz RP, et al (2016) Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). BMJ. 353:i1246.

Rasmussen BM, Vessby B, Uusitupa M, Berglund L, Pedersen E, Riccardi G, et al (2006) Effects of dietary saturated, monounsaturated, and n-3 fatty acids on blood pressure in healthy subjects. Am J Clin Nutr. 83(2):221-226.

Roberts C, Steer T, Mapelthorpe N, Cox L, Meadows S, Nicholson S, et al (2018) National Diet and Nutrition Survey, Results from Years 7 and 8 (combined) of the Rolling Programme (2014/2015 to 2015/2016).

SACN (2003) Salt and Health The Stationery Office (TSO). Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338782/SACN_Salt_and_Health_report.pdf

SACN (2012) SACN framework for the evaluation of evidence. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/480493/SACN_Framework_for_the_Evaluation_of_Evidence.pdf

SACN (2015) Carbohydrates and Health The Stationery Office. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf

Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 375(9733):2215-2222.

Schwab U, Lauritzen L, Tholstrup T, Haldorssoni T, Riserus U, Uusitupa M, et al (2014) Effect of the amount and type of dietary fat on cardiometabolic risk factors and risk of developing type 2 diabetes, cardiovascular diseases, and cancer: a systematic review. Food & nutrition research. 58.

Siri-Tarino PW, Sun Q, Hu FB & Krauss RM (2010) Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. American Journal of Clinical Nutrition. 91(3):535-546.

Skeaff CM & Miller J (2009) Dietary fat and coronary heart disease: Summary of evidence from prospective cohort and randomised controlled trials. Annals of Nutrition and Metabolism. 55(1-3):173-201.

Smith-Warner A, Ritz J, Hunter J, Albanes D, Beeson WL, van AP, et al (2002) Dietary fat and risk of lung cancer in a pooled analysis of prospective studies. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 11(10):987.

Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, Van PAB, Folsom AR, et al (2001) Types of dietary fat and breast cancer: A pooled analysis of cohort studies. International Journal of Cancer. 92(5):767-774.

Sprecher H (2002) The roles of anabolic and catabolic reactions in the synthesis and recycling of polyunsaturated fatty acids. Prostaglandins, Leukotrienes and Essential Fatty Acids. 67(2):79-83.

Stampfer M, Sacks F, Salvini S, Willett W & Hennekens C (1991) A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. N Engl J Med. 325:373-381.

Stuebe AM, Oken E & Gillman MW (2009) Associations of diet and physical activity during pregnancy with risk for excessive gestational weight gain. Am J Obstet Gynecol. 201(1):58.e51-58.

Tang JL, Armitage JM, Lancaster T, Silagy CA, Fowler GH & Neil HAW (1998) Systematic review of dietary intervention trials to lower blood total cholesterol in free-living subjects. British Medical Journal. 316(7139):1213-1219.

Tariq S, Sidys M, Toth P & Boden W (2014) HDL hypothesis: where do we stand now? Curr Atheroscler Rep. 14.

Te Morenga L & Montez J (2017a) Health effects of saturated and trans-fatty acid intake in children and adolescents: Systematic review and meta-analysis. . PLoS ONE. 12.

Te Morenga L & Montez JM (2017b) Health effects of saturated and trans-fatty acid intake in children and adolescents: Systematic review and meta-analysis. PLoS One. 12(11):e0186672.

Tielemans J, Garcia H, Peralta Santos A, Bramer M, Luksa N, Luvizotto J, et al (2016) Macronutrient composition and gestational weight gain: a systematic review. The American journal of clinical nutrition. 103(1):83.

Turner B (2011) A meta-analysis of fat intake, reproduction, and breast cancer risk: an evolutionary perspective. American journal of human biology : the official journal of the Human Biology Council. 23(5):601.

Uusitalo U, Arkkola T, Ovaskainen ML, Kronberg-Kippila C, Kenward MG, Veijola R, et al (2009) Unhealthy dietary patterns are associated with weight gain during pregnancy among Finnish women. Public Health Nutr. 12(12):2392-2399.

Van Horn L, McCoin M, Kris-Etherton M, Burke F, Carson SA, Champagne M, et al (2008) The evidence for dietary prevention and treatment of cardiovascular disease. Journal of the American Dietetic Association. 108(2):287.

Wakai K, Naito M, Date C, Iso H & Tamakoshi A (2014) Dietary intakes of fat and total mortality among Japanese populations with a low fat intake: the Japan Collaborative Cohort (JACC) Study. Nutr Metab (Lond). 11(1):12.

WCRF (2014) World Cancer Research Fund UK Annual Report 2014-2015.

Whalley LJ, Deary IJ, Starr JM, Wahle KW, Rance KA, Bourne VJ, et al (2008) n-3 Fatty acid erythrocyte membrane content, APOE varepsilon4, and cognitive variation: an observational follow-up study in late adulthood. American Journal of Clinical Nutrition. 87(2):449-454.

WHO (2006) Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia.

WHO (2007a) Prevention of Cardiovascular Disease, Guidelines for assessment and management of cardiovascular risk. Available from: http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf

WHO (2011) Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Available from: http://www.who.int/diabetes/publications/report-hba1c_2011.pdf?ua=1

WHO (2016) Global Health Observatory (GHO) data; Raised blood pressure. Available from: http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/

WHO Expert Panel on Detection E, and Treatment of High Blood Cholesterol in Adults, (2001) Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama. 285(19):2486-2497.

Woodhill J, Palmer A, Leelarthaepin B, McGilchrist C & Blacket R (1978) Low fat, low cholesterol diet in secondary prevention of coronary heart disease. . Advances in Experimental Medicine and Biology. 109:317-330.

Xia H, Ma S, Wang S & Sun G (2015) Meta-Analysis of Saturated Fatty Acid Intake and Breast Cancer Risk. Medicine. 94(52).

Xu C, Han FF, Zeng XT, Liu TZ, Li S & Gao ZY (2015a) Fat intake is not linked to prostate cancer: A systematic review and dose-response meta-analysis. PLoS ONE. 10(7).

Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al (2015b) Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 86(12):1299-1306.

Yao X & Tian Z (2015) Saturated, monounsaturated and polyunsaturated fatty acids intake and risk of pancreatic cancer: Evidence from observational studies. PLoS ONE. 10(6).

Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S & Kris-Etherton PM (1999) Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: A meta-analysis. American Journal of Clinical Nutrition. 69(4):632-646.

Yu JT, Tan L & Hardy J (2014) Apolipoprotein E in Alzheimer's disease: an update. Annual Review of Neuroscience. 37:79-100.

Annexes

ANNEX 1: Search terms

	Embase	Medline	Cochrane	Scopus
fats	*SATURATED FAT/ OR *SATURATED FATTY ACID/ saturate* AND (fat* or "fatty acid*" or lipid*)	saturate* AND (fat* or "fatty acid*" or lipid*)	saturated AND (fat* or "fatty acid*" or lipid*)	saturated AND (fat* or "fatty acid*" or lipid*)
sources	(saturat* OR type* OR source* OR animal OR dairy) ADJ2 (fat* OR lipid* OR "fatty acid*")	(saturat* OR type* OR source* OR animal OR dairy) ADJ2 (fat* OR lipid* OR "fatty acid*")	(saturat* OR type* OR source* OR animal OR dairy) NEAR (fat* OR lipid* OR "fatty acid*")	(saturat* OR type* OR source* OR animal OR dairy) W/2 (fat* OR lipid* OR "fatty acid*")
study type filters (terms)	SYSTEMATIC REVIEW/			
	systematic ADJ2 (review* or overview*)	systematic ADJ2 (review* or overview*)		systematic W/2 (review* or overview*)
	META-ANALYSIS/			
	"meta analys*" or meta-analys*	"meta analys*" or meta-analys*		"meta analys*" or meta-analys*
	pooled ADJ (analys* OR mean OR estimate*)	pooled ADJ (analys* OR mean OR estimate*)		pooled W/0 (analys* OR mean OR estimate*)
study type filters (database)			Cochrane reviews	
			other reviews	
date filter	1991-current	1991-current	1991-current	1991-current

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Cardiovascular diseases

Table A2.1 Characteristics of meta-analyses and systematic reviews

Study	Research methods	Analysis	Results	Comments
Muto & Ezaki (2018a) (systematic review with meta-analysis) Funding source: Not reported Declarations of interest: A lecture fee from ONO Pharmaceutical Co Ltd	Research question Examine the association between saturated fats and the risks to stroke subtypes in PCS separated by ethnic Japanese and non-Japanese Selection criteria *Search dates:* inception to 3 March 2016 *Study design:* PCS *Inclusion criteria:* cohort design used to examine the association between the intake of saturated fats and the incidence of death of intracerebral haemorrhage or ischemic stroke, CT, MRI or autopsy findings were used for diagnosis. Studies on mortality in which stroke was classified by death certificate were also included if they were conducted since the 1980s when CT or MRI became available. *Exclusion criteria:* total stroke (if hemorrhagic and ischemic strokes were not separated). Stroke diagnosis by clinical image and not on CT or MRI. Dietary assessment method FFQ, 24-hr recall	Analysis Random-effects model was used except when the number of samples was 2 and then fixed-effects model was used. Evaluation of study quality Publication bias measured by Egger's test.	11 PCS; n= 423,870 (range 832 to 87,025); duration: 7.6 to 20y; age: 35 to 83y; sex: M (2), W (3), M/W (6); country: Japan (5), USA (4), Sweden (2). Primary outcome Hemorrhagic stroke (5 PCS; n=265,593; strokes n=2538) HR 0.69 (95% CI 0.48 to 1.0) p=0.048, I^2=58% Ischaemic stroke (11 PCS; n=419,095; strokes n=5,365) HR 0.89 (95% CI 0.82 to 0.96) p=0.004, I^2=39% Secondary outcome Hemorrhagic stroke Japanese: ↓ in hemorrhagic stroke risk with higher saturated fat intake (3 PCS; n=145,159; stroke n=2231) HR 0.55 (95% CI 0.32 to 0.94) p=0.03, I^2=67% Non-Japanese: no association (2 PCS; n=120,434; stroke n=307) HR 0.98 (95%CI 0.62 to 1.53) p=0.91, I^2=38% Ischaemic stroke Japanese: ↓ in ischemic stroke risk with higher saturated fat intake (4 PCS; n=146,398; stroke n=82,387) HR 0.82 (95%CI 0.71 to0.93) p=0.003, I^2=19% Non-Japanese: no association (7 PCS; n=272,697, stroke n=4015) HR 0.93 (95%CI 0.84 to 1.03) p=0.17, I^2=42%	Findings suggest that a high intake of saturated fats was associated with a reduction in hemorrhagic and ischaemic stroke. In the secondary analysis there was an association between high intake of saturated fats and reduced risk of hemorrhagic and ischaemic stroke in Japanese participants living in Japan only. Limitations Differences in dietary patterns and stroke aetiology in Japanese populations living in Japan.

Study	Research methods	Analysis	Results	Comments
Hamley (2017a) (meta-analysis) Funding source: Not applicable Declaration of interest: None declared	Research question To account for the differences not related to saturated fats or mostly n-6 PUFA intake in the diet heart trials and to emphasise the results from those trials that most accurately test the effect of replacing saturated fats with mostly n-6 PUFA Selection criteria *Search dates:* (trials taken from previous meta-analyses) *Study design:* RCTs *Inclusion criteria:* trials that reported on CHD events, CHD mortality or total mortality and substituting saturated fats with mostly n-6 PUFA *Exclusion criteria:* trials that did not have an intervention group that had a simultaneous decrease in saturated fats and increase in PUFA of at least 20% Dietary assessment methods Not reported	Analysis Random effects model was used to calculate RR for: overall pooled effect for all trials; the adequately randomised trials; the adequately controlled trials; the inadequately controlled trials; the adequately controlled trials where Sydney Diet Heart Study (SDHS) was excluded in a sensitivity analysis (due to unknown intake of trans fats). Evaluation of study quality PRISMA	11 RCTs; n=26,054; age 30 to >70y; sex: M(7), W(0), M/W(3). Major CHD events (includes myocardial infarction and sudden death) 1069 major CHD events (inc MI and sudden death) in 17077 participants Adequately controlled trials (n=5)[35] RR 1.06 (95% CI 0.86 to 1.31) p=0.59, I^2=46% Sensitivity analysis (excluding SDHS) RR 0.98 (95% CI 0.83 to1.16) p=0.80, I^2=not reported Inadequately controlled trials (n=6)[36] RR 0.64 (95% CI 0.47 to 0.87) p=0.004, I^2=38% All trials RR 0.87 (95% CI 0.70 to 1.07) p=0.19, I^2=60% Total CHD events (also includes angina) 1349 total CHD events in 17072 participants Adequately controlled trials (n=5) RR 1.02 (95% CI 0.84 to 1.23) p=0.85, I^2=45% Sensitivity analysis (excluding SDHS) RR 0.95 (95% CI 0.83 to 1.09) p=0.45, I^2=not reported Inadequately controlled trials (n=6) RR 0.60 (95 %CI 0.46 to 0.79) p=0.0002, I^2=59% All trials RR 0.80 (95%CI 0.65 to 0.98) p=0.03, I^2=72% CHD mortality 924 deaths in 24022 participants Adequately controlled trials (n=5)	Findings suggest that there is no effect of substituting saturated fats with mainly n-6 PUFA on CHD events, CHD mortality or total mortality from adequately controlled trials. When all trials are pooled together there is an effect of substituting saturated fats with n-6 PUFA on total CHD events, but not major CHD events, CHD mortality or total mortality.

[35] Definition of 'adequately controlled': most accurately test the effect of replacing SFA with mostly n-6 PUFA (Rose Corn Oil Trial (RCOT), Medical Research Council Trial (MRCT), Sydney Diet Heart Study (SDHS), Minnesota Coronary Survey (MCS), Diet and Reinfarction Trial (DART)

[36] Definition of 'inadequately controlled': have too many dietary and/or non-dietary differences between the groups to be considered a valid test of replacing SFA with mostly n-6 PUFA

Study	Research methods	Analysis	Results	Comments
			RR 1.13 (95%CI 0.91 to 1.40) p=0.29, I^2=19% Sensitivity analysis (excluding SDHS) RR 1.04 (95% CI 0.85 to 1.27) p=0.71, I^2=not reported Inadequately controlled trials (n-=5) RR 0.66 (95%CI 0.54 to 0.81) p<0.0001, I^2=11% All trials RR 0.90 (95%CI 0.70 to1.17) p=0.43, I^2=65% <u>Total mortality</u> 2614 deaths in 24022 participants Adequately controlled trials RR 1.07 (95%CI 0.90 to 1.26) p=0.45, I^2=23% Inadequately controlled trials RR 0.95 (95%CI 0.82 to 1.10) p=0.48, I^2=35% All trials RR 1.00 (95%CI 0.90 to 1.10) p=0.99, I^2=26%	

Study	Research methods	Analysis	Results	Comments
Harcombe et al, (2017) (systematic review with meta-analysis) Funding source Not reported Declarations of interest: ZH receives income from writing and from two small self-employment businesses: The Harcombe Diet Co. and Columbus Publishing.	Research question To re-examine the totality of PCS evidence relating to the current dietary fat guidelines. Selection criteria *Search dates:* Inception to 30 September 2015 *Study design:* PCS *Inclusion criteria:* prospective cohort studies, participants were human adults, primary study outcome was CHD mortality, data related to dietary fat consumption were available, data on CHD mortality and serum cholesterol measurements were available. *Exclusion criteria:* clinical trials, cross-sectional studies, case-control studies Dietary assessment method Not reported	Analysis Random-effects meta-analysis. Evaluation of study quality Publication bias was estimated using Funnel plot and Egger's regression intercept	7PCS; n=89,801; 2024 CHD deaths; duration: 6-20y; age: 30-79y; sex: M (4), M/W (3). Primary outcome *CHD mortality:* no association (7 PCS) RR 1.08 (95% CI 0.94 to 1.25) p=0.265	Authors suggest that epidemiological evidence to date found no significant difference in CHD mortality and saturated fat intake thus does not support the present dietary fat guidelines. The evidence per se lacks generalisability for population-wide guidelines. Limitations Currently available epidemiological evidence lacks generalisability. Unreliable dietary information collection methods.

Study	Research methods	Analysis	Results	Comments
Cheng et al, (2016) (systematic review with meta-analysis) Funding source: Supported by a grant from the National Natural Science Foundation of China Declaration of interest: None declared	Research question To conduct a meta-analysis to summarise the available evidence on the relationship between saturated fat intake and stroke risk. Selection criteria *Search dates:* Up to 2016 *Study design:* PCS *Inclusion criteria:* PCS study design; relative risks (RRs) and their corresponding 95% CIs of stroke relating to saturated fat intake were provided; (3) covariates (such as alcohol, smoking, and blood pressure) were controlled in the multivariate analysis; only the most recent publication, or the one with the longest follow-up period, was included when duplicate reports based on the same cohort occurred. *Exclusion criteria:* non prospective cohort study design; reviews; non-human studies; conference abstracts or reports lacking of RRs and the corresponding 95 % CIs of stroke relating to saturated fats intake. Dietary assessment methods FFQ, 24-hr recall, diet history method	Analysis Random-effects model was used except when I^2 <50% then fixed-effects model was used. Evaluation of study quality Sensitivity analysis was conducted to detect potential bias of studies in the meta-analysis. Publication bias assessed by using funnel plots and Egger's test.	15 PCS; n=476,569 (range 832 to 87,025); stroke = 11,074; duration: 7.6 to 23 years; age: 20 to 89 years; sex: M (5), W (3), M/W (7); country: USA (5), Japan (5), Sweden (2), Israel (1), UK (1), Greece (1). **Primary outcome** Overall stroke: ↓ with higher saturated fat intake (15 PCS) RR = 0.89 (95% CI 0.82 to 0.96) p=0.002, I^2=37.4% Fatal stroke: ↓ with higher saturated fat intake (4 PCS) RR 0.75 (95% CI 0.59 to 0.94) p=0.014, I^2=0% **Subgroup analysis** East Asian: ↓ stroke risk with higher saturated fat intake (6 PCS) RR = 0.79 (95% CI 0.69 to 0.90) p=0.001, I^2=42.4% Non East Asian: no association (9 PCS) RR = 0.94 (95% CI 0.86 to 1.02) p=0.143, I^2= 17.2% Dose <25g/day: ↓ stroke risk with higher saturated fat intake (6 PCS) RR=0.81 (95% CI 0.71 to 0.92) p=0.001, I^2=45.3% Dose ≥ 25g/day: no association (5 PCS) RR 1.02 (95% CI 0.89 to 1.15) p=0.808, I^2=2.7% Men: ↓in stroke risk with higher saturated fat intake (6 PCS) RR 0.85 (95% CI 0.75 to 0.96) p=0.008, I^2=0% Women: no association (4 PCS) RR = 1.04 (95% CI 0.91 to 1.18) p=0.587, I^2=0% BMI<24 kg/m^2: ↓in stroke risk with higher saturated fat intake (5 PCS) RR – 0.75 (95% CI 0.65 to 0.87) p<0.001, I^2=34.1% BMI ≥ 24 kg/m^2: no association (5 PCS) RR = 0.94 (95% CI 0.84 to 1.04) p=0.212, I^2=41.5%	Findings suggest that higher saturated fat intake reduces the risk of overall stroke and fatal stroke. Subgroup analysis suggests that higher saturated fat intake was associated with reduced risk of stroke in East Asian populations living in East Asia, in populations with doses ≤ 25g/day, men and in participants with BMI <24 kg/m^2. Limitations Possibility of differing degrees of adjustment for potential confounders in each study included in the meta-analysis. Midpoint of BMI 24kg/m^2 was used, as the upper limit of normal BMI for Asian populations is 23 kg/m^2, and an upper limit of normal BMI issued by WHO guidelines is 25 kg/m^2.

Study	Research methods	Analysis	Results	Comments
Harcombe et al (2016a) (Systematic review) Funding source None declared. Declarations of interest Z Harcombe: receives income from writing and from two small self-employment businesses: The Harcombe Diet Co and Columbus Publishing.	Research question Assess if the published prospective cohort studies available to the dietary committees supported their recommendations on dietary fat. Selection criteria *Search dates:* Up to 5 September 1983. *Study design:* PCS. *Inclusion criteria:* Participants were human adults; primary study outcome was CHD mortality; data related to dietary fat consumption were available; data on CHD mortality and serum cholesterol measurements were available. *Exclusion criteria:* Clinical trials, cross-sectional studies, case-control studies. Dietary assessment method Not reported.	Analysis Available data did not allow a meta-analysis. Evaluation of study quality Author judgement for each study on whether: cohort appropriately reflected wider population; blinding of outcome assessment; incomplete outcome data; selective reporting.	6 PCS; n=31,445 (range 337 to 12,770); duration: 4 to 20y (mean 7.5±6.2y (weighted mean [person years by participants] 5.6±0.8y)); age: 30 to 67y; sex: men only; health at baseline: without previous heart disease (5), with previous heart disease (1); country: USA (2), UK (1), Puerto Rico (1), multi-country (2). CHD mortality 360 deaths from CHD (1.14%), mean follow-up 7.5±6.2y. 1 PCS found statistically significant association between CHD deaths and saturated fat intake.	No prospective cohort study available to dietary guideline committees found any association between saturated fat intake and deaths from heart disease in the same population. Limitations All evidence was undertaken on men. Evidence available at the time could not be generalised to women.

Study	Research methods	Analysis	Results	Comments
Harcombe et al (2016b) (Systematic review with meta-analysis) <u>Funding source</u> None declared. <u>Declarations of interest</u> None declared.	<u>Research question</u> To extend the Harcombe et al, (2015) report, and re-examine the totality of RCT evidence relating to the current dietary fat guidelines. <u>Selection criteria</u> *Search dates:* Not specified. *Study design:* RCTs *Inclusion criteria:* Randomised dietary intervention study; study hypothesis relating to a reduction or modification of dietary fat; participants were human adults; study was a minimum of 1 year in duration; primary study outcome was all-cause and CHD mortality; data on all-cause mortality, CHD mortality, and cholesterol measurements were available. *Exclusion criteria:* Study being observational; non-randomised and/or multi factorial in design. <u>Dietary assessment method</u> Not reported.	<u>Analysis</u> Random-effects meta-analysis. Heterogeneity and bias: I^2 and T^2 calculations. Publication bias: Funnel plot methodology and Effer's regression intercept were calculated. <u>Evaluation of study quality</u> Risk of bias assessed using the Cochrane Collaboration assessment tool for selection bias, performance/detection bias, attrition bias, and reporting bias. Sensitivity analysis of the exclusion of any one study.	10 RCTs; n=62,421; duration: 2 to 11y (mean 4.7±3.3y(weighted mean [person years by participants] 6.8±2y)); age: 30 to 70y; sex: M(8), W(1), M/W(1); health at baseline: primary and secondary prevention (2), primary prevention (1), secondary prevention (7); country: USA (3), UK (5), Norway (1), Australia (1). 6 RCTs did not examine total fat or saturated fat intakes of 30% and 10% of total energy respectively. 4 RCTs examined vegetable oil. 2 RCTs examined a diet of 10% energy as saturated fat (higher incidence of total and CHD mortality in intervention group in 1 RCT; no difference in total and CHD mortality in 1 RCT). <u>CHD mortality: no effect</u> 1218 deaths from CHD. RR 0.98 (95% CI 0.88 to 1.08); Q-value=9.173; I^2=0.000; T^2=0.000. Excluding Women's Health Initiative (78% of the total participants, n=13,586), RR 0.96 (95% CI 0.85 to 1.09)	RCT evidence does not support the current dietary fat guidelines. The reduction in serum cholesterol does not appear to translate into an improved survival from CHD.

Study	Research methods	Analysis	Results	Comments
Ramsden et al (2016) (Systematic review and meta-analysis) <u>Funding source</u> US Public Health Service; National Heart Institute; The Intramural Program of the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health; University of North Carolina Program on Integrative Medicine (National Institutes of Health). <u>Declarations of interest</u> None declared.	<u>Research question</u> Does replacement of saturated fat with linoleic acid rich vegetable oils decrease CHD and all-cause mortality by reducing serum LDL and total cholesterol? <u>Selection criteria</u> *Search dates:* 1950 to September 2015. *Study design:* RCTs. *Inclusion criteria:* Serum cholesterol-lowering RCTs published in English that: randomised participants; provided linoleic acid rich vegetable oil intervention in place of saturated fats, compared to usual care control diet; not confounded by addition of large quantities of n-3 EPA and DHA or other major concomitant interventions (e.g. complex dietary pattern changes) or unequal intensity of medical management (e.g. smoking cessation advice or blood pressure control); reported deaths due to CHD or all causes. *Exclusion criteria*: Excluded from main analysis, studies that: provided large quantities of EPA and DHA or advice only without provision of linoleic acid rich oils; only provided biochemical or intermediate endpoints. Sensitivity analyses included studies in: 1) exclusion criteria that otherwise met the inclusion and exclusion criteria.	<u>Analysis</u> Pooled risk estimates calculated for CHD death using random effects model. Heterogeneity: I^2 statistic and Tau-squared, and stratification by study oil. Publication bias: funnel plot visual inspection of treatment effect vs standard error. Sources of heterogeneity explored using stratified fixed effects meta-analysis (PUFA) and inverse variance weighted meta-regression (between group cholesterol reduction and increases in dietary linoleic acid). <u>Evaluation of study quality</u> Considerations included: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessments; selective reporting; systematic differences in between-group medical care; study-specific sources of potential bias.	5 RCTs; n=10,808; duration: ≤2 to ≤7y; age: not reported; sex: M (4), W (0), M/W (1); health at baseline: with or without CHD (2), history of CHD (3); country: USA (2), UK (2), Australia (1). <u>Saturated fats substitution with linoleic acid or linoleic acid-rich vegetable oil</u> The mean change in serum cholesterol concentration in RCTs ranged from 7.8-13.8% lower in the intervention vs. the control groups. *CHD Mortality:* no effect (5 RCTs) HR 1.13 (95% CI 0.83 to 1.54) I^2 = 45.1% *Provision or advice to replace saturated fats with linoleic acid rich oils, with or without confounding by n-3 EPA+DHA* (8 RCTs) *CHD mortality:* no effect (8 RCTs) HR 1.00 (95% CI 0.81 to 1.24) I^2 = 37.5%	Replacement of saturated fat in the diet with linoleic acid lowers serum cholesterol but does not lower risk of death from CHD. <u>Limitations</u> Small number of RCTs; one trial (Minnesota Coronary Experiment) accounted for about 80% of participants; differences in methodological quality and design and population characteristics of individuals in trials.

Study	Research methods	Analysis	Results	Comments
	Dietary assessment method Not reported.			

Study	Research methods	Analysis	Results	Comments
de Souza et al (2015) (Systematic review with meta-analysis) <u>Funding source</u> World Health Organization. <u>Declarations of interest</u> RJ de Souza: received a Canadian Institutes for Health Research postdoctoral fellowship. V Ha: received a Province of Ontario graduate scholarship and research support from the Canadian Institutes for Health Research. AI Cozma: received a Province of Ontario graduate scholarship.	<u>Research question</u> Systematically review associations between saturated fat and trans fats intake and total mortality, CVD and associated mortality, CHD and associated mortality, ischemic stroke, type 2 diabetes. <u>Selection criteria</u> *Search period*: Up to 1 May 2015. *Study design:* observational studies. *Inclusion criteria*: Observational studies in humans; report a measure of association between intakes of saturated fats or trans fats (measured by self-report or a biomarker) and total mortality, CVD and associated mortality, CHD and associated mortality, ischemic stroke, T2DM (measured by self-report and/or confirmed by medical records or registry linkage). *Exclusion criteria*: Not reported. <u>Dietary assessment methods</u> FFQ, SQFFQ, 24 hr recall, dietary recall, 7 day food diary, weighted food diary, diet history, 4 day prospective diet record, cross check diet history method.	<u>Analysis</u> Principle association measures were RRs between highest and lowest intakes. ≥ 2 studies a random effects meta-analysis was performed. ≤ 3 studies fixed effect estimates also considered. Heterogeneity: Cochran's Q test (significant at P<0.10), quantified with the I^2 statistic. If ≥ 10 studies and substantial heterogeneity (I^2 > 60% or P_Q < 0.10) Meta-regression was used to explore heterogeneity. <u>Evaluation of study quality</u> The Newcastle-Ottawa scale was used to measure the risk of bias of included studies. The GRADE approach was used to assess confidence in the effect estimates derived from the body of evidence.	41 PCS; n= 90,501 to 339,090; duration: 1 to 32y; age 15 to 89y; sex: not reported; health at baseline: healthy; country: US (17), UK (4), Japan (4), Sweden (4), Israel (1), Finland (3), Denmark (1), Canada (1), China (1), Greece (1), Australia (1). <u>Highest vs lowest saturated fat intake</u> *CVD mortality:* no association (3 PCS) Most adjusted RR 0.97 (95% CI 0.84 to 1.12) p=0.69; I^2=19% Least adjusted RR 0.97 (95% CI 0.84 to 1.12) p=0.69; I^2=19% *Total CHD*: no association (12 PCS 17 comparisons - 3 could not be included in analysis) Most adjusted RR 1.06 (95% CI 0.95 to 1.17) p=0.29; I^2=47% Least adjusted RR 1.12 (95% CI 1.00 to 1.26) p=0.05; I^2=63% Risk estimates for 3 comparisons could not be extracted and so those reported in another meta-analysis were used; when removed RR 1.08 (95% CI 0.97 to 1.20) p=0.18; I^2=51%, P_{het}=0.01. *CHD mortality:* no association (11 PCS 15 comparisons) Most adjusted RR 1.15 (95% CI 0.97 to 1.36) p=0.10; I^2=70% Least adjusted RR 1.20 (95% CI 1.02 to 1.41; P=0.02; I^2=74% Risk estimates for 4 comparisons could not be extracted and so those reported in another meta-analysis were used; when removed RR 1.26 (95% CI 0.98 to 1.62) p=0.07; I^2=74% RR shifted to 1.20 (95% CI 1.01 to 1.42) p=0.04; I^2=68%, when 2 comparisons were removed.	Saturated fat intake is not associated with total mortality, CVD, CHD, stroke or type 2 diabetes, but the evidence considered is heterogeneous with methodological limitations. <u>Limitations</u> Comparison of higher fat and lower fat obscures the importance of reciprocal and possibly heterogeneous decreases in other macronutrients that accompany high saturated fat intake. Most studies did not model the effect of nutrient substitution.

Study	Research methods	Analysis	Results	Comments
Hooper et al (2015) (Systematic review and meta-analysis) <u>Funding source</u> L Hooper: Studentship, Systematic Reviews Training, Institute of Child Health, University of London, UK. <u>Declarations of interest</u> None declared.	<u>Research question</u> What is the effect of reducing saturated fat intake and replacing it with carbohydrate, PUFA, MUFA and/or protein on mortality and cardiovascular morbidity? <u>Selection criteria</u> *Search dates:* July 2010 to March 2014 (plus search from Hooper 2012 – inception to June 2010). *Study design:* RCTs only. *Inclusion criteria:* >18yrs at any risk of CVD, with/without existing CVD, using/not using lipid-lowering medication; aim to reduce saturated fat intake or alter dietary fats and achieve reduction in saturated fats; intervention dietary advice, supplementation of fats, oils or modified or low-fat foods or a provided diet and the control group usual diet, placebo or a control diet; duration ≥ 24 months; mortality or cardiovascular morbidity data available; no language restrictions. *Exclusion criteria*: Pregnant, acutely ill or breastfeeding subjects; allocation not truly randomised; multifactorial trials. <u>Dietary assessment methods</u> Not reported.	<u>Analysis</u> Random effects meta-analysis to assess risk ratios. Low vs high % of energy from saturated fats. Incremental changes in % of energy from saturated fats. *Subgroup analysis* Saturated fats substitution with PUFA, MUFA, carbohydrate or protein. <u>Evaluation of study quality</u> Cochrane 'risk of bias' tool used. Additional characteristics assessed include: studies being free of systematic differences in care, a study aiming to reduce saturated fat intake, achieving saturated fats reduction, and achieving total serum cholesterol reduction. Evidence assessed using GRADE system, sensitivity analyses, and heterogeneity examined using I^2 test.	12 RCTs; n=59,000; duration: 2 to >8y; age: 45-66y; sex: M(7), W(3), M/W(5); health at baseline: with or without CVD; country: USA (7), Europe (8), Australia/New Zealand (2). <u>Lowest saturated fat compared with usual saturated fat</u> *CVD mortality:* no effect (10 RCTs) RR 0.95 (95% CI 0.80 to 1.12), p=0.51; I^2=30% (Random-effects) RR 0.95 (95% CI 0.85 to 1.07), p>0.05; I^2=30% (Mantel-Haenszel fixed-effects) RR 0.95 (95% CI 0.84 to 1.08), p>0.05; I^2=41% (Peto fixed-effects) *CVD events:* ↓ events with lower saturated fat intake (11 RCTs) RR 0.83 (95% CI 0.72 to 0.96), p=0.01; I^2=65% (Random effects) RR 0.93 (95% CI 0.88 to 0.98), p<0.05; I^2=65% (Mantel-Haenszel fixed-effects) RR 0.92 (95% CI 0.86 to 0.98), p<0.05; I^2=72% (Peto fixed-effects) *Myocardial infarction (MI) (fatal and non-fatal):* no effect (11 RCTs) RR 0.90 (95% CI 0.80 to 1.01), p=0.90; I^2=10% (Random-effects) RR 0.92 (95% CI 0.84 to 1.01), p>0.05; I^2=10% (Mantel-Haenszel fixed-effects) RR 0.92 (95% CI 0.83 to 1.01), p>0.05; I^2=31% (Peto fixed-effects) *Non-fatal MI:* no effect (9 RCTs) RR 0.95 (95% CI 0.80 to 1.13), p=0.57; I^2 =27% (Random-effects) RR 0.94 (95% CI 0.85 to 1.05), p>0.05; I^2=27% (Mantel-Haenszel and Peto fixed-effects) *CHD mortality:* no effect (10 RCTs) RR 0.98 (95% CI 0.84 to 1.15), p=0.78; I^2 =21% (Random-effects) RR 0.98 (95% CI 0.86 to 1.12), p>0.05; I^2 =21% (Mantel-Haenszel fixed-effects)	Findings suggest reduction in risk of CVD and CHD events on reduction of saturated fat intake. Replacing energy from saturated fats with PUFA appears to be a useful strategy but replacement with carbohydrate appears to be less useful. Effects of replacement with MUFA unclear due to inclusion of only one trial. <u>Limitations</u> Although the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched, due to limited resources, filters were applied to limit to core clinical journals (MEDLINE) and priority journals (EMBASE). .

Study	Research methods	Analysis	Results	Comments
			RR 0.98 (95% CI 0.85 to 1.13), p>0.05; I^2=21% (Peto fixed-effects) *CHD events:* ↓ events with lower saturated fat intake (12 RCTs) RR 0.87 (95% CI 0.74 to 1.03), p=0.07; I^2=66% (Random-effects) RR 0.93 (95% CI 0.87 to 0.99), p<0.05; I^2=66% (Mantel-Haenszel fixed-effects) RR 0.92 (95% CI 0.86 to 0.99), p<0.05; I^2=72% (Peto fixed-effects) *Strokes (any type, fatal or non-fatal)*: no effect (7 RCTs) RR 1.00 (95% CI 0.89 to 1.12), p>0.05; I^2=0% (Random-effects) RR 0.99 (95% CI 0.89 to 1.11), p>0.05; I^2=0% (Mantel-Haenszel fixed-effects) RR 0.99 (95% CI 0.88 to 1.13), p>0.05; I^2=18% (Peto fixed-effects) <u>Subgroup analysis</u> <u>Substitution of saturated fats with PUFA (Random-effects)</u> *CVD mortality:* no effect (7 RCTs) RR 0.95 (95% CI 0.73 to 1.25), p>0.05; I^2=55% *CVD events:* ↓ events (7 RCTs) RR 0.73 (95% CI 0.58 to 0.92), p<0.05; I^2=69% *Fatal or non-fatal MI:* no effect (10 RCTs) RR 0.83 (95% CI 0.67 to 1.02); I^2=29% *Non-fatal MI:* no effect (10 RCTs) RR 0.80 (95% CI 0.63 to 1.03); I^2=0% *CHD mortality:* no effect (10 RCTs) RR 0.98 (95% CI 0.74 to 1.28); I^2=49% *CHD events:* ↓ events (10 RCTs) RR 0.76 (95% CI 0.57 to 1.00); I^2=71% *Strokes (any type, fatal or non-fatal):* no effect (4 RCTs) RR 0.68 (95% CI 0.37 to 1.27); I^2 =0% <u>Substitution of saturated fats with MUFA (Random-effects)</u>	

Study	Research methods	Analysis	Results	Comments
			CVD mortality: no effect (1 RCT) RR 3.0 (95% CI 0.33 to 26.99), p>0.05. *CVD events:* no effect (1 RCT) RR 1.00 (95% CI 0.53 to 1.89), p>0.05. *Fatal or non-fatal MI:* no effect (1 RCT) RR 1.40 (95% CI 0.51 to 3.85) *Non-fatal MI*: no effect (1 RCT) RR 1.20 (95% CI 0.42 to 3.45) *CHD mortality:* no effect (1 RCT) RR 3.00 (95% CI 0.33 to 26.99) *CHD events:* no effect (1 RCT) RR 1.55 (95% CI 0.62 to 3.61) <u>Substitution of saturated fats with carbohydrates (Random-effect</u> *CVD mortality:* no effect (6 RCTs) RR 0.99 (95% CI 0.86 to 1.14), p>0.05; I^2 =0%; *CVD events:* no effect (6 RCTs) RR 0.93 (95% CI 0.79 to 1.08), p>0.05; I^2 =57% *Fatal or non-fatal MI:* no effect (10 RCTs) RR 0.96 (95% CI 0.86 to 1.06); I^2=0% *Non-fatal MI:* no effect (5 RCTs) RR 0.99 (95% CI 0.73 to 1.35); I^2=0% *CHD mortality:* no effect (3 RCTs) RR 1.01 (95% CI 0.86 to 1.18); I^2=0% *CHD events:* no effect (5 RCTs) RR 0.98 (95% CI 0.83 to 1.14); I^2=0% *Strokes (any type, fatal or non-fatal):* no effect (4 RCTs) RR 1.01 (95% CI 0.90 to 1.13); I^2 =0% <u>Substitution of saturated fats with proteins (Random-effect</u> *CVD mortality:* no effect (5 RCTs) RR 0.99 (95% CI 0.86 to 1.14) I^2 =0% *CVD events:* no effect (6 RCTs) RR 0.98 (95% CI 0.90 to 1.06); I^2 =15% *Fatal or non-fatal MI:* no effect (3 RCTs) RR 0.96 (95% CI 0.86 to 1.07); I^2=0%	

Study	Research methods	Analysis	Results	Comments
			Non-fatal MI: no effect (3 RCTs) RR 0.99 (95% CI 0.73 to 1.35); I^2=75% *CHD mortality:* no effect (3 RCTs) RR 1.01 (95% CI 0.86 to 1.18); I^2=0% *CHD events:* no effect (4 RCTs) RR 0.99 (95% CI 0.88 to 1.12); I^2=41% *Strokes (any type, fatal and non-fatal):* no effect (3 RCTs) RR 1.01 (95% CI 0.89 to 1.15); I^2=11%	

Study	Research methods	Analysis	Results	Comments
Chowdhury et al (2014) (Systematic review and meta-analysis) <u>Funding source</u> British Heart Foundation (BHF); Medical Research Council (MRC); Cambridge National Institute for Health Research Biomedical Research Centre; Gates Cambridge. <u>Declarations of interest</u> Grants: Nestle; Metagenics; Pfizer; Merck Sharp & Dohme; Novartis; MRC; BHF; Cancer Research UK; British United Provident Association Foundation; diaDexus; European Research Council; European Union; Evelyn	<u>Research question</u> What is the association between fatty acids and coronary disease? *Specific*: What is the association between saturated fats and coronary disease? <u>Selection criteria</u> *Search dates:* Inception to end June 2013. *Study design:* PCS and RCTs. *Inclusion criteria:* Studies reporting on association of dietary fatty acid intake, fatty acids biomarkers or fatty acids intervention (dietary or supplement) with risk of coronary disease; observational studies with at least 1y follow-up; intervention studies – randomised and recorded coronary outcomes endpoint of interest; observational studies: participants from general populations or with stable CVD at study entry (defined as diagnosis made at least 30 days prior to baseline sampling). *Exclusion criteria:* Not reported.	<u>Analysis</u> Highest vs lowest 1/3 of saturated fat intake compared. Where RR adjusted, version not adjusting for blood lipids and/or circulating fatty acids was used. Random-effects model including between study heterogeneity used to pool RRs. Spearman's correlation coefficients using random-effects meta-analysis calculated for dietary fatty acid intake and circulating fatty acids. Heterogeneity: between studies, chi-squared and I^2 statistic. Newcastle-Ottawa Scale score using meta-regression. Publication bias: funnel plots and Egger tests. <u>Evaluation of study quality</u> Newcastle-Ottawa Scale for PCS. Cochrane Collaboration's tool for assessing risk of bias for RCTs.	20 PCS for saturated fats only (45 PCS for all fatty acids); n=283,963; 10,518 cases; follow-up 5 to 20 years; age: not reported; sex: not reported; health at baseline: healthy (40), with CVD (22), with elevated risk factors for CVD (10); country: North America (19), Europe (42), Asia-Pacific region (9), multinational (2). <u>Intake of saturated fats highest vs lowest intake</u> *CHD outcomes:*↓ outcomes with lower saturated fat intake (20 PCS) RR 1.02 (95% CI 0.97 to 1.07) (random-effects) RR 1.04 (95% CI 1.01 to 1.07), p<0.05 (fixed-effects)	Current evidence does not clearly support cardiovascular guidelines that encourage high consumption of PUFAs and low consumption of total saturated fats. <u>Limitations</u> Lack of repeat assessments of dietary intake; inability to adjust consistently for potential confounding factors across all studies.

Study	Research methods	Analysis	Results	Comments
Trust; Fogarty International Centre; GlaxoSmithKline; National Heart, Lung and Blood Institute; National Institute of Neurological Disorders and Stroke; National Health Service Blood and Transplant; University of British Columbia; University of Sheffield; Wellcome Trust; UK Biobank. Personal fees: Roche Pharmaceuticals; Bunge; Pollock Institute; Quaker Oats; Life Sciences Research Organization; Foodminds; Nutrition Impact; Amarin; AstraZeneca; Winston & Strawn; Unilever North American Scientific Advisory Board; UpToDate online chapter; Merck		<u>Dietary assessment method</u> FFQs, 7-day food diary, 7-day weighted food record, 24-hour dietary recall, 4-day food record, 7-day food record, diet-history interview.		

Study	Research methods	Analysis	Results	Comments
Sharp & Dohme UK Atherosclerosis Advisory Board; Novartis Cardiovascular & Metabolic Advisory Board; Pfizer Population Research Advisory Panel; Sanofi Advisory Board. Royalties: Elsevier (France).				

Study	Research methods	Analysis	Results	Comments
Farvid et al (2014) (Systematic review with meta-analysis) <u>Funding source</u> National Institutes of Health grants. <u>Declarations of interest</u> Received research support from California Walnut Commission.	<u>Research question</u> *General*: does dietary linoleic acid intake reduce CHD risk? *Specific*: does replacement of dietary saturated fat with dietary linoleic acid reduce CHD risk? <u>Selection criteria</u> *Search dates:* Inception to June 2013. *Study design:* PCS. *Inclusion criteria:* Studies provided multivariate adjusted risk estimates (RR or HR) for dietary linoleic acid consumption as the exposure and CHD endpoints; *Exclusion criteria:* Retrospective, cross-sectional or ecological studies; studies in non-adults (< 19 years old); non-original papers (reviews, editorials, letters), meeting abstracts and duplicated publications; studies conducted in patients with known CHD at baseline. <u>Dietary assessment method</u> FFQ (9); diet/7-day weighed food record (1); diet history (1); diet/24-hour recall (1); FQ/7-day menu book (1).	<u>Analysis</u> RR calculated using fixed-effect models; random effects models for sensitivity analysis. Heterogeneity: I^2 statistic, stratified analysis and meta-regression. Multivariate model included: total energy, age, smoking, BMI, education level, alcohol intake, hypertension, fibre intake, % of energy from saturated fats, trans fats, MUFAs, α-linoleic acid, PUFAs other than linoleic acid and α-linoleic acid and protein intake. Publication bias: visual inspection of funnel plot and Begg test. <u>Evaluation of study quality</u> No information provided; however the "study quality score" was used to assess heterogeneity between studies.	13 PCS; n=310,602 (range 1643 to 84,566); duration: 5.3 to 30y; age 20 to 75y; sex: M(4), W(3), M/W(6); health at baseline: without known CHD; country: USA (6), Finland (2), Sweden (2), The Netherlands (1), Denmark (1),Israel (1). <u>Substituting 5% energy from saturated fats with linoleic acid</u> *CHD mortality:* ↓ deaths (10 PCS) RR 0.87 (95% CI 0.82 to 0.94), p<0.05; I^2=0.0% (fixed-effects) RR 0.90 (95% CI 0.80 to 1.01) (random-effects) *CHD events:* ↓ events (8 PCS) RR 0.91 (95% CI 0.87 to 0.96), p=0.012; I^2=55.9% (fixed-effects) RR 0.90 (95%CI 0.80 to 1.01) (random-effects)	Dietary linoleic acid is inversely associated with CHD risk in a dose-response manner. <u>Limitations</u> Most studies used FFQs to assess dietary intake, thus measurement errors may be introduced by under- or over-reporting of the amounts of food groups usually eaten by day; intake levels of linoleic acid may be underestimated in some studies that did not query brand names of some linoleic acid containing foods in the FFQ.

Study	Research methods	Analysis	Results	Comments
Schwab et al (2014) (Systematic narrative review) <u>Funding source</u> Supported by the Nordic Council of Ministers. <u>Declarations of interest</u> None declared.	<u>Research question</u> What are the effects of intake of total fat and various combinations and proportions of fatty acid classes in the diet, considering intake of other nutrients on: a. well-established indicators of clinical outcomes such as plasma or serum total lipids and lipoprotein concentrations, plasma or serum glucose and insulin concentrations and blood pressure? b. clinical outcomes including body weight, type 2 diabetes, CVD, and cancer? <u>Selection criteria</u> *Search dates:* January 2000- February 2012. *Study designs:* RCT and PCS. *Inclusion criteria:* 18-70y, healthy (subjects with dyslipidaemia, glucose intolerance, or overweight (mean BMI of study population not exceeding 30kg/m^2) were included); ≥10 participants for RCTs; dietary assessment method: food record, FFQ, dietary recall, biomarkers; duration <u>≥</u> 4 weeks (RCTs), <u>≥</u>6 months (body weight and body composition studies); PCS follow-up >4y, studies >5y for cancers; RCT dropout <30% in 6 months, <40% on 12 months, <50% in 24 months; intervention: amount and/or quality of dietary fat; updated/relevant nutrient databases. *Exclusion criteria*: Studies without Caucasians or Caucasians a clear minority;	<u>Analysis</u> Narrative review, results of the quality assessment of the individual studies were summarised to evaluate the quality and strength of the overall evidence in relation to the posed research questions. The evidence for each exposure-outcome association was categorised according to predetermined categories: convincing, probable, limited-suggestive, and limited-no conclusion. <u>Evaluation of study quality</u> Primary evidence assessed for quality but method not reported. Quality categories included: A) high quality with very low risk of bias; B) good quality, some risk of bias but not enough to invalidate results; C) low quality with significant bias and weaknesses which may invalidate results.	5 PCS (6 publications); n=185,049; duration: 7 to 22y; age: 30 to 84y; sex: M (1), W (2), M/W (3); health at baseline: healthy (6); country: USA (4), Denmark (2). 1 RCT; n=48,835; duration: 8.1y; age: 50-79y; sex: women only; health at baseline: healthy; country: USA. Majority of PCS – no association between intake of saturated fats and risk of CVD outcomes (grade B evidence). *Secondary analysis* RCT: Lower saturated fat intake associated with decreased risk of CHD in women (men not included in RCT), (grade B evidence). 2 PCS: saturated fats reduced, and replaced with carbohydrate: associated with increased risk of CVD outcomes (grade B evidence). 1 PCS: Increased risk of CVD outcomes with simple carbohydrate (high glycaemic index) but not complex carbohydrate (low glycaemic index) (grade B evidence).	<u>Limitations</u> Focus on new evidence since previous edition of Nordic Nutrition Recommendations (NNR), hence why studies pre 2000 not included, however several systematic reviews and meta-analyses included in previous publications. Strict criteria for both study quality and evidence grading resulting in a relatively conservative estimate of the evidence. Many questions remain unresolved due to conflicting results from studies and lack of high quality controlled studies.

Study	Research methods	Analysis	Results	Comments
	study aim outside scope of review; exposure food pattern or a whole food; included non-healthy subjects, obese subjects. <u>Dietary assessment methods</u> Food record, FFQ, dietary recall, valid biomarkers.			

Study	Research methods	Analysis	Results	Comments
Ramsden et al (2013) (Systematic review with meta-analysis) <u>Funding source</u> The Life Insurance Medical Research Fund of Australia and New Zealand; The Intramural Program of the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health. <u>Declarations of interest</u> None declared	<u>Research question</u> Are longitudinal dietary changes in PUFAs and saturated fats associated with mortality outcomes? <u>Selection criteria</u> *Search dates:* Not specified. *Study design:* RCTs *Inclusion criteria:* RCTs in which PUFA were increased in place of saturated fats; CHD mortality, CVD mortality and/or total mortality reported. *Exclusion criteria*: No randomisation; disproportionate CHD risk factors reported in different arms; dietary information necessary to classify experimental diets as either n-6 specific PUFA or mixed n-3/n-6 PUFA was not available. <u>Dietary assessment method</u> Not reported.	<u>Analysis</u> Fixed effects meta-analyses for linoleic acid-selective and mixed n-3/n-6 PUFA intervention datasets for CHD mortality, CVD mortality and total mortality. Test of heterogeneity performed to determine whether effects of linoleic acid-selective and mixed n-3/n-6 PUFA intervention datasets should be evaluated separately. Potential for publication bias assessed by visual inspection of a funnel plot of the treatment effect versus standard error. Sensitivity analysis performed. <u>Evaluation of study quality</u> Not systematically assessed.	7 RCTs; n=11,275; duration: 2 to ≤8y; age: not reported; sex: M (7), W (1); health at baseline: with CHD (5), with or without CHD (3); country: USA (3), UK (3), Norway (1), Australia (1). <u>Saturated fats substitution with PUFA</u> *CVD mortality:* no effect (7 RCTs) HR 0.97 (95% CI 0.82 to 1.15) I^2=46.9% <u>Saturated fats substitution with n-6 PUFA</u> *CVD mortality:* no effect (4 RCTs) HR 1.27 (95% CI 0.98 to 1.65) p=0.07; I^2=22% <u>Saturated fats substitution with n-6 and n-3 PUFA (combined)</u> *CVD mortality:* ↓ deaths *(4 RCTs)* HR 0.79 (95% CI 0.63 to 0.99) p=0.04; I^2=0% HR 0.81 (95% CI 0.64 to 1.03) p=0.08; I^2=0%	An updated meta-analysis of linoleic acid intervention trials showed no evidence of CVD benefits. Selective substitution of n-6 PUFA for saturated fats is unlikely to be beneficial particularly in patients with established heart disease. <u>Limitations</u> Relatively small number of trials investigating PUFA interventions and differences in design and population characteristics of each trial.

Study	Research methods	Analysis	Results	Comments
Micha & Mozaffarian (2010) (Systematic review) Funding source Searle Funds at The Chicago Community Trust; the Bill & Melinda Gates Foundation/World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study. Declarations of interest Consulting honoraria (modest) from Nutrition Impact, Unilever and SPRIM.	Research question Elucidate effects of saturated fat consumption on CVD risk based on the most current evidence. Selection criteria *Search period*: Inception to September 2009. *Study design*: RCT and PCS. *Inclusion*: Adults; evaluating saturated fat intake and risk of CHD, stroke, type 2 diabetes, related risk pathways including lipids and lipoproteins, systemic inflammation, vascular function, insulin resistance. *Exclusion*: A priori animal studies, ecological studies, commentaries, general reviews, case reports. Dietary assessment methods Not reported.	Analysis Narrative review. Evaluation of study quality Not reported.	Characteristics of identified studies not summarised. Substitution of saturated fats with MUFA *CHD events* Effect/association on CHD risk uncertain. Substitution of saturated fats with carbohydrates *CHD events* No benefit effect on CHD risk.	Replacement with carbohydrate has no benefit. Replacement with MUFA has uncertain effects. Advice to reduce saturated fat intake without considering the replacement may have little or no effects on disease risk.

Study	Research methods	Analysis	Results	Comments
Mozaffarian et al (2010) (Systematic review with meta-analysis) <u>Funding source</u> National Heart, Lung and Blood Institute, National Institute of Health; Searle Scholar Award from the Searle Funds at the Chicago Community Trust. <u>Declarations of interest</u> Research grants: US National Institutes of Health; Searle Funds at the Chicago Community Trust; Genes and Environment Initiative; Gates Foundation/WHO Global Burden of Diseases, Injuries and Risk Factors Study;	<u>Research question</u> What is the impact of increased PUFA consumption, as a replacement for saturated fats, on CHD endpoints? <u>Selection criteria</u> *Search dates:* Inception to June 2009. *Study design:* RCTs. *Inclusion criteria:* Interventions that randomised adults to increased total or n-6 PUFA consumption for at least 1y without other major concomitant interventions; an appropriate control group; sufficient data to calculate risk estimates with SE for effects on occurrence of "hard" CHD events; primary or secondary prevention trials; feeding trials and trials that utilised dietary advice. *Exclusion criteria*: Observational or non-randomised studies; tested mainly n-3 rather than total or n-6 PUFAs; studies that evaluated only intermediate endpoints (e.g. angina); or were commentaries, reviews or duplicate publications from the same study. <u>Dietary assessment method</u> Direct analysis of provided food (4), multiple serial weighted diet records (1), 7-14 day weighed diet records in a subset (1), questionnaire validated against 7-day weighed diet records (1), clinical interviews about dietary compliance (1).	<u>Analysis</u> The overall pooled effect was calculated using random effects meta-analysis. Heterogeneity between studies was evaluated using the I^2 statistic and meta-regression. Pre-specified potential sources of heterogeneity were explored using stratified inverse-variance weighted random effects meta-analysis and inverse-variance weighted meta-regression including trial duration, study population and overall quality score. <u>Evaluation of study quality</u> The validated Jadad score was used to assess quality, which includes criteria relating to randomisation, blinding, and withdrawals and dropouts that are together summed to generate an overall quality score between 0 and 5.	8 RCTs; n=13,614; duration: 2 to 8y; age: not reported; sex: M(6), W(1), M/W(1); health at baseline: with or without CHD (1), without CHD (3), history of CHD (4); country: USA (2), UK (3), Finland (2), Norway (1). <u>Saturated fats substitution with PUFA intake</u> *CHD events:* ↓risk (7 RCTs) RR 0.81 (95% CI 0.70 to 0.95), p=0.008 <u>For each 5% of energy increased PUFA in place of saturated fats</u> *CHD events*: ↓events RR 0.90 (95% CI 0.83 to 0.97) A number of sub-group analyses were performed, none of which were significantly different from the main pooled result.	Consuming PUFA in place of saturated fats reduces CHD events in RCTs. <u>Limitations</u> Many of the included RCTs had important design limitations: some provided all or most meals limiting generalisability while others only provided dietary advice; some trials were not double-blinded; the methods of estimating and reporting saturated fats and PUFA varied between trials; some trials included sources of marine n-3 PUFA.

Study	Research methods	Analysis	Results	Comments
GlaxoSmithKline; Sigma Tau and Pronova. Honoraria and travel expenses: US Food and Drug Administration; International Life Sciences Institute; Aramark; Unilever; SPRIM; Nutrition Impact, WHO.				

Study	Research methods	Analysis	Results	Comments
Siri-Tarino et al (2010) (Systematic review with meta-analysis) <u>Funding source</u> National Dairy Council; National Center for Research Resources; National Institutes of Health; National Institute of Health Roadmap for Medical Research; Postdoctoral Fellowship from Unilever Corporate Research. <u>Declarations of interest</u> None declared.	<u>Research question</u> What is the evidence related to the association of dietary saturated fat with risk of CHD, stroke and CVD in prospective epidemiological studies? <u>Selection criteria</u> *Search dates:* Inception to 17 September 2009. *Study design: PCS.* *Inclusion criteria:* Data available on dietary consumption of saturated fats; specifically investigating association of saturated fat with fatal or non-fatal CVD events; participants were generally healthy adults. *Exclusion criteria*: Investigating CVD risk factors. <u>Dietary assessment method</u> FFQs, 24-hour recalls, interview and multiple daily food records (1day, 7day).	<u>Analysis</u> RRs and 95% CIs were log transformed to derive corresponding SEs for β-coefficients by using Greenland's formula. Risk estimates for the most fully adjusted models used to estimate pooled RR. Meta-analyses performed with a random effects model. Influence of individual studies on the pooled estimated were examined. Examined whether the size of the effect depended on characteristics of each study, including age, sex, sample size, duration of follow-up, whether disease outcomes were confirmed by medical record and a score evaluating overall study quality. *Secondary analysis*: age and sex effects; effects of replacing saturated fats with carbohydrate or PUFA. <u>Study quality</u> Studies were given a quality score derived	21 PCS (16 CHD, 8 Stroke); n=347,747 (total) (range: 266-85,764); duration: 6-23y; age: ~30-89y; sex: M(11), W(2), M/W(8); health at baseline: healthy; country: North America (12), Europe (6), Japan (2), Israel (1). <u>Highest vs lowest saturated fat intake</u> *CVD events:* no association (21 cohorts) RR 1.00 (95% CI 0.89 to 1.11) p=0.95; I^2=56% *CVD events by sex*: no association *Men* (14 PCS) RR 0.97 (95% CI 0.87 to 1.08) p=0.60; I^2=34% *Women* (6 PCS) RR 1.06 (95% CI 0.86 to 1.32) p=0.57; I^2=1% *CVD events by age*: no association *<60y* (15 PCS) RR 0.98 (95% CI 0.84 to 1.13) p=0.77; I^2=50% *≥60y* (10 PCS) RR 0.98 (95% CI 0.86 to 1.10) p=0.69; I^2=0% *CHD events:* no association (16 PCS) RR 1.07 (95% CI 0.96 to 1.19) p=0.22; I^2=41% *Stroke:* no association (8 PCS) RR 0.81 (95% CI 0.62 to 1.05) p=0.11; I^2=61% <u>Adjusted for total energy intake and energy from protein, carbohydrate and fats (except PUFA)</u> *CVD events:* no association RR 0.97 (95% CI 0.86 to 1.10) p=0.66; I^2=0%; *CHD events:* no association (4 PCS) RR 0.98 (95% CI 0.86 to 1.13) p=0.83; I^2=0%	There is insufficient evidence from prospective epidemiological studies to conclude that dietary saturated fat is associated with an increased risk of CHD, stroke or CVD. <u>Limitations</u> The meta-analysis relies on the accuracy of dietary assessments of the component studies. Only a limited number of studies provided data that enabled the evaluation of the effects of isoenergetically replacing saturated fats with carbohydrate or PUFA and therefore the statistical power was diminished for the secondary analysis restricted to these studies. The funnel plot analysis suggests publication bias; studies with significant associations tended to be received more favourably for publication.

Study	Research methods	Analysis	Results	Comments
		from the dietary assessment method, the number of dietary assessments and the number of adjusted established risk factors for CVD.	*Stroke:* no association (3 PCS) RR 0.93 (95% CI 0.71 to 1.21) p=0.58; I^2=0%	

Study	Research methods	Analysis	Results	Comments
Jakobsen et al (2009) (Pooled analysis) <u>Funding source</u> National Heart, Lung and Blood Institute, National Institutes of Health; Danish Heart Foundation. <u>Declarations of interest</u> None declared.	<u>Research question</u> Should energy from unsaturated fatty acids or carbohydrate replace energy from saturated fats to prevent CHD? <u>Selection criteria</u> *Search dates:* Not reported. *Study design:* PCS. *Inclusion criteria:* Published follow-up study with ≥ 150 incident coronary events; availability of usual dietary intake; a validation or repeatability study of the diet-assessment method used. *Exclusion criteria*: Age < 35 years; history of CVD, diabetes or cancer (other than non-melanoma skin cancer); and extreme energy intake (i.e. > or < 3 SDs form the study-specific log-transformed mean energy intake of the population). <u>Dietary assessment method</u> FFQs and diet history interview.	<u>Analysis</u> HRs with 95% CI for the incidence of a coronary event and of mortality from CHD were calculated using Cox proportional hazards regression. Studies with follow-up periods >10y were truncated to reduce possible effect modification by time. Two models were used to investigate whether energy intake from unsaturated fatty acids or carbohydrate should replace energy intake from saturated fats to prevent coronary events: *Model 1* included intakes of MUFAs, PUFAs, trans fats, carbohydrate and protein expressed as percentages of total energy intake. *Model 2* included variables in model 1 and CHD risk factors measured at baseline: smoking, BMI, physical activity, highest attained educational level, alcohol intake, history of hypertension and energy adjusted quintiles of fibre intake	11 PCS; n=344,696 (range 3324 to 143,121); duration: 4 to 10y; age: 47 to 61y (median at baseline); sex: M(3), F(3), M/F(5) (71% of total participants were women); health at baseline: healthy, no history of CVD, diabetes or cancer; country: USA (6), Finland (2), Sweden (1), Denmark (1), Israel (1). <u>5% lower energy intake from saturated fats and a concomitant higher energy intake from PUFA</u> *CHD mortality:* ↓ deaths (11 PCS) HR 0.74 (95% CI 0.61 to 0.89), no p value reported *CHD events:* ↓events (11 PCS) HR 0.87 (95% CI 0.77 to 0.97), no p value reported <u>5% lower energy intake from saturated fats and a concomitant higher energy intake from MUFA</u> *CHD mortality:* no association (11 PCS) HR 1.01 (95% CI 0.73 to1.41), no p value reported *CHD events:* ↑events (11 PCS) HR 1.19 (95% CI 1.00 to 1.42), no p value reported <u>5% lower energy intake from saturated fats and a concomitant higher energy intake from carbohydrates</u> *CHD mortality:* no association (11 PCS) HR 0.96 (95% CI 0.82 to 1.13), no p value reported *CHD events:*↑events HR 1.07 (95% CI 1.01 to 1.14), no p value reported No effect modification by sex or age was found.	The associations suggest that replacing saturated fats with PUFAs rather than MUFAs or carbohydrate prevent CHD over a wide range of intakes. <u>Limitations</u> Although the study suggests that to lower the risk of CHD, saturated fats should not be replaced with carbohydrate, the authors acknowledged that the effect of substitution may vary depending on the type of carbohydrate consumed as the study did not consider different types of carbohydrate. Only baseline information was available regarding dietary habits.

Study	Research methods	Analysis	Results	Comments
		(g/day) and cholesterol (mg/day). A random effects model was used to provide a pooled estimate of HRs. Between study heterogeneity was assessed using the Q statistic. <u>Evaluation of study quality</u> Not reported.		

Study	Research methods	Analysis	Results	Comments
Mente et al (2009) (Systematic review) <u>Funding source</u> Heart and Stroke Foundation of Canada Postdoctoral Research Fellowship; Canadian Institutes of Health Research Clinician-Scientist Phase 2 Award; Heart and Stroke Foundation of Ontario Michael G. DeGroote Research Chair in Population Health Research; Canadian Institutes of Health Research Canada Graduate Scholarship Doctoral Award. <u>Declarations of interest</u> None declared.	<u>Research question</u> Systematically evaluate dietary exposures and CHD using the Bradford Hill criteria; determine which dietary exposures have been studied sufficiently in RCTs and found to support the findings of PCS; identify dietary exposures deemed to have insufficient evidence to be conclusive. <u>Selection criteria</u> *Search period*: 1950 – June 2007. *Study designs:* PCS and RCTs. *Inclusion criteria*: English language; investigating dietary exposures in relation to CHD, with ≥ 1 year follow-up; PCS include estimates of dietary intake measured using conventional dietary assessment tools; RCTs randomised and compare dietary exposure with control diet or placebo. *Exclusion criteria*: Crossover trials that did not evaluate plasma biomarkers or atherosclerotic indicators. <u>Dietary assessment methods</u> FFQ, food records, 24-hour diet recall.	<u>Analysis</u> Summary estimates were calculated using a general variance-based method (random-effects model) with 95% CIs. <u>Evaluation of study quality</u> Not reported.	11 PCS; n=160,673 (saturated fat cohorts); median duration: 11y (range 2.8 to 28y); mean age: 53 y; sex: 41% women; country: USA (201), Europe (130), Asia (12). <u>Highest vs lowest intake of saturated fats</u> *Coronary outcomes:* no association (11 sub-cohorts) RR = 1.06 (95% CI 0.96 to 1.15) <u>Bradford Hill Criteria</u> Weak evidence (≤ 2 criteria) for association between saturated fats and CHD.	Strong evidence for a causal association for protective factors including intake of vegetables, nuts, monounsaturated fatty acids, Mediterranean and high quality dietary patterns, and harmful factors including foods with a high glycaemic index, trans fats and a western dietary pattern. Among these factors, only a Mediterranean dietary pattern was associated with CHD in RCTs. <u>Limitations</u> Created arbitrary definitions for evidence and scoring system, but has been validated. Derived RR cut-off points to define a strong association from the distribution of RR values in cohort studies because the true cut-off points for defining clinically meaningful effects are not known. Heterogeneity of cohort studies may have influenced results.

Study	Research methods	Analysis	Results	Comments
Skeaff & Miller (2009) (Systematic review with Meta-analysis) <u>Funding source</u> None declared. <u>Declarations of interest</u> Funding received from Unilever and Fonterra.	<u>Research question</u> What is the relationship between dietary fat and risk of CHD? <u>Selection criteria</u> *Search dates:* Not reported. *Study design:* PCS and RCTs. *Inclusion criteria:* Studies in which dietary fat exposure was assessed by dietary assessment measures or fatty acid biomarkers. *Exclusion criteria*: Cohort studies that did not report a RR associated with intake of dietary fats; studies where MUFA exposure was assessed using fatty acid biomarkers. <u>Dietary assessment method</u> 24-hour recall, diet records, diet histories and FFQs.	<u>Analysis</u> *PCS*: random effects meta-analysis to calculate summary estimates of RR of CHD in high vs low exposure to dietary fat or its components. Separate meta-analysis performed for summary estimates of risk for 5% energy increments for saturated fats. *RCTs: meta-analysis* of results from RCTs based on diets involving a change in the PUFA to saturated fats ratio of the diet, with or without reduction in total fat intake. <u>Evaluation of study quality</u> Not systematically assessed. Commentary in discussion section.	<u>Hghest vs lowest saturated fat intake.</u> 8 PCS; n=415 to 78,778; duration: 5 to 20y; age: 30 to 79y; sex: M (3), W (1), M/W (4); health at baseline: healthy (5), high risk (smokers) (1), clinically established coronary artery disease (1), not reported (1); country: USA (4), UK (1), Finland (2), Denmark (1). *CHD Mortality:* no association (6 PCS) RR 1.14 (95% CI 0.82 to 1.60) p=0.431; I^2 = 72.1% *CHD Events:* no association (5 PCS) RR 0.93 (95% CI 0.83 to 1.05) p=0.269; I^2 = 0.09% <u>Per 5% total energy increment in saturated fat intake</u> *CHD Mortality:* no association (2 PCS) RR 1.11 (95% CI 0.75 to 1.65) p=0.593; I^2 = 62.8% *CHD Events:* no association (3 PCS) RR 1.03 (95% CI 0.87 to 1.22) p=0.723; I^2 = 34.3% <u>RCTs: Increased PUFA and decreased saturated fat</u> 8 RCTs; n=90 to 9057; duration: 2 to 6y; age: 30 to 64y; sex: M (6), F (1), M/F (1); health at baseline: previous MI (3), with CHD (1), hospitalised patients (3), not reported (1); country: USA (2), UK (4), Norway (1), Finland (1). *CHD Mortality:* no effect (5 RCTs) RR 0.84 (95% CI 0.62 to 1.12) p=0.867; I^2 = 12.4% *CHD Events:* ↓events (8 RCTs) RR 0.83 (95% CI 0.69 to 1.00), p=0.050; I^2 = 44.2% *Only trials where mean serum cholesterol concentration was significantly lowered in the intervention group* *CHD Mortality:* ↓deaths (3 RCTs) RR 0.52 (95% CI 0.30 to 0.87), p=0.014; I^2 = 0.0% *CHD Events:* ↓events (5 RCTs) RR 0.68 (95% CI 0.49 to 0.94), p=0.020; I^2 = 40.3%	The available evidence from PCS and RCTs is unsatisfactory and unreliable to make judgement about and substantiate the effects of dietary fat on risk of CHD. The null results of observational studies reflect the combined effects of limitations of dietary assessment methods, inadequate numbers of participants studied and the prolonged follow-up of individuals.

Table A2.2 RCTs assessing the relationship between dietary saturated fat intake and cardiovascular diseases in each review article

Study name[1] / first author (publication dates)	**Harcombe et al, (2016b)**	**Ramsden et al, (2016)**	**Hooper et al, (2015)[2]**	**Schwab et al, (2014)[3]**	**Ramsden et al, (2013)**	**Micha and Mozaffarian (2010)[3]**	**Mozaffarian et al, (2010)**	**Skeaff and Miller (2009)**
A, cardiovascular disease; B, coronary heart disease; C, stroke; d number of deaths; t number of events.								
Total primary studies (publications)	10	5 (21)	12		7 (25)	9	8	8
Howard 2006	B^{d}		$A^{dt}B^{dt}$			$AB^{t}C$		
Ley 2004			$A^{dt}B^{dt}$					
Sydney Diet-Heart Study	B^{d}	B^{d}	$A^{t}B^{d}$		$A^{d}B^{d}$			
Moy 2001			A^{t} B^{dt}					
Black 1994			C^{td}					
STARS Watts 1992 Watts 1994	B^{d}		C^{dt}		$A^{d}B^{d}$ $A^{d}B^{d}$	B^{t}	B^{t}	B^{dt}
DART Study								
Burr 1989			$A^{dt}B^{dt}$			B^{t}	B^{t}	B^{dt}
Burr 1968	B^{d}							
Minnesota Coronary Experiment	B^{d}	B^{d}			$A^{d}B^{d}$	B^{t}	B^{t}	B^{t}
Houtsmuller 1979			A^{t} B^{dt}					
Finnish Mental Hospital Study						B^{t}	B^{t}	B^{dt}

Study name[1] / first author (publication dates)	**Harcombe et al, (2016b)**	**Ramsden et al, (2016)**	**Hooper et al, (2015)[2]**	**Schwab et al, (2014)[3]**	**Ramsden et al, (2013)**	**Micha and Mozaffarian (2010)[3]**	**Mozaffarian et al, (2010)**	**Skeaff and Miller (2009)**
Oslo Diet-Heart Study								
Leren 1970	B^{d}				$A^{d}B^{d}$	B^{t}	B^{t}	B^{dt}
Leren 1966			$A^{dt}B^{dt}$		$A^{d}B^{d}$			
Los Angeles Veterens Admin	B^{d}	B^{d}	$A^{dt}B^{dt}$		$A^{d}B^{d}$	B^{t}	B^{t}	B^{t}
Research Committee 1965	B^{d}							
Rose 1965	B^{d}	B^{d}	$A^{dt}B^{dt}$		$A^{d}B^{d}$			B^{t}

Outcomes measured by study: A, cardiovascular disease; B, coronary heart disease; C, stroke; ^{d} number of deaths; ^{t} number of events.

[1] Study name is only provided when two or more publications for that study are used in any of the reviews.

[2] Hooper et al, (2015) presents publications used in the analyses by study name and identifies a main study publication along with all supplementary publications for the study. It is not possible to know which exact publication the data has come from, therefore, the main study publication has been used in the table above.

[3] Micha & Mozaffarian (2010) also discusses the reviews by Jakobsen et al (2009), Mente et al (2009), Siri-Tarino et al (2010) and Mozaffarian et al (2010), however, these are included as separate reviews in this report.

Table A2.3 PCS assessing the relationship between dietary saturated fat intake and cardiovascular diseases in each review article

Study name[1] / first author (publication dates)	**Muto et al, (2018)**	**Harcombe et al, (2017)**	**Cheng et al, (2016)**	**Harcombe et al, (2016a)**	**de Souza et al, (2015)**	**Chowdhury et al, (2014)**	**Farvid et al, (2014)**	**Schwab et al, (2014)[2]**	**Micha and Mozaffarian (2010)**	**Siri-Tarino et al, (2010)**	**Jakobsen et al, (2009)**	**Mente et al, (2009)**
A, cardiovascular disease; B, coronary heart disease; C, stroke; d number of deaths; t number of events.												
Total primary studies (publications)	11	6	15	6	29 (36)	20 (25)	13	6	5	21	11	9
De Goede 2014					B^{t}							
Japan Collaboration Cohort Study	C		C		$AB^{dt}C$	B			C			
Larsson et al, 2012	C		C									
Virtanen 2014					B^{dt}							
Pientinen 1997		B^{d}			B^{dt}	B	B^{dt}			B^{t}	B^{dt}	B^{d}
De Oliveira 2012					A^{t}			A				
European Prospective Investigation into Cancer and Nutrition (EPIC)												

Study name[1] / first author (publication dates)	**Muto et al, (2018)**	**Harcombe et al, (2017)**	**Cheng et al, (2016)**	**Harcombe et al, (2016a)**	**de Souza et al, (2015)**	**Chowdhury et al, (2014)**	**Farvid et al, (2014)**	**Schwab et al, (2014)[2]**	**Micha and Mozaffarian (2010)**	**Siri-Tarino et al, (2010)**	**Jakobsen et al, (2009)**	**Mente et al, (2009)**
Misirli 2012			C		C							
Trichopoulou 2006					B^{d}	B						
De Goede 2012							B^{t}					
Malmo Diet and Cancer Study	C		C		$A^{d}B^{t}C$	B	B^{dt}			$B^{d}C$		
Yaemsiri 2012	C		C		C							
Caerphilly Prospective Study Atkinson 2011 Fehily 1993			C		C B^{t}	B				B^{t}		
Vedtofte 2011							B^{t}					
Jakobsen 2010					B^{t}			A				
Wang 2010								A				
Jakobsen 2009							B^{dt}					
Howard 2006					B^{t}							
Wiberg 2006					C							
Xu 2006		B^{d}			B^{dt}	B				B^{t}		
Health Professionals Follow-up Study		B^{d}			B^{dt}	B	B^{dt}	A		B^{t}	B^{dt}	B^{dt}

Study name[1] / first author (publication dates)	**Muto et al, (2018)**	**Harcombe et al, (2017)**	**Cheng et al, (2016)**	**Harcombe et al, (2016a)**	**de Souza et al, (2015)**	**Chowdhury et al, (2014)**	**Farvid et al, (2014)**	**Schwab et al, (2014)[2]**	**Micha and Mozaffarian (2010)**	**Siri-Tarino et al, (2010)**	**Jakobsen et al, (2009)**	**Mente et al, (2009)**
Laaksonen 2005						B						
Nurses' Health Study	C		C		$A^{dt}B^{dt}C$	B	B^{dt}			B^{t}	B^{dt}	B^{t}
Tucker 2005					B^{d}	B				B^{d}		B^{d}
Jakobsen 2004					B^{t}	B		A		B^{t}	B^{dt}	
Sauvaget 2004	C		C		C					C		
Erkkila 2003						B						B^{d}
Hallmans 2003							B^{dt}				B^{dt}	
He 2003	C		C		C					C		
Iso 2003	C		C						C	C		
Boniface and Tefft 2002		B^{d}			B^{d}	B				B^{d}		B^{d}
Liu 2002							B^{dt}				B^{dt}	
Iso 2001								A	C	C		
Keys 1970				B^{d}								
Folsom 1997							B^{dt}				B^{dt}	
Gillman 1997	C		C		C				C	C		
Mann 1997					B^{d}	B				B^{d}		B^{t}
Seino 1997	C		C		C				C			
Esrey 1996		B^{d}			B^{d}	B				B^{d}		

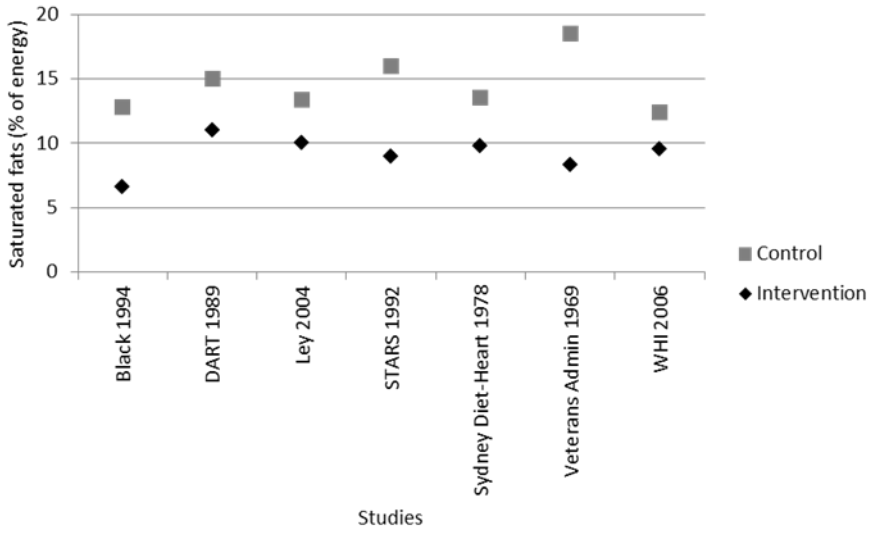
Study name[1] / first author (publication dates)	**Muto et al, (2018)**	**Harcombe et al, (2017)**	**Cheng et al, (2016)**	**Harcombe et al, (2016a)**	**de Souza et al, (2015)**	**Chowdhury et al, (2014)**	**Farvid et al, (2014)**	**Schwab et al, (2014)[2]**	**Micha and Mozaffarian (2010)**	**Siri-Tarino et al, (2010)**	**Jakobsen et al, (2009)**	**Mente et al, (2009)**
Kushi 1996							B^{d}					
Knekt 1994							B^{dt}				B^{dt}	
Goldbourt 1993			C		B^{d} C	B	B^{d}			B^{dt} C	B^{dt}	
Dolecek 1992							B^{d}					
Fraser 1992											B^{dt}	
Framingham Heart Study Posner 1991					B^{t}	B				B^{t}		B^{t}
Gordon 1970				B^{d}								
Honolulu Heart Programme McGee 1985					B^{t} C							
Kagan 1974				B^{d}								
Kushi 1985					B^{d}	B				B^{d}	B^{d}	B^{d}
McGee 1984			C			B				B^{t} C		
Shekelle 1981					B^{d}	B				B^{d}		
Morris 1977				B^{d}								
Garcia-Palmieri 1969				B^{d}								

Study name[1] / first author (publication dates)	Muto et al, (2018)	Harcombe et al, (2017)	Cheng et al, (2016)	Harcombe et al, (2016a)	de Souza et al, (2015)	Chowdhury et al, (2014)	Farvid et al, (2014)	Schwab et al, (2014)[2]	Micha and Mozaffarian (2010)	Siri-Tarino et al, (2010)	Jakobsen et al, (2009)	Mente et al, (2009)
Nagata 2012		B[d]										
Paul 1963				B[d]								

[2] Schwab et al (2014) also discusses the reviews by Jakobsen et al (2009), Mozaffarian et al (2010), and Hooper et al (2015), however, these are included as separate reviews in this report.

[3] Micha & Mozaffarian (2010) also discusses the reviews by Jakobsen et al (2009), Mente et al (2009), Siri-Tarino et al (2010), and Mozaffarian et al (2010), however, these are included as separate reviews in this report.

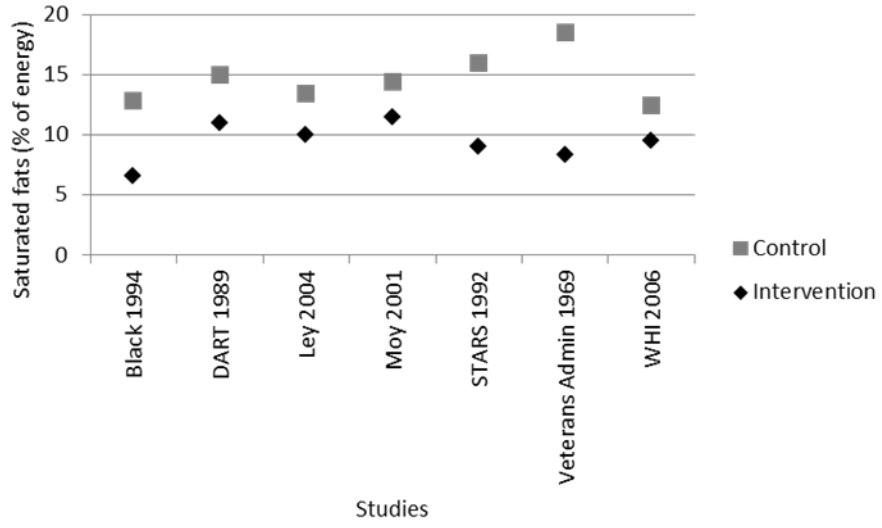
Figure A2.1 Mean intakes of saturated fats from individual RCTs that examined the effect of reduced intake of saturated fats on CVD mortality



Note:

- Data on mean intakes of saturated fats obtained from individual RCTs included in the Hooper et al, (2015) review
- Hooper et al, 2015 examined 10 RCTs; 7 RCTs reported mean intakes of saturated fats
- Intakes of saturated fats ranged from 6.6-11.0% of energy (intervention) and 12.4-18.5% of energy (control)

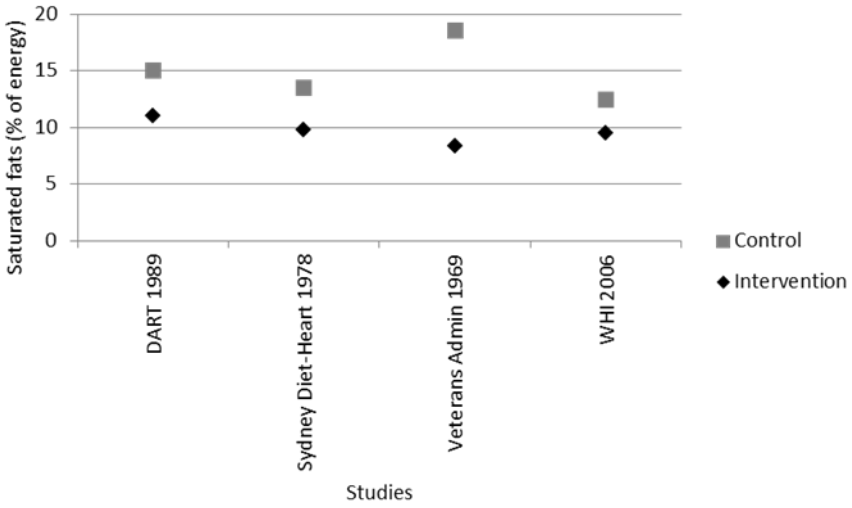
Figure A2.2 Mean intakes of saturated fats from individual RCTs that examined the effect of reduced intakes of saturated fats on CVD events



Note:

- Data on mean intakes of saturated fats obtained from individual RCTs included in the Hooper et al, (2015) review
- Hooper et al, 2015 examined 11 RCTs; 7 RCTs reported mean intakes of saturated fats
- Intakes of saturated fats ranged from 6.6-11.5% of energy (intervention) and 12.4-18.5% of energy (control)

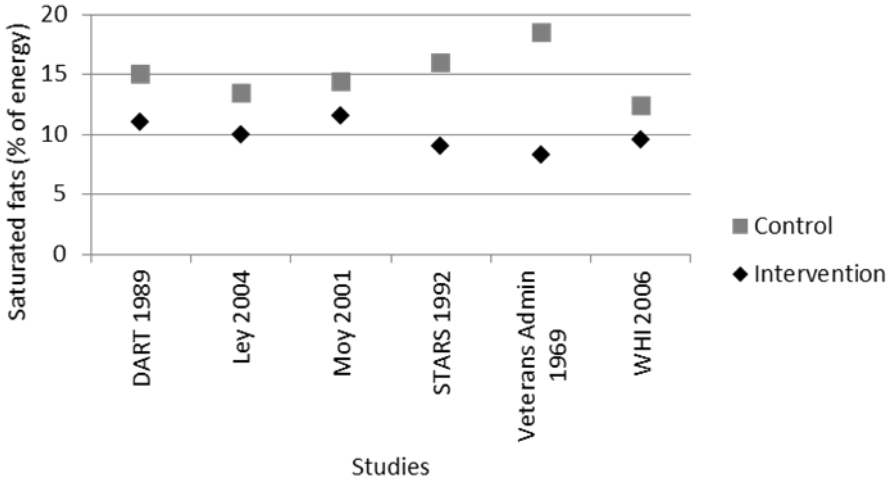
Figure A2.3 Mean intakes of saturated fats from individual RCTs that examined the effect of reduced intakes of saturated fats on CHD mortality



Note:

- Data on mean intakes of saturated fats obtained from individual RCTs included in the Hooper et al, (2015) review
- Hooper et al, 2015 examined 10 RCTs; 4 RCTs reported mean intakes of saturated fats
- Intakes of saturated fats ranged from 8.3-11.0% of energy (intervention) and 12.4-18.5% of energy (control)

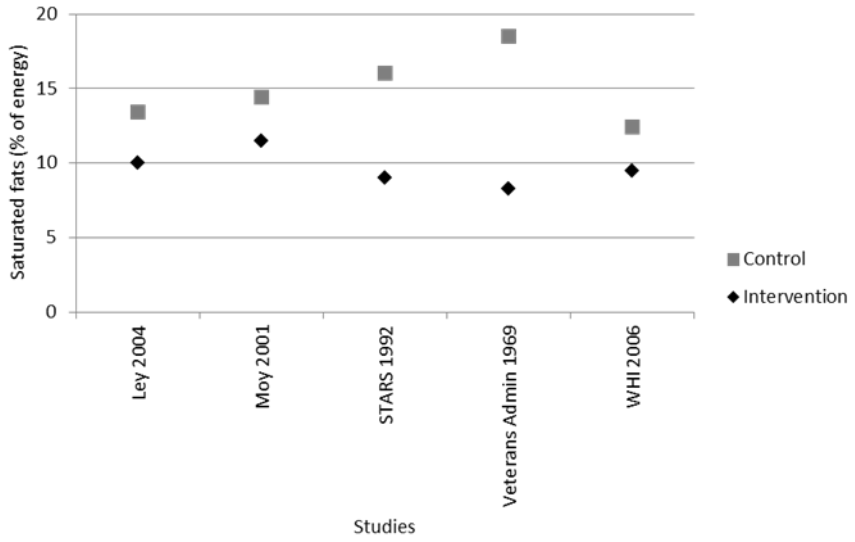
Figure A2.4 Mean intakes of saturated fats from individual RCTs that examined the effect of reduced intakes of saturated fats on CHD events



Note:

- Data on mean intakes of saturated fats obtained from individual RCTs included in the Hooper et al, (2015) review
- Hooper et al, 2015 examined 12 RCTs; 6 RCTs reported mean intakes of saturated fats
- Intakes of saturated fats ranged from 8.3-11.5% of energy (intervention) and 12.4-18.5% of energy (control)

Figure A2.5 Mean intakes of saturated fats from individual RCTs that examined the effect of reduced intakes of saturated fats on strokes



Note:

- Data on mean intakes of saturated fats obtained from individual RCTs included in the Hooper et al, (2015) review
- Hooper et al,, 2015 examined 7 RCTs; 5 RCTs reported mean intakes of saturated fats
- Intakes of saturated fats ranged from 6.6-11.0% of energy (intervention) and 12.4-18.5% of energy (control)

Blood lipids

Table A2.4 Characteristics of meta-analyses and systematic reviews

Study	Research methods	Analysis	Results	Comments
Hannon et al (2017) (Systematic review with meta-analysis) Funding source: None declared Declaration of interest: None declared	Research question What is the effect of saturated fats replacement with unsaturated fats in metabolically healthy adults with overweight and obesity on markers of dyslipidemia and body composition? Selection criteria *Search dates:* inception to June 24 2016 *Study design:* RCTs only *Inclusion criteria:* >18y with BMI >25 kg/m^2 or waist circumference >94 cm for men or >80cm for women, or waist-to-hip ratio >0.96 for men or >0.81 for women without diagnosis of metabolic disease, enrolled in RCT interventions that included dietary replacement of saturated fats with unsaturated fats within the setting of a controlled feeding study or among free-living individuals *Exclusion criteria:* Interventions that focused on management of chronic conditions such as CVD or diabetes; short term studies with intervention duration less than 1 week Dietary assessment methods 3 day food records, 18 day food records, controlled feeding study	Analysis For studies with substantial heterogeneity, random effects model was used. Fixed effects models were used when I^2 was <50%. Evaluation of study quality 7 dichotomous questions were used to assess individual study quality, including: use of control group; statistically nonsignificant differences between control and intervention group at baseline; use of high saturated fats run in period before randomisation; measurement tools for data collection were clearly explained in the methods section; all potential confounders controlled for; study procedures defined and bias adequately controlled. Cochrane Risk of Bias tool was used to assess individual study bias.	8 RCTs; n=663; duration: 4 to 28 weeks; age: not reported; sex: M(3), M/F(5); controlled feeding study (5). Saturated fats substitution with unsaturated fats TC: ↓with saturated fats substitution with unsaturated fats -10.68 mg/dL (95% CI -21.90 to 0.53) p=0.06, I^2=95%, LDL: no effect with saturated fats substitution with unsaturated fats -8.70 mg/dL (95% CI -19.17 to 1.77) p=0.10, I^2=96% HDL: no effect with saturated fats substitution with unsaturated fats 1.15 mg/dL (95% CI -4.57 to 6.86) p=0.22, I^2=98% TAG: no effect with saturated fats substitution with unsaturated fats -9.07 mg/dL (95%CI -23.55 to 5.42) p=0.22, I^2=96% Subgroup analysis Energy restriction interventions TC: -12.13 mg/dL (95% CI -27.13 to 2.88) p=0.11, I^2=97% LDL: -8.52 mg/dL (95% CI -22.12 to 5.08) p=0.22, I^2=97%	Findings suggest that saturated fats substitution with unsaturated fats results in a non-significant reduction in TC, LDL and TAG and a non-significant increase in HDL Limitations Only 8 studies with small to moderate sample size included. Study findings only applicable to adults with overweight and obesity. High study heterogeneity.

Study	Research methods	Analysis	Results	Comments
			HDL-C: -0.79 mg/dL (95% CI -2.34 to0.77) p=0.32, I^2=71% TG: -14.66 mg/dL (95%CI-38.20 to 8.87) p=0.22, I^2=95%CI Energy balanced interventions TC: -10.48 mg/dL (95%CI -27.28 to 6.31) p=0.22, I^2=80% LDL-C: -9.21 mg/dL (95%CI -23.19 to 4.76) p=0.2, I^2=75.4% HDL-C: 5.84 mg/dL (95%CI -10.74 to 22.41) p=0.49, I^2=98% TG: -2.12 mg/dL (95%CI not reported), p=0.74, I^2= 95%	

Study	Research methods	Analysis	Results	Comments
Te Morenga & Montez (2017b) (systematic review with meta-analysis) Funding source: The University of Otago and the WHO Declarations of interest: None declared	Research question Examine the evidence for health effects associated with reducing saturated fats and trans fats intake in free living children, adolescents and young adults aged 2 to 19 years of age Selection criteria *Search dates:* inception to July 2016 *Study design:* RCTs and PCS (PCS not included in meta-analysis) *Inclusion criteria:* children, adolescents and young adults aged 2 to 19 years, healthy individuals as well as individuals with or at risk of hyperlipidaemia, hypertension or diabetes (type 1 & 2), or who were overweight or obese. RCTs with intervention duration of at least 2 weeks with primary intention of reducing saturated fats or trans fats directly or through reduction in total fat intake. *Exclusion criteria:* studies targeting those that were pregnant, acutely ill or with chronic infection such as HIV. Trials where weight loss was primary outcome and trials involving multifactorial interventions where the effect of saturated fats or trans fats reduction could not be separated from the effect of other changes such as physical activity level Dietary assessment methods 24hr dietary recalls, product inventory; daily consumption checklists; 3-day diet records, FFQ, biomarker assessment (pentadecanoic acid)	Analysis Random effects meta-analysis (data pooled using inverse variance models) Evaluation of study quality Cochrane criteria used to assess risk of bias. Evidence assessed using GRADE system. Evidence summaries and GRADE assessments were discussed and reviewed by the WHO Nutrition Guidance Expert Advisory Group Subgroup on Diet and health as part of WHO's guideline development process. Heterogeneity examined using I^2 test.	8 RCTs; n=2430; duration: 5 weeks – 19y; age 2-16y; gender: M/F (8); health at baseline: healthy and hyperlipidemic; country: US (4), Spain (1), Australia (1), Finland (1), China (1) Reduced saturated fats TC: ↓ with reduced saturated fats (7 RCTs; n=2372) MD -0.16 (95% CI -0.25 to -0.07), p=0.0004; I^2=64% LDL-C: ↓ with reduced saturated fats (7 RCTs; n=2004) MD -0.13 (95% CI -0.22 to -0.03), p=0.01; I^2=77% HDL-C: no effect (6 RCTs; n=1565) MD 0.00 (95%CI -0.02 to 0.02), p=0.82; I^2=23% TAG: no effect (6 RCTs; n=1565) MD -0.02 (95%CI -0.06 to 0.01), p=0.22; I^2=20% Subgroup analysis 2 cross-over RCTs Saturated fats substituted with PUFA (through provision of fat containing foods) TC: ↓with saturated fats substituted with PUFA MD -0.30 (95%CI -0.39 to -0.21) LDL-C: ↓with saturated fats substituted with PUFA MD -0.28 (95%CI -0.36 to -0.20) 6 parallel RCTs Saturated fats substituted with PUFA (through provision of general advice on substituting saturated fats).	Findings suggest that reduced saturated fat intake compared to the control diet reduced total and LDL cholesterol. There was no effect of reduced saturated fat intake on HDL cholesterol or triacylglycerol. Limitations Difficulties in obtaining reliable dietary intake data, maintain the blind among participants and personnel and variation in the nature and quality of the interventions.

Study	Research methods	Analysis	Results	Comments
Hooper et al (2015) (Systematic review with meta-analysis) <u>Funding source</u> L Hooper: Studentship, Systematic Reviews Training, Institute of Child Health, University of London, UK. <u>Declarations of interest</u> None declared.	<u>Research question</u> What is the effect of reducing saturated fat intake and replacing it with carbohydrate, PUFA, MUFA and/or protein on mortality and cardiovascular morbidity? <u>Selection criteria</u> *Search dates:* July 2010 to March 2014 (plus search from Hooper 2012 – inception to June 2010). *Study design:* RCTs only. *Inclusion criteria:* >18yrs at any risk of CVD, with/without existing CVD, using/not using lipid-lowering medication; aim to reduce saturated fat intake or alter dietary fats and achieve reduction in saturated fats; intervention dietary advice, supplementation of fats, oils or modified or low-fat foods or a provided diet and the control group usual diet, placebo or a control diet; duration ≥ 24 months; mortality or cardiovascular morbidity data available; no language restrictions. *Exclusion criteria*: Pregnant, acutely ill or breastfeeding subjects; allocation not truly randomised; multifactorial trials. <u>Dietary assessment methods</u> Not reported.	<u>Analysis</u> Random effects meta-analysis to assess risk ratios. Low vs high % of energy from saturated fats. Incremental changes in % of energy from saturated fats. *Subgroup analysis* Saturated fat substitution with PUFA, MUFA, carbohydrate. <u>Evaluation of study quality</u> Cochrane 'risk of bias' tool used. Additional characteristics assessed include: studies being free of systematic differences in care, a study aiming to reduce saturated fat intake, achieving saturated fats reduction, and achieving total serum cholesterol reduction. Evidence assessed using GRADE system, sensitivity analyses, and heterogeneity examined using I^2 test.	15 RCTs; n=56,568; duration: 1.6 to 8.1y; age 46 to 66y; sex: M(8), F(3), M/F(4); health at baseline: high risk of CVD (4), previous MI (6), diabetic / impaired glucose intolerance (3), angina (2), breast cancer (1), siblings of people with CHD, with at least one CVD risk factor (1); country: USA (5), UK (6), The Netherlands (1), Norway (1), New Zealand (1), Australia (1). <u>Reduced saturated fats compared to usual diet</u> TC: ↓ with reduced saturated fats (13 RCTs; n=7115) MD -0.24mmol/L (95% CI -0.36 to -0.13), p<0.001; I^2=60% No clear differential effect on TC depending on the replacement for saturated fats. LDL-C:↓ with reduced saturated fats (5 RCTs; n=3291) MD -0.19mmol/L (95% CI -0.33 to -0.05), p<0.05; I^2=37% No clear differential effect on LDL-C depending on the replacement for saturated fats. HDL-C: no effect (7 RCTs; n=5147) MD -0.01mmol/L (95% CI -0.02 to 0.01), p=0.21; I^2=0% No clear differential effect on HDL-C depending on the replacement for saturated fats. TC:HDL-C ratio: no effect (3 RCTs; n=2985) MD -0.10mmol/L (95% CI -0.33 to 0.13) I^2=24% No clear differential effect on TC:HDL ratio depending on the replacement for saturated fats. TAG: no effect (7 RCTs; n=3845) MD -0.08mmol/L (95% CI -0.21 to 0.04) I^2=51% No clear differential effect on TAG depending on the replacement for saturated fats.	Findings suggest reducing saturated fat intake reduces TC and LDL-C but not HDL-C, TC:HDL-C ratio or TAG. No differential effect of replacement type was observed. <u>Limitations</u> Although the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched, due to limited resources, filters were applied to limit to core clinical journals (MEDLINE) and priority journals (EMBASE). Blood lipids were a secondary outcome and not included in the original search.

Study	Research methods	Analysis	Results	Comments
Schwab et al (2014) (Systematic narrative review) <u>Funding source</u> Supported by the Nordic Council of Ministers. <u>Declarations of interest</u> None declared.	<u>Research question</u> What are the effects of intake of total fat and various combinations and proportions of fatty acid classes in the diet, considering intake of other nutrients on: a. well-established indicators of clinical outcomes such as plasma or serum total lipids and lipoprotein concentrations, plasma or serum glucose and insulin concentrations and blood pressure? b. clinical outcomes including body weight, type 2 diabetes, CVD, and cancer? <u>Selection criteria</u> *Search dates:* January 2000- February 2012. *Study designs:* RCTs and PCS. *Inclusion criteria:* 18-70y, healthy (subjects with dyslipidaemia, glucose intolerance, or overweight (mean BMI of study population not exceeding 30kg/m^2) were included); ≥10 participants for RCTs; dietary assessment method: food record, FFQ, dietary recall, biomarkers; duration ≥ 4 weeks (RCTs), ≥6 months (BW and body composition studies); PCS follow-up >4y, studies >5y for cancers; RCT dropout <30% in 6 months, <40% on 12 months, <50% in 24 months; intervention: amount and/or quality of dietary fat; updated/relevant nutrient databases. *Exclusion criteria*: Studies without Caucasians or Caucasians a clear minority;	<u>Analysis</u> Narrative review, results of the quality assessment of the individual studies were summarised to evaluate the quality and strength of the overall evidence in relation to the posed research questions. The evidence for each exposure-outcome association was categorised according to predetermined categories: convincing, probable, limited-suggestive, and limited-no conclusion. <u>Evaluation of study quality</u> Primary evidence assessed for quality but method not reported. Quality categories included: A) high quality with very low risk of bias; B) good quality, some risk of bias but not enough to invalidate results; C) low quality with significant bias and weaknesses which may invalidate results.	9 RCTs; n=976; duration: 5 to 18wks; age 18 to 65y; sex: M(2), W(0), M/W(7); health at baseline: healthy (6), diabetic (1), obese/overweight (2); country: USA (3), UK (2), The Netherlands (2), Sweden (1), Czech Republic (1). <u>High MUFA and/or PUFA diet compared with high saturated fat diet</u> Saturated fat vs MUFA diet: saturated fat 13-19% of energy, MUFA 14-21% of energy. Saturated fat vs PUFA diets: saturated fat 20% of energy or 52% of total fat in diet, PUFA 9% of energy or 41% of total fat in diet. *Fasting plasma/serum TC* (9 RCTs, n=476) All RCTs: ↓TC. Convincing evidence of an effect; grade B evidence. *Fasting plasma/serum LDL-C* (9 RCTs, n=not reported). 8 RCTs: ↓ LDL-C. 1 RCT: no effect. Convincing evidence of an effect; grade B evidence. *Fasting plasma/serum HDL-C* (9 RCTs, n=476) 3 RCTs: ↓ HDL-C 1 RCT: ↑ HDL-C. 5 RCTs: no effect. Limited evidence-no conclusion; grade B evidence. *Fasting plasma/serum total TAGs* (8 RCTs, n=456) 2 RCTs: ↓ total TAGs. 6 RCTs: no effect. Effect unlikely; grade B evidence.	Substitution of saturated fats with MUFA and/or PUFA convincingly decreases concentration of total and LDL-C but is unlikely to affect total triglycerides. <u>Limitations</u> Focus on new evidence since previous edition of Nordic Nutrition Recommendations (NNR), hence why studies pre 2000 not included, however several systematic reviews and meta-analyses included in pervious publications. Strict criteria for both study quality and evidence grading resulting in a relatively conservative estimate of the evidence. Many questions remain unresolved due to conflicting results from studies and lack of high quality controlled studies.

Study	Research methods	Analysis	Results	Comments
	study aim outside scope of review; exposure food pattern or a whole food; included non-healthy subjects, obese subjects. <u>Dietary assessment methods</u> Food record, FFQ, dietary recall, valid biomarkers.			

Study	Research methods	Analysis	Results	Comments
Micha & Mozaffarian (2010) (Systematic review with meta-analysis) <u>Funding source</u> Searle Funds at The Chicago Community Trust; the Bill & Melinda Gates Foundation/WHO Global Burden of Diseases, Injuries, and Risk Factors Study. <u>Declarations of interest</u> Consulting honoraria (modest) from Nutrition Impact; Unilever; SPRIM.	<u>Research question</u> Elucidate effects of saturated fat consumption on CVD risk based on the most current evidence. <u>Selection criteria</u> *Search period*: Inception to September 2009. *Study design*: RCTs and PCS. *Inclusion criteria*: Adults; evaluating saturated fat intake and risk of CHD, stroke, type 2 diabetes, related risk pathways including lipids and lipoproteins, systemic inflammation, vascular function, insulin resistance. *Exclusion criteria*: A priori animal studies, ecological studies, commentaries, general reviews, case reports. <u>Dietary assessment methods</u> Not reported.	<u>Analysis</u> Narrative review. <u>Evaluation of study quality</u> Not reported.	Number of publications not mentioned for this analysis; characteristics of identified studies not summarised. <u>Increased intake of PUFA in the diet as substitution for saturated fats</u> TC, LDL-C, TC:HDL-C ratio, TAG: ↓ HDL-C: "slight lowering" ↓ <u>Increased intake of MUFA in the diet as substitution for saturated fats</u> TC, LDL-C, TC:HDL-C ratio, TAG: ↓ <u>Increased intake of carbohydrates in the diet as a substitution for saturated fats</u> TC, HDL-C: ↓ LDL-C: ↓ β=-0.032 mmol/L, p<0.05; 0.032 mmol/L decrease in serum LDL cholesterol for 1% isoenergetic substitution of saturated fats with carbohydrates TC:HDL-C ratio: no effect TAG: ↑	Substantial evidence indicating that reducing saturated fat has varying effects depending on the substitution nutrient. Substituting with PUFA or MUFA lowers total, LDL, HDL (PUFA only) cholesterol and the ratio. No effect on tryglycerides. Substituting with carbohydrate lowers total and LDL cholesterol and tryglycerides and increases HDL cholesterol. No effect on the ratio. Authors conclude that advice to reduce saturated fat intake without considering the replacement may have little or no effects on disease risk.

Study	Research methods	Analysis	Results	Comments
Van Horn et al (2008) (Systematic narrative review) <u>Funding source</u> None declared. <u>Declarations of interest</u> None declared.	<u>Research question</u> Review of the evidence associated with key dietary factors and risk of CVD. <u>Selection criteria</u> *Search period:* First review 1991-2001; update review 2001-2004; supplementary search in 2006. *Study Design:* Not detailed. *Inclusion criteria:* Human subjects; English language; articles in ADA evidence analysis library. *Exclusion criteria:* Sample size <10 in each treatment group; drop-out rate >20%. Provided more than 1000 papers, additional criteria applied but not detailed. <u>Dietary assessment method</u> Not reported.	<u>Analysis</u> Expert panel identified and evaluated current research, limited details provided. <u>Evaluation of study quality</u> Not reported.	*Saturated fat* 4 RCTs; n=25-290; duration: 4 to 8 wk; other study characteristics not reported. <u>Low saturated fats diet (<7% of energy)</u> reduced LDL-C by 9-12% (4 RCTs), and HDL-C (3 RCTs). Population studies (number and characteristics not reported): associations between diets high in saturated fats and increased TC, LDL-C, and HDL-C concentrations. *Isoenergetic replacement of saturated fat (2 RCTs)* Isoenergetic replacement of saturated fats with PUFA and MUFA decreases TC, LDL-C, and TC:HDL-C ratio.	To reduce the risk of CVD, dietary saturated fat should be replaced isoenergetically with complex carbohydrate and/or unsaturated fatty acids including both MUFA (<20% of energy) and PUFA (<10% of energy).

Study	Research methods	Analysis	Results	Comments
Mensink et al (2003) (Systematic review with meta-analysis) <u>Funding source</u> Maastricht University; Wageningen University; Wageningen Centre for Food Sciences. <u>Declarations of interest</u> None declared.	<u>Research question</u> Evaluate the effect of individual fatty acids on TC:HDL-C and on serum lipoproteins. <u>Selection criteria</u> *Search period:* January 1970- December 1998. *Study design:* Parallel, crossover or Latin-square design control trials. *Inclusion criteria:* Dietary fatty acids sole variable; controlled consistent dietary cholesterol intake; feeding period > 13 days; adult subjects >17 years; non disturbances of lipid metabolism or diabetes; English language only. *Exclusion criteria:* Very long chain PUFAs (n-3) e.g. fish oils; medium-chain fatty acids (too few studies to allow stats analysis); sequential study design; subjects with diabetes. <u>Dietary assessment method</u> Not reported.	<u>Analysis</u> Data points: Independent variable – fatty acid composition of the diet; Dependent variable - mean serum TC:HDL-C, mean serum lipid, or apolipoprotein concentration; of a group of subjects, at end of dietary period. Regression coefficients are predicted change in TC:HDL-C, serum lipid, or apolipoprotein, concentrations, when carbohydrate intake decreases by 1% of energy and the fatty acid increases by the same amount. Model estimated effects on a particular outcome of all fatty acids (saturated fats, *cis* MUFAs, n-6 *cis* PUFAs). Dependent variable: absolute lipid or apolipoprotein concentrations during the diets rather than changes induced by diets. Cook's distances and visual inspection of plots used for validity. Random-effect model not used as standard error not provided in the studies. <u>Evaluation of study quality</u> Not reported.	60 RCTs; n=1672; duration: 13 to 91days; age: 21 to 72y (reported in 51 RCTs); sex: 70% men; health at baseline: trials on inpatients (11), used liquid formulas (6); country: USA (34), The Netherlands (8), Denmark (4), Canada (3), Finland (2), Israel (2), Malaysia (2), Norway (2), Germany (1), Italy (1), UK (1). 40 RCTs reported mean pre study TC, range: 3.7 to 6.5mmol/L. <u>Substitution of saturated fats with PUFA</u> 1% of energy replaced from saturated fats with equal percentage of PUFA HDL-C: ↓ TC:HDL-C: ↓ <u>Substitution of saturated fats with MUFA</u> 1% of energy replaced from saturated fats with equal percentage of MUFA HDL-C: ↓ by 0.002mmol/L TC:HDL-C: ↓ <u>Isoenergetic substitution of carbohydrate with saturated fats</u> HDL-C: ↑ β =0.010mmol/L (95% CI 0.007 to 0.013) TC:HDL-C: no effect TAG: ↓ β = -0.021 (95% CI -0.027 to -0.015)	Efficacy of replacing saturated fats with carbohydrate depends on the effect on body weight in the long term and effect is uncertain. Replacement of saturated fats with *cis* unsaturated fatty acids reduce coronary artery disease risk. <u>Limitations</u> Effect of sex could not be examined as many studies combine results from men and women.

Study	Research methods	Analysis	Results	Comments
Yu-Poth et al (1999) (Systematic review with meta-analysis) <u>Funding source</u> None declared. <u>Declarations of interest</u> None declared.	<u>Research question</u> Evaluate the effects of different dietary interventions (National Cholesterol Education programs Step 1 and Step 2 dietary interventions) on major CVD risk factors in healthy and high-risk subjects using meta-analysis. <u>Selection criteria</u> *Search dates:* 1981-1997. *Study design:* RCTs (sequential, randomised, parallel-arm). *Inclusion criteria:* Aim to lower blood cholesterol concentrations or reduce body weight for primary purpose of preventing CVD; a Step 1 diet (all intervention groups: total fat ≤30% of energy; saturated fats ≤10% of energy; ≤ 300mg dietary cholesterol/d), a Step 2 diet (saturated fats ≤7% of energy; ≤200mg dietary cholesterol/d) or both were part of dietary intervention; subjects free-living, prepared own food and counselled by dietitians/professionals about low-fat diets; intervention ≥3 weeks to stabilise plasma cholesterol concentrations. *Exclusion criteria:* Not reported. <u>Dietary assessment method</u> 24 hour recall, 3-7 day food record and FFQ.	<u>Analysis</u> Changes in plasma TC, LDL-C, HDL-C and TAG after Step 1 and Step 2 dietary interventions assessed. Analysis of variance to compare effects of Step 1 with Step 2. Changes in plasma TC, LDL-C, HDL-C and TAG with changes in saturated fats evaluated by regression analysis. <u>Evaluation of study quality</u> Not reported.	37 RCTs; n=9276 (intervention), n=2310 (control); duration: 3wk to 4y; age: not reported; sex: M(9), W(7), M/W(21); health at baseline: healthy and high-risk subjects; country: not reported. Range of dietary interventions and experimental designs (% saturated fat of total energy <6% to <10%); had control group (19 RCTs) (maintained habitual lifestyle and food consumption during study); included exercise intervention (13 RCTs). *Step 1 intervention: lipids decreased by* TC: ↓ MD 0.63 ± 0.06mmol/L (10%) p<0.01 LDL-C: ↓ MD 0.49 ± 0.05mmol/L (12%) p<0.01 HDL-C: 0.04 ± 0.02mmol/L (1.5%) p not reported TC:HDL-C: ↓ MD 0.50 ± 0.11mmol/L (10%) p<0.01 TAG: ↓ MD 0.17 ± 0.04mmol/L (8%) p<0.01 *Step 2 intervention: lipids decreased by* TC: ↓ MD 0.81 ± 0.12mmol/L (13%) (p<0.01) LDL-C: ↓ MD 0.65 ± 0.09mmol/L (16%) (p<0.01) HDL-C: ↓ MD 0.09 ± 0.03mmol/L (7%) (p<0.01) TC:HDL-C: ↓ MD 0.34 ± 0.12mmol/L (7%) (p<0.01) TAG: ↓ MD 0.19 ± 0.14mmol/L (8%)(p<0.01) <u>Changes in lipids in men vs women</u> *Step 1 intervention* TAG: Women 0.01mmol/L (2.4%) Men -0.21mmol/L (-10.4%) *Step 2 intervention* HDL-C: Women -0.10mmol/L (-6.7%) Men -0.03mmol/L (-2.2%) p<0.05 TAG: Women 0.07mmol/L (5.4%) Men -0.03mmol/L (-1.5%)	Reduction in dietary fat and saturated fat has beneficial effects on CVD risk factors in free-living subjects. Plasma TC, LDL-C, and TAG concentrations and TC:HDL-C significantly decreased after both Step 1 and Step 2 diets. Weight loss and exercise combined can increase the effect.

Study	Research methods	Analysis	Results	Comments
			<u>Multiple regression analysis with body weight as a co-variable, every 1% decrease in energy from saturated fats resulted in:</u> TC: -0.056mmol/L (-0.77%) (r^2 =0.59 , p=0.001) LDL-C: -0.056mmol/L (-1.07%) HDL-C: -0.012mmol/L (-0.6%) TAG: no effect	

Study	Research methods	Analysis	Results	Comments
Tang et al (1998) (Systematic review with meta-analysis) <u>Funding source</u> Funded by a project grant from the nutrition programme phase 1 of the Department of Health and Medical Research Council. Authors supported by the British Heart Foundation and Imperial Cancer Research Fund. <u>Declarations of interest</u> None declared.	<u>Research Question</u> Estimate the efficacy of dietary advice to lower blood TC concentration in free-living subjects and to investigate the efficacy of different dietary recommendations. <u>Selection criteria</u> *Search period:* Inception to 1996. *Study Design:* RCTs. *Inclusion criteria:* Two groups, one a control, treatment assignment by random allocation; intervention was a global dietary modification (changes to various food components of the diet to achieve desired targets); lipid concentration measured before and after intervention. *Exclusion criteria:* Specific supplementation diets (e.g. specific oils, garlic); multifactorial interventions trials; trials aimed primarily at lowering body weight or blood pressure; interventions that lasted <4 weeks; randomisation of workplace or general practice. <u>Dietary assessment method</u> Not reported.	<u>Analysis</u> Absolute difference (mmol/L) in mean change in blood TC between control and intervention groups. % reduction cholesterol concentrations at end of trial or 12 months, whichever was earlier. SE of the difference for each comparison. Similar methods applied to changes in dietary intakes. Heterogeneity tested by comparing observed results in different categories of trials grouped according to type of diet, intensity of advice, and type of patients. <u>Evaluation of study quality</u> Not reported.	19 RCTs; n=40-2033; duration: 6wk to 5y; age: not reported; sex: M(7), W(2), M/W(10); health at baseline: CHD patients with aim of secondary prevention (5), raised cholesterol (4), raised blood pressure (3), healthy adults (4), women at increased risk of breast cancer (2), children (1); country: not reported. Average baseline blood TC concertation 6.3mmol/L. <u>Overall effect of dietary advice on TC</u> TC: ↓ (19 RCTs) MD 5.3% (95% CI 4.7 to 5.9). <u>Reduction in TC by category of diet</u> • American Heart Association Step 1 or equivalent diets (9 RCTs): MD -3.0% (95% CI 1.8 to 4.1), no significant heterogeneity ($X^2_4 = 6$, P>0.1), but estimate heavily depends on one large trial. • American Heart Association Step 2 or equivalent diets (8 RCTs): MD -5.6% (95% CI 4.7 to 6.5), significant heterogeneity of effects of Step 2 diets ($X^2_7 = 45$, p<0.001), includes one trial in children (aged 8- 10y). <u>Reduction in TC by duration of intervention</u> Overall reduction in blood TC concentration attributable to dietary advice was 6.6% at about 6 weeks, 8.5% at about 3 months, 6.8% at 6 months, 5.5% at 112 months and 4.4% at 24 months. <u>Compliance with dietary advice</u> Fat intake of control groups ranged from 29 to 42% of total energy intake. Two trials of Step 1 diets met target for saturated fat (<10% of total fat), both achieved the largest reduction in blood TC concentration.	Suggests that dietary advice to free-living subjects can be expected to reduce blood TC by only 3 to 6%. Step 1 diet only has a small cholesterol lowering effect even among those with evidence of CHD. <u>Limitations</u> Excluded trials in which dietary advice was given together with other interventions. Publication bias- unable to identify any unpublished trials. Limited analysis to published, tabulated data by approaching investigators and experts in the subject to obtain extra unpublished data or clarify areas of uncertainty, but was largely unsuccessful.

Study	Research methods	Analysis	Results	Comments
Clarke et al (1997) (Systematic review with meta-analysis) <u>Funding source</u> British Heart Foundation and Medical Research Council. <u>Declarations of interest</u> None declared.	<u>Research Question</u> Determine the quantitative importance of dietary fatty acids and dietary cholesterol to blood concentrations of TC, LDL-C and HDL-C. <u>Selection criteria</u> *Search period:* Not specified. *Study Design:* Metabolic ward studies. *Inclusion criteria:* Diets persisting for minimum 2 weeks; solid food studies (liquid diets considered separately); healthy volunteers. *Exclusion criteria:* Subjects selected for some disorder (e.g. diabetes or dyslipidaemia); dietary changes deliberately confounded by other interventions (e.g. weight reduction or exercise); no data available about dietary fatty acids or dietary cholesterol; poor compliance. <u>Dietary assessment method</u> Not reported.	<u>Analysis</u> Multilevel regression analyses (included: age, weight, dietary intake of nutrients, and one unique term per study to ensure people within any other one study were compared directly only with each other). Analyses assessed different sources of variability: (a) within group, between experiments; (b) within study, between matched groups; (c) within study, between unmatched groups; and (d) between studies. <u>Evaluation of study quality</u> Not reported.	No study characteristics reported. TC, LDL-C and HDL-C (395 RCTs). <u>Substitution of saturated fats with unsaturated fats</u> TC: ↓ (no data provided) <u>Substitution of saturated fats equivalent to 10% of dietary calories by carbohydrates</u> TC: ↓ -0.52mmol/L (SE 0.03) (95% CI 0.58 to 0.43), p<0.001 LDL-C: ↓ (227 RCTs) -0.36mmol/L (SE 0.05) (95% CI -0.046 to -0.026), p<0.001 HDL-C: ↓ (227 RCTs) -0.13mmol/L (SE 0.02) (95% CI -0.017 to -0.009), p<0.001	Substitution of saturated fats with unsaturated fats reduced total cholesterol. Substitution of saturated fats with carbohydrate reduces total, LDL and HDL cholesterol. <u>Limitations</u> Restricted to metabolic ward studies as non-experimental dietary studies in community subjects may chiefly reflect poor compliance.

Study	Research methods	Analysis	Results	Comments
Howell et al (1997) (Systematic review with meta-analysis) <u>Funding source</u> Supported by a grant-in-aid from the American Egg Board administered through the Egg Nutrition Center and by funds from The University of Arizona Agricultural Experiment Station. <u>Declarations of interest</u> None declared.	<u>Research Question</u> Investigate the extent to which study and subject characteristics, initial serum lipid concentrations, interactions of dietary manipulations, and the duration of treatment influenced the predictive models. Develop a more broadly applicable model, spanning a diversity of study designs and types of subjects, to predict more appropriately the extent to which meeting the National Cholesterol Education Program (NCEP) Steps 1 and 2 national dietary guidelines could be expected to affect changes in blood lipid concentrations of the American population. <u>Selection criteria</u> *Search period:* January 1966-February 1994. *Study Design:* Not reported. *Inclusion criteria:* English language; adults >18 years; studies reporting single-group or multiple-group repeated-measures comparisons; studies reporting quantitative measures of manipulated dietary components including one or more of the following: cholesterol, total fat (% of energy), saturated fats, PUFAs, and MUFAs (% of energy); studies reporting group means ± SDs or SEMs for quantitative measures of response variables including any or all of the following: serum TC, LDL-C, HDL-C, VLDL-C and serum TAG.	<u>Analysis</u> Study groups were weighted proportionally to their size and inversely to the number of times observed. Difference between the final and initial values of dietary cholesterol (mg/day) and total fat, PUFA, MUFA and saturated fats (% of energy), computed to create dietary change variables. Bivariate Pearson correlations described relations between dietary variables and response variables. Stepwise-multiple-regression analysis used to identify best linear prediction equations for response measures, evaluating combined and independent contributions of specified dietary variables. Forward stepwise variable selection to describe relations and control for problems of linear dependence. Effects of dietary manipulations explored using modified linear predication model into a nonlinear. Nonlinear least squares estimates significantly different from 0 taken as indicative of a discernible treatment duration effect.	224 studies; n=8143 (in 366 independent groups including 878 diet-blood lipid comparisons were presented for the weighted least square regression analyses); duration: not reported; age: 18 to 69y: sex: M (70% in independent groups); health at baseline: healthy (81%), coronary artery disease (19%); country: not reported. 10% studies where blinded (7% double blinded, 3% single blinded). <u>Saturated fats intake</u> *Bivariate relations between variables* TC: (r=0.80, p<0.0005) LDL-C: (r=0.79, p<0.0005) HDL-C: (r=0.60, p<0.0005) TAG: (r=-0.20, p=0.807) <u>Prediction equations</u> 1% change in total energy from saturated fats will result in 49.1µmol/L change in serum TC. 1% change in total energy from saturated fats will result in 46.5mmol/L. change in LDL-C. 1% change in total energy from saturated fats will result in 0.007mmol/L change in HDL-C.	Some individuals can lower their plasma cholesterol concentrations by decreasing dietary saturated fat and cholesterol intakes.

Study	Research methods	Analysis	Results	Comments
	Exclusion: Large clinical trials with multiple interventions; studies reporting data on weight reduction diets; fish oils, trans fat and hydrogenated fats were excluded. Dietary assessment method Weighed/measured intake, subject reported intake records, subject recall.	Evaluation of study quality Internal validity was assed as high, medium or low; 9% of studies were rated as having high internal validity.		

Table A2.5 RCTs assessing the relationship between dietary saturated fat intake and blood lipids in each review article

Study name[1] / first author (publication dates)	**Hannon et al, (2017)**	**Te Morenga et al, (2017)**	**Hooper et al, (2015)[2]**	**Schwab et al, (2014)**	**Van Horn et al, (2008)[3]**	**Mensink et al, (2003)[4]**	**Yu-Poth et al, (1999)**	**Tang et al, (1998)**
C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.								
Total primary studies (publications)	8	8 (21)[5]	14	9	8	60 (65)	37	19 (21)
Moreira 2014	C, H, L, T							
Noakes 2014	C, H, L, T							
Hendrie 2011		C,H,L,T						
Bos 2010	C, H, L, T			C, H, L, T				
Hartwich 2009	C, H, L, T							
van Dijk 2009	C, H, L			C, H, L				
Lesna 2008				C, H, L, T				
Chlebowski 2006			C					
Howard 2006			C, H, L, T, R					
Krauss 2006	C, H, L, T							
Jenkins 2006					L			
Appel 2005					H, L, T			
Lefevre 2005				C, H, L, T				
Healthy Start		C						

Study name[1] / first author (publication dates)	**Hannon et al, (2017)**	**Te Morenga et al, (2017)**	**Hooper et al, (2015)[2]**	**Schwab et al, (2014)**	**Van Horn et al, (2008)[3]**	**Mensink et al, (2003)[4]**	**Yu-Poth et al, (1999)**	**Tang et al, (1998)**
C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.								
Ley 2004			C, H, L, T, R					
Piers 2003	C, H, L, T							
Jenkins 2003					L			
Zhu et al, 2003		C, H, L, T						
Vessby 2001				C, H, L, T				
Smith 2003				C, H, L, T				
Judd 2002					L			
Lichtenstein 2002					H, L, T			
Lovejoy 2002				C, H, L, T				
Summers 2002				C, H, L, T				
Dietary Intervention Study in Children (DISC) Obarzanek 2001 DISC Collaboration writing group 1995		C, H, L, T			C, H, L, T			C
Kriketos 2001	C, H, L, T							
Moy 2001			H, L, T					
Denke 2000		C, H, L, T		C, H, L, T				
Yu-Poth 2000					L, H			

Study name[1] / first author (publication dates)	Hannon et al, (2017)	Te Morenga et al, (2017)	Hooper et al, (2015)[2]	Schwab et al, (2014)	Van Horn et al, (2008)[3]	Mensink et al, (2003)[4]	Yu-Poth et al, (1999)	Tang et al, (1998)
C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.								
Estevez-Gonzalez 1998		C,H,L,T						
Ginsberg 1998					H, L, T	X		
Judd 1998						X		
Muller 1998						X		
Tholstrup 1998						X		
Aro 1997						X		
Cater 1997						X		
Knopp 1997							C, H, L, T	
Mazier 1997						X		
McCarron 1997							C, H, L, T	
Simon 1997			C, H, L, T					
Kasim 1993							C, H, L, T	
Walden 1997							C, H, L, T	
Davidson 1996							C, H, L, T	
Fox 1996							C, H, L, T	
Park 1996						X		
Siggaard 1996							C, H, L, T	
Almendingen 1995						X		
Dengel 1995							C, H, L, T	

Study name[1] / first author (publication dates)	Hannon et al, (2017)	Te Morenga et al, (2017)	Hooper et al, (2015)[2]	Schwab et al, (2014)	Van Horn et al, (2008)[3]	Mensink et al, (2003)[4]	Yu-Poth et al, (1999)	Tang et al, (1998)
C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.								
Dougherty 1995						X		
Fielding 1995						X		
Geil 1995							C, H, L, T	
Howard 1995						X		
Jeffery 1995							C, H, L, T	
Katzel 1995							C, H, L, T	
Nelson 1995						X		
Raben 1995							C, H, L, T	
Sundram 1995						X		
Special Turku Coronary Risk Factor Intervention Project (STRIP)		C,H,L,T						
Children's Health Project		L						
de Lorgeril 1994							C, H, L, T	
Burr 1989			C, H					C
Denke 1994							C, H, L, T	
Ginsberg 1994						X		
Haskell 1994							C, H, L, T	
Judd 1994						X		

Study name[1] / first author (publication dates)	Hannon et al, (2017)	Te Morenga et al, (2017)	Hooper et al, (2015)[2]	Schwab et al, (2014)	Van Horn et al, (2008)[3]	Mensink et al, (2003)[4]	Yu-Poth et al, (1999)	Tang et al, (1998)
C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.								
Lichtenstein 1994a						X		
Lichtenstein 1994b						X		
Sarkkinen 1994								C
Shah 1994							C, H, L, T	
Sundram 1994						X		
Tholstrup (b) 1994						X		
Tholstrup (a) 1994						X		
Zock 1994						X		
Baer 1993							C, H, L, T	
Derr 1993						X		
Hunninghake 1993								C
Kris-Etherton 1993						X		
Lichtenstein 1993						X		
Schlundt 1993							C, H, L, T	
Singh 1993							C, H, L, T	
Anderson 1992								C
Barnard 1992							C, H, L, T	
Barr 1992						X		
Berry 1992						X		

Study name[1] / first author (publication dates)	Hannon et al, (2017)	Te Morenga et al, (2017)	Hooper et al, (2015)[2]	Schwab et al, (2014)	Van Horn et al, (2008)[3]	Mensink et al, (2003)[4]	Yu-Poth et al, (1999)	Tang et al, (1998)
C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.								
Bonanome 1992						X		
Denke 1992						X		
Marckmann 1992						X		
Schuler 1992							C, H, L, T	
Sciarrone 1992								C
Seim 1992							C, H, L, T	
Singh (a) 1992							C, H, L, T	
Singh (b) 1992							C, H, L, T	
Valsta 1992						X		
Wahrburg 1992						X		
Watts 1992			C, H, L, T, R					C
Zock 1992						X		
Bae 1991							C, H, L, T	
Barnard 1991							C, H, L, T	
Berry 1991						X		
Bloemberg 1991								C
Chan 1991						X		
Iacano 1991						X		
Kwon 1991						X		
Nikolaus 1991							C, H, L, T	

Study name[1] / first author (publication dates)	Hannon et al, (2017)	Te Morenga et al, (2017)	Hooper et al, (2015)[2]	Schwab et al, (2014)	Van Horn et al, (2008)[3]	Mensink et al, (2003)[4]	Yu-Poth et al, (1999)	Tang et al, (1998)
C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.								
Shepherd 1991							C, H, L, T	
Tremblay 1991							C, H, L, T	
Wardlaw 1991						X		
Wood 1991							C, H, L, T	
Baron 1990								C
Boyd 1990							C, H, L, T	
Denamark-Wahrenfreid 1990								C
Dreon 1990								C
Ginsberg 1990						X		
Insull 1990								C
Mensink 1990						X		
Ornish 1990							C, H, L, T	
Hockaday 1978			C					
Wardlaw 1990						X		
McDonald 1989						X		
Mensink 1989a						X		
Mensink 1989b						X		
Oslo Diet-Heart Study Bonanome 1988			C			X		C

Study name[1] / first author (publication dates)	Hannon et al, (2017)	Te Morenga et al, (2017)	Hooper et al, (2015)[2]	Schwab et al, (2014)	Van Horn et al, (2008)[3]	Mensink et al, (2003)[4]	Yu-Poth et al, (1999)	Tang et al, (1998)
C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.								
Boyd 1988								C
Grundy 1988						X		
Judd 1988						X		
Katan 1988						X		
Mensink 1987						X		
Grundy 1986a						X		
Grundy 1986b						X		
Marshall 1986						X		
Arntzenius 1985							C, H, L, T	
Kuusi 1985							C, H, L, T	C
Mattson 1985						X		
McPherson 1995						X		
Reiser 1985						X		
Ehnholm 1984							C, H, L, T	
Becker 1983						X		
Harris 1983						X		
Wolf 1983						X		
Brussard 1982						X		
Ehnholm 1982							C, H, L, T	C
Laine 1982						X		

Study name[1] / first author (publication dates)	Hannon et al, (2017)	Te Morenga et al, (2017)	Hooper et al, (2015)[2]	Schwab et al, (2014)	Van Horn et al, (2008)[3]	Mensink et al, (2003)[4]	Yu-Poth et al, (1999)	Tang et al, (1998)
C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.								
Hjermann 1981							C, H, L, T	
Lewis 1981						X		
Brussaard 1980						X		
Houtsmuller 1979			C, T					
Woodhill 1978			C, T					C
Anderson 1976						X		
MRC 1968			C					
Grande 1972						X		
Grande 1970						X		
Dayton 1969			C					
American National Heart Study 1968								C
Research Committee 1965								C
Rose 1965			C					

Outcomes measured by study: C, total cholesterol (TC); H, high density lipoprotein cholesterol (HDL-C); L, low density lipoprotein cholesterol (LDL-C); T, triacylglycerol (TAG); R, TC to HDL-C ratio.

[1] Study name is only provided when two or more publications for that study are used by the reviews. Micha and Mozaffarian (2010), Clarke et al, (1997), Howell et al, (1997): unclear which primary studies were included in reviews.

[2] Hooper et al, (2015) presents publications used in the analyses by study name and identifies a main study publication along with all supplementary publications for the study. It is not possible to know which exact publication the data has come from, therefore, the main study publication has been used in the table above.

[3] Van Horn et al, (2008) also includes the review by Yu-Poth (1999).

[4] Unclear in review which papers relate to each outcome measured.

[5] Te Morenga and Montez (2017) included 8 RCTs reported in 21 publications, study name only provided when 2 or more publication for that study are used by the reviews.

Blood pressure

Table A2.6 Characteristics of meta-analyses and systematic reviews

Study	Research methods	Analysis	Results	Comments
Te Morenga & Montez (2017b) (systematic review with meta-analysis) Funding source: The University of Otago and the WHO Declarations of interest: None declared	Research question Examine the evidence for health effects associated with reducing saturated fats and trans fats intake in free living children, adolescents and young adults aged 2 to 19 years of age Selection criteria *Search dates:* inception to July 2016 *Study design:* RCTs *Inclusion criteria:* children, adolescents and young adults aged 2 to 19 years, healthy individuals as well as individuals with or at risk of hyperlipidaemia, hypertension or diabetes (type 1 & 2), or who were overweight or obese. RCTs with intervention duration at least 2 weeks with primary intention of reducing saturated fats or trans fats directly or through reduction in total fat intake. *Exclusion criteria:* studies targeting those that pregnant, acutely ill or with chronic infection such as HIV. Trials where weight loss was primary outcome or involving multifactorial interventions where effect of saturated fats or trans fats reduction could not be separated from the effect of other changes such as physical activity level	Analysis Random effects meta-analysis (data pooled using inverse variance models) Evaluation of study quality Cochrane criteria used to assess risk of bias. Evidence assessed using GRADE system. Evidence summaries and GRADE assessments were discussed and reviewed by the WHO Nutrition Guidance Expert Advisory Group Subgroup on Diet and health as part of WHO's guideline development process.	2 RCTs; n=1106; duration: 3y to 19y; age 3 to 10y; sex: M/W (2); health at baseline: hyperlipidemic (1), not specified (1); country: US (1), Finland (1). Reduced saturated fats Systolic BP: no effect (2 RCTs; n=1106) MD -0.68 (95% CI -1.71 to 0.35), p=0.19, I^2=0% Diastolic BP: ↓with reduced saturated fat intake (2 RCTs; n=1106) MD -1.45 (95% CI -2.34 to -0.56), p=0.001, I^2=0%	Findings suggest that reduced saturated fat intake compared to the control diet reduced diastolic blood pressure but not systolic blood pressure. Limitations Difficulties in obtaining reliable dietary intake data, maintain the blind among participants and personnel and variation in the nature and quality of the interventions.

Study	Research methods	Analysis	Results	Comments
	Dietary assessment methods 24hr dietary recalls, product inventory; daily consumption checklists; 3-day diet records, FFQ, biomarker assessment (pentadecanoic acid)			

Study	Research methods	Analysis	Results	Comments
Hooper et al (2015) (Systematic review with meta-analysis) <u>Funding source</u> L Hooper: Studentship, Systematic Reviews Training, Institute of Child Health, University of London, UK. <u>Declarations of interest</u> None declared.	<u>Research question</u> What is the effect of reducing saturated fat intake and replacing it with carbohydrate, PUFA, MUFA and/or protein on mortality and cardiovascular morbidity? <u>Selection criteria</u> *Search dates:* July 2010 to March 2014 (plus search from Hooper 2012 – inception to June 2010). *Study design:* RCTs only. *Inclusion criteria:* >18yrs at any risk of CVD, with/without existing CVD, using/not using lipid-lowering medication; aim to reduce saturated fat intake or alter dietary fats and achieve reduction in saturated fats; intervention dietary advice, supplementation of fats, oils or modified or low-fat foods or a provided diet and the control group usual diet, placebo or a control diet; duration ≥ 24 months; mortality or cardiovascular morbidity data available; no language restrictions. *Exclusion criteria*: Pregnant, acutely ill or breastfeeding subjects; allocation not truly randomised; multifactorial trials. <u>Dietary assessment methods</u> Not reported.	<u>Analysis</u> Random effects meta-analysis to assess risk ratios. Low vs high % of energy from saturated fats. Incremental changes in % energy from saturated fats. *Subgroup analysis:* Saturated fat substitution with PUFA, MUFA, carbohydrate. <u>Evaluation of study quality</u> Cochrane 'risk of bias' tool used. Additional characteristics assessed include: studies being free of systematic differences in care, a study aiming to reduce saturated fat intake, achieving saturated fats reduction, and achieving total serum cholesterol reduction. Evidence assessed using GRADE system, sensitivity analyses, and heterogeneity examined using I^2 test.	5 RCTs; n=3812 participants; duration: 3.8 to 8.1y; age: 30 to 67y; sex: M(3), W(1), M/W(1); health at baseline: high risk of CVD (1), previous MI (3), diabetic/impaired glucose intolerance (1); country: USA (1), UK (1), Norway (1), Australia (1), New Zealand (1). <u>Reduced saturated fats</u> Systolic blood pressure: no effect MD = -0.19 mmHg, 95% CI -1.36 to 0.97, P=0.97, I^2 0% Diastolic blood pressure: no effect MD = -0.36 mmHg, 95% CI -1.03 to 0.32, P=1.00, I^2 0%	Reducing saturated fats has no effect on systolic or diastolic blood pressure. <u>Limitations</u> Although the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched, due to limited resources, filters were applied to limit to core clinical journals (MEDLINE) and priority journals (EMBASE). As a secondary outcome, blood pressure was not included in the original search.

Study	Research methods	Analysis	Results	Comments
Schwab et al (2014) (Systematic narrative review) <u>Funding source</u> Supported by the Nordic Council of Ministers. <u>Declarations of interest</u> None declared.	<u>Research question</u> What are the effects of intake of total fat and various combinations and proportions of fatty acid classes in the diet, considering intake of other nutrients on: a. well-established indicators of clinical outcomes such as plasma or serum total lipids and lipoprotein concentrations, plasma or serum glucose and insulin concentrations and blood pressure? b. clinical outcomes including body weight, type 2 diabetes, CVD, and cancer? <u>Selection criteria</u> *Search dates:* January 2000- February 2012. *Study designs:* RCTs and PCS. *Inclusion criteria:* 18 to 70y, healthy (subjects with dyslipidaemia, glucose intolerance, or overweight (mean BMI of study population not exceeding 30kg/m^2) were included); ≥10 participants for RCTs; dietary assessment method: food record, FFQ, dietary recall, biomarkers; duration <u>≥</u> 4 weeks (RCTs), <u>≥</u>6 months (body weight and body composition studies); PCS follow-up >4y, studies >5y for cancers; RCT dropout <30% in 6 months, <40% on 12 months, <50% in 24 months; intervention: amount and/or quality of dietary fat; updated/relevant nutrient databases.	<u>Analysis</u> Narrative review, results of the quality assessment of the individual studies were summarised to evaluate the quality and strength of the overall evidence in relation to the posed research questions. The evidence for each exposure-outcome association was categorised according to predetermined categories: convincing, probable, limited-suggestive, and limited-no conclusion. <u>Evaluation of study quality</u> Primary evidence assessed for quality but method not reported. Quality categories included: A) high quality with very low risk of bias; B) good quality, some risk of bias but not enough to invalidate results; C) low quality with significant bias and weaknesses which may invalidate results.	3 RCTs; n=647; duration: 8 wks to 3 months; age: 30 to 70y; sex: M (0), W (0), M/W (3); health at baseline: healthy (2), impaired glucose tolerance but not diabetic (1); country: The Netherlands (1), Europe (1), Europe/Australia (1). 1 PCS; n=28,100; durations: 12.9y; age: ≥39y; sex: F; health at baseline: healthy; country: USA. 3 RCTs and 1 PCS compared MUFA and saturated fats. Saturated fats replaced with MUFA (20-21% of energy) resulted in lower blood pressure in two of the RCTs. 1 RCT found the response to a MUFA-enriched diet (21% of energy) was pronounced when total fat was <37% of energy, compared with total fat intake >37% of energy. PCS found no effect on blood pressure. 1 RCT found fish oil 12 g/day resulted in lower mean arterial blood pressure than saturated fats in an energy-restricted setting.	Evidence for an association between total fat, proportions of saturated fats, MUFA or total unsaturated fat and blood pressure was 'limited-no conclusion'. <u>Limitations</u> Focus on new evidence since previous edition of Nordic Nutrition Recommendations (NNR), hence why studies pre 2000 not included, however several systematic reviews and meta-analyses included in previous publications. Strict criteria for both study quality and evidence grading resulting in a relatively conservative estimate of the evidence. Many questions remain unresolved due to conflicting results from studies and lack of high quality controlled studies.

Study	Research methods	Analysis	Results	Comments
	Exclusion criteria: Studies without Caucasians or Caucasians a clear minority; study aim outside scope of review; exposure food pattern or a whole food; included non-healthy subjects, obese subjects. <u>Dietary assessment methods</u> Food record, FFQ, dietary recall, valid biomarkers.			

Study	Research methods	Analysis	Results	Comments
Micha & Mozaffarian (2010) (Systematic review) Funding source Searle Funds at The Chicago Community Trust; the Bill & Melinda Gates Foundation/WHO Global Burden of Diseases, Injuries, and Risk Factors Study. Declarations of interest Consulting honoraria (modest) from Nutrition Impact, Unilever and SPRIM.	Research question Elucidate effects of saturated fat consumption on CVD risk based on the most current evidence. Selection criteria *Search period*: Inception to September 2009. *Study design*: RCTs and PCS. *Inclusion criteria*: Adults; evaluating saturated fat intake and risk of CHD, stroke, type 2 diabetes, related risk pathways including lipids and lipoproteins, systemic inflammation, vascular function, insulin resistance. *Exclusion criteria*: A priori animal studies, ecological studies, commentaries, general reviews, case reports. Dietary assessment methods Not reported.	Analysis Narrative review. Evaluation of study quality Not reported.	Characteristics of identified studies not summarised. 7 out of the 9 RCTs observed no differences between diets that differed in saturated fat intakes and replacement nutrients. 1 of the 5 RCTs including a comparison to PUFA found an improvement (decrease) in blood pressure (4 RCTs found no effect). 2 of the 5 RCTs including a comparison to MUFA found an improvement (decrease) in blood pressure (3 RCTs found no effect). All of the 4 RCTs including a comparison to carbohydrate found no effect.	Varying saturated fat consumption intake has no clear effect on blood pressure.

Table A2.7 RCTs assessing the relationship between dietary saturated fat intake and blood pressure in each review article

Study name / first author (publication dates)	**Te Morenga et al, (2017)**	**Hooper et al, (2015)[1]**	**Schwab et al, (2014)**	**Micha and Mozaffarian (2010)**
Total primary studies (publications)	2	5	3	9
Bos 2010			X	
Gulseth 2010			X	
Sanders 2009				X
STRIP Niinikoski et al, 2009	X			
Howard 2006		X		
Rasmussen 2006			X	X
Dyerberg 2004				
Ley 2004		X		
Piers 2003				X
Lahoz 1997				X
Storm 1997				X
DISC 1995	X			
Uusitupa 1994				X
Sacks 1987				X
Margetts 1985				X
Puska 1985				X
Woodhill 1978		X		
MRC 1968		X		
Leren 1966		X		

[1] Hooper et al, (2015) presents publications used in the analyses by study name and identifies a main study publication along with all supplementary publications for the study. It is not possible to know which exact publication the data has come from, therefore, the main study publication has been used in the table above.

Table A2.8 PCS assessing the relationship between dietary saturated fat intake and blood pressure in each review article

Study name / first author (publication dates)	**Schwab et al, (2014)**
Total primary studies (publications)	1
Wang 2010	X

Type 2 Diabetes and markers of glycaemic control

Table A2.9 Characteristics of meta-analyses and systematic reviews

Study	Research methods	Analysis	Results	Comments
Type 2 diabetes				
de Souza et al (2015) (Systematic review with meta-analysis) Funding source World Health Organization. Declarations of interest Canadian Institutes for Health Research postdoctoral fellowship; Province of Ontario graduate scholarship; Canadian Institutes for Health Research.	Research question Systematically review associations between saturated fat and trans fats intake and total mortality, CVD and associated mortality, CHD and associated mortality, ischemic stroke, type 2 diabetes. Selection criteria *Search period*: Up to 1 May 2015. *Study design:* Observational studies. *Inclusion criteria*: Observational studies in humans; report a measure of association between intakes of saturated fats or trans fats (measured by self-report or a biomarker) and total mortality, CVD and associated mortality, CHD and associated mortality, ischemic stroke, type 2 diabetes (measured by self-report and/or confirmed by medical records or registry linkage). *Exclusion criteria*: Not reported. Dietary assessment methods FFQ, SQFFQ, 24 hr recall, dietary recall, 7 day food diary, weighted food diary, diet history, 4 day prospective diet record, cross check diet history method.	Analysis The principle association measures were RRs between highest and lowest intakes. ≥ 2 studies a random effects meta-analysis was performed. ≤ 3 studies fixed effect estimates were also considered. Heterogeneity measured using Cochran's Q test (significant at P<0.10), quantified with the I^2 statistic. If ≥ 10 studies and substantial heterogeneity (I^2 > 60% or P_Q < 0.10) meta-regression was used to explore heterogeneity. Evaluation of study quality The Newcastle-Ottawa scale was used to measure the risk of bias of included studies. The GRADE approach was used to assess confidence in the effect estimates derived from the body of evidence.	8 PCS; n=522 to 84,204; duration: 5 to 14y; age: 34 to 75y; sex: M (3), W (4), M/W (1); health at baseline: not reported; country: USA (4), Finland (3), Australia (1). Type 2 diabetes (8 cohorts) *Highest vs lowest saturated fat intake* Most adjusted: RR 0.95 (95% CI 0.88 to 1.03) p=0.20; I^2=0%, P_{het}=0.61 Least adjusted: RR 1.23 (95% CI 0.98 to 1.52) p=0.07; I^2=91%, P_{het}<0.00001	Saturated fat intake is not associated with type 2 diabetes, but the evidence considered is heterogeneous with methodological limitations. Limitations Comparison of higher fat and lower fat obscures the importance of reciprocal and possibly heterogeneous decreases in other macronutrients that accompany high saturated fat intake. Most studies did not model the effect of nutrient substitution.

Study	Research methods	Analysis	Results	Comments
Hooper et al (2015) (Systematic review with meta-analysis) Funding source L Hooper: Studentship, Systematic Reviews Training, Institute of Child Health, University of London, UK. Declarations of interest None declared.	Research question What is the effect of reducing saturated fat intake and replacing it with carbohydrate, PUFA, MUFA and/or protein on mortality and cardiovascular morbidity? Selection criteria *Search dates:* July 2010 to March 2014 (plus search from Hooper 2012 – inception to June 2010). *Study design:* RCTs only. *Inclusion criteria:* >18yrs at any risk of CVD, with/without existing CVD, using/not using lipid-lowering medication; aim to reduce saturated fat intake or alter dietary fats and achieve reduction in saturated fats; intervention dietary advice, supplementation of fats, oils or modified or low-fat foods or a provided diet and the control group usual diet, placebo or a control diet; duration ≥ 24 months; mortality or cardiovascular morbidity data available; no language restrictions. *Exclusion criteria*: Pregnant, acutely ill or breastfeeding subjects; allocation not truly randomised; multifactorial trials. Dietary assessment methods Not reported.	Analysis Random effects meta-analysis to assess risk ratios. Low vs high % of energy from saturated fats. Incremental changes in % of energy from saturated fats. *Subgroup analysis:* Saturated fat substitution with PUFA, MUFA, carbohydrate. Evaluation of study quality Cochrane 'risk of bias' tool used. Additional characteristics assessed include: studies being free of systematic differences in care, a study aiming to reduce saturated fat intake, achieving saturated fats reduction, and achieving total serum cholesterol reduction. Evidence assessed using GRADE system, sensitivity analyses, and heterogeneity examined using I^2 test.	Type 2 diabetes, new diagnoses 1 RCT; n=48,835, reported on diagnosis. No clear effect of reducing saturated fat intakes (compared with usual diet) on diagnosis of diabetes RR: 0.96, (95%CI 0.90 to 1.02), P= 0.21	No clear effect of reducing saturated fats on diabetes diagnoses. Limitations Although the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched, due to limited resources, filters were applied to limit to core clinical journals (MEDLINE) and priority journals (EMBASE).

Study	Research methods	Analysis	Results	Comments
Schwab et al (2014) (Systematic narrative review) <u>Funding source</u> Supported by the Nordic Council of Ministers. <u>Declarations of interest</u> None declared.	<u>Research question</u> What are the effects of intake of total fat and various combinations and proportions of fatty acid classes in the diet, considering intake of other nutrients on: a. well-established indicators of clinical outcomes such as plasma or serum total lipids and lipoprotein concentrations, plasma or serum glucose and insulin concentrations and blood pressure? b. clinical outcomes including body weight, type 2 diabetes, CVD, and cancer? <u>Selection criteria</u> *Search dates:* January 2000-February 2012. *Study designs:* RCTs and PCS. *Inclusion criteria:* 18-70y, healthy (subjects with dyslipidaemia, glucose intolerance, or overweight (mean BMI of study population not exceeding 30kg/m^2) were included); n≥10 participants for RCTs; dietary assessment method: food record, FFQ, dietary recall, biomarkers; duration<u>≥</u>4w (RCTs), <u>≥</u>6 months (body weight and body composition studies); PCS follow-up >4y, studies >5y for cancers; RCT dropout <30% in 6m, <40% 12m, <50% 24m; intervention: amount and/or quality of dietary fat; updated/relevant nutrient databases. *Exclusion criteria*: Studies without Caucasians or Caucasians a clear minority; study aim outside scope of review; exposure food pattern or a whole food;	<u>Analysis</u> Narrative review, results of the quality assessment of the individual studies were summarised to evaluate the quality and strength of the overall evidence in relation to the posed research questions. The evidence for each exposure-outcome association was categorised according to predetermined categories: convincing, probable, limited-suggestive, and limited-no conclusion. <u>Evaluation of study quality</u> Primary evidence assessed for quality but method not reported. Quality categories included: A) high quality with very low risk of bias; B) good quality, some risk of bias but not enough to invalidate results; C) low quality with significant bias and weaknesses which may invalidate results.	<u>Type 2 diabetes</u> *Saturated fat intake (2 PCS)* No association *Substituting PUFA for saturated fats (3-6% of energy)* (2 PCS) 1 PCS reported reduced risk of type 2 diabetes: RR 0.84 (95% CI 0.71 to 0.98) 1PCS reported no association with type 2 diabetes with changing the PUFA:saturated fat ratio (OR 0.91, 95% CI 0.81 to 1.03), although the association was significant when model was not adjusted for BMI or waist:hip ratio (OR 0.88, 95% CI 0.78 to 0.99). Evidence graded limited to draw conclusions between saturated fat intake and type 2 diabetes.	<u>Limitations</u> Focus on new evidence since previous edition of Nordic Nutrition Recommendations (NNR), hence why studies pre 2000 not included, however several systematic reviews and meta-analysis included in previous publications. Strict criteria for both study quality and evidence grading resulting in a relatively conservative estimate of the evidence. Many questions remain unresolved due to conflicting results from studies and lack of high quality controlled studies.

Study	Research methods	Analysis	Results	Comments
	included non-healthy subjects, obese subjects. Dietary assessment methods Food record, FFQ, dietary recall, valid biomarkers.			

Study	Research methods	Analysis	Results	Comments
Alhazmi et al (2012) (Systematic review with meta-analysis) Funding source A Alhazmi supported by scholarship from the government of Saudi Arabia. Declarations of interest None declared.	Research question Association between macronutrient intake and type 2 diabetes risk. Selection criteria *Search dates*: Up to July 2012. *Study designs*: PCS. *Inclusion criteria*: Cohorts that examined the relationship between dietary macronutrient intake or macronutrient sub-types and type 2 diabetes and if included healthy participants at baseline with no history of type 2 diabetes at baseline assessment; studies that report RR, OR or HRs and 95%CIs for comparison of type 2 diabetes risk between the highest and lowest levels of macronutrient consumption were included; required a minimum score of 7 on JBI check list for quality; human studies only; no language restriction. *Exclusion criteria:* Reviews, case-control, case studies, editorial or statistical analysis. Dietary assessment methods FFQs.	Analysis RRs (95% CI) comparing type 2 diabetes risk between highest and lowest quintiles of macronutrient intake. A random effects meta-analysis model, which takes into account within- and between-study variations, was applied. Sub-group analysis conducted by length of follow-up period (<10y or ≥10y), sex and use of follow-up or baseline only FFQ. Heterogeneity between studies was measured using I^2 statistic. Evaluation of study quality JBI checklist.	7 PCS for saturated fat intake and type 2 diabetes risk; n=2724 to 84,360; duration: 6 to 14y; age: 34 to 75y; sex: M(1), F(5), M/F(1); health at baseline: healthy with no history of diabetes; country: USA (6), Europe (1). Saturated fat intakes Type 2 diabetes risk: no association RR: 0.99 (95% CI 0.91 to 1.07), I^2=0.0%, p=0.75	Saturated fat intake was not significantly associated with type 2 diabetes risk. Limitations It is possible that the observed effects between macronutrient intake and the risk of type 2 diabetes could be due to residual or unmeasured confounding factors in PCS.

Study	Research methods	Analysis	Results	Comments
Micha & Mozaffarian (2010) (Systematic review) Funding source Searle Funds at The Chicago Community Trust; the Bill & Melinda Gates Foundation/WHO Global Burden of Diseases, Injuries, and Risk Factors Study. Declarations of interest Consulting honoraria (modest) from Nutrition Impact, Unilever and SPRIM.	Research question Elucidate effects of saturated fat consumption on CVD risk based on the most current evidence. Selection criteria *Search period*: Inception to September 2009. *Study design*: RCTs and PCS. *Inclusion criteria*: Adults; evaluating saturated fat intake and risk of CHD, stroke, type 2 diabetes, related risk pathways including lipids and lipoproteins, systemic inflammation, vascular function, insulin resistance. *Exclusion criteria*: A priori animal studies, ecological studies, commentaries, general reviews, case reports. Dietary assessment methods Not reported.	Analysis Narrative review. Evaluation of study quality Not reported.	1 RCT, 4 PCS; study characteristics not summarised. Type2 diabetes *4 PCS: N*o association with saturated fat intake. *1 RCT* (Women's Health Initiative: n=45,887, saturated fat intake reduced from 12.7 to 9.5% of energy over 8 years, mainly replaced with carbohydrate, total fat also reduced): No effect on incident diabetes : RR = 0.95 (95% CI 0.90 to 1.03)	Several long-term observational studies and one large RCT suggest no effect of saturated fat consumption on onset of diabetes.

Study	Research methods	Analysis	Results	Comments
Markers of glycaemic control				
Te Morenga & Montez (2017b) (systematic review with Meta-analysis) Funding source: The University of Otago and the WHO Declarations of interest: None declared.	Research question Examine the evidence for health effects associated with reducing saturated fats and trans fats intake in free living children, adolescents and young adults aged 2 to 19 years of age Selection criteria *Search dates:* inception to July 2016 *Study design:* RCTs *Inclusion criteria:* children, adolescents and young adults aged 2 to 19 years, healthy individuals as well as individuals with or at risk of hyperlipidaemia, hypertension or diabetes (type 1 & 2), or who were overweight or obese. RCTs with intervention duration of at least 2 weeks with primary intention of reducing saturated fats or trans fats directly or through reduction in total fat intake. *Exclusion criteria:* studies targeting those that were pregnant, acutely ill or with chronic infection such as HIV. Trials where weight loss was primary outcome and trials involving multifactorial interventions where the effect of saturated fats or trans fats reduction could not be separated from the effect of other changes such as physical activity level Dietary assessment methods 24hr dietary recalls, product inventory; daily consumption checklists; 3-day diet records, FFQ, biomarker assessment (pentadecanoic acid)	Analysis Only 1 RCT Evaluation of study quality Cochrane criteria used to assess risk of bias. Evidence assessed using GRADE system. Evidence summaries and GRADE assessments were discussed and reviewed by the WHO Nutrition Guidance Expert Advisory Group Subgroup on Diet and health as part of WHO's guideline development process.	1 RCT; n=437; duration 19y; age 19 to 20y; sex: M/W (1); country: Finland (1). Reduced saturated fats Insulin resistance (HOMA): improvement in insulin resistance with reduced saturated fat intake MD – 0.14 (95%CI -0.28 to 0.01), p=0.06, I^2=not reported	Findings suggest reduced saturated fat intake improved insulin sensitivity as measured by HOMA. Limitations Difficulties in obtaining reliable dietary intake data, maintain the blind among participants and personnel and variation in the nature and quality of the interventions.

Study	Research methods	Analysis	Results	Comments
Imamura et al (2016) (Systematic review with meta-analysis) <u>Funding source</u> Support received from Medical Research Council Epidemiology Unit Core Support; The National Institute of Health. <u>Declarations of interest</u> Support received from Unilever R&D. Consulting honoraria from Boston Heart Diagnostics; Haas Avocado Board; Astra Zeneca; GOED; DSM; Life Sciences Research Organization. Chapter royalties from UpToDate; scientific advisory board Elysium Health. Listed on a patent assigned to	<u>Research Question</u> Quantify effects of isoenergetic replacement of major macronutrient intake, focusing on different types of fatty acids, on fasting glucose, fasting insulin and insulin resistance. <u>Disease outcome/intermediate risk factors</u> Isoenergetic exchange of saturated fats. <u>Selection criteria</u> *Search dates:* Up to 26th November 2015. *Study designs:* RCTs. *Inclusion criteria:* RCTs in adults (≥18y) of isoenergetic exchange of different types of dietary fat, carbohydrate or total protein; reporting different types of dietary fat intake and examining post-intervention values or changes in the values of fasting glucose ,fasting insulin or measures of insulin resistance as effects of dietary modification on glucose homeostasis. *Exclusion criteria:* Insufficient information on macronutrient composition or glycaemic outcomes; studies of supplements or dietary advice only; studies of acute (single meal) post-prandial effects only; pregnant women or children (aged <18years). <u>Dietary assessment methods</u> Not reported.	<u>Analysis</u> Evaluated post intervention values of trial arms as the primary outcomes. Between arms correlations in trials using either crossover or Latin-square design were estimated and incorporated in meta-analysis by using reported p values and outcome measures based on the function of within individual correlations, interventional effects, their standard error or deviations, and p values. Estimated dose-response effects of replacement among carbohydrate, saturated fat, MUFA and PUFA using multiple-treatment meta-regression. Heterogeneity was tested using the standard Q-statistics. <u>Evaluation of study quality</u> Examined using the Jadad scale.	102 RCTs; n=4220; duration: 3 to 168 days (median 28 days); age <30y (18), 30 to 49.9y (29), ≥50y (55); sex: M (45%), W (55%); health at baseline: healthy and diabetics; country: USA and Canada (35), Europe, Australia, and New Zealand (57), Asia (7), Central or South America and Africa (3). <u>Effect of isoenergetic replacement of 5% dietary energy</u> *Glucose mmol/L* (99 RCTs, n=4144) Saturated fat to PUFA: -0.04 (95% CI -0.07 to -0.01), p<0.05 Saturated fat to MUFA: -0.02 (95% CI -0.04 to 0.00) Carbohydrate to saturated fat: 0.02 (95% CI -0.01 to 0.04) *Fasting insulin, pmol/L* (90 RCTs, n=3774) Saturated fat to PUFA: -0.5 (95% CI -2.0 to 1.1) Saturated fat to MUFA: 1.2 (95% CI 0.6 to 1.8), p<0.001 Carbohydrate to saturated fat: -1.1 (95% CI -1.7 to -0.5), p<0.01 *Glycated haemoglobin (HbA1c)*, % (23 RCTs, n=618) Saturated fat to PUFA: -0.15 (95% CI -0.23 to -0.06), p<0.001 Saturated fat to MUFA: -0.12 (95% CI -0.19 to -0.05), p<0.001 Carbohydrate to saturated fat: 0.03 (95% CI -0.02 to 0.09) *2 h glucose, mmol/L* (11 RCTs, n=615) Saturated fat to PUFA: 0.26 (95% CI -0.34 to 0.85) Saturated fat to MUFA: -0.10 (95% CI-0.91 to 0.70) Carbohydrate to saturated fat: -0.04 (95% CI -0.39 to 0.31)	Increasing MUFA in place of saturated fats has beneficial effects to improve glycaemia and insulin resistance, with possibly stronger effects among patients with type 2 diabetes. Increasing PUFA intake in the general population to improve long-term glycaemic control, insulin resistance, and insulin secretion capacity, in place of saturated fats. <u>Limitations</u> Data from feeding trails which is included in this data may not be generalisable to the effects of long term habitual diet. Not all RCTs were double blinded. This study showed that replacing saturated fats with MUFA was shown to lower fasting glucose, 2h glucose, 2h insulin and HOMA-IR in trials implementing blinding intervention but not in trials blinding for participants.

Study	Research methods	Analysis	Results	Comments
Harvard University for use of trans-palmitoleic acid in identifying and treating metabolic disease.			*HOMA-IR, % change* (30 RCTs, n=1801) Saturated fat to PUFA: -4.1 (95% CI -6.4 to -1.6) p<0.05 Saturated fat to MUFA: -3.1 (95% CI -5.8 to -0.4) p<0.01 Carbohydrate to saturated fat: 0.7 (95% CI -1.6 to 3.1) *Insulin sensitivity index, 10-5/(pmol/L)/min* (13 RCTs, n=1292) Saturated fat to PUFA: 0.24 (95% CI -0.13 to 0.61) Saturated fat to MUFA: 0.08 (95% CI -0.01 to 0.17) Carbohydrate to saturated fat: -0.10 (95% CI -0.21 to 0.02) *2 hr insulin, pmol/L* (11 RCTs, n=598) Carbohydrate to saturated fat: 1.9 (95% CI -19.3, 23.1) Saturated fat to MUFA:-22.2 (95% CI -49.1 to 4.6) Saturated fat to PUFA: -26.8 (95% CI -72.5 to 18.9) *C-peptide, nmol/L* (7 RCTs, n=175) Carbohydrate to saturated fat: 0.03 (95%CI -0.00 to 0.05) p<0.05 Saturated fat to MUFA: -0.01 (95%CI -0.03 to 0.01) Saturated fat to PUFA: -0.07 (95%CI -0.14 to -0.01) p<0.05 *Acute insulin response, pmol/L/min* (10 RCTs, n=1204) Carbohydrate to saturated fat: -0.02 (95% CI -0.11, 0.07) Saturated fat to MUFA: -0.01 (95% CI -0.08 to 0.06) Saturated fat to PUFA: 0.51 (95% CI -0.20 to 0.82) p<0.01	

Study	Research methods	Analysis	Results	Comments
Hooper et al (2015) (Systematic review with meta-analysis) Funding source L Hooper: Studentship, Systematic Reviews Training, Institute of Child Health, University of London, UK. Declarations of interest None declared.	Research question What is the effect of reducing saturated fat intake and replacing it with carbohydrate, PUFA, MUFA and/or protein on mortality and cardiovascular morbidity? Selection criteria *Search dates:* July 2010 to March 2014 (plus search from Hooper 2012 – inception to June 2010). *Study design:* RCTs only. *Inclusion criteria:* >18yrs at any risk of CVD, with/without existing CVD, using/not using lipid-lowering medication; aim to reduce saturated fat intake or alter dietary fats and achieve reduction in saturated fats; intervention dietary advice, supplementation of fats, oils or modified or low-fat foods or a provided diet and the control group usual diet, placebo or a control diet; duration ≥ 24 months; mortality or cardiovascular morbidity data available; no language restrictions. *Exclusion criteria*: Pregnant, acutely ill or breastfeeding subjects; allocation not truly randomised; multifactorial trials. Dietary assessment methods Not reported.	Analysis Random effects meta-analysis to assess risk ratios. Low vs high % of energy from saturated fats. Incremental changes in %of energy from saturated fats. *Subgroup analysis:* Saturated fat substitution with PUFA, MUFA, carbohydrate. Evaluation of study quality Cochrane 'risk of bias' tool used. Additional characteristics assessed include: studies being free of systematic differences in care, a study aiming to reduce saturated fat intake, achieving saturated fats reduction, and achieving total serum cholesterol reduction. Evidence assessed using GRADE system, sensitivity analyses, and heterogeneity examined using I^2 test.	4 RCTs; n=3081; duration: 3 to 8.1y; age: 48 to 62y; sex: M(1), W(1), M/W(2); health at baseline: high risk of CVD (1), diabetic/impaired glucose intolerance (2), angina (1); country: USA (1), UK (1), The Netherlands (1), New Zealand (1). Reduced saturated fat intake Glucose tolerance: ↓ with ↓ saturated fat (3 RCTs, n=249) MD: -1.69mmol/L (95% CI -2.55 to -0.82), p=0.0001; I^2=45%,. Homeostatic model assessment (HOMA): no effect (1 RCT, n=2832) MD: 0.00 (95%CI -0.04 to 0.04), I2=93%, p=1.00.	No clear effect of reducing saturated fats on HOMA, but a suggestion of reduction in glucose two hours after a glucose load. Limitations Although the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched, due to limited resources, filters were applied to limit to core clinical journals (MEDLINE) and priority journals (EMBASE).

Study	Research methods	Analysis	Results	Comments
Schwab et al (2014) (Systematic narrative review) <u>Funding source</u> Supported by the Nordic Council of Ministers. <u>Declarations of interest</u> None declared.	<u>Research question</u> What are the effects of intake of total fat and various combinations and proportions of fatty acid classes in the diet, considering intake of other nutrients on: a. well-established indicators of clinical outcomes such as plasma or serum total lipids and lipoprotein concentrations, plasma or serum glucose and insulin concentrations and blood pressure? b. clinical outcomes including body weight, type 2 diabetes, CVD, and cancer? <u>Selection criteria</u> *Search dates:* January 2000- February 2012. *Study designs:* RCTs and PCS. *Inclusion criteria:* 18-70y, healthy (subjects with dyslipidaemia, glucose intolerance, or overweight (mean BMI of study population not exceeding 30kg/m^2) were included); ≥10 participants for RCTs; dietary assessment method: food record, FFQ, dietary recall, biomarkers; duration ≥ 4 weeks (RCTs), ≥6 months (body weight and body composition studies); PCS follow-up >4y, studies >5y for cancers; RCT dropout <30% in 6 months, <40% on 12 months, <50% in 24 months; intervention: amount and/or quality of dietary fat; updated/relevant nutrient databases. *Exclusion criteria*: Studies without Caucasians or Caucasians a clear minority; study aim outside scope of review;	<u>Analysis</u> Narrative review, results of the quality assessment of the individual studies were summarised to evaluate the quality and strength of the overall evidence in relation to the posed research questions. The evidence for each exposure-outcome association was categorised according to predetermined categories: convincing, probable, limited-suggestive, and limited-no conclusion. <u>Evaluation of study quality</u> Primary evidence assessed for quality but method not reported. Quality categories included: A) high quality with very low risk of bias; B) good quality, some risk of bias but not enough to invalidate results; C) low quality with significant bias and weaknesses which may invalidate results. <u>Dietary assessment methods</u> Food record, FFQ, dietary recall, valid biomarkers.	9 RCTs; n=17 to 154; duration: 4wk (crossover) to 6m; age: 30 to 65y; sex: M/W (9); health at baseline; healthy (4), obese (4), diabetic or at risk (1); country: not reported. <u>Fatsing glucose</u> PUFA vs saturated fats: no effect (1 RCT) MUFA vs saturated fats: no effect (6 RCTs), ↓ (1 RCT) Carbohydrate vs saturated fats: no effect (4 RCTs) <u>Fasting insulin</u> PUFA vs saturated fats: no effect (1 RCT) MUFA vs saturated fats: ↑ with higher saturated fats (5 RCTs), no effect (2 RCTs) Carbohydrate vs saturated fats: ↑ with saturated fats (2 RCTs <u>Glycated haemoglobin (HbA1c)</u> MUFA vs saturated fats: ↑ with higher saturated fats (1 RCT) Carbohydrate vs saturated fats: ↑ with higher saturated fats (1 RCT) <u>Insulin resistance</u> PUFA vs saturated fats: ↑ with higher saturated fats (1 RCT) Carbohydrate vs saturated fats: ↑ with higher saturated fats (1 RCT)	Compared to MUFA saturated fats increased fasting glucose, fasting insulin and HbA1c. Compared to PUFA saturated fats increased insulin resistance, but no effect on fasting insulin or glucose. Compared to carbohydrate saturated fats increased fasting insulin, HbA1c and insulin resistance but had no effect on fasting glucose. <u>Limitations</u> Focus on new evidence since previous edition of Nordic Nutrition Recommendations (NNR), hence why studies pre 2000 not included, however several systematic reviews and meta-analyses included in pervious publications. Strict criteria for both study quality and evidence grading resulting in a relatively conservative estimate of the evidence. Many questions remain unresolved due to

Study	Research methods	Analysis	Results	Comments
	exposure food pattern or a whole food; included non-healthy subjects, obese subjects.			conflicting results from studies and lack of high quality controlled studies.

Study	Research methods	Analysis	Results	Comments
Micha & Mozaffarian (2010) (Systematic narrative review) <u>Funding source</u> Searle Funds at The Chicago Community Trust; the Bill & Melinda Gates Foundation/WHO Global Burden of Diseases, Injuries, and Risk Factors Study. <u>Declarations of interest</u> Consulting honoraria (modest) from Nutrition Impact, Unilever and SPRIM.	<u>Research question</u> Elucidate effects of saturated fat consumption on CVD risk based on the most current evidence. <u>Selection criteria</u> *Search period*: Inception to September 2009. *Study design*: RCTs and PCS. *Inclusion criteria*: Adults; evaluating saturated fat intake and risk of CHD, stroke, type 2 diabetes, related risk pathways including lipids and lipoproteins, systemic inflammation, vascular function, insulin resistance. *Exclusion criteria*: A priori animal studies, ecological studies, commentaries, general reviews, case reports. <u>Dietary assessment methods</u> Not reported.	<u>Analysis</u> Narrative review. <u>Evaluation of study quality</u> Not reported.	Characteristics of the identified studies not summarised. Saturated fat consumption inconsistently affects insulin resistance in controlled trials and has not been associated with incident diabetes in PCS. Among healthy individuals, most RCTs show no difference in markers of glucose-insulin homeostasis comparing different intakes of saturated fats vs MUFA, PUFA, or carbohydrate. Findings mixed among individuals having or predisposed to insulin resistance: improvements in markers of glucose-insulin homeostasis were seen in 3out of 5 RCTs with comparison to MUFA, 1 out of 3 RCTs comparison to PUFA, 1 RCT including a comparison to carbohydrate.	Some evidence from short-term RCTs that saturated fat consumption in place of MUFA may worsen glucose-insulin homeostasis, especially among individuals predisposed to insulin resistance. <u>Limitations</u> Majority of studies were short-term (up to several weeks) and <20 subjects. Two largest trials (n = 163 and 59) found saturated fats to worsen glucose-insulin homeostasis in comparison to MUFA (both) and carbohydrate (1 trial). Further confirmatory results required in appropriately powered studies.

Table A2.10 RCTs assessing the relationship between dietary saturated fat intake and type 2 diabetes and markers of glycaemic control in each review article

Study name[1] / first author (publication dates)	**Te Morenga & Montez (2017)**	**Hooper et al, (2015)[2]**	**Schwab et al, (2014)**	**Micha and Mozaffarian (2010)**
D, incident type 2 diabetes; G, markers of glycaemic control				
Total primary studies (publications)	1 (2)	4 (5)	11	12
STRIP Oranta 2013 Kaitosaari 2006	 G G			
Women's Health Initiative Tinker 2008 Howard 2006		 D, G		 D, G
Ley 2004		G		
Song 2004				
Lovejoy 2002			G	G
Vessby 2001			G	G
Watts 1992		G		
Houtsmuller 1979 Bos 2010		G	 G	
Van Dijk 2009			G	
Sloth 2009			G	
Due 2009			G	
Due 2008 (a)			G	
Due 2008 (b)			G	
Lithander 2008				G
Paniagua 2007				G

Study name[1] / first author (publication dates)	Te Morenga & Montez (2017)	Hooper et al, (2015)[2]	Schwab et al, (2014)	Micha and Mozaffarian (2010)
D, incident type 2 diabetes; G, markers of glycaemic control				
Vega-Lopez 2006				G
Summers 2002			G	G
Perez-Jimenez 2001			G	G
Louheranta 2000			G	G
Christiansen 1997				G
Fasching 1995				G
Schwab 1995				G

Outcome measured by study: D, incident type 2 diabetes; G, markers of glycaemic control.

[1] Study name is only provided when two or more publications for that study are used in any of the reviews. Imamura et al, (2016): unclear which primary studies were included in the review.

[2] Hooper et al, (2015) presents publications used in the analyses by study name and identifies a main study publication along with all supplementary publications for the study. It is not possible to know which exact publication the data has come from, therefore, the main study publication has been used in the table above.

Table A2.11 PCS assessing the relationship between dietary saturated fat intake and type 2 diabetes and markers of glycaemic control in each review article

Study name[1] / first author (publication dates)	**de Souza et al, (2015)**	**Schwab et al, (2014)**	**Alhazmi et al, (2012)**	**Micha and Mozaffarian (2010)**
D, incident type 2 diabetes; G, markers of glycaemic control				
Total primary studies (publications)	8	3	7	4
Alhazmi 2014	D			
Korger 2011			D	
Harding 2004		D		D
Song 2004	D		D	
Mahendran 2014	D			
Simila 2012	D			
Lindstrom 2006	D			
van Dam 2002	D		D	D
Meyer 2001	D	D	D	D
Salmeron 2001	D	D	D	D
Salmeron 1997			D	
Colditz 1992			D	

Outcome measured by study: D, incident type 2 diabetes; G, markers of glycaemic control.

[1] Study name is only provided when two or more publications for that study are used in any of the reviews. Imamura et al, (2016): unclear which primary studies were included in review.

[2] Hooper et al, (2015) presents publications used in the analyses by study name and identifies a main study publication along with all supplementary publications for the study. It is not possible to know which exact publication the data has come from, therefore, the main study publication has been used in the table above.

Anthropometry

Table A2.12 Characteristics of meta-analyses and systematic reviews

Study	Research methods	Analysis	Results	Comments
Hannon et al (2017b) (Systematic review with meta-analysis) Funding source: None declared Declaration of interest: None declared	Research question What is the effect of saturated fats replacement with unsaturated fats in metabolically healthy adults with overweight and obesity on markers of dyslipidemia and body composition? Selection criteria *Search dates:* inception to June 24 2016 *Study design:* RCTs only *Inclusion criteria:* >18y with BMI >25 kg/m^2 or waist circumference >94 cm for men or >80cm for women, or waist-to-hip ratio >0.96 for men or >0.81 for women without diagnosis of metabolic disease, enrolled in RCT interventions that included dietary replacement of saturated fats with unsaturated fats within the setting of a controlled feeding study or among free-living individuals. *Exclusion criteria:* Interventions that focused on management of chronic conditions such as CVD or diabetes; short term studies with intervention duration less than 1 week. Dietary assessment methods Not Reported	Analysis For studies with substantial heterogeneity, random effects model was used. Fixed effects models were used when I^2 was <50%. Evaluation of study quality 7 dichotomous questions were used to assess individual study quality, including: use of control group; statistically nonsignificant differences between control and intervention group at baseline; use of high saturated fats run in period before randomisation; measurement tools for data collection were clearly explained in the methods section; all potential confounders controlled for; study procedures defined and bias adequately controlled. Cochrane Risk of Bias tool was used to assess individual study bias. Heterogeneity examined using I^2 test.	8 RCTs; n=663; duration: 4 to 28 weeks; age >18y; BMI >25, sex: M(3), M/W(5). Saturated fats substitution with unsaturated fats Body weight: no effect (6 RCTs; n=387) MD -0.60 (95% CI -2.10 to 0.91) p=0.44, I^2=0.0% (fixed-effect model) Body fat %: no effect (3 RCTs; n=230) MD 0.14 (95%CI -0.86 to 1.14) p=0.79, I^2=27% (fixed-effect model) Fat mass: no effect (2 RCTs; n=60) MD 0.84 (95%CI -1.08 to 2.75) p=0.39, I^2=76% Waist circumference: no effect (3 RCTs; n=117) MD 1.24 (95% CI -0.15 to 2.64) p=0.08, I^2=0.0% (fixed-effect model) Subgroup analysis **Energy restriction interventions** Body fat %: no effect (2 RCTs; n=60) MD 0.36 (95 % CI -0.87 to 1.59) p=0.57, I^2=58% (fixed-effect model) Body weight kg: no effect (3 RCTs, n=132) MD -0.31 (95% CI -2.77 to 2.15) p=0.80, I^2=27% (random-effects model)	Findings suggest there was no effect of saturated fats substitution with unsaturated fats and body composition measurements. Limitations Only 8 studies with small to moderate sample size included. Study findings only applicable to adults with overweight and obesity. High study heterogeneity.

Study	Research methods	Analysis	Results	Comments
			Waist circumference: significant effect (2 RCTs, n= 60) MD 1.58 (95% CI 0.28 to 2.88) p=0.02, I^2=37% (fixed-effect model) **Energy balanced interventions** Body weight kg: no effect (3 RCTs, n=255) MD 0.12 (95% CI -4.03 to 4.26) p=0.96, I^2=0.0 (random-effects model)	

Study	Research methods	Analysis	Results	Comments
Te Morenga & Montez (2017b) (systematic review with meta-analysis) Funding source: The University of Otago and the WHO Declarations of interest: None declared	Research question Examine the evidence for health effects associated with reducing saturated fats and trans fats intake in free living children, adolescents and young adults aged 2 to 19 years of age Selection criteria *Search dates:* inception to July 2016 *Study design:* RCTs *Inclusion criteria:* children, adolescents and young adults aged 2 to 19 years, healthy individuals as well as individuals with or at risk of hyperlipidaemia, hypertension or diabetes (type 1 & 2), or who were overweight or obese. RCTs with intervention duration of at least 2 weeks with primary intention of reducing saturated fats or trans fats directly or through reduction in total fat intake. *Exclusion criteria:* studies targeting those that were pregnant, acutely ill or with chronic infection such as HIV. Trials where weight loss was primary outcome and trials involving multifactorial interventions where the effect of saturated fats or trans fats reduction could not be separated from the effect of other changes such as physical activity level Dietary assessment methods 24hr dietary recalls, product inventory; daily consumption checklists; 3-day diet records, FFQ, biomarker assessment (pentadecanoic acid)	Analysis Random effects meta-analysis (data pooled using inverse variance models) Evaluation of study quality Cochrane criteria used to assess risk of bias. Evidence assessed using GRADE system. Evidence summaries and GRADE assessments were discussed and reviewed by the WHO Nutrition Guidance Expert Advisory Group Subgroup on Diet and health as part of WHO's guideline development process	5 RCTs; n=1597; duration 5 weeks to 19 years (follow up); age 4 to 16y; sex: M/W (5); health at baseline: hyperlipidemic (2), not specified (3); country: US (3), Australia (1), Finland (1) Reduced saturated fats BMI: no effect (3 RCTs; n=1189) MD -0.10 (95% CI -0.32 to 0.12), p=0.36; I^2=0% Body weight: no effect (4RCTs; n=1419) MD -0.03 (95% CI -0.13 to 0.07), p=0.55; I^2=0% Waist circumference: no effect (2 RCTs; n=576) MD -0.20 (95% CI -1.38 to 0.98), p=0.28; I^2=0%	Findings suggest no effect between reduced saturated fat intake and anthropometric measurements.

Study	Research methods	Analysis	Results	Comments
Tielemans et al, (2016) (Systematic review) <u>Funding source</u> Supported by Nestle Nutrition, Metagenics Inc. and AXA. <u>Declarations of interest</u> None declared.	<u>Research question</u> Assess whether energy intake and macronutrient intake during pregnancy were associated with gestational weight gain. <u>Selection criteria</u> *Search dates*: Up to 12th August 2015. *Study design*: RCTs and PCS. *Inclusion criteria*: Studies recruited women with singleton pregnancy either healthy or diseased; protein, fat, carbohydrate or energy intake was measured or supplemented as the exposure or intervention; reported outcome was gestational weight gain (measured or self-reported) or the adequacy of gestational weight gain; studies that measured weight shortly after birth; any language. *Exclusion criteria*: Studies that included only mothers who had given birth to newborns with birth defects or to extremely preterm newborns (<28wk of gestation); studies restricted to adolescents and studies in which the mean age total population was <18y; intervention studies in which the exclusive effects of macronutrients could not be determined (e.g. intervention combined with micronutrients or physical activity); studies on dietary counselling when actual dietary intake was not measured. <u>Dietary assessment methods</u> FFQ, 24 hr recall, weighed food record, dietary interview.	<u>Analysis</u> Narrative review. Studies were stratified by the income level of the country in which the study was performed on the basis of the World Bank list of economies. <u>Evaluation of study quality</u> Quality of each study given a score based on: study design, population size, exposure measurement (or in intervention studies the adequacy of blinding), outcomes measurement and adjustment for confounders and energy adjustment (or in intervention studies the adequacy of random assignment). Studies were considered of high quality when the score was ≥7 (out of 10).	8 PCS (for saturated fat intake); n=39 to 3360; duration: not reported; age: 16 to 43y; sex: all women; health at baseline: healthy (6), obese women (1), women carrying newborns with increased risk of type 1 diabetes (1); country: USA (3), The Netherlands (1), Finland (1), Denmark (1), Australia (1), Brazil (1). <u>Saturated fat intake and gestational weight gain</u> *2 high quality PCS* 1 PCS reported marginally higher gestational weight gain with higher saturated fat intake. 1 PCS reported no association. *6 low quality PCS* 1 PCS reported a positive association. 5 PCS reported no association.	The effects of macronutrients on gestational weight gain are inconclusive and inconsistent. Higher intake of fat, mainly saturated fat, might be associated with higher gestational weight gain, however the included studies had a low quality. <u>Limitations</u> Overall low quality of studies and the insufficient adjustment for confounding factors in many of the included studies. Therefore, residual confounding might remain.

Study	Research methods	Analysis	Results	Comments
Hooper et al (2015) (Systematic review with meta-analysis) <u>Funding source</u> L Hooper: Studentship, Systematic Reviews Training, Institute of Child Health, University of London, UK. <u>Declarations of interest</u> None declared.	<u>Research question</u> What is the effect of reducing saturated fat intake and replacing it with carbohydrate, PUFA, MUFA and/or protein on mortality and cardiovascular morbidity? <u>Selection criteria</u> *Search dates:* July 2010 to March 2014 (plus search from Hooper 2012 – inception to June 2010). *Study design:* RCTs only. *Inclusion criteria:* >18yrs at any risk of CVD, with/without existing CVD, using/not using lipid-lowering medication; aim to reduce saturated fat intake or alter dietary fats and achieve reduction in saturated fats; intervention dietary advice, supplementation of fats, oils or modified or low-fat foods or a provided diet and the control group usual diet, placebo or a control diet; duration ≥ 24 months; mortality or cardiovascular morbidity data available; no language restrictions. *Exclusion criteria*: Pregnant, acutely ill or breastfeeding subjects; allocation not truly randomised; multifactorial trials. <u>Dietary assessment methods</u> Not reported.	<u>Analysis</u> Random effects meta-analysis to assess risk ratios. Low vs high % of energy from saturated fats. Incremental changes in % of energy from saturated fats. *Subgroup analysis* Saturated fat substitution with PUFA, MUFA, carbohydrate. <u>Evaluation of study quality</u> Cochrane 'risk of bias' tool used. Additional characteristics assessed include: studies being free of systematic differences in care, a study aiming to reduce saturated fat intake, achieving saturated fats reduction, and achieving total serum cholesterol reduction. Evidence assessed using GRADE system, sensitivity analyses, and heterogeneity examined using I^2 test.	6 RCTs; n=194 to 2439; duration: 1.8 to 9.3y; age: 45 to 65y; sex: M(1), W(3), M/W(2); health at baseline: high risk of CVD (1), previous MI (1), diabetic/impaired glucose intolerance (1), breast cancer (2), siblings of people with CHD, with at least one CVD risk factor (1); country: USA (4), UK (1), Australia (1). <u>Reduced saturated fat intake</u> *Body weight:* ↓ (6 RCTs, n=4541) MD -1.97kg (95% CI -3.67 to -0.27), I^2=72%. *BMI:* ↓(6 RCTs, n=5553) MD -0.50 kg/m^2 (95% CI -0.82 to -0.19), I^2=55%.	Small reductions in body weight and BMI with advice to reduce saturated fat intake. <u>Limitations</u> Although the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched, due to limited resources, filters were applied to limit to core clinical journals (MEDLINE) and priority journals (EMBASE). As secondary outcomes, body weight and BMI were not included in the original search, and not reported in all studies.

Study	Research methods	Analysis	Results	Comments
Fogelholm et al (2012b) (Systematic narrative review) <u>Funding source</u> Review was part of the Nordic Nutrition Recommendations 2012 project, with financial support from the Nordic Council of Ministers. <u>Declarations of interest</u> None declared.	<u>Research question</u> 1. Primary prevention of obesity The effect of different dietary macronutrient composition on long-term (≥1y) change in weight/waist circumference/body fat in adult population. 2. Prevention of weight regain after weight loss The effect of different dietary macronutrient composition on long-term (≥1y) change in weight/waist circumference/body fat in individuals who have deliberately reduced their weight by at least 5%. <u>Selection criteria</u> *Search period:* 2000 onwards. *Study design:* PCS, case-control studies, weight maintenance interventions (intentional mean weight loss at least 5%; at least 6 months follow up). *Inclusion criteria:* Adults 18-70 years, PCS with a minimum follow-up of 1y. *Exclusion criteria:* Cross-sectional studies, adults >70 years, studies without Caucasians or with Caucasians as a minority group. <u>Dietary assessment methods</u> FFQ.	<u>Analysis</u> Narrative review. <u>Evaluation of study quality</u> Principles of the Nordic Nutrition Recommendation 2012 working group was used to assess the quality of the papers. The papers were evaluated according to a 3-scale grading.	<u>Saturated fats and change in weight or waist circumference</u> 2 PCS; n=89,432 to 130,950; duration: 3.7 to 10y; age: 41 to 68y; sex: M(0), W(1), M/W(1); health at baseline: healthy (2); country: USA (1), Europe (1). *Saturated fats and change in weight* 2 PCS: 1 PCS reported a positive association between saturated fats and weight gain 1 PCS reported no association between saturated fats and weight change *Saturated fats and change in waist circumference* 1 PCS found no association	Limited evidence, no conclusion can be drawn from the 2 studies, as 1 reported a positive association of saturated fat with body weight and 1 study found no significant association of saturated fat with body weight or waist circumference.

Study	Research methods	Analysis	Results	Comments
Micha & Mozaffarian (2010) (Systematic narrative review) Funding source Searle Funds at The Chicago Community Trust and; the Bill & Melinda Gates Foundation/WHO Global Burden of Diseases, Injuries, and Risk Factors Study. Declarations of interest Consulting honoraria (modest) from Nutrition Impact, Unilever and SPRIM.	Research question Elucidate effects of saturated fat consumption on CVD risk based on the most current evidence. Selection criteria *Search period*: Inception to September 2009. *Study design*: RCTs and PCS. *Inclusion criteria*: Adults; evaluating saturated fat intake and risk of CHD, stroke, type 2 diabetes, related risk pathways including lipids and lipoproteins, systemic inflammation, vascular function, insulin resistance. *Exclusion criteria*: A priori animal studies, ecological studies, commentaries, general reviews, case reports. Dietary assessment methods Not reported.	Analysis Narrative review. Evaluation of study quality Not reported.	2 PCS; characteristics of identified studies not summarised. *Waist circumference* Men, 9y follow-up. Positive association with saturated fat intake. *Body weight* Women, 8y follow-up; adjusted for other risk factors, lifestyle and dietary behaviours. Positive association with saturated fat intake compared with carbohydrate intake.	Limited evidence for independent effects of saturated fats on weight gain or adiposity.

Table A2.13 RCTs assessing the relationship between dietary saturated fat intake and anthropometry in each review article

Study name / first author (publication dates)	**Hannon et al, (2017)**	**Te Morenga & Montez (2017)**	**Hooper et al, (2015)[1]**
% BF, percentage body fat; H, height; BMI, body mass index; C, waist circumference; GWG, gestational weight gain; WC, weight change			
Total primary studies	8	5	6
Blumfield 2015			
Renault 2015			
Shin 2014			
Maple-Brown 2013			
Costa 2011			
Howard 2006			BMI, WC
Martins and Benicio 2011			
Bos 2010	WC		
Althuizen 2009			
Forouhi 2009			
Stuebe 2009			
Van Dijk 2009	WC		
Field 2007			
Chlebowski 2006			BMI, WC
Krauss 2006	%BF, WC		
Koh-Banerjee 2003			
Piers 2003	%BF, FM, C, WC		

Study name / first author (publication dates)	Hannon et al, (2017)	Te Morenga & Montez (2017)	Hooper et al, (2015)[1]
% BF, percentage body fat; H, height; BMI, body mass index; C, waist circumference; GWG, gestational weight gain; WC, weight change			
Hendrie 2001		H, WC, BMI, C	
Kriketos 2001	%BF, FM, C, WC		
Moy 2001			BMI
Denke 2000		WC	
Noakes 2000	WC		
Simon 1997			WC
Hockaday 1978			BMI
Woodhill 1978			BMI, WC
DISC		H, WC, BMI	
Children's Health Project		WC	
STRIP		H, WC, C	

Outcomes measured by study: % BF, percentage body fat; H, height; BMI, body mass index; C, waist circumference; GWG, gestational weight gain; WC, weight change.

[1] Hooper et al, (2015) presents publications used in the analyses by study name and identifies a main study publication along with all supplementary publications for the study. It is not possible to know which exact publication the data has come from, therefore, the main study publication has been used in the table above.

Table A2.14 PCS assessing the relationship between dietary saturated fat intake and anthropometry in each review article

Study name / first author Publication year	Tielemans et al, (2016)	Fogelholm et al, (2012)	Micha and Mozaffarian (2010)
% BF, percentage body fat; H, height; BMI, body mass index; C, waist circumference; GWG, gestational weight gain; WC, weight change.			
Total primary studies	8	2	2
Blumfield 2015	GWG		
Renault 2015	GWG		
Shin 2014	GWG		
Maple-Brown 2013	GWG		
Costa 2011	GWG		
Martins and Benicio 2011	GWG		
Althuizen 2009	GWG		
Forouhi 2009		WC, C	
Stuebe 2009	GWG		
Field 2007		WC	WC
Koh-Banerjee 2003			C

Outcomes measured by study: % BF, percentage body fat; H, height; BMI, body mass index; C, waist circumference; GWG, gestational weight gain; WC, weight change.

Cancers

Table A2.15 Characteristics of meta-analyses and systematic reviews

Study	Research methods	Analysis	Results	Comments
Cao et al (2016) (Systematic review with meta-analysis) <u>Funding source</u> None declared. <u>Declarations of interest</u> L Hou received a grant from the Natural Science Foundation of Shandong Province.	<u>Research question</u> Assess the association between dietary total fat and fatty acids intake and breast cancer risk. <u>Selection criteria</u> *Search dates:* Inception to September 2015. *Study designs:* PCS. *Inclusion criteria:* PCS or nested case-control study in which total fat and fatty acids consumption precedes breast cancer incidence; exposure of interest was dietary total fat, fatty acids intake or serum fatty acids; the outcome of interest was breast cancer; RR, HR, ORs with 95% CI provided. *Exclusion criteria:* Not reported. <u>Dietary assessment methods</u> FFQ (22), food record and 24 hour recall (2).	<u>Analysis</u> Pooled measure was calculated as the inverse variance weighted mean of the logarithm of RR with 95% CI to assess the strength of association. A random-effect model was used as the pooling method, which considers both within and between study variations. I^2 statistic was used to evaluate heterogeneity. <u>Evaluation of study quality</u> 9-star Newcastle-Ottawa Scale was used to evaluate study quality.	<u>Breast cancer</u> 24 PCS (20 for saturated fat); n=1,220,608 (38,262 breast cancer cases); duration: 2 to 25y; age: 20 to 74y; sex: women only; health at baseline: not specified; country: USA (11), Canada (1), Sweden (3), The Netherlands (1), Finland (1), Norway (1), Italy (1), France (1), Japan (2), China (1), multinational (1). <u>Highest vs lowest dietary saturated fat intake and breast cancer (20 PCS)</u> RR 1.08 (95% CI 0.99 to 1.18); I^2= 58.81% <u>Sub-group analysis</u> Positive association between saturated fat intake and breast cancer for: *Estrogen receptor positive breast cancer (3 PCS)* RR 1.29 (95% CI 1.04 to 1.60); I^2=0.00% *Studies conducted in Europe (8 PCS)* RR 1.16 (95% CI 1.06 to 1.26); I^2=0.00% *Studies with follow-up duration <10y (12 PCS)* RR 1.13 (95% CI 1.02 to 1.24); I^2=16.28% *Studies with subjects with mean age >50y (14 PCS)* RR 1.09 (95% CI 1.00 to 1.19); I^2=43.67% *Studies that did not adjust for family history of breast cancer (9 PCS)* RR 1.15 (95% CI 1.08 to 1.23); I^2=0.00%	No association was observed between saturated fat intake and risk of breast cancer. <u>Limitations</u> Some of the sub-group analyses included data from a limited number of studies; adjustment of several covariates could influence the fat-breast cancer association.

Study	Research methods	Analysis	Results	Comments
Brennan et al (2015) (Systematic review with meta-analysis) <u>Funding source</u> SF Brennan: PhD studentship from the Department of Employment and Learning, Northern Ireland. <u>Declarations of interest</u> None declared.	<u>Research question</u> Clarify the association between dietary fat and breast cancer mortality. <u>Selection criteria</u> *Search dates:* Up to March 2012. *Study designs*: PCS. *Inclusion criteria:* English language; reported risk estimates (HRs, ORs and RRs); measures of variability (SEs, 95% CIs); all-cause and/or breast cancer mortality according to total fat and/or saturated fat intake. *Exclusion criteria*: not reported. <u>Dietary assessment methods</u> FFQs (3), diet histories (1).	<u>Analysis</u> All data converted to g/day by calculation or by requesting the results from the authors. Meta-analyses were conducted to evaluate the risk of all-cause or breast cancer specific death in women, comparing highest and lowest intakes of fat and saturated fat. Regression analysis of HRs, to calculate linear increase in risk of breast cancer and all-cause death per percentile increase in total fat and saturated fat. Multivariable adjusted HRs, ORs or RR with 95% CIs from individual studies were weighted and combined using an inverse-variance weighted random-effects model to produce pooled estimates. Heterogeneity was tested with the chi-squared test and measured using the I^2 statistic. Sub-group analyses were conducted for studies which did and did not have energy intake adjusted and type of dietary assessment method, pre vs post-diagnosis diet. <u>Evaluation of study quality</u> Not reported.	<u>Breast cancer</u> 15 PCS (4 PCS for saturated fats); n=149 to 11,302; duration: 3 to 26y; age: 19 to 79y; sex: women only; health at baseline: not reported; country: USA (8), Canada (4), Australia (1), Denmark (1), Belgium (1). *Highest vs lowest saturated fat intake and breast cancer mortality (4 PCS)* HR 1.51 (95% CI: 1.09 to 2.09) p=0.317; I^2=15% *Breast cancer specific mortality with 20g increase in saturated fat intake (4 PCS)* HR 1.03 (95%CI 0.77 to 1.38), p=0.80; I^2=75%, p<0.01	Saturated fat intake negatively impacts upon breast cancer survival. <u>Limitations</u> Adjustment for confounders was inconsistent between studies resulting in the potential for residual confounding.

Study	Research methods	Analysis	Results	Comments
Xia et al (2015) (Systematic review with meta-analysis) <u>Funding source</u> None declared. <u>Declarations of interest</u> None declared.	<u>Research question</u> Determine the quantitative relations between dietary saturated fat intake and incidence of breast cancer. <u>Selection criteria</u> *Search dates*: Up to April 2015. *Study designs*: Cohort, case-control. *Inclusion criteria*: Published in English; human studies only; published openly; evaluated the association between saturated fat intake from food and the incidence of female breast cancer only; specified diagnosis of breast cancer; containing ORs, RRs or HRs with corresponding 95%CIs or data could be estimated; selected when data were most sufficient if they were from the same population. *Exclusion criteria:* Animal or vitro experiments; review articles, repeated literatures, or mechanism studies; not related to human subjects; not of appropriate control groups; without analysis method provided; and were excluded when lack of access to full texts. <u>Dietary assessment methods</u> FFQs, diet history, 24 hour recall.	<u>Analysis</u> Used RR as an approximate for HR in the cohort studies. Adjusted ORs or RRs comparing highest versus lowest category of dietary saturated fat intake were gathered with the corresponding 95% CIs as possible and meanwhile were calculated by the logarithmic transformation of RRs and ORs with the corresponding 95% CIs. Fixed effects model was used when I^2 was lower than 50% and P of the value of heterogeneity was ≥ 0.05. Otherwise the random-effects model was used. <u>Evaluation of study quality</u> Assessed using the Newcastle-Ottawa scale.	<u>Breast cancer</u> 24 PCS; n=1,786,537 (35,651 breast cancer cases); duration: 3.3 to 20y; age: not reported; sex: women only; health at baseline: not reported; country: USA (14), Sweden (2), UK (1), Finland (1), Norway (1), The Netherlands (2), Canada (1), Japan (1), Europe- multi country (1). <u>Pooled RR of breast cancer incidence for highest vs lowest saturated fat intake (24 PCS)</u> Pooled RR 1.04 (95%CI 0.97 to 1.11); I^2=59.9% <u>Sub-group analysis</u> *Menopause status:* Pre-menopausal (5 PCS) Pooled RR 1.01 (95%CI 0.92 to 1.10); I^2= 0% Post-menopausal (13 PCS) Pooled RR 1.04 (95%CI 0.95 to 1.13); I^2=63.4% *Recruit source:* Population (17 PCS) RR 1.11(95% CI 1.01 to 1.21); I^2=48.3% Hospital (7 PCS) RR 0.96 (0.91 to 1.00); I^2=35%	No association was found between saturated fat intake and breast cancer in PCS.

Study	Research methods	Analysis	Results	Comments
Xu et al (2015a) (Systematic review with meta-analysis) Funding source None declared. Declarations of interest None declared.	Research question Assess relationship between fat intake and prostate cancer risk. Selection criteria *Search dates:* Up to 1st March 2015. *Study designs:* PCS. *Inclusion criteria:* PCS assessing the relationship between any stage of prostate cancer and total fat, saturated fat or unsaturated fat intake; studies reporting animal fat (expect for fish oil) categorised as saturated fats. *Exclusion criteria:* Secondary tumours from other organs not considered; vegetable and oils; grey literature; meeting papers; animal studies. Dietary assessment methods Not reported	Analysis Dose response meta-analysis conducted in two steps: first, the generalised least squares method estimated the coefficient per unit increment of exposure within each study. Second, the regression coefficients were combined in a random-effect model with the weight calculated by inverse variance. Random-effects meta-regression was used to assess which covariates in the subgroup analysis influenced the intervention effect. Egger's test used to determine publication bias, I^2 statistic used to assess heterogeneity. Evaluation of study quality Quality assessed using the Newcastle-Ottawa Scale.	Prostate cancer 9 PCS; n=751,030 (37,349 prostate cancer cases); duration: 5 to 17.4y; age: 40 to 75y; sex: men only; health at baseline: not reported; country: USA/Canada (7), Finland (3), Sweden (1), The Netherlands (1), Norway (1), multi European countries (1). Saturated fat intake and prostate cancer risk per 28.35g increment (9 PCS) RR 1.00 (95% CI 1.00 to 1.00); p = 0.72; I^2 = 14.3% Saturated fat intake and advanced or high grade prostate cancer risk per 28.35g increment (6 PCS) RR 0.96 (95%CI 0.84 to 1.11); p = 0.61; I^2 = 70.4% Sub-group analysis *Area of country* America (6 PCS) RR 1.00 (95%CI 1.00 to 1.00); p = 0.98, I^2 = 17.70% Europe (3 PCS) RR 1.00 (95%CI 1.00 to 1.00); p = 0.29, I^2 = 0.00% *Adjusted for BMI* Adjusted (6 PCS) RR 1.00 (95% CI 1.00 to 1.00); p=0.41; I^2=43.80% Non-adjusted (3 PCS) RR 1.00 (95% CI 1.00 to 1.00); p=0.76; I^2=0.00% Confounders adjusted for in primary studies include age, race, family history of prostate cancer, education, marital status, prostate specific antigen (PSA) testing in past 3 years, physical activity, diabetes, socioeconomic status, BMI, age 21 BMI, waist circumference, birth country, vasectomy status, energy intake, intakes of calcium, fruit and vegetables, red meat, alcohol and tomatoes.	Current published cohort studies suggest no association between saturated fat intake and the risk of prostate cancer. Limitations Meta-analysis is on a limited number of studies and there is considerable heterogeneity; studies conducted in American and European populations only.

Study	Research methods	Analysis	Results	Comments
Yao & Tian (2015) (Systematic review with meta-analysis) <u>Funding source</u> None declared. <u>Declarations of interest</u> None declared.	<u>Research question</u> Role of different fatty acids on the risk of pancreatic cancer. <u>Selection criteria</u> *Search dates*: Until end of June 2014. *Study designs*: PCS. *Inclusion criteria*: Study had to be a cohort/case-cohort/nested case-control/case-control study design; exposure was dietary saturated fat, MUFA or PUFA intake; the outcome was the incidence of pancreatic cancer; provided RR, OR, HR with 95% CI. *Exclusion criteria*: Not provided. <u>Dietary assessment methods</u> FFQs.	<u>Analysis</u> Random or fixed effects models were used to estimate RR with 95% CI. Galbraith plot used to depict heterogeneity, I^2 statistics to evaluate heterogeneity among studies, Higgins and Thompson fixed-effects model where non-significant heterogeneity. DerSimonian and laird random-effects model if significant heterogeneity. <u>Evaluation of study quality</u> Scoring system with 9-star on the strength of the Newcastle-Ottawa Scale.	<u>Pancreatic cancer</u> 6 PCS; n = 1,130,815 participants (3072 cases of pancreatic cancer); duration: 8 to 22y; age: not reported; sex: M (1), W (1), M/W (5); health at baseline: not reported; country: USA (5), The Netherlands (1), Finland (1). <u>Highest vs lowest saturated fat intake</u> Pancreatic cancer: no association (6 PCS) RR 1.04 (95% CI 0.81 to 1.35); I^2 = 74.2%	No statistically significant relationship between saturated fat intake and pancreatic cancer risk. <u>Limitations</u> Could not control for confounders not adjusted for in the individual studies. A few studies adjusted for BMI and alcohol intake, the majority adjusted for age, cigarette smoking and total energy intake, however, residual or unmeasured confounding cannot be excluded. Some degree of misclassification of fatty acids intake could be prone to overestimation of the range of intake and underestimation of the magnitude of the association between dietary intake and risk of cancer.

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Schwab et al (2014) (Systematic narrative review) <u>Funding source</u> Supported by the Nordic Council of Ministers. <u>Declarations of interest</u> None declared.	<u>Research question</u> What are the effects of intake of total fat and various combinations and proportions of fatty acid classes in the diet, considering intake of other nutrients on: a. well-established indicators of clinical outcomes such as plasma or serum total lipids and lipoprotein concentrations, plasma or serum glucose and insulin concentrations and blood pressure? b. clinical outcomes including body weight, type 2 diabetes, CVD, and cancer? <u>Selection criteria</u> *Search dates*: Jan 2000 to Feb 2012. *Study designs*: RCTs and PCS. *Inclusion criteria:* 18-70y, healthy (subjects with dyslipidaemia, glucose intolerance, or overweight (mean BMI of study population not >30kg/m^2) were included); n ≥10 for RCTs; dietary assessment method: food record, FFQ, dietary recall, biomarkers; duration≥4w (RCTs), ≥6 months (body weight and body composition studies); PCS follow-up >4y, studies >5y for cancers; RCT dropout <30% in 6m, <40% 12m, <50% 24m; intervention: amount and/or quality of dietary fat; updated/relevant nutrient databases. *Exclusion criteria*: Studies without Caucasians or a clear minority. Study aim outside scope of review. Studied exposure was a food pattern or whole food. Included non-healthy, obese subjects.	<u>Analysis</u> Narrative review, results of the quality assessment of the individual studies were summarised to evaluate the quality and strength of the overall evidence in related tot the posed research questions. The evidence for each exposure-outcome association was categorising according to pre demented categories: convincing, probable, limited-suggestive, and limited- no conclusion. <u>Evaluation of study quality</u> The primary evidence was assessed for quality but method not reported. Quality categories included A: high quality with very low risk of bias; B: good quality, some risk of bias but not enough to invalidate results; C: low quality with significant bias and weaknesses which may invalidate results.	<u>Colorectal cancer</u> 1 PCS; n=37,547; duration: 8.7y: age: ≥45y; sex: F. No significant association with saturated fat intake. <u>Pancreatic cancer</u> 4 PCS; n=831,931; duration: 6.3 to 18y; age: 30 to 75y; sex: M (1), W (1), M/W (2). 2 PCS: found no significant associations with saturated fat intake. 2 PCS: found positive associations with saturated fat intake. Limited evidence – no conclusion; grade B evidence. <u>Breast cancer</u> 6 PCS; n=659,782; duration: 7.8 to 20y; age: 25 to 75y; sex: W (6). 5 PCS: no significant associations with saturated fat intake. 1 PCS: found a positive association among menopausal women who did not use hormone replacement therapy. <u>Prostate cancer</u> 3 PCS; n=235,568; duration: 8 to 11y; age: 45 to 73y; sex: M. No significant associations with saturated fat intake observed.	Limited evidence, no conclusion. <u>Limitations</u> Focus on new evidence since previous edition of Nordic Nutrition Recommendations (NNR), hence why studies pre 2000 not included. Strict criteria for both study quality and evidence grading resulting in a relatively conservative estimate of the evidence.

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	Dietary assessment methods Food record, FFQ, dietary recall, valid biomarkers.			

Study	Research methods	Analysis	Results	Comments
Makarem et al (2013) (Systematic narrative review) <u>Funding source</u> Financial support from the American Cancer Society and the National Cancer Institute. <u>Declarations of interest</u> None declared.	<u>Research question</u> Assess epidemiological evidence on the impact of total dietary fat and fat subtypes, measured pre- and/or post cancer diagnosis, in relation to breast cancer-specific and all-cause mortality among breast cancer survivors. <u>Selection criteria</u> *Search dates:* Up to 30th May 2012. *Study designs:* Cross-sectional, case-control, cohort and experimental studies *Inclusion criteria:* English language; sample size ≥200 subjects; presented HR/RR for recurrence, disease specific mortality, or all-cause mortality among breast cancer patients; conducted follow-up in cancer cases; presented multivariate analysis. *Exclusion criteria:* Univariate analysis. <u>Dietary assessment methods</u> FFQ.	<u>Analysis</u> Narrative review. <u>Evaluation of study quality</u> Not reported.	<u>Breast cancer</u> 4 PCS; n=212-678; duration: not reported; age: 19 to 75y; sex: women only; health at baseline: not reported; country: Canada (3), Japan (1). <u>Saturated fat intake</u> *Evaluation of association between saturated fat intake assessed before diagnosis and breast cancer mortality (2 PCS)* Significant increased risk of breast cancer mortality when treated as a continuous variable and when comparing highest vs lowest quartile of saturated fat intake. Statistically significant linear trend across the quartiles of intakes were observed in a Canadian cohort for saturated fat expressed as % of total fat and as % of total energy. <u>5% increase in saturated fat intake as a % of total energy</u> Associated with approx. 65% increased risk of breast cancer mortality in models including estrogen receptor status as a covariate (HR 1.65, 95%CI 1.07 to 2.56), and the association was borderline significant in models excluding estrogen receptor status (HR 1.55, 95% CI 1.00 to 2.37). <u>Post diagnostic saturated fat intake and breast cancer mortality</u> 2 PCS suggested an increased risk of 55% and 65% increased risk, albeit confidence intervals included the null. 1 PCS showed a non-significant 23% increased risk when comparing women with the highest consumption of saturated fat to the lowest.	Inconsistent and limited evidence warrants research to assess the impact of consumption of fat subtypes on breast cancer recurrence and mortality. <u>Limitations</u> One issue relates to the measurements of dietary fat intake using different dietary assessment methods. Deaths from breast cancer may have been miss-reported as other causes. Selection bias may have occurred.

Study	Research methods	Analysis	Results	Comments
			1 PCS reported a statistically significant 41% elevation in risk of death. 1 PCS reported a non-significant increase in risk with lowest intake compare to the highest intake of saturated fat.	

Study	Research methods	Analysis	Results	Comments
Liu et al (2011) (Systematic review with meta-analysis) <u>Funding source</u> None declared. <u>Declarations of interest</u> None declared.	<u>Research question</u> Evaluate the association between total dietary fat and risk of colorectal cancer. <u>Selection criteria</u> *Search dates*: Up to 1st May 2009. *Study designs*: PCS. *Inclusion criteria*: PCS that reported an association between total dietary fat and risk of colorectal cancer; reported RR and 95% CI according to highest vs. lowest level of intake. *Exclusion criteria*: No details of inclusion and exclusion criteria in studies; data were repeatedly reported; the study was a review, comment, editorial or letter. <u>Dietary assessment methods</u> FFQ (ranged from 50 to 276 items).	<u>Analysis</u> Combined RR and 95% CI used to measure the impact of the highest vs. lowest level of fat and colorectal cancer risk. RR and 95% CI for each study transferred into a logarithm for combined analysis. Random-effects model used to analyse statistical significance. Stratified analyses were performed for types of fat (including saturated fats). Heterogeneity assessed using Q test and I^2. Publication bias evaluated by visual inspection of funnel plots, Begg rank correlation and Egger weighted regression method. <u>Evaluation of study quality</u> Not reported	<u>Colorectal cancer</u> 12 PCS; n= 459,910 participants (3635 cases of colorectal cancer); duration: 3 to 32y; age: not reported; health at baseline: not reported; country: USA (5), UK (1), Finland (2), The Netherlands (1), Norway (1), Japan (2), Singapore (1). <u>Highest vs lowest intake of saturated fat</u> Colorectal cancer risk: no association (12 PCS) RR 1.00 (95% CI 0.90 to 1.12), p=0.89; I^2=0% Stratified analysis according to sex, ethnicity, country, tumour location, follow-up duration, number of items included in FFQ and age showed that saturated fat intake was not associated with the risk of colorectal cancer.	No associations between saturated fat intake and risk of colorectal cancer found. <u>Limitations</u> Probable bias caused by measurement error, needs to be adjusted in future studies. Ten out of 13 studies performed in Europe and USA, therefore extrapolation to Asian populations difficult.

Study	Research methods	Analysis	Results	Comments
Turner (2011) (Systematic review with meta-analysis) <u>Funding source</u> None declared. <u>Declarations of interest</u> None declared.	<u>Research question</u> Identify relationships between dietary fat and fat subtypes, with risk of breast cancer in women. <u>Selection criteria</u> *Search dates:* Up to May 2010. *Study designs*: Cohort and case-control studies. *Inclusion criteria*: Human subjects only. *Exclusion criteria*: Not specified. <u>Dietary assessment methods</u> FFQ (17), diet history (1), serum fatty acid analysis (1).	<u>Analysis</u> Inverse variance method was used for pooling and subsequent random effects meta-analysis. Additional sub-grouping and regression analyses were conducted to identify significant difference between studies. Heterogeneity identified significant variability between studies. <u>Evaluation of study quality</u> Not reported.	<u>Breast cancer</u> 19 PCS for saturated fat; n=1,379,666 (24,257 cases of breast cancer); duration: not reported; age: pre-menopausal (2), post-menopausal (12), both pre- and post-menopausal (5); sex: women only; health at baseline: not reported; country: USA (13), Sweden (2), Singapore (1), Netherlands (1), Italy (1), multiple (1). <u>Highest vs lowest quartile of saturated fat intake</u> Breast cancer risk: no association (19 PCS) RR 0.99 (95% CI 0.94 to 1.05)	Data from cohort studies suggest that intakes of saturated fats were associated with decreased risk of breast cancer, but not significantly. <u>Limitations</u> Small sample of pre-menopausal studies. Study results were based on estimated RR extracted from published studies.

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Dennis et al (2004) (Systematic review with meta-analysis) <u>Funding source</u> Research supported by the National Cancer Institute grants. <u>Declarations of interest</u> None declared.	<u>Research question</u> Examine both the strength and the consistency of the observed associations between aspects of dietary fat and prostate cancer. <u>Selection criteria</u> *Search dates*: 1966 to end of October 2003. *Study designs*: Case control and cohort studies. *Inclusion criteria*: Non-English language publications. *Exclusion criteria*: Animal and therapy studies; no relevant dietary intake data; included populations already reported on; studies that concentrated on % of fatty acids in adipose tissue or serum rather than on intake; ecological studies. <u>Dietary assessment methods</u> FFQs, 24 hour recall.	<u>Analysis</u> Examined RR where available across multiple ordinal categories of the exposures. Where multiple RRs were presented the most adjusted for greatest number of confounders were included. Pooled estimates of risk were then obtained from random-effects models applied to the study-specific slopes. Heterogeneity assessed using Cochran's chi-square test (Q) to assess consistency of associations. I^2 was calculated as the relative difference between Q statistic and its expected value. <u>Evaluation of study quality</u> Not reported	<u>Prostate cancer</u> 3PCS for saturated fat; n = 130,875 participants (2536 cases prostate cancer); duration: 4 to 21y; age: 16 to 75y; health at baseline: not reported; country: USA (2), Netherlands (1), Norway (1). <u>per 25g/day unit change in saturated fats</u> Prostate cancer risk: no association (4 PCS) RR 1.00 (95%CI 0.87 to 1.16), p = 0.81; I^2 = 0% *Adjusted for energy (3 PCS)* RR 1.03 (95%CI 0.73 to 1.46), p = 0.63; I^2 = 0% Confounders adjusted for in primary studies include age; family history of prostate cancer; socioeconomic status; BMI; age 21 BMI; vasectomy status; energy intake; intakes of phosphorous, vitamin D, Vitamin E, lycopene, fructose and calcium.	No significant association between saturated fat intake and prostate cancer. <u>Limitations</u> Inconsistencies in assessments of dietary fat intake.

Study	Research methods	Analysis	Results	Comments
Boyd et al (2003) (Systematic review with meta-analysis) <u>Funding source</u> Supported by Department of Medical Biophysics, University of Toronto; Institute of Medical Sciences, University of Toronto. <u>Declarations of interest</u> None declared.	<u>Research question</u> Examine the association of dietary fat or fat containing foods with risk of breast cancer. <u>Selection criteria</u> *Search dates*: From January 1966 up to July 2003. *Study designs*: Cohort and case-control studies. *Inclusion criteria:* Not specified. *Exclusion criteria*: Not specified. <u>Dietary assessment methods</u> Diet history (12), FFQs (32), 24 hour diet recall (1), food records and food frequency questionnaire (1). *Cohort only:* FFQ (10), diet history (3), 24 hour diet recall (1).	<u>Analysis</u> Data for case-control and cohort were analysed separately and together. To account for sources of variation in this meta-analysis, the method of DerSimonian and Laird was used. The magnitude of the heterogeneity was estimated, and accounted for by assigning a greater variability to the estimate of the overall effect. Regression analysis was used to examine independent factor contributions. <u>Evaluation of study quality</u> Calculated for each study independently by 4 investigators using predetermined methodological standards and any difference resolved by discussion. Quality scores were used to divide studies into groups for stratified analysis.	<u>Breast cancer</u> 14 PCS; n=568,549 (8735 breast cancer cases); duration: not reported; age: not reported; sex: women only; health at baseline: not reported; country: USA (7), UK (1), Canada (1), Finland (1), France (1), Sweden (1), The Netherlands (1), Norway (1). <u>RR of breast cancer and saturated fat intake</u> Breast cancer: ↑ risk (12 PCS) RR 1.15 (95% CI 1.02 to 1.30)	Saturated fat intake was significantly associated with breast cancer risk in cohort studies. <u>Limitations</u> Homogeneity of fat intake within population, error in measurement of fat intake, as FFQ may lead to overestimation of the range of intakes.

Study	Research methods	Analysis	Results	Comments
Smith-Warner et al (2002) (Pooled analysis) Funding source National Institutes of Health. Declarations of interest None declared.	Research Question Examine the relationship between lung cancer and intakes of total and specific types of fat and cholesterol. Selection criteria *Search dates:* Not specified. *Study designs:* PCS. *Inclusion criteria:* At least 200 incident breast cancer cases; assessment of long term dietary intake; validation of the diet assessment method or a closely related instrument; at least 50 incident lung cancer cases; assessment of smoking history at baseline. *Exclusion criteria:* Excluded data on participants that had reported energy intakes greater or less than 3 SDs from the study specific $\log_e$-transformed mean energy intake of the baseline population; reported a history of cancer (except non-melanoma skin cancer) at baseline; no information on smoking habits. Dietary assessment methods FFQ (the number of items included in the questionnaires ranged from 45 to 276; portion sizes not given in 2 PCS; specified by participants in 3 PCS; specified on the questionnaire in 3 PCS).	Analysis Cox proportional hazards model used to calculate study-specific RRs. Analysed associations for intakes of saturated fats as a percentage of total calories. In the multivariate analyses smoking habits, education, BMI, alcohol consumption, fruit and vegetable consumption, and energy intake included as covariates. Two sided 95% CIs were calculated. Pooled RRs were calculated using a random effects model. Heterogeneity among studies assessed using asymptotic DerSimonian and Laird Q statistics. Analyses for specific types of fat were conducted by including saturated fat, MUFA and PUFA, protein and alcohol intakes in the same multivariate model, in addition to the other covariates. In this model, the RRs for the specific types of fat are adjusted for each other and have the interpretation of being compared with an identical decrease in the % of energy from carbohydrates. Evaluation of study quality Not reported.	Lung cancer 8 PCS; n = 280,419 women, n =149,862 men, 3188 cases of lung cancer (1395 in women, 1793 in men); duration: 6 to 16y; age: 15 to 107y; sex: M(2), W(3), M/W(3); country: USA/Canada (6), The Netherlands (1), Finland (1). Quartile of saturated fat intake Lung cancer: no association (8 PCS) Q1 vs Q2: RR 0.94 (95% CI 0.81 to 1.10) Q1 vs Q3: RR 0.99 (95% CI 0.87 to 1.11) Q1 vs Q4: RR 1.01 (95% CI 0.89 to 1.14) P, test for trend = 0.57 P, test for between study heterogeneity = 0.40 *RR of lung cancer for saturated fat (5% of energy increase)* Age adjusted: RR 1.21 (95% CI 1.08 to 1.36), p=0.001 (when adjusted for education, BMI, alcohol consumption, fruit and vegetable consumption and energy intake the association were attenuated but still statistically significant). Multivariate-adjusted: RR 1.03 (95% CI 0.96 to 1.11), p=0.35. (P, test for between study heterogeneity = 0.60) *RR of lung cancer for intake of saturated fats (5% of energy increase) by smoking status* Current: RR 1.02 (95% CI 0.92 to 1.13) Past: RR 1.10 (95% CI 0.91 to 1.33) Never: RR 0.97 (95% CI 0.74 to 1.27)	No evidence of an association between saturated fat intake and risk of lung cancer risk. Findings consistent with evidence from cohort studies but not case-control studies which indicate positive associations between saturated fat intake and lung cancer risk. Limitations Fat intake measurement error induced by use of FFQ compared with other studies where fat intake has been measured more precisely, thereby resulting in an underestimate of association.

Study	Research methods	Analysis	Results	Comments
			Greater saturated fat intakes not significantly associated with higher risk of lung cancer in any of the individual cohorts in the multivariate analysis. When intakes of saturated fat, MUFA and PUFA were mutually adjusted by including them simultaneously in the multivariate model as continuous variables, there was no significant association between saturated fat and lung cancer risk.	

Study	Research methods	Analysis	Results	Comments
Smith-Warner et al (2001) (Pooled analysis) Funding source Supported by research grants from National Institute of health; Cancer Research Foundation of America; American Society of Preventive Oncology Research Fellowship; American Cancer Society. Declarations of interest None declared.	Research question Investigate the independent association between intakes of specific types of fat and breast cancer risk. Selection criteria *Search dates:* Not reported. *Study designs:* PCS. *Inclusion criteria:* At least 200 incident breast cancer cases; assessment of usual intake of foods and nutrients; a validation study of the diet assessment method or a closely related instrument. *Exclusion criteria:* Excluded data on participants if they reported energy intakes greater or less than 3 SDs from study specific $\log_e$-transformed mean energy intake of the baseline population, had missing alcohol intake data or reported history of cancer (expect non-melanoma skin cancer) at baseline. Dietary assessment methods FFQ (the number of items included in the questionnaires ranged from 45 to 150; portion sizes not given in 2 PCS; specified by participants (as small medium and large relative to a standard size) in 2 PCS; specified on the questionnaire in 3 PCS).	Analysis Holding total energy intake constant, RRs for increments of 5% of energy for each type of fat compared with an equivalent amount of energy from carbohydrates or from other types of fat were calculated. Study-specific RRs were combined using a random effects model. Evaluation of study quality Not specified.	8 PCS; n = 351,821 participants, 7329 cases of invasive breast cancer; duration: 6 to 16y; age: 28 to 93y; sex: women only; country: USA/Canada (6), The Netherlands (1), Sweden (1). Range of median total fat intake: 30-41% of total energy. Range of median saturated fat intake: 10-16% of total energy. 5% of energy increase from saturated fats (continuous model) Breast cancer risk: no association RR 1.03 (95% CI 0.95 to 1.10; p, test for heterogeneity = 0.04) Premenopausal: RR 1.10 (95% CI 0.91 to1.35) Postmenopausal: RR 1.07 (95% CI 0.93 to 1.24) Quartile of saturated fat intake Breast cancer risk: no assocaition Q1 vs Q2: RR 0.99 (95% CI 0.91 to 1.08) Q1 vs Q3: RR 0.95 (95% CI 0.87 to 1.04) Q1 vs Q4: RR 1.01 (95% CI 0.89 to 1.16) P, test for trend = 0.85 Substituting 5% of energy from saturated fat Breast cancer risk: no assocaition PUFA: 0.98 (95% CI 0.85 to 1.12) MUFA: RR 1.18 (95% CI 0.99 to 1.42) Carbohydrate: RR 1.09 (95% CI 1.00 to 1.19);	No association between saturated fat intake and substitutions and breast cancer risk. Limitations Fat consumption is measured with error in cohort studies. Cohort studies frequently measure dietary intake using FFQs which lead to underestimation of fat intake

Table A2.16 PCS assessing the relationship between dietary saturated fat intake and cancers in each review article

Study name[1] / first author (publication dates)	**Cao et al (2016)**	**Brennan et al (2015)**	**Xia et al (2015)**	**Xu et al (2015a)**	**Yao & Tian (2015)**	**Schwab et al (2014)**	**Makarem et al (2013)**	**Liu et al (2011)**	**Turner (2011)**	**Dennis et al (2004)**	**Boyd et al (2003)**	**Smith-Warner et al (2002)**	**Smith-Warner et al, (2001)**
C, colorectal cancer; Pa, pancreatic cancer; L, lung cancer; B, breast cancer; Pr, prostate cancer													
Total primary studies (publications)	20	4	24	9	6	14	3 (4)	12	19	4	14	8	8
Boeke 2014	B		B										
Farvid 2014			B										
Sieri 2014	B												
Arem 2013					Pa								
NIH-AARP Diet and Health Study													
Pelser 2013				Pr									
Thiebaut 2009					Pa	Pa							
Park 2012	B		B			B							
Sczaniecka 2012	B		B										
Linos 2010						B			B				
Netherland's Cohort Study on Diet and Cancer													
Heinen 2009					Pa								
Kushi 1992											B	B	
Butler 2008								C					
European Prospective Into Cancer and Nutrition (EPIC)													
Crowe 2008				Pr		Pr							
Willett 1987									B				
Sieri 2008			B			B							
Lof 2007	B		B			B			B				
Neuhouser 2007				Pr									
Park 2007				Pr		Pr							
Thiebaut 2007	B		B						B				
Wallstrom 2007				Pr		Pr							
Freedman 2006	B												
Kim 2006			B			B			B				

Study name[1] / first author (publication dates)	Cao et al (2016)	Brennan et al (2015)	Xia et al (2015)	Xu et al (2015a)	Yao & Tian (2015)	Schwab et al (2014)	Makarem et al (2013)	Liu et al (2011)	Turner (2011)	Dennis et al (2004)	Boyd et al (2003)	Smith-Warner et al (2002)	Smith-Warner et al, (2001)
C, colorectal cancer; Pa, pancreatic cancer; L, lung cancer; B, breast cancer; Pr, prostate cancer													
Oba 2006								C					
Nothlings 2005					Pa	Pa							
Wakai 2005	B		B										
Borugian 2004		B					B						
Lin 2004						C		C					
Nurses Health Study Frazier 2004			B										
Mills 1989												B	
Saadatian-Elahi 2004									B				
Bingham 2003			B								B		
Cho 2003			B			B			B		B		
Flood 2003								C					
Gago-Dominguez 2003									B				
Michaud 2003					Pa	Pa							
Byrne 2002			B						B				
New York University Women's Health Study													
Horn-Ross 2002	B								B				
Kato 1997								C					
Sieri 2002	B								B				
Stolzenberg-Solomon 2002					Pa	Pa							
Voorrips 2002	B		B						B				
Wirfalt 2002	B								B				
Jarvinen 2001								C					
Feskanaich 2000													L
Rohan 2000													L
Velie 2000	B		B						B		B		
Kristal 2010				Pr									
Pietinen 1999								C					
Schuurman 1999										Pr			
Holmes 1999		B	B						B		B	B	L
Wolk 1998	B		B								B	B	
Jain and Milier 1997							B						

Study name[1] / first author (publication dates)	Cao et al (2016)	Brennan et al (2015)	Xia et al (2015)	Xu et al (2015a)	Yao & Tian (2015)	Schwab et al (2014)	Makarem et al (2013)	Liu et al (2011)	Turner (2011)	Dennis et al (2004)	Boyd et al (2003)	Smith-Warner et al (2002)	Smith-Warner et al, (2001)
C, colorectal cancer; Pa, pancreatic cancer; L, lung cancer; B, breast cancer; Pr, prostate cancer													
Jain 1994		B					B						
Veierod 1997				Pr						Pr			
Gaard 1996								C					
Hunter 1996									B				
Gaard 1995	B		B								B		
Kushi 1995	B								B				
ATBC Cancer prevention Study Group 1994													L
Bostick 1994								C					
Giovannucci 1994								C					
Goldbohm 1994								C					
Toniolo 1994	B		B						B		B	B	
Giovannucci 1993				Pr						Pr			
van den Brandt (a) 1993													L
van den Brandt (b) 1993			B								B	B	
Rohan 1993		B											
Graham 1992											B	B	L
Kushi 1992													L
Kyogoku 1992							B						
Willett 1992			B						B				
Howe 1991	B		B								B	B	
Howe (b) 1991											B		
Knekt 1990	B		B								B		
Willett 1990								C					
Mills 1989													L
Severson 1989				Pr						Pr			
Jones 1987	B		B								B		

[1] Study name is only provided when two or more publications for that study are used in any of the reviews.

Cognitive impairment and dementias

Table A2.17 Characteristics of a meta-analysis and systematic reviews

Study	Research methods	Analysis	Results	Comments
Xu et al (2015b) (Systematic review with meta-analysis) Funding source None declared. Declarations of interest None declared.	Research question To carry out the most extensive and comprehensive systematic review and meta-analysis to date, which employs a full-scale search of observational studies to calculate effect sizes of various modifiable risk factors for Alzheimer's disease. Selection criteria *Search dates:* Up to 15th July 2014. *Study designs:* PCS and retrospective case-control studies. *Inclusion criteria:* Original data concerning OR or RR of Alzheimer's disease; study population representative of the general population; exposures considered to be positively or negatively associated with later diagnosis of Alzheimer's disease are potentially modifiable. *Exclusion criteria:* Non English-written publications; about genetic risk factors; without dementia specification; statistically non-significant; special population or population not representing general people; relative of Alzheimer's disease patients or individuals with another disease as control; Alzheimer's disease	Analysis Where an exposure of interest was reported by 2 studies in a consistent way, these were combined. Pooled effect size calculated and 95% CI. Heterogeneity between studies: I^2 statistic, where significant ($p<0.05$), it was further analysed. When heterogeneity could not be explained, random effect model used. Publication bias: evaluated using Egger test, where significant, trim and fill method used. Evaluation of study quality Grade I evidence: pooled population >5000, lower heterogeneity $I^2<50\%$; Grade II-A evidence: pooled population >5000, higher heterogeneity $I^2 \geq 50\%$; Grade II-B evidence: pooled population <5000, lower heterogeneity $I^2 \geq 50\%$;	3 PCS; n=7894 (244 cases); duration: 2.1 to 21y; age: 67.7y mean age in 1 PCS (not reported in 2 PCS); sex: M (2), W (0), M/W (1); health at baseline: not reported; country: USA (1), The Netherlands (1), Finland (1). RR of Alzheimer's disease for highest vs lowest saturated fat intake *Fixed effect analysis:* RR 1.35 (95% CI -0.03 to 2.74), p=0.619; $I^2=0\%$ One cohort study adjusted for APOE status.	No association found.

Study	Research methods	Analysis	Results	Comments
	progression or Alzheimer's disease has happened. <u>Dietary assessment methods</u> FFQ, SQFFQ and structured questionnaire and interview.	Grade III evidence: pooled population <5000, higher heterogeneity.		

Study	Research methods	Analysis	Results	Comments
Barnard et al (2014) (Narrative systematic review) <u>Funding source</u> None declared. <u>Declarations of interest</u> ND Barnard writes books and articles and gives lectures related to nutrition and health and has received royalties and honoraria from these sources. Authors affiliated with the Physicians Committee for Responsible Medicine, which promotes the use of low-fat, plant-based diets and discourages the use of animal-derived, fatty and sugary foods.	<u>Research question</u> Identify the strength of associations between saturated fat intake or trans fats intake and the risk of Alzheimer's disease and other forms of dementia. <u>Selection criteria</u> *Search dates*: Inception until July 2012. *Study designs*: PCS, RCTs. *Inclusion criteria*: Exposure to saturated or trans fats was quantified (at any adult age); endpoints included incident dementia, Alzheimer's disease or mild cognitive impairment; or cognitive decline; the outcome was identified in older age; in PCS, an interval of at least 1 year occurred between dietary assessment and determination of cognitive outcome or in studies assessing cognitive decline, between 2 or more assessments of cognitive status. *Exclusion criteria*: Case reports, case series, case-control studies, studies limited to individuals with medical conditions likely to influence cognitive status and intervention trials including non-dietary methods (e.g. exercise). <u>Dietary assessment methods</u> All used FFQ, except one study - shortened questionnaire specific to dairy products and spreads.	<u>Analysis</u> Narrative review, data not combined. <u>Evaluation of study quality</u> Study reports were examined for means of dietary assessment, diagnosis and cognitive assessment, sample size, baseline dietary variability, attrition, and statistical measures.	9 PCS (13 publications); n=278 to 6183; duration: 2.6 to 21y; age: mean 50.2 to 73.1y; sex: M (0), W (2), M/W (10); health at baseline: not reported; country: USA (6), Finland (2), Italy (2), The Netherlands (1), Australia (1). <u>Incident Alzheimer's disease and other forms of dementia (4 PCS)</u> *Alzheimer's disease:* 1 PCS reported high saturated fat intake was associated with an increased risk. 1 PCS reported high saturated fat was associated with a reduced risk. 2 PCS found no association. *Total dementia:* 2 PCS found no association. 1 PCS found APOE e4 allele carriers at increased risk of dementia and Alzheimer's disease with moderate (second quartile) saturated fat intake: OR 3.16 (95% CI 1.12 to 8.91). <u>Incident mild cognitive impairment (4 PCS)</u> 1 PCS found saturated fat intake was positively associated with risk of mild cognitive impairment limited to those with APOE e4 allele: OR 5.06 (95% CI 1.35 to 18.94). 3 PCS found no association; did not test for APOE status or adjust for it in analysis. <u>Cognitive decline (4 PCS)</u> 2 PCS found higher saturated fat intake was associated with increased risk; APOE status not measured. 2 PCS found no association; APOE status reported in 1 PCS, no effect on association.	Not all PCS indicate relationships between saturated fat intake and risk of cognitive problems. <u>Limitations</u> Limited number of studies and no RCTs reflect challenges of completing these studies and need for caution in drawing conclusions. Individuals with cognitive problems are more likely to be lost to follow-up.

Study	Research methods	Analysis	Results	Comments
Lee et al (2010) (Narrative systematic review) <u>Funding source</u> Health Promotion Fund and partial support from the Clinical Research Center for Dementia, Ministry for Health, Welfare and Family Affairs, Republic of Korea. <u>Declarations of interest</u> None declared.	<u>Research question</u> Provide an update on the evidence on major health behavioural factors affecting cognitive function, cognitive impairment, and dementia in older people living in the community. Five health behaviours considered: physical activity, smoking, alcohol drinking, BMI, diet and nutrition). <u>Selection criteria</u> *Search dates*: Inception until August 2008 *Study designs*: PCS *Inclusion criteria*: Predominantly aged over 65 years; from a community representative population; could include institutionalised patients as a minority in a larger community based sample. *Exclusion criteria*: Only involving those aged less than 65 years; non-representative samples; non-cognitive outcomes; cross sectional or retrospective study design; congress proceedings and abstracts. <u>Dietary assessment methods</u> Not reported.	<u>Analysis</u> Narrative review. <u>Evaluation of study quality:</u> Assessed based on a 'priori' internal and external validity criteria, incorporating representativeness of the study sample, sample size, follow-up rate and period, outcome and predictor measurements, and controlled confounders.	1 PCS (3 publications); n=1449 to 1589; duration: mean 20.9y (72.5% attrition rate); age: 39 to 64y; sex: M/F; health at baseline: not reported; country: Finland. Adjusted for sociodemographic, health-related variables, APOE status. <u>OR for mild cognitive impairment for highest vs lowest intake of saturated fats</u> *Saturated fat from milk, sour milk, and spreads* ↑SF ↑risk: OR 2.36 (95% CI 1.17 to 4.74) <u>OR for total dementia and Alzheimer's disease for saturated fat intake (2nd quartile vs 1st quartile)</u> *Saturated fat from milk, sour milk, and spreads* Total dementia: OR 2.45 (95% CI 1.10 to 5.47) Alzheimer's disease: OR 3.82 (95% CI 1.48 to 9.87) *Saturated fat from spreads* ↑ saturated fat ↑ risk of total dementia and Alzheimer's disease: OR 2.54 (95% CI 1.13 to 5.68) APOE $_e$4 carriers: OR 4.34 (95% CI 1.28 to 14.68)	Saturated fat intake increased the risk of mild cognitive impairment and dementia.

Study	Research methods	Analysis	Results	Comments
Patterson et al (2007) (Narrative systematic review) Funding source Financial support from the Institute of Advanced Studies, University of Bologna, Italy; CIHR New Investigator Award. Declarations of interest Support received from: Janssen-Ortho; Pfizer; Novartis; Lundbeck; Alzheimer Society of Nova Scotia; Voyager Pharmaceuticals; Myriad; Neurochem.	Research question To identify and quantify general (non-genetic) risk factors for all-cause dementia, Alzheimer's disease, and vascular dementia. Selection criteria *Search dates*: From 1966 to December 2005. *Study designs*: Longitudinal cohort studies. *Inclusion criteria*: Longitudinal cohort studies; population broadly representative of Canadian demographics; dementia, Alzheimer's disease, or vascular dementia as outcome; general risk factors identified (e.g. hypertension, educational status, occupation, chemical exposure). *Exclusion criteria*: Genetic risk factors. Dietary assessment methods Not reported.	Analysis Narrative review. Evaluation of study quality Categorised as good, fair, or poor based on a criteria considering: population characteristics, follow-up, exposure risk factors, outcomes, analysis.	Characteristics of identified studies not summarised. RR of all-cause dementia with total fat intake >85.5 g/day vs total fat intake <75.5 g/day (1 PCS) RR 2.4 (95% CI 1.1 to 5.4) Increased amounts of saturated fat and cholesterol were not established as definite risk factors in 1PCS from The Netherlands (unclear if other studies were identified).	Limitations 1 PCS with very limited description.

Study	Research methods	Analysis	Results	Comments
Ernst (1999) (Narrative systematic review) <u>Funding source</u> None declared. <u>Declarations of interest</u> None declared.	<u>Research question</u> Summarise present knowledge of the relationship of dietary factors and dementias. <u>Selection criteria</u> *Search dates*: Inception to the end of 1997. *Study designs*: Cross-sectional or longitudinal. *Inclusion criteria*: Articles had to include either cross-sectional or longitudinal data on dietary factors and relate these to dementias of either vascular or degenerative type; human subjects. *Exclusion criteria*: Not reported. <u>Dietary assessment methods</u> FFQ.	<u>Analysis</u> Narrative review. <u>Evaluation of study quality</u> Not reported.	1 PCS for saturated fat; n=5386; duration: 2.1y; mean age: 67.7y; sex: not reported; health at baseline: not reported; country: The Netherlands. Adjustments made for age, sex, education, energy intake. Results suggested saturated fat intake was a risk factor for dementia RR 1.9 (95% CI not reported)	<u>Limitations</u> Saturated fat and dementia association found during post hoc analysis. Only one study looked into the association.

Table A2.18 PCS assessing the relationship between dietary saturated fat intake and cognitive impairment and dementias in each review article

Study name[1] / first author (publication dates)	**Xu et al (2015b)**	**Barnard et al (2014)**	**Lee et al (2010)**	**Patterson et al (2007)**	**Ernst (1999)**
AD, Alzheimer's disease; CD, cognitive decline; MCI, mild cognitive disorder; TD, total dementia.					
Total primary studies (publications)	3	9 (13)	1 (3)	1	1
Cherbuin and Anstey 2012		MCI			
Okereke 2012		CD			
Roberts 2012		MCI			
Naqvi 2011		CD			
Cardiovascular risk factors, Ageing and Dementia					
Eskelinen 2008		MCI	MCI		
Kivipelto 2008			AD, TD		
Laitenen 2006	AD	AD, TD	AD, TD		
Italian Longitudinal Study on Ageing					
Solfrizzi 2006		MCI			
Solfrizzi 2006		CD			
Chicago Health and Ageing Project					
Morris 2004		CD			
Morris 2003	AD	AD			
Luchsinger 2002		AD			
Rotterdam Study					
Engelhart 2002		AD, TD			
Kalmijin 1997	AD	AD, TD		TD	TD

Outcome measured by the study: AD, Alzheimer's disease; CD, cognitive decline; MCI, mild cognitive disorder; TD, total dementia.

[1] Study name is only provided when two or more publications for that study are used in any of the reviews.

ANNEX 3: Intakes and sources of dietary fats

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Table A3.1 Average daily intake of saturated fats (g/day and % total energy) by age in children and adults from 4 years of age

NDNS RP years 7-8 (2014/15-2015/16)

Aged 4 years and over % exceeding DRV from NDNS RP years 5-6 (2012/13-2013/14)

	Saturated fatty acids	
Age group (years) [Bases unweighted]	g/day	% total energy[1]
Children 4-10 years [n=514]		
Mean	20.9	13.0
Median	19.9	12.9
SD	7.1	2.7
2.5th percentile	8.8	7.7
97.5th percentile	36.7	18.3
% exceeding the DRV[2]		89.3
Children 11-18 years [n=542]		
Mean	24.2	12.4
Median	22.4	12.4
SD	11.7	2.9
2.5th percentile	7.6	7.1
97.5th percentile	49.9	18.6
% exceeding the DRV[2]		84.7
Adults 19-64 years [n=1082]		
Mean	25.1	11.9
Median	23.8	11.7
SD	11.5	3.4
2.5th percentile	6.5	5.6
97.5th percentile	50.4	18.9
% exceeding the DRV[2]		74.5

	Saturated fatty acids	
Age group (years) [Bases unweighted]	g/day	% total energy[1]
Adults 65 years and over [n=335]		
Mean	24.3	13.3
Median	23.1	12.7
SD	10.4	3.8
2.5th percentile	8.4	7.4
97.5th percentile	49.6	20.9
% exceeding the DRV[2]		83.3
Adults 65-74 years [n=181][3]		
Mean	23.7	12.5
Median	22.3	12.1
SD	9.9	3.6
2.5th percentile	8.2	6.6
97.5th percentile	45.8	19.2
Adults 75 years and over [n=154][3]		
Mean	25.1	14.3
Median	24.4	14.0
SD	11.0	3.9
2.5th percentile	8.3	8.0
97.5th percentile	50.7	22.2

Note:

[1] Total energy intake includes energy from alcohol

[2] The dietary reference value for saturated fats is 10% of total dietary energy (11% of energy from food and drinks excluding alcohol) (COMA 1994). All calculations weighted. Data source: NDNS: years 5&6 (2012/13-2013/14)

[3]Data on the % exceeding the DRV is not available for Adults 65-74 years or Adults 75 years and over

Table A3.2 Percentage contribution of food groups to average daily saturated fats intake by age in children and adults from 4 years of age

Aged 4 years and over NDNS RP years 7-8 (2014/15-2015/16)

Food group[a]	Age group (years)				
	4-10	11-18	19-64	65-74	75+
	%	%	%	%	%
Cereals and cereal products	27	28	21	21	20
of which:					
Pasta, rice, pizza and other miscellaneous cereals	6	8	6	1	2
White bread	3	3	2	1	1
Wholemeal bread	0	0	1	1	1
Brown, granary and wheatgerm bread	0	0	0	0	0
High fibre breakfast cereals	1	1	1	2	2
Other breakfast cereals	1	1	0	0	0
Biscuits	8	7	5	6	6
Buns, cakes, pastries and fruit pies	7	6	4	6	6
Puddings	2	2	1	2	3
Milk and milk products	30	22	21	24	27
of which:					
Whole milk (3.8% fat)	7	3	2	1	4
Semi skimmed milk (1.8% fat)	5	5	4	6	5
Other milk and cream	2	1	2	1	2
Cheese	8	8	9	10	11
of which					
Cheddar cheese	5	7	6	7	7
Other cheese	3	2	3	3	4
Yoghurt, fromage frais and other dairy desserts	4	2	2	3	3
Ice cream	4	2	1	2	2
Eggs and egg dishes	2	3	3	4	4

Food group[a]	Age group (years)				
	4-10	11-18	19-64	65-74	75+
	%	%	%	%	%
Fat spreads[b]	8	7	9	13	16
of which:					
Butter	4	4	6	8	11
Reduced fat spread polyunsaturated (41-75% fat)	1	0	0	1	1
Reduced fat spread not polyunsaturated (41-75% fat)	2	2	2	4	3
Low fat spread polyunsaturated (18-39% fat)	0	0	0	0	0
Low fat spread not polyunsaturated (18-39% fat)	0	0	0	0	0
Meat and meat products	17	22	24	21	18
of which:					
Bacon and ham	1	2	2	2	2
Beef, veal and dishes	2	4	4	4	4
Lamb and dishes	1	1	2	1	2
Pork and dishes	1	1	1	1	1
Coated chicken and turkey	1	2	1	0	0
Chicken, turkey and dishes	3	4	5	3	3
Liver and dishes	0	0	0	0	1
Burgers and kebabs	1	2	1	1	0
Sausages	4	3	3	3	2
Meat pies and pastries	2	4	3	3	3
Other meat, meat products and dishes	1	0	1	1	1
Fish and fish dishes	2	2	3	4	4
of which:					
White fish coated or fried including fish fingers	1	1	1	1	1
Other white fish, shellfish or fish dishes and canned tuna	0	0	1	1	1
Oily fish	0	0	1	2	2

Food group[a]	Age group (years)				
	4-10	11-18	19-64	65-74	75+
	%	%	%	%	%
Vegetables and potatoes	4	5	6	4	3
of which:					
Vegetables (not raw) including vegetable dishes	1	1	3	2	1
Chips, fried and roast potatoes and potato products	2	3	3	2	1
Other potatoes, potato salads and dishes	0	0	1	0	1
Savoury snacks	2	1	1	0	0
Nuts and seeds	1	1	2	2	1
Fruit	0	0	1	1	0
Sugar, preserves and confectionery	8	7	5	4	3
of which:					
Sugars, including table sugar, preserves and sweet spreads	1	1	0	0	0
Sugar confectionery	0	0	0	0	0
Chocolate confectionery	6	6	4	4	3
Non-alcoholic beverages[c]	0	0	1	1	0
of which:					
Tea, coffee and water	0	0	1	1	0
Alcoholic beverages	0	0	0	0	0
Miscellaneous[d]	1	2	3	3	3
of which:					
Dry weight beverages	0	0	0	1	1
Soup, manufactured/retail and homemade	0	0	1	1	1
Savoury sauces, pickles, gravies and condiments	1	2	2	1	1
Commercial toddler foods	0	0	0	0	0

Food group[a]	Age group (years)				
	4-10	11-18	19-64	65-74	75+
	%	%	%	%	%
Average daily saturated fatty acids intake g	20.9	24.2	25.1	23.7	25.1
Bases (unweighted)	*514*	*542*	*1082*	*181*	*154*

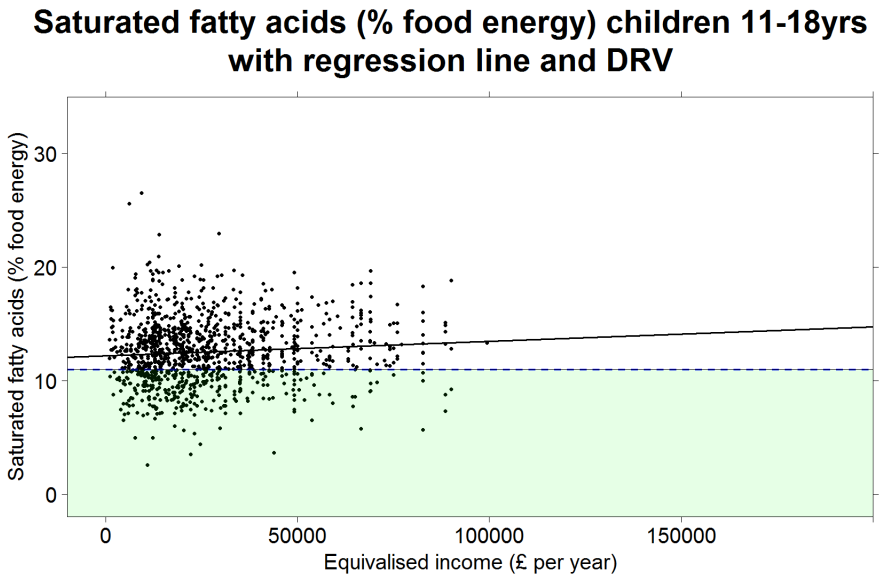
[a] Sub food groups that contribute <0.5% to intake across all age/sex groups are excluded from the table. All other food groups are included.

[b] Some oils which are used as a condiment on bread or salads are included in this food group; however this food group does not include oils or fats used in cooking.

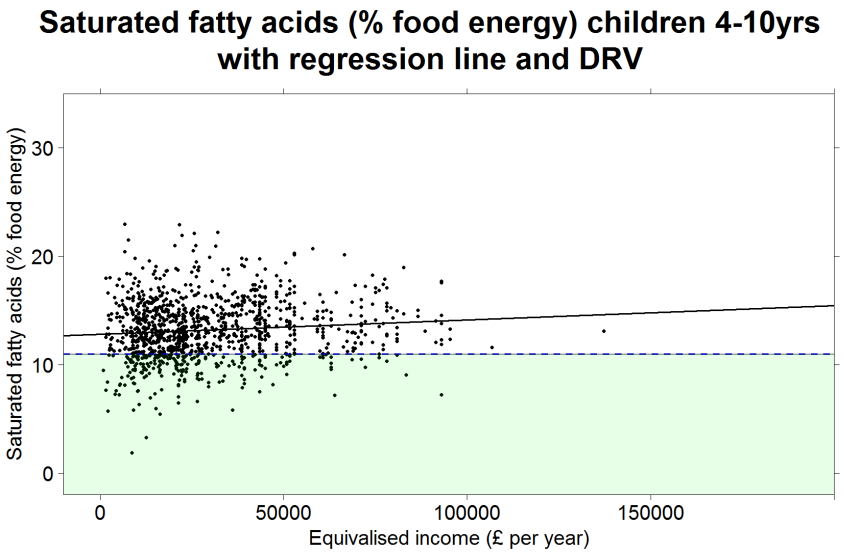
[c] Non-alcoholic beverages are reported as consumed with diluent water.

[d] In addition to dry weight beverages; soup, manufactured/retail and homemade; savoury sauces, pickles, gravies and condiments; and commercial toddler foods, Miscellaneous also includes nutrition powders and drinks.

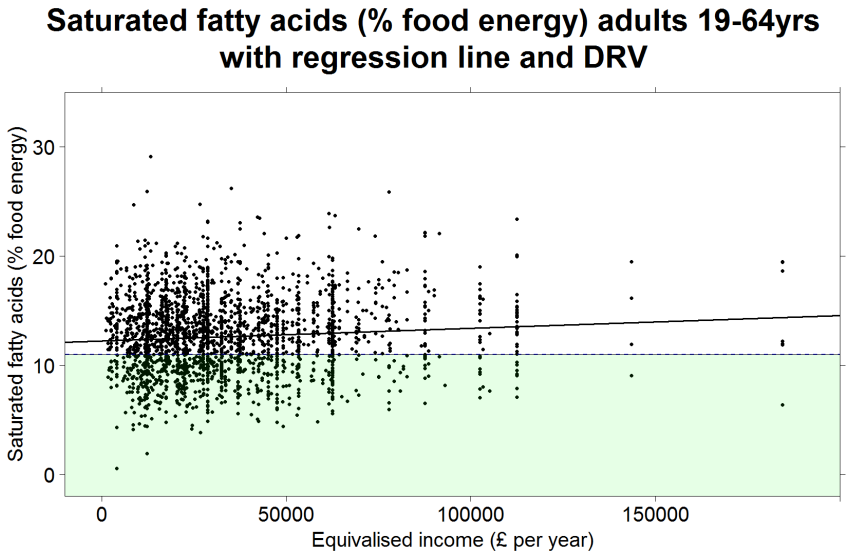
Figure A3.1 Saturated fatty acids intake (% food energy) equivalised income analysis - UK Years 5-9



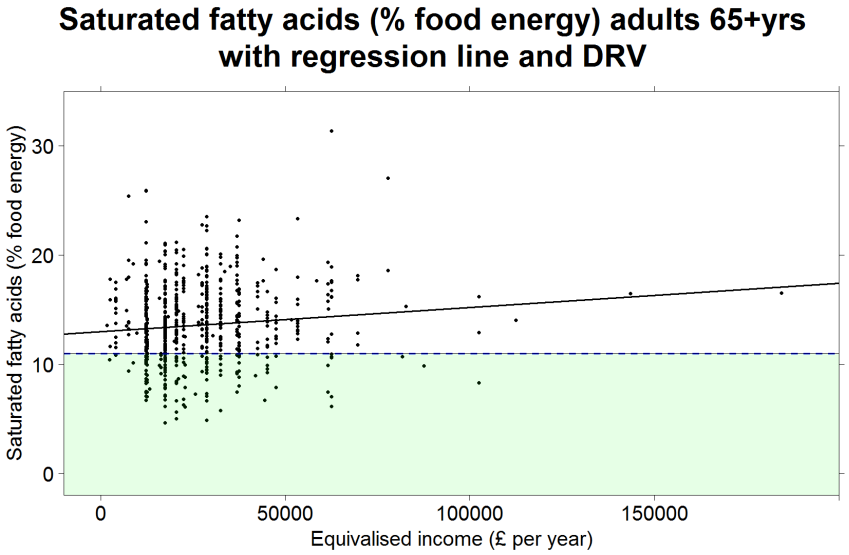
Average change per £10,000 (percentage points) 0.1 (95% CI 0.0 to 0.2)



Average change per £10,000 (percentage points) 0.1 (95% CI 0.0 to 0.2)



Average change per £10,000 (percentage points) 0.1 (95% CI 0.0 to 0.2)



Average change per £10,000 (percentage points) 0.2 (95% CI 0.0 to 0.4)

Key

Green area – meeting the DRV

Blue dashed line – DRV

Black line – regression line using individual participant response

Individual participant response plotted at participants' equivalised income response

Table A3.3 Average daily intake of polyunsaturated fats (g/day and % total energy) by age and sex in children and adults from 4 years of age

Aged 4 years and over

National Diet and Nutrition Survey Rolling Programme Years 1, 2, 3 and 4 (2008/09 - 2011/12)

	Sex and age group (years)													
	Boys		Total	Men		Girls		Total	Women		Total			
	4-10	11-18	boys	19-64	65+	4-10	11-18	girls	19-64	65+	4-10	11-18	19-64	65+
***Cis* n-3 polyunsaturated fats (g/day)**														
Mean	1.4	1.9	1.7	2.2	2.3	1.3	1.6	1.5	1.8	1.8	1.4	1.8	2.0	2.0
Median	1.3	1.7	1.5	2.0	2.1	1.2	1.5	1.4	1.6	1.6	1.3	1.6	1.8	1.8
SD	0.6	0.9	0.8	1.1	1.2	0.6	0.8	0.8	1.0	1.0	0.6	0.8	1.1	1.1
Upper 2.5 percentile	2.7	4.2	3.6	4.9	5.7	2.9	3.4	3.3	4.2	4.4	2.8	3.8	4.7	4.5
Lower 2.5 percentile	0.6	0.6	0.6	0.7	0.8	0.6	0.5	0.5	0.5	0.7	0.6	0.6	0.6	0.7
% total energy[a]														
Mean	0.8	0.9	0.8	0.9	1.1	0.8	0.9	0.9	1.0	1.1	0.8	0.9	1.0	1.1
Median	0.8	0.8	0.8	0.9	0.9	0.7	0.9	0.8	0.9	0.9	0.8	0.8	0.9	0.9
SD	0.3	0.3	0.3	0.4	0.5	0.3	0.4	0.3	0.4	0.5	0.3	0.3	0.4	0.5
Upper 2.5 percentile	1.5	1.7	1.5	1.9	2.3	1.4	1.8	1.7	2.1	2.4	1.5	1.8	2.0	2.3
Lower 2.5 percentile	0.4	0.4	0.4	0.4	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
***Cis* n-6 polyunsaturated fats (g/day)**														
Mean	7.6	10.0	8.9	11.2	10.1	7.4	8.5	8.0	8.8	7.7	7.5	9.2	10.0	8.7
Median	7.3	9.3	8.4	10.6	9.4	6.7	8.0	7.5	8.2	7.3	7.0	8.8	9.2	8.1
SD	2.7	3.7	3.5	4.7	4.4	3.1	3.5	3.4	3.9	3.0	2.9	3.7	4.5	3.9
Upper 2.5 percentile	13.9	18.2	16.9	23.3	20.5	16.4	16.8	16.8	17.4	13.9	14.2	17.3	20.7	19.0
Lower 2.5 percentile	3.6	3.9	3.8	3.8	3.5	3.1	3.1	3.1	2.7	3.2	3.3	3.4	3.1	3.3
% total energy[a]														
Mean	4.4	4.6	4.5	4.8	4.7	4.4	4.8	4.6	4.9	4.6	4.4	4.7	4.8	4.6
Median	4.3	4.4	4.4	4.6	4.5	4.2	4.7	4.5	4.6	4.4	4.2	4.5	4.6	4.4
SD	1.2	1.2	1.2	1.5	1.4	1.3	1.3	1.4	1.6	1.7	1.3	1.3	1.6	1.6
Upper 2.5 percentile	7.2	7.1	7.1	8.2	8.1	7.6	8.1	8.0	8.6	7.5	7.5	7.6	8.4	7.7
Lower 2.5 percentile	2.5	2.7	2.6	2.4	2.4	2.6	2.7	2.6	2.4	2.4	2.5	2.7	2.4	2.4
Bases (unweighted)	*665*	*744*	*1409*	*1126*	*317*	*612*	*753*	*1365*	*1571*	*436*	*1277*	*1497*	*2697*	*753*

Note:

[a] Total energy intake includes energy from alcohol.

Source:

National Diet and Nutrition Survey. Results from Years 1,2,3 and 4 (combined) of the Rolling Programme (2008/09 – 2011/12).

Table A3.4 Average daily intake of monounsaturated fats (g/day and % total energy) by age and sex in children and adults from 4 years of age

Aged 4 years and over

National Diet and Nutrition Survey Rolling Programme Years 1, 2, 3 and 4 (2008/09 - 2011/12)

	Sex and age group (years)													
	Boys		Total	Men		Girls		Total	Women		Total			
	4-10	11-18	boys	19-64	65+	4-10	11-18	girls	19-64	65+	4-10	11-18	19-64	65+
***Cis* monounsaturated fats (g/day)**														
Mean	21.0	27.6	24.6	28.5	25.8	20.0	22.7	21.5	21.7	19.6	20.5	25.2	25.1	22.3
Median	20.5	27.2	23.4	27.4	25.0	19.6	22.0	20.4	20.9	18.7	20.0	24.2	23.6	21.4
SD	6.1	9.3	8.6	11.3	9.4	6.6	8.4	7.7	8.7	6.8	6.3	9.2	10.6	8.6
Upper 2.5 percentile	34.7	49.8	43.2	53.9	45.4	34.7	39.4	37.9	41.5	33.2	34.7	45.3	48.3	42.7
Lower 2.5 percentile	10.6	12.7	11.1	9.8	10.1	9.9	9.1	9.2	6.9	8.6	9.9	9.7	7.5	9.4
% total energy[a]														
Mean	12.0	12.5	12.3	12.0	11.9	12.0	12.8	12.5	11.9	11.5	12.0	12.7	12.0	11.7
Median	11.8	12.5	12.2	12.0	11.6	11.9	12.7	12.4	11.8	11.5	11.9	12.6	11.9	11.6
SD	2.0	2.3	2.2	2.8	2.6	2.2	2.6	2.5	2.9	2.6	2.1	2.5	2.8	2.6
Upper 2.5 percentile	15.9	17.2	16.9	17.5	17.2	16.5	18.3	17.7	17.7	16.8	16.1	17.7	17.7	16.8
Lower 2.5 percentile	8.2	7.8	8.1	6.5	7.4	7.5	8.0	7.7	6.1	6.6	7.9	7.9	6.4	7.1
Bases (unweighted)	*665*	*744*	*1409*	*1126*	*317*	*612*	*753*	*1365*	*1571*	*436*	*1277*	*1497*	*2697*	*753*

Note:

[a] Total energy intake includes energy from alcohol.

Source:

National Diet and Nutrition Survey. Results from Years 1,2,3 and 4 (combined) of the Rolling Programme (2008/09 – 2011/12).

Table A3.5 Average daily intake of saturated fats (g/day and % total energy) adults (19-64 years[a]) at six NDNS time points

Aged 16-64 years

	NDNS Year					
	1986/87[a]	2000/01[b]	Years 1-2 (2008/09 - 2009/10)[b]	Years 3-4 (2010/11 - 2011/12)[b]	Years 5-6 (2012/13 - 2013/14)[b]	Years 7-8 (2014/15-2015/16)[b]
Saturated fats (g/day)[1]						
Mean	36.6	27.3	26.0	24.5	25.2	25.1
Median	35.6	26.0	24.7	22.6	24.2	23.8
SD	11.9	12.6	12.1	10.7	10.8	11.5
2.5th percentile	15.5	8.0	7.5	7.7	7.7	6.5
97.5th percentile	62.0	56.1	52.8	48.7	48.4	50.4
Saturated fats (% total energy)[1,2]						
Mean	16.0	12.6	12.2	11.9	12.1	11.9
Median	15.9	12.5	12.0	11.8	12.0	11.7
SD	3.2	3.4	3.4	3.2	3.3	3.4
2.5th percentile	10.0	6.3	5.6	6.4	6.0	5.6
97.5th percentile	22.3	19.6	19.4	18.9	18.8	18.9
Bases (unweighted)	*2197*	*1724*	*1254*	*1443*	*965*	*1082*

Notes:

a The 1986/87 Dietary and Nutritional Survey of British Adults collected data for adults aged 16-64 years

b Standard deviation (sd) was calculated from the Standard Error of the Mean (SE) where sd=SE x√N. sd shown is the average of published figures for men and women.

[1] tatistical comparisons were performed for Years 3-4 vs Years 1-2, Years 5-6 vs Years 1-2 and Years 7-8 vs Years 1-2.Comparisons were only performed where the goodness-of-fit statistic R-squared was above 5%' Results were not statistically significant.

[2] Total energy intake includes energy from alcohol.

Data sources:

National Diet and Nutrition Survey years 1-8 (2008/09-2015/16)

National Diet and Nutrition Survey: adults aged 19 to 64 years (2000/01)

Dietary and nutritional survey of British Adults 1986/87

Table A3.6 Average daily intake of saturated fats (g/day and % total energy) in adults aged 65years and over at fiveNDNS time points

Aged 65 years and over *2008/09-2015/16*

		NDNS RP survey years			
	NDNS: 65 years and over 1994/95	Years 1-2 (2008/09 - 2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
Saturated fats (g/day)[1]					
Mean	27.2	26.6	24.3	23.7	24.3
Median	25.4	25.7	22.0	22.3	23.1
SD	10.7	10.5	10.7	9.1	10.4
2.5th percentile	9.5	9.1	9.7	8.1	8.4
97.5th percentile	52.4	48.6	48.5	44.0	49.6

		NDNS RP survey years			
	NDNS: 65 years and over 1994/95	Years 1-2 (2008/09 - 2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
Saturated fats (% total energy)[1,2]					
Mean	15.0	13.8	12.8**	12.9**	13.3
Median	14.7	13.9	12.7	12.8	12.7
SD	3.9	3.6	3.4	3.3	3.8
2.5th percentile	8.2	6.6	7.6	6.8	7.4
97.5th percentile	23.2	20.4	20.7	20.4	20.9
Bases (unweighted)	*1275*	*359*	*394*	*323*	*335*

[1] Statistical comparisons were performed for Years 3-4 vs Years 1-2, Years 5-6 vs Years 1-2 and Years 7-8 vs Years 1-2 where * indicates p<0.05 and ** indicates p<0.01. Comparisons were only performed where the goodness-of-fit statistic R-squared was above 5%'.

[2] Total energy intake includes energy from alcohol.

Data sources:

National Diet and Nutrition Survey: years 1-8 (2008/09-2015/16)

National Diet and Nutrition Survey: people aged 65 years and over (1994/95)

Table A3.7 Average daily intake of saturated fats (g/day and % total energy) in adults aged 65-74 years at four NDNS time points

Aged 65-74 years *2008/09-2015/16*

	NDNS RP survey years			
	Years 1-2 (2008/09 - 2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
Saturated fats (g/day)[1]				
Mean	26.6	24.1	23.9	23.7
Median	26.0	21.8	22.6	22.3
SD	10.1	11.5	9.5	9.9
2.5th percentile	9.8	9.5	8.0	8.2
97.5th percentile	45.8	50.4	45.0	45.8

	NDNS RP survey years			
	Years 1-2 (2008/09 - 2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
Saturated fats (% total energy)[1,2]				
Mean	13.3	12.3*	12.5*	12.5
Median	13.2	12.3	12.2	12.1
SD	3.3	3.3	3.3	3.6
2.5th percentile	6.9	6.1	6.7	6.6
97.5th percentile	19.9	18.4	20.2	19.2
Bases (unweighted)	*192*	*228*	*200*	*181*

[1] Statistical comparisons were performed for Years 3-4 vs Years 1-2, Years 5-6 vs Years 1-2 and Years 7-8 vs Years 1-2.Comparisons were only performed where the goodness-of-fit statistic R-squared was above 5%' Results were not statistically significant.

[2] Total energy intake includes energy from alcohol.

Table A3.8 Average daily intake of saturated fats (g/day and % total energy) in adults aged 75+ years at four NDNS time points

Aged 75 years and above *2008/09-2015/16*

	NDNS RP survey years			
	Years 1-2 (2008/09 - 2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
Saturated fats (g/day)[1]				
Mean	26.6	24.6	23.5	25.1
Median	25.3	22.4	22.2	24.4
SD	11.1	9.4	8.3	11.0
2.5th percentile	9.0	10.3	9.4	8.3
97.5th percentile	50.3	44.0	39.3	50.7

	NDNS RP survey years			
	Years 1-2 (2008/09 - 2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
Saturated fats (% total energy)[1,2]				
Mean	14.6	13.5	13.7	14.3
Median	14.6	13.3	13.5	14.0
SD	3.9	3.4	3.3	3.9
2.5th percentile	6.4	7.7	7.4	8.0
97.5th percentile	21.0	20.2	20.3	22.2
Bases (unweighted)	*167*	*166*	*123*	*154*

[1] Statistical comparisons were performed for Years 3-4 vs Years 1-2, Years 5-6 vs Years 1-2 and Years 7-8 vs Years 1-2.Comparisons were only performed where the goodness-of-fit statistic R-squared was above 5%' Results were not statistically significant.

[2] Total energy intake includes energy from alcohol.

Table A3.9 Percentage contribution of food groups to average daily saturated fat intake in adults (19-64 years) by survey year using NDNS data at six time points

Food groups	**Survey year**					
	1986/7	**2000/01**	**2008/09-2009/10**	**2010/11-2011/12**	**2012/13-2013/14**	**2014/15-2015/16**
	16-64yrs	19-64yrs	19-64yrs	19-64 years	19-64 years	19-64 years
Cereals and cereal products	18	18	19	20	22	21
of which:						
Biscuits	4	4	4	5	5	5
Buns, cakes, pastries and fruit pies	6	4	4	6	5	4
Milk and milk products	23	24	22	22	22	21
of which:						
Whole milk (3.8% fat)	11	4	2	2	2	2
Cheese	9	10	10	11	10	9
Eggs and egg dishes	3	3	4	3	4	3
Fat spreads [b]	17	11	10	10	10	9
of which:						
Butter	10	6	5	5	6	6
Meat and meat products	23	22	25	24	22	24
of which:						
Bacon and ham	3	2	2	2	2	2
Beef, veal and dishes	4	4	5	4	4	4
Meat pies and pastries	4	4	3	3	3	3
Fish and fish dishes	2	2	3	3	3	3

Food groups	Survey year					
	1986/7	**2000/01**	**2008/09-2009/10**	**2010/11-2011/12**	**2012/13-2013/14**	**2014/15-2015/16**
	16-64yrs	19-64yrs	19-64yrs	19-64 years	19-64 years	19-64 years
Vegetables, potatoes and savoury snacks	6	9	7	7	6	7
Fruit, Nuts and seeds	0	1	1	1	2	2
Sugar, preserves and confectionery	4	5	5	4	5	5
Beverages	0	2	1	0	1	1
Miscellaneous[d]	3	3	3	3	3	3
Average daily saturated fat intake g	36.5	27.3	26.0	24.5	25.2	25.1
Bases (unweighted)	*2197*	*1724*				

Note:

[b] Some oils which are used as a condiment on bread or salads are included in this food group; however this food group does not include oils or fats used in cooking.

[d] In addition to dry weight beverages; soup, manufactured/retail and homemade; savoury sauces, pickles, gravies and condiments; and commercial toddler foods, Miscellaneous also includes nutrition powders and drinks.

Sources:

National Diet and Nutrition Survey. Years 1-8 (2008/09-2015/16)

National Diet and Nutrition Survey: Adults aged 19 to 64 years, 2000/01

The Dietary and Nutritional Survey of British Adults, 1986/87

Table A3.10 Percentage contribution of food groups to average daily saturated fat intake in adults (19-64 years) by survey year using NDNS data at four time points

Aged 19-64 years *2008/09-2015/16*

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Cereals and cereal products	19	20	22	21
of which:				
Pasta, rice, pizza and other miscellaneous cereals	5	5	6	6
White bread	2	2	2	2
Wholemeal bread	1	1	0	1
Brown, granary and wheatgerm bread	0	0	0	0
High fibre breakfast cereals	1	1	1	1
Other breakfast cereals	0	0	0	0
Biscuits	4	5	5	5
Buns, cakes, pastries and fruit pies	4	5	5	4
Puddings	1	1	1	1

Aged 19-64 years *2008/09-2015/16*

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Milk and milk products	22	22	22	21
of which:				
Whole milk (3.8% fat)	2	2	2	2
Semi skimmed milk (1.8% fat)	4	4	4	4
Other milk and cream	2	2	2	2
Cheese	10	11	10	9
of which				
Cheddar cheese	0	8	7	6
Other cheese	10	3	3	3
Yoghurt, fromage frais and other dairy desserts	2	2	2	2
Ice cream	1	1	2	1
Eggs and egg dishes	4	3	4	3

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Fat spreads[b]	10	10	10	9
of which:				
Butter	5	5	6	6
Reduced fat spread polyunsaturated (41-75% fat)	1	1	1	0
Reduced fat spread not polyunsaturated (41-75% fat)	4	3	3	2
Low fat spread polyunsaturated (18-39% fat)	0	0	0	0
Low fat spread not polyunsaturated (18-39% fat)	0	0	0	0
Meat and meat products	25	24	22	24
of which:				
Bacon and ham	2	2	2	2
Beef, veal and dishes	5	4	4	4
Lamb and dishes	2	2	2	2
Pork and dishes	1	1	1	1
Coated chicken and turkey	1	1	1	1
Chicken, turkey and dishes	4	5	4	5
Liver and dishes	0	0	0	0
Burgers and kebabs	1	2	2	1
Sausages	3	3	3	3

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Meat pies and pastries	3	3	3	3
Other meat, meat products and dishes	1	1	1	1
Fish and fish dishes	3	3	3	3
of which:				
White fish coated or fried including fish fingers	1	1	1	1
Other white fish, shellfish or fish dishes and canned tuna	1	1	1	1
Oily fish	1	1	1	1
Vegetables and potatoes	6	6	5	6
of which:				
Vegetables (not raw) including vegetable dishes	2	2	2	3
Chips, fried and roast potatoes and potato products	3	3	2	3
Other potatoes, potato salads and dishes	1	1	1	1
Savoury snacks	1	1	1	1
Nuts and seeds	1	1	1	2
Fruit	0	0	1	1
Sugar, preserves and confectionery	5	4	5	5
of which:				
Sugars, including table sugar,	0	0	0	0

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
preserves and sweet spreads				
Sugar confectionery	0	0	0	0
Chocolate confectionery	4	4	5	4
Non-alcoholic beverages[c]	1	0	1	1
of which:				
Tea, coffee and water	1	0	1	1
Alcoholic beverages	0	0	0	0
Miscellaneous[d]	3	3	3	3
of which:				
Dry weight beverages	0	0	0	0
Soup, manufactured/retail and homemade	1	1	1	1
Savoury sauces, pickles, gravies and condiments	2	2	2	2
Commercial toddler foods	0	0	0	0
Average daily saturated fatty acids intake g	26.0	24.5	25.2	25.1
Bases (unweighted)	*1254*	*1443*	*965*	*1082*

[a] Sub food groups that contribute <0.5% to intake across all age/sex groups are excluded from the table. All other food groups are included.

[b] Some oils which are used as a condiment on bread or salads are included in this food group; however this food group does not include oils or fats used in cooking.

[c] Non-alcoholic beverages are reported as consumed with diluent water.

[d] In addition to dry weight beverages; soup, manufactured/retail and homemade; savoury sauces, pickles, gravies and condiments; and commercial toddler foods, Miscellaneous also includes nutrition powders and drinks.

Table A3.11 Percentage contribution of food groups to average daily saturated fat intake in adults (65+ years) by survey year using NDNS data at four time points

Aged 65 years and over *1994/95-2015/16*

	NDNS RP survey years and age group (years)				
Food group	1994/95	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%	%
Cereals and cereal products	19	18	19	21	21
of which:					
Biscuits	5	5	5	5	6
Buns, cakes, pastries and fruit pies	6	6	6	7	6
Milk and milk products	27	26	25	24	25
of which:					
Whole milk (3.8% fat)	10	4	2	2	2
Cheese	8	10	10	9	10
Eggs and egg dishes	3	4	3	4	4
Fat spreads[a]	20	15	16	14	14
of which:					
Butter	13	10	10	8	9
Meat and meat products	19	20	19	22	19
of which:					
Bacon and ham	2	2	2	3	2
Beef, veal and dishes	3	4	4	4	4
Meat pies and pastries	5	4	2	4	3
Fish and fish dishes	2	4	5	4	4
Vegetables, potatoes and savoury snacks	5	5	5	4	4
Fruit, nuts and seeds	0	1	1	1	2
Sugar, preserves and confectionery	2	2	2	3	3
Beverages[b]	0	0	0	1	1
Miscellaneous[c]	3	3	4	3	3

Food group	NDNS RP survey years and age group (years)				
	1994/95	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%	%
Average daily saturated fatty acids intake g	27.2	26.6	24.3	23.7	24.3
Bases (unweighted)	*1275*	*359*	*394*	*323*	*335*

[a] Some oils which are used as a condiment on bread or salads are included in this food group; however this food group does not include oils or fats used in cooking.

[b] Non-alcoholic beverages are reported as consumed with diluent water.

[c] In addition to dry weight beverages; soup, manufactured/retail and homemade; savoury sauces, pickles, gravies and condiments; and commercial toddler foods, Miscellaneous also includes nutrition powders and drinks.

Table A3.12 Percentage contribution of food groups to average daily saturated fat intake in adults (65-74 years) by survey year using NDNS data at four time points

Aged 65-74 years *2008/09-2015/16*

	NDNS RP survey years and age group (years)			
Food group[a]	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Cereals and cereal products	18	19	20	21
of which:				
Pasta, rice, pizza and other miscellaneous cereals	2	2	2	1
White bread	1	1	1	1
Wholemeal bread	1	1	1	1
Brown, granary and wheatgerm bread	0	1	1	0
High fibre breakfast cereals	1	2	2	2
Other breakfast cereals	0	0	0	0
Biscuits	4	5	4	6
Buns, cakes, pastries and fruit pies	6	6	7	6
Puddings	2	1	2	2
Milk and milk products	25	24	23	24
of which:				
Whole milk (3.8% fat)	3	1	1	1
Semi skimmed milk (1.8% fat)	5	6	6	6
Other milk and cream	2	2	2	1
Cheese	11	10	10	10
of which				
Cheddar cheese	0	7	7	7
Other cheese	10	3	3	3
Yoghurt, fromage frais and other dairy desserts	2	3	2	3
Ice cream	2	2	2	2

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Eggs and egg dishes	4	4	4	4
Fat spreads[b]	14	16	14	13
of which:				
Butter	9	9	8	8
Reduced fat spread polyunsaturated (41-75% fat)	1	1	1	1
Reduced fat spread not polyunsaturated (41-75% fat)	3	5	3	4
Low fat spread polyunsaturated (18-39% fat)	1	1	1	0
Low fat spread not polyunsaturated (18-39% fat)	0	0	0	0
Meat and meat products	20	19	23	21
of which:				
Bacon and ham	2	2	3	2
Beef, veal and dishes	4	5	4	4
Lamb and dishes	3	1	1	1
Pork and dishes	1	1	1	1
Coated chicken and turkey	0	1	1	0
Chicken, turkey and dishes	2	2	4	3
Liver and dishes	0	1	1	0
Burgers and kebabs	1	0	0	1
Sausages	2	3	3	3
Meat pies and pastries	3	2	4	3
Other meat, meat products and dishes	1	0	1	1
Fish and fish dishes	4	5	4	4
of which:				

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
White fish coated or fried including fish fingers	1	1	1	1
Other white fish, shellfish or fish dishes and canned tuna	1	1	1	1
Oily fish	2	3	2	2
Vegetables and potatoes	6	5	4	4
of which:				
Vegetables (not raw) including vegetable dishes	2	2	2	2
Chips, fried and roast potatoes and potato products	2	2	2	2
Other potatoes, potato salads and dishes	1	2	1	0
Savoury snacks	0	0	0	0
Nuts and seeds	1	1	1	2
Fruit	1	1	0	1
Sugar, preserves and confectionery	2	3	3	4
of which:				
Sugars, including table sugar, preserves and sweet spreads	0	0	0	0
Sugar confectionery	0	0	0	0
Chocolate confectionery	2	2	3	4
Non-alcoholic beverages[c]	1	0	1	1
of which:				
Tea, coffee and water	1	0	1	1
Alcoholic beverages	0	0	0	0
Miscellaneous[d]	4	4	3	3
of which:				
Dry weight beverages	1	1	1	1

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Soup, manufactured/retail and homemade	1	1	1	1
Savoury sauces, pickles, gravies and condiments	2	2	1	1
Commercial toddler foods	0	0	0	0
Average daily saturated fatty acids intake g	26.6	24.1	23.9	23.7
Bases (unweighted)	*192*	*228*	*200*	*181*

[a] Sub food groups that contribute <0.5% to intake across all age/sex groups are excluded from the table. All other food groups are included.

[b] Some oils which are used as a condiment on bread or salads are included in this food group; however this food group does not include oils or fats used in cooking.

[c] Non-alcoholic beverages are reported as consumed with diluent water.

[d] In addition to dry weight beverages; soup, manufactured/retail and homemade; savoury sauces, pickles, gravies and condiments; and commercial toddler foods, Miscellaneous also includes nutrition powders and drinks.

Table A3.13 Percentage contribution of food groups to average daily saturated fat intake in adults (75 years and over) by survey year using NDNS data at four time points

Aged 75 years and over *2008/09-2015/16*

	NDNS RP survey years and age group (years)			
Food group[a]	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Cereals and cereal products	19	20	22	20
of which:				
Pasta, rice, pizza and other miscellaneous cereals	1	1	2	2
White bread	1	1	1	1
Wholemeal bread	0	1	1	1
Brown, granary and wheatgerm bread	0	0	0	0
High fibre breakfast cereals	2	2	2	2
Other breakfast cereals	0	0	0	0
Biscuits	5	5	6	6
Buns, cakes, pastries and fruit pies	6	7	6	6
Puddings	3	2	4	3

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Milk and milk products	26	26	24	27
of which:				
Whole milk (3.8% fat)	4	4	3	4
Semi skimmed milk (1.8% fat)	6	5	5	5
Other milk and cream	4	2	3	2
Cheese	8	9	9	11
of which				
Cheddar cheese	0	7	5	7
Other cheese	8	2	3	4
Yoghurt, fromage frais and other dairy desserts	1	3	2	3
Ice cream	3	3	2	2
Eggs and egg dishes	3	2	3	4
Fat spreads[b]	17	16	14	16
of which:				
Butter	12	10	7	11
Reduced fat spread polyunsaturated (41-75% fat)	1	1	2	1
Reduced fat spread not polyunsaturated (41-75% fat)	3	3	4	3
Low fat spread polyunsaturated (18-39% fat)	1	0	1	0
Low fat spread not polyunsaturated (18-39% fat)	0	1	0	0

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Meat and meat products	20	19	21	18
of which:				
Bacon and ham	2	2	2	2
Beef, veal and dishes	4	4	3	4
Lamb and dishes	2	3	3	2
Pork and dishes	1	1	1	1
Coated chicken and turkey	0	0	0	0
Chicken, turkey and dishes	2	2	2	3
Liver and dishes	1	1	1	1
Burgers and kebabs	0	0	0	0
Sausages	3	2	3	2
Meat pies and pastries	4	2	3	3
Other meat, meat products and dishes	1	2	2	1
Fish and fish dishes	4	5	4	4
of which:				
White fish coated or fried including fish fingers	1	1	1	1
Other white fish, shellfish or fish dishes and canned tuna	1	2	1	1
Oily fish	1	2	2	2

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Vegetables and potatoes	5	4	4	3
of which:				
Vegetables (not raw) including vegetable dishes	2	2	1	1
Chips, fried and roast potatoes and potato products	2	1	2	1
Other potatoes, potato salads and dishes	1	1	1	1
Savoury snacks	0	0	0	0
Nuts and seeds	0	1	0	1
Fruit	0	0	1	0
Sugar, preserves and confectionery	2	2	3	3
of which:				
Sugars, including table sugar, preserves and sweet spreads	0	0	0	0
Sugar confectionery	0	0	0	0
Chocolate confectionery	2	2	3	3
Non-alcoholic beverages[c]	0	0	0	0
of which:				
Tea, coffee and water	0	0	0	0
Alcoholic beverages	0	0	0	0

	NDNS RP survey years and age group (years)			
Food group[a]	Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
	%	%	%	%
Miscellaneous[d]	3	3	4	3
of which:				
Dry weight beverages	1	1	1	1
Soup, manufactured/retail and homemade	1	2	2	1
Savoury sauces, pickles, gravies and condiments	1	1	1	1
Commercial toddler foods	0	0	0	0
Average daily saturated fatty acids intake g	26.6	24.6	23.5	25.1
Bases (unweighted)	*167*	*166*	*123*	*154*

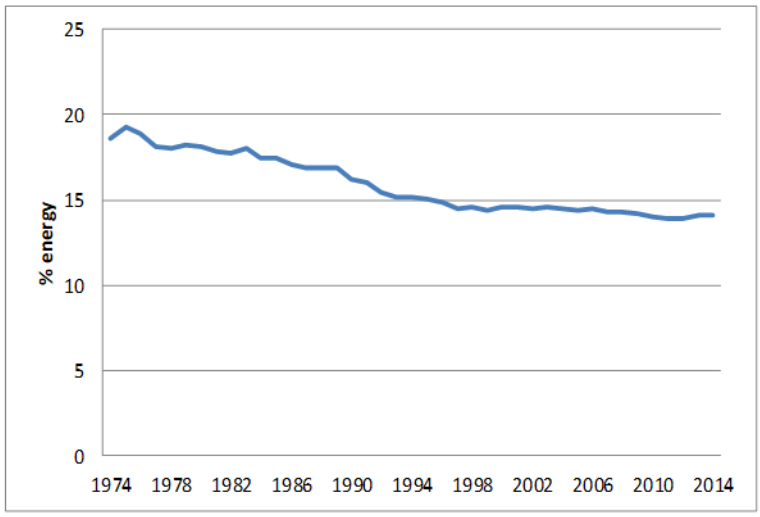
[a] Sub food groups that contribute <0.5% to intake across all age/sex groups are excluded from the table. All other food groups are included.

[b] Some oils which are used as a condiment on bread or salads are included in this food group; however this food group does not include oils or fats used in cooking.

[c] Non-alcoholic beverages are reported as consumed with diluent water.

[d] In addition to dry weight beverages; soup, manufactured/retail and homemade; savoury sauces, pickles, gravies and condiments; and commercial toddler foods, Miscellaneous also includes nutrition powders and drinks.

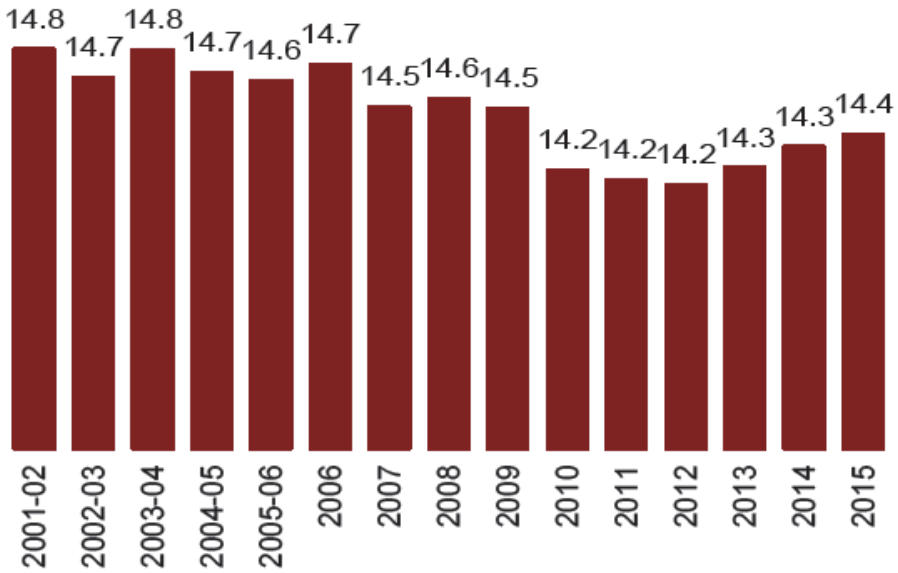
Figure A3.2 Long term trend in the percentage of energy derived from saturated fats from household food and drink purchases



Note: Pre-1992 energy intakes excluded alcohol, soft drinks and confectionery

Source: https://www.gov.uk/government/statistical-data-sets/family-food-datasets

Figure A3.3 Recent trend in the percentage of food energy derived from saturated fats from household and eating out food and drink



Source: Family Food 2015

Table A3.14 Trans fats intake (g/day and % total energy) in adults (16-64 years) by survey year using NDNS data at five time points

Aged 19-64 years *1986/87-2015/16*

			NDNS years			
	1986/87[a]	2000/01[b]	Years 1-2 (2008/09 - 2009/10)[b]	Years 3-4 (2010/11 - 2011/12)[b]	Years 5-6 (2012/13 - 2013/14)[b]	Years 7-8 (2014/15- 2015/16)[b]
Trans fats (g/day)						
Mean	4.8	2.4	1.5	1.0	1.0	1.0
Median	4.5	2.2	1.4	1.0	0.9	0.9
SD	2.3	1.5	0.8	0.6	0.5	0.5
2.5th percentile	1.5	0.5	0.3	0.2	0.2	0.2
97.5th percentile	10.1	6.0	3.5	2.4	2.3	2.2

			NDNS years			
	1986/87[a]	2000/01[b]	Years 1-2 (2008/09 - 2009/10)[b]	Years 3-4 (2010/11 - 2011/12)[b]	Years 5-6 (2012/13 - 2013/14)[b]	Years 7-8 (2014/15-2015/16)[b]
Trans fats (% total energy)[1]						
Mean	2.1	1.1	0.7	0.5	0.5	0.5
Median	2.0	1.1	0.7	0.5	0.5	0.4
SD	0.7	0.5	0.3	0.2	0.2	0.2
2.5th percentile	0.9	0.3	0.2	0.1	0.1	0.1
97.5th percentile	3.9	2.2	1.3	1.0	1.0	0.9
Bases (unweighted)	*2197*	*1724*	*1254*	*1443*	*965*	*1082*

[1] Total energy intake includes energy from alcohol.

[a] Age group: 16-64 years

[b] Age group: 19-64 years

Table A3.15 Trans fats intake (g/day and % total energy) in adults aged 65 years and over by five time points

Aged 65 years and over — *2008/09-2015/16*

		NDNS RP survey years			
		Years 1-2	Years 3-4	Years 5-6	Years 7-8
	1994/95	(2008/09 - 2009/10)	(2010/11 - 2011/12)	(2012/13 - 2013/14)	(2014/15-2015/16)
Trans fats (g/day)					
Mean	2.8	1.6	1.0	1.0	1.0
Median	2.6	1.5	1.0	0.9	0.9
SD	1.3	0.8	0.6	0.5	0.5
2.5th percentile	0.9	0.4	0.3	0.3	0.3
97.5th percentile	5.6	3.2	2.4	2.2	2.2
Trans fats (% total energy)[1]					
Mean	1.5	0.8	0.6	0.5	0.5
Median	1.5	0.8	0.5	0.5	0.5
SD	0.5	0.3	0.2	0.2	0.2
2.5th percentile	0.6	0.3	0.2	0.2	0.2
97.5th percentile	2.7	1.5	1.1	1.1	1.0
Bases (unweighted)	*1275*	*359*	*394*	*323*	*335*

[1] Total energy intake includes energy from alcohol.

Table A3.16 Trans fats intake (g/day and % total energy) in adults (65-74 years) by survey year using NDNS data at four time points

Aged 65-74 years *2008/09-2015/16*

	NDNS RP survey years			
	Years 1-2 (2008/09 - 2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15- 2015/16)
Trans fats (g/day)				
Mean	1.6	1.0	1.0	0.9
Median	1.4	0.9	0.9	0.9
SD	0.7	0.6	0.5	0.4
2.5th percentile	0.5	0.2	0.3	0.3
97.5th percentile	3.1	2.4	2.2	2.0
Trans fats (% total energy)[1]				
Mean	0.8	0.5	0.5	0.5
Median	0.7	0.5	0.5	0.5
SD	0.3	0.2	0.2	0.2
2.5th percentile	0.3	0.2	0.2	0.1
97.5th percentile	1.5	1.0	1.0	0.9
Bases (unweighted)	*192*	*228*	*200*	*181*

[1] Total energy intake includes energy from alcohol.

Table A3.17 Trans fats intake (g/day and % total energy) in adults (75 years and over) by survey year using NDNS data at four time points

Aged 75+ years *2008/09-2015/16*

	NDNS RP survey years			
	Years 1-2 (2008/09 - 2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15- 2015/16)
Trans fats (g/day)				
Mean	1.7	1.1	1.0	1.1
Median	1.6	1.0	0.9	0.9
SD	0.8	0.6	0.5	0.6
2.5th percentile	0.3	0.3	0.3	0.2
97.5th percentile	3.2	2.4	2.2	0.4
Trans fats (% total energy)[1]				
Mean	0.9	0.6	0.6	0.6
Median	0.9	0.6	0.5	0.6
SD	0.3	0.3	0.2	0.3
2.5th percentile	0.3	0.2	0.3	0.2
97.5th percentile	1.7	1.3	1.1	1.1
Bases (unweighted)	*167*	*166*	*123*	*154*

[1] Total energy intake includes energy from alcohol.

Table A3.18 Percentage contribution of food groups to trans fats intake in adults (19-64 years) at six data points

Aged 19-64 years *2008/09-2015/16*

Food group	1986/87[a]	2000/01	NDNS RP survey years and age group (years) Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
			%	%	%	%
Cereals and cereal products	27	26	17	16	18	18
of which:						
Biscuits	7	9	3	1	1	1
Buns, cakes, pastries and fruit pies	14	8	4	4	5	4
Milk and milk products	10	16	23	30	31	30
of which:						
Whole milk (3.8% fat)	4	1	1	2	2	2
Cheese	4	8	12	16	16	14
Eggs and egg dishes	2	3	3	2	2	2
Fat spreads[b]	30	18	9	8	9	9
of which:						
Butter	5	4	5	6	7	7
Meat and meat products	18	21	25	28	27	28
of which:						
Meat pies and pastries	7	7	3	2	1	1
Fish and fish dishes	1	3	4	3	2	2
Vegetables and potatoes and savoury snacks	6	7	9	6	5	5

Food group	1986/87[a]	2000/01	NDNS RP survey years and age group (years) Years 1-2 (2008/09-2009/10)	Years 3-4 (2010/11 - 2011/12)	Years 5-6 (2012/13 - 2013/14)	Years 7-8 (2014/15-2015/16)
			%	%	%	%
Sugar, preserves and confectionery	3	4	3	2	2	2
Miscellaneous[d]	2a	3	5	4	3	3
Average daily *trans* fatty acids intake g	4.8	2.4	1.5	1.0	1.0	1.0
Bases (unweighted)	*2197*	*1724*	*1254*	*1443*	*965*	*1082*

[a] Age group: 16-64 years

[b] Some oils which are used as a condiment on bread or salads are included in this food group; however this food group does not include oils or fats used in cooking.

[c] Non-alcoholic beverages are reported as consumed with diluent water.

[d] In addition to dry weight beverages; soup, manufactured/retail and homemade; savoury sauces, pickles, gravies and condiments; and commercial toddler foods, Miscellaneous also includes nutrition powders and drinks

Table A3.19 Percentage contribution of food groups to trans fats intake in adults (19-64 years) by survey year using NDNS data at four time points

Aged 19-64 years *2008/09-2015/16*

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	**Years 3-4 (2010/11 - 2011/12)**	**Years 5-6 (2012/13 - 2013/14)**	**Years 7-8 (2014/15-2015/16)**
	%	%	%	%
Cereals and cereal products	17	16	18	18
of which:				
Pasta, rice, pizza and other miscellaneous cereals	4	4	6	6
White bread	2	3	3	3
Wholemeal bread	1	1	1	1
Brown, granary and wheatgerm bread	0	1	1	1
High fibre breakfast cereals	0	1	1	1
Biscuits	3	1	1	1
Buns, cakes, pastries and fruit pies	4	4	5	4
Puddings	1	2	1	1
Milk and milk products	23	30	31	30
of which:				
Whole milk (3.8% fat)	1	2	2	2
Semi skimmed milk (1.8% fat)	5	7	7	7
Other milk and cream	1	2	2	2
Cheese	12	16	16	14
Cheddar cheese	0	12	11	10
Other cheese	12	5	5	4
Yoghurt, fromage frais and other dairy desserts	1	2	2	2
Ice cream	2	1	1	1

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	**Years 3-4 (2010/11 - 2011/12)**	**Years 5-6 (2012/13 - 2013/14)**	**Years 7-8 (2014/15-2015/16)**
	%	%	%	%
Eggs and egg dishes	3	2	2	2
Fat spreads[b]	9	8	9	9
of which:				
Butter	5	6	7	7
Reduced fat spread polyunsaturated (41-75% fat)	1	0	0	0
Reduced fat spread not polyunsaturated (41-75% fat)	3	1	1	1
Low fat spread polyunsaturated (18-39% fat)	0	0	0	0
Meat and meat products	25	28	27	28
of which:				
Bacon and ham	1	1	1	1
Beef, veal and dishes	8	9	8	8
Lamb and dishes	4	4	5	5
Pork and dishes	1	1	1	1
Coated chicken and turkey	1	1	1	1
Chicken, turkey and dishes	3	5	4	5
Burgers and kebabs	2	3	2	2
Sausages	2	2	2	2
Meat pies and pastries	3	2	1	1
Other meat, meat products and dishes	1	1	1	1

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	**Years 3-4 (2010/11 - 2011/12)**	**Years 5-6 (2012/13 - 2013/14)**	**Years 7-8 (2014/15-2015/16)**
	%	%	%	%
Fish and fish dishes	4	3	2	2
of which:				
White fish coated or fried including fish fingers	3	2	1	1
Other white fish, shellfish or fish dishes and canned tuna	1	1	1	1
Oily fish	0	0	0	1
Vegetables and potatoes	9	6	5	5
of which:				
Salad and other raw vegetables	0	0	0	0
Vegetables (not raw) including vegetable dishes	1	2	2	2
Chips, fried and roast potatoes and potato products	6	3	2	2
Other potatoes, potato salads and dishes	1	1	1	1
Savoury snacks	0	0	0	1
Nuts and seeds	0	0	0	0
Fruit	0	0	0	0
Sugar, preserves and confectionery	3	2	2	2
of which:				
Sugar confectionery	0	0	0	0
Chocolate confectionery	3	2	2	2
Non-alcoholic beverages[c]	1	0	1	1
of which:				
Tea, coffee and water	1	0	1	1
Alcoholic beverages	0	0	0	0

Food group[a]	NDNS RP survey years and age group (years)			
	Years 1-2 (2008/09-2009/10)	**Years 3-4 (2010/11 - 2011/12)**	**Years 5-6 (2012/13 - 2013/14)**	**Years 7-8 (2014/15-2015/16)**
	%	%	%	%
Miscellaneous[d]	5	4	3	3
of which:				
Dry weight beverages	0	0	0	0
Soup, manufactured/retail and homemade	2	1	1	1
Savoury sauces, pickles, gravies and condiments	3	2	2	2
Commercial toddler foods	0	0	0	0
Average daily *trans* fatty acids intake g	1.5	1.0	1.0	1.0
Bases (unweighted)	*1254*	*1443*	*965*	*1082*

[a] Sub food groups that contribute <0.5% to intake across all age/sex groups are excluded from the table. All other food groups are included.

[b] Some oils which are used as a condiment on bread or salads are included in this food group; however this food group does not include oils or fats used in cooking.

[c] Non-alcoholic beverages are reported as consumed with diluent water.

[d] In addition to dry weight beverages; soup, manufactured/retail and homemade; savoury sauces, pickles, gravies and condiments; and commercial toddler foods, Miscellaneous also includes nutrition powders and drinks

Table A3.20 Trans fats content of fat spreads analysed in 1991, 1992 and 2000

Composite samples analysed 2009/10[1]	**Examples of products included**	**Total fat g/100g**	**Trans fat g/100g**
Low fat spreads (26-39%) not polyunsaturated (including dairy type)	I can't believe it's not butter light; own brand equivalents	39.0	0.12
Low fat spread (26-39%) not polyunsaturated, olive oil	Bertolli Light; own brand equivalents	38.9	0.14
Low fat spread (26-39%) polyunsaturated	Flora Light; own brand equivalents	36.9	0.05
Hard block margarine	Stork margarine block. Own brand equivalents	76.4	0.07
Compound cooking fat, not polyunsaturated	Cookeen, Crisp n dry, Trex	100.0	0.06
Ghee from vegetable oil	Khanum, Taj Mahal, Pride	100.0	0.08
Reduced fat spread (41-62%) polyunsaturated	Flora Original, Vitalite; own brand equivalents	59.2	0.13
Reduced fat spread (41-62%) not polyunsaturated	I can't believe it's not butter, Utterly Butterly; Stork; own brand equivalents	60.6	0.15
Reduced fat spread (41-62%) not polyunsaturated, olive oil	Bertoli; Own brand equivalents	59.1	0.11
Reduced fat spread (62-75%) not polyunsaturated	Clover; own brand equivalents	73.2	0.14
Composite samples analysed 1992[2]			
Reduced fat spread 70-80% fat polyunsaturated	I can't believe it's not butter	77.0	5.9
Reduced fat spread 60% fat made with olive oil	Olivio and own brand equivalents	62.7	6.1
Vegetable ghee	Khanum, Pride	99.4	1
Catering margarine	Chef's Choice, Family Choice	81.7	12.6
Samples analysed 1991[3]			
Soft margarine not polyunsaturated	own brands; Stork SB, Blue Band	79-83	7-4-11.7
Soft margarine polyunsaturated (sunflower)	own brands; Vitalite	81-82	3.3-5.6
Hard margarine	Echo	79.4	14.4
Compound cooking fat	White Flora, Cookeen, White Cap	99.9	7.5-17.0
Reduced fat spreads 70% fat not polyunsaturated	Krona, Clover, Summer County	70-74	1.8-7.6
Reduced fat spreads 60% fat not polyunsaturated	Mello, Stork Light Blend	60	4.4-7.2
Reduced fat spreads 60% fat polyunsaturated	Vitalite Light	60.8	3.3
Low fat spread polyunsaturated	Flora Extra Light, Shape Sunflower	38-39	2.2-2.8
Low fat spread not polyunsaturated	Gold, Clover Light, Delight	39-41	3.4-4.4
Very low fat spread not polyunsaturated	Outline, Gold Lowest	23-28	1.9-2.9

References
1 Department of Health. Nutrient analysis of processed foods with special reference to trans fatty acids. Analysis of composite samples of different brands. https://www.gov.uk/government/publications/nutrient-analysis-of-processed-foods-including-trans-fats
2 Ministry o fAgriculture , Fisheries and Food . Fatty acids in foods. Nutrient analysis project. RHM. 1992. Analysis of com posite samples of different brands
3 Ministry of Agriculture, Fisheries and Food. Fat, fatty acids, fat soluble vitamins and sodium composition of yellow fats . 1990/91. Laboratory of the Government Chemist. Analysis of single brands. Analytical values are shown as a range of the products analy sed in each category

Table A3.21 Blood lipids analysis among adults (16-64 years) by sex and age using NDNS data at six time points

Aged 19-64 years

Blood analyte	**NDNS RP survey years**						**NDNS RP survey years**					
			Years 1-2	**Years 3-4**	**Years 5-6**	**Years 7-8**			**Years 1-2**	**Years 3-4**	**Years 5-6**	**Years 7-8**
	1986/87[a,b,e]	**2000/01[a,b,f]**	**(2008/09 - 2009/10)[c,d,f]**	**(2010/11 - 2011/12)[c,d,f]**	**(2012/13 - 2013/14)[c,d,f]**	**(2014/15-2015/16)[c,d,f]**	**1986/87[a,b,e]**	**2000/01[a,b,f]**	**(2008/09 - 2009/10)[c,d]**	**(2010/11 - 2011/12)[c,d,f]**	**(2012/13 - 2013/14)[c,d,f]**	**(2014/15-2015/16)[c,d,f]**
	Men						Women					
Total cholesterol (mmol/L)												
Mean	5.8	5.2	5.1	5.2	4.9	4.7	5.8	5.3	5.2	5.2	5.0	4.8
Median	5.8	5.1	5.0	5.1	4.9	4.5	5.6	5.2	5.2	5.0	4.9	4.6
SD	1.2	1.2	1.0	1.1	1.1	0.9	1.4	1.2	1.1	1.1	1.0	1.1
2.5th percentile	*	3.2	3.4	3.4	2.8	3.0	*	3.3	3.2	3.4	3.4	2.8
97.5th percentile	*	7.6	7.7	7.3	6.7	6.6	*	8.0	7.7	7.5	7.1	7.4
% between 5.2mmol/L and 6.4mmol/L[1,2]	*	*	35.9	32.9	38.0	24.2	*	*	39.7	31.6	31.2	28.4
% between 6.5mmol/L and 7.8mmol/L[1,2]	*	*	8.3	12.7	5.9	2.9	*	*	9.3	13.4	8.9	5.5
% above 7.8mmol/L[1,2]	*	*	1.6	1.1	0.0	0.0	*	*	2.2	2.3	0.7	0.7
Bases (unweighted)	*923*	*618*	*252*	*308*	*210*	*225*	*809*	*659*	*344*	*445*	*327*	*301*

Aged 19-64 years

Blood analyte	NDNS RP survey years						NDNS RP survey years					
			Years 1-2	Years 3-4	Years 5-6	Years 7-8			Years 1-2	Years 3-4	Years 5-6	Years 7-8
	1986/87[a,b,e]	2000/01[a,b,f]	(2008/09 - 2009/10)[c,d,f]	(2010/11 - 2011/12)[c,d,f]	(2012/13 - 2013/14)[c,d,f]	(2014/15-2015/16)[c,d,f]	1986/87[a,b,e]	2000/01[a,b,f]	(2008/09 - 2009/10)[c,d]	(2010/11 - 2011/12)[c,d,f]	(2012/13 - 2013/14)[c,d,f]	(2014/15-2015/16)[c,d,f]
	Men						Women					
Serum high density lipoprotein-cholesterol (mmol/L)												
Mean	1.2	1.1	1.3	1.3	1.3	*	1.4	1.3	1.6	1.6	1.5	*
Median	1.1	1.0	1.3	1.3	1.2	*	1.4	1.3	1.6	1.5	1.5	*
SD	0.3	0.3	0.3	0.4	0.4	*	0.3	0.4	0.4	0.5	0.4	*
2.5th percentile	*	0.6	0.8	0.8	0.7	*	*	0.7	1.0	0.9	0.8	*
97.5th percentile	*	1.7	2.1	2.2	2.2	*	*	2.3	2.6	2.6	2.5	*
Bases (unweighted)	*919*	*617*	*252*	*308*	*210*	*n/a*	*806*	*659*	*344*	*445*	*327*	*n/a*

Aged 19-64 years

Blood analyte	NDNS RP survey years						NDNS RP survey years					
			Years 1-2	Years 3-4	Years 5-6	Years 7-8			Years 1-2	Years 3-4	Years 5-6	Years 7-8
	1986/87[a,b,e]	2000/01[a,b,f]	(2008/09 - 2009/10)[c,d,f]	(2010/11 - 2011/12)[c,d,f]	(2012/13 - 2013/14)[c,d,f]	(2014/15-2015/16)[c,d,f]	1986/87[a,b,e]	2000/01[a,b,f]	(2008/09 - 2009/10)[c,d]	(2010/11 - 2011/12)[c,d,f]	(2012/13 - 2013/14)[c,d,f]	(2014/15-2015/16)[c,d,f]
	Men						Women					
Total cholesterol to high density lipoprotein (HDL) cholesterol ratio												
Mean	*	*	4.0	4.2	4.1	4.2	*	*	3.3	3.4	3.5	3.5
Median	*	*	4.0	4.0	3.8	4.0	*	*	3.1	3.2	3.2	3.2
SD	*	*	1.2	1.4	1.4	1.4	*	*	1.0	1.1	1.1	1.4
2.5th percentile	*	*	2.1	2.0	2.0	2.2	*	*	2.0	1.9	2.0	2.0
97.5th percentile	*	*	6.6	7.4	7.2	7.7	*	*	6.1	5.8	6.1	7.7
Bases (unweighted)	*n/a*	*n/a*	*252*	*308*	*210*	*225*	*n/a*	*n/a*	*344*	*445*	*327*	*301*

Aged 19-64 years

Blood analyte	NDNS RP survey years						NDNS RP survey years					
			Years 1-2	Years 3-4	Years 5-6	Years 7-8			Years 1-2	Years 3-4	Years 5-6	Years 7-8
	1986/87[a,b,e]	2000/01[a,b,f]	(2008/09 - 2009/10)[c,d,f]	(2010/11 - 2011/12)[c,d,f]	(2012/13 - 2013/14)[c,d,f]	(2014/15-2015/16)[c,d,f]	1986/87[a,b,e]	2000/01[a,b,f]	(2008/09 - 2009/10)[c,d]	(2010/11 - 2011/12)[c,d,f]	(2012/13 - 2013/14)[c,d,f]	(2014/15-2015/16)[c,d,f]
	Men						Women					
Low density lipoprotein (LDL) cholesterol (mmol/L)												
Mean	4.7	4.2	3.1	3.2	3.0	2.8	4.4	4.0	3.1	3.1	3.0	2.9
Median	4.6	4.1	3.1	3.2	3.1	2.8	4.2	3.8	3.1	3.0	3.0	2.7
SD	1.2	1.2	0.88	0.97	0.92	0.78	1.40	1.20	0.98	0.99	0.86	0.93
2.5th percentile	*	2.1	1.5	1.6	1.2	1.4	*	2.1	1.4	1.6	1.7	1.4
97.5th percentile	*	6.6	5.1	5.3	4.9	4.4	*	6.8	5.2	5.3	4.9	5.3
Bases (unweighted)	*919*	*618*	*243*	*299*	*208*	*220*	*806*	*659*	*340*	*438*	*327*	*301*

[1] The British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association, have issued guidance published in the article 'Joint British recommendations on prevention of coronary heart disease in clinical practice'. Heart, 1998; 80: 1–29.

[2] The evidence for this threshold is confined mainly to (non-elderly) adults.

[a] Blood samples were not fasting samples

[b] LDL was calculated by sub subtracting HDL from total cholesterol uncorrected for plasma triglycerides (not measured).

[c] LDL was calculated using the Friedewald equation: LDL (mmol/L) = Total Cholesterol – HDL Cholesterol – (triglycerides/2.2). LDL was not calculated for samples with triglyceride values greater than 4.5mmol/L.

[d] Blood samples were fasting samples

[e] Age group 16-64 years;

[f] Age group 19-64 years

* Data not available

Table A3.22 Blood lipids analysis among adults (65+ years) by sex using NDNS data at five time points

Aged 65 years and over

Blood analyte	NDNS RP survey years					NDNS RP survey years				
		Years 1-2	Years 3-4	Years 5-6	Years 7-8		Years 1-2	Years 3-4	Years 5-6	Years 7-8
	1994/95[a]	(2008/09 - 2009/10)[b]	(2010/11 - 2011/12)[b]	(2012/13 - 2013/14)[b]	(2014/15-2015/16)[b]	1994/95[a]	(2008/09 - 2009/10)[b]	(2010/11 - 2011/12)[b]	(2012/13 - 2013/14)[b]	(2014/15-2015/16)[b]
	Men					Women				
Total cholesterol (mmol/L)										
Mean	5.6	4.6	4.7	4.6	4.2	6.2	5.4	5.6	5.3	5.3
Median	5.6	4.2	4.7	4.4	4.2	6.1	5.7	5.4	5.3	5.3
SD	1.1	1.2	1.1	1.2	1.0	1.5	1.1	1.2	1.1	1.3
2.5th percentile	3.3	2.6	2.9	2.6	1.9	3.5	3.6	3.6	3.3	2.8
97.5th percentile	8	7.1	7.0	7.1	6.0	9.3	7.3	8.2	7.6	7.7
% between 5.2mmol/L and 6.4mmol/L[1,2]	*	24	24	16	21	*	51	30	37	38
% between 6.5mmol/L and 7.8mmol/L[1,2]	*	10	6	8	0	*	11	25	17	11
% above 7.8mmol/L[1,2]	*	0	2	2	0	*	2	5	1	3
Bases (unweighted)	*458*	*69*	*76*	*71*	*63*	*428*	*98*	*104*	*102*	*89*

Aged 65 years and over

Blood analyte	NDNS RP survey years					NDNS RP survey years				
	1994/95[a]	Years 1-2 (2008/09 - 2009/10)[b]	Years 3-4 (2010/11 - 2011/12)[b]	Years 5-6 (2012/13 - 2013/14)[b]	Years 7-8 (2014/15-2015/16)[b]	1994/95[a]	Years 1-2 (2008/09 - 2009/10)[b]	Years 3-4 (2010/11 - 2011/12)[b]	Years 5-6 (2012/13 - 2013/14)[b]	Years 7-8 (2014/15-2015/16)[b]
	Men					Women				
High density lipoprotein cholesterol (mmol/L)										
Mean	1.2	1.3	1.3	1.3	*	1.4	1.6	1.7	1.6	*
Median	1.1	1.3	1.2	1.3	*	1.3	1.5	1.7	1.5	*
SD	0.5	0.4	0.4	0.4	*	0.5	0.4	0.4	0.4	*
2.5th percentile	0.5	0.8	0.8	0.6	*	0.7	0.9	1.1	0.8	*
97.5th percentile	2.3	2.1	2.3	2	*	2.5	2.4	2.6	2.5	*
Bases (unweighted)	*458*	*69*	*76*	*71*	*n/a*	428	98	104	102	n/a

Aged 65 years and over

Blood analyte	NDNS RP survey years					NDNS RP survey years				
	1994/95[a]	Years 1-2 (2008/09 - 2009/10)[b]	Years 3-4 (2010/11 - 2011/12)[b]	Years 5-6 (2012/13 - 2013/14)[b]	Years 7-8 (2014/15-2015/16)[b]	1994/95[a]	Years 1-2 (2008/09 - 2009/10)[b]	Years 3-4 (2010/11 - 2011/12)[b]	Years 5-6 (2012/13 - 2013/14)[b]	Years 7-8 (2014/15-2015/16)[b]
	Men					Women				
Total cholesterol to high density lipoprotein (HDL) cholesterol ratio										
Mean	*	3.6	3.8	3.7	3.7	*	3.5	3.4	3.6	3.6
Median	*	3.5	3.6	3.6	3.3	*	3.3	3.2	3.3	3.4
SD	*	1.2	1.1	1.0	1.2	*	1.0	1.0	1.2	1.2
2.5th percentile	*	1.9	2.3	2.1	2.2	*	2.0	2.0	2.0	2.1
97.5th percentile	*	6.0	6.1	6.0	6.4	*	5.4	5.5	6.6	6.3
Bases (unweighted)	*n/a*	*69*	*76*	*71*	*63*	*n/a*	*98*	*104*	*102*	*89*

Aged 65 years and over

Blood analyte	NDNS RP survey years					NDNS RP survey years				
	1994/95[a]	Years 1-2 (2008/09 - 2009/10)[b]	Years 3-4 (2010/11 - 2011/12)[b]	Years 5-6 (2012/13 - 2013/14)[b]	Years 7-8 (2014/15- 2015/16)[b]	1994/95[a]	Years 1-2 (2008/09 - 2009/10)[b]	Years 3-4 (2010/11 - 2011/12)[b]	Years 5-6 (2012/13 - 2013/14)[b]	Years 7-8 (2014/15- 2015/16)[b]
	Men					Women				
Low density lipoprotein (LDL) cholesterol (mmol/L)										
Mean	4.4	2.8	2.9	2.8	2.4	4.8	3.2	3.4	3.2	3.1
Median	4.4	2.5	2.8	2.7	2.3	4.8	3.5	3.4	3.0	2.9
SD	1.1	1.2	0.9	1.0	0.8	1.5	1.0	1.1	1.0	1.2
2.5th percentile	2	0.8	1.4	1.2	0.5	2.2	1.2	1.9	1.5	1.4
97.5th percentile	6.9	5.0	4.8	5.2	3.7	8.1	5.0	6.1	5.1	5.6
Bases (unweighted)	*458*	*68*	*75*	*71*	*63*	*428*	*95*	*104*	*101*	*89*

[1] The British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association, have issued guidance published in the article 'Joint British recommendations on prevention of coronary heart disease in clinical practice'. Heart, 1998; 80: 1–29.

[2] The evidence for this threshold is confined mainly to (non-elderly) adults.

[a] LDL was calculated by sub subtracting HDL from total cholesterol uncorrected for plasma triglycerides (not measured).

[b] LDL was calculated using the Friedewald equation: LDL (mmol/L) = Total Cholesterol – HDL Cholesterol – (triglycerides/2.2). LDL was not calculated for samples with triglyceride values greater than 4.5mmol/L.

* Data not available.

ANNEX 4: AMSTAR assessment summary tables for all included meta-analyses and systematic reviews

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Cao et al (2016) (Meta-analysis)	No	1) Yes 2) Yes 3) No	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes- in online supplement. 6) Yes	No	1) Yes 2) No	Yes- in online supplement	1) Yes - Newcastle Ottawa Scale 2) No	No	Two stage random effects dose-response meta-analysis. Heterogeneity: I^2 statistic.	1) Yes 2) Egger regression test.	1) Yes 2) No 3) Not reported.
Cheng et al, (2016) (Systematic review with meta-analysis)	No	1) No 2) Yes 3) Yes	Yes 1) Yes 2) No 3) Yes 4) Yes 5) Yes 6) Yes	No	1) Yes 2) no	Yes	1) Yes - Newcastle Ottawa Scale 2) No	No	Random-effects model was used except when I2 <50% then fixed-effects model was used. Heterogeneity: I^2 statistic.	1) Yes 2) Funnel plots and Egger's test.	1) Yes 2) No 3) National Natural Science Foundation of China
Hamley et al, (2017) (meta-analysis)	No	1) No 2) No 3) No	No 1) No 2) No 3) No 4) No 5) No 6) Yes	No	1) No 2) No	Yes	1) No 2) No	Yes – by author's own criteria	Random-effects meta-analysis. Heterogeneity and bias: I2 and T2 calculations.	1) Yes 2) Funnel plot	1) Yes 2) No 3) No funding support

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Hannon et al, (2017) (Systematic review with meta-analysis)	No	1) Yes 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	No	1) Yes 2) Yes	Yes	1) Yes 2) Yes	Yes	For studies with substantial heterogeneity, random effects model was used. Fixed effects models were used when I2 was <50%.	1) Yes 2) Funnel plot, Begg's test & Egger's test	1) Yes 2) No 3) Not reported
Harcombe et al, (2017) Systematic review with meta-analysis	No	1) No 2) Yes 3) No	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) No	No	1) Yes 2) No	Yes	1) Yes – Cochrane Collaboration assessment 2) Yes	Yes	Random-effects meta-analysis. Heterogeneity and bias: I2 and T2 calculations.	1) Yes 2) Funnel plots and Egger's test.	1) Yes 2) Z Harcombe receives income from 2 small self-employment businesses: The Harcombe Diet Co and Columbus Publishing. 3) Not reported
Harcombe et al, (2016a) (Systematic review)	Yes	1) Yes 2) No 3) No	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) No	No	1) Yes 2) No	Yes	1) Yes – Cochrane Collaboration assessment 2) Yes	No	Narrative systematic review – available data did not allow for a meta-analysis.	1) No 2) N/A	1) Yes 2) Z Harcombe receives income from 2 small self-employment businesses: The Harcombe Diet Co and Columbus Publishing. 3) Not reported

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Harcombe et al, (2016b) (Systematic review with meta-analysis)	Yes	1) Yes 2) No 3) No	Yes 1) Yes 2) No 3) Yes 4) Yes 5) Yes 6) No	No	1) Yes 2) No	Yes	1) Yes – Cochrane Collaboration assessment 2) Yes	No	Random-effects meta-analysis. Heterogeneity and bias: I^2 and T^2 calculations.	1) Yes 2) Funnel plots and Egger's test.	1) Yes 2) Z Harcombe receives income from 2 small self-employment businesses: The Harcombe Diet Co and Columbus Publishing. 3) No funding support

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Imamura et al (2016) (Systematic review with meta-analysis)	Yes	1) No 2) Yes 3) No	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	Yes	1) Yes 2) No	Yes - in online supplement.	1) Yes- 2) Yes- in online supplement.	Yes	Primary outcome: post intervention values. Meta-analysis: between arm correlations from crossover/Latin-square design – p-values and outcome measures, within individual correlations, interventional effects (SD or SE). Dose-response replacement nutrient estimated multiple treatments meta-regression. Heterogeneity: Q-statistics.	1) Yes 2) Examined plots and Egger's test.	1) Yes 2) Yes - support/consulting: Hass Avocado board Boston Heart Diagnostics, GOED, DSM, Life Science Research Organization, Elysium Health, Astra Zeneca, Unilever R&D 3) Medical Research Council Epidemiology Unit Core Support, National Institute of Health in the US

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Muto et al, (2017) (Systematic review with meta-analysis)	No	1) Yes 2) No 3) No	No 1) No 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	No	1) Yes 2) No	Yes	1) No 2) No	No	Random-effects model was used except when the number of samples was 2 and then fixed-effects model was used. Heterogeneity and bias: I^2 and T^2 calculations.	1) Yes 2) Funnel plots and Egger's test.	1) Yes 2) Yes –a lecture fee from Ono Pharmaceutical Co. Ltd 3) No
Ramsden et al (2016) (Systematic review and meta-analysis) (all information provided in the supplementary material)	Can't answer	1) Yes 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	Yes	1) Yes 2) Yes	Yes	1) Yes 2) Yes	Yes	Pooled risk estimates calculated for CHD death and all-cause mortality using a random effects model. Heterogeneity: I^2 statistic and Tau-squared.	1)Yes 2) Visual inspection of a funnel plot. Trim and fill analysis then performed.	1) Yes 2) No 3) US Public Health Service, National Heart Institute, National Institute of Alcohol Abuse and Alcoholism, National Institute of Health, University of North Carolina.

Study	**Was an 'a priori' design provided?**	**Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?**	**Was a comprehensive literature search performed?** **1) ≥2 electronic databases searched** **Reported:** **2) Search period** **3) Databases searched** **4) Key words / MESH terms** **5) Search strategy** **6) Reference lists searched**	**Was the status of publication (i.e. grey literature) used as an inclusion criterion?**	**Was a list of 1) included studies and 2) excluded studies provided?**	**Were the characteristics of the included studies provided?**	**Was the scientific quality of the included studies 1) assessed and 2) documented?**	**Was the scientific quality of the included studies used appropriately in formulating conclusions?**	**Were the methods used to combine the findings of studies appropriate?**	**1) Was the likelihood of publication bias assessed? 2) how was it assessed?**	**1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?**
Tielemans et al (2016) (Narrative systematic review)	Yes	1) Yes 2) No 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes- in supplement. 5) Yes-in supplement. 6) Yes but only in the 20% most recent publications.	Yes	1) Yes 2) No	Yes	1) Yes 2) Yes- in supplement.	Yes	N/A - narrative systemic review.	1) No 2) N/A	1) Yes 2) Yes (funding source) 3) Nestle Nutrition, Metagenics and AXA.
Te Morenga & Montez (2017) (Systematic review with meta-analysis)	No	1) Yes 2) Yes 3) No	Yes 1) Yes 2) Yes 3) Yes 4) Yes – online supplement 5) Yes 6) Yes	No	1) Yes 2) No	Yes	1) Yes 2) Yes	Yes	Random-effects meta-analysis. Heterogeneity and bias; I^2 and T^2 calculations.	1) No – too few studies identified 2) N/A	1) Yes 2) No 3) The University of Otago and the WHO
Brennan et al (2015) (Systematic review with meta-analysis)	No	1) Yes 2) No 3) No	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) No 6) Yes	No	1) Yes 2) No included a list of some excluded studies.	Yes	1) No 2) N/A	N/A	Meta-analysis and variance weighted least squares linear regression analysis of HRs. Heterogeneity: X^2 and I^2 statistic.	1) Yes 2) Inspection, funnel plots, Begg's and Egger's tests.	1) Yes 2) No 3) PhD studentship funding from Department of Employment and Learning.

Study	**Was an 'a priori' design provided?**	**Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?**	**Was a comprehensive literature search performed?** **1) ≥2 electronic databases searched** **Reported:** **2) Search period** **3) Databases searched** **4) Key words / MESH terms** **5) Search strategy** **6) Reference lists searched**	**Was the status of publication (i.e. grey literature) used as an inclusion criterion?**	**Was a list of 1) included studies and 2) excluded studies provided?**	**Were the characteristics of the included studies provided?**	**Was the scientific quality of the included studies 1) assessed and 2) documented?**	**Was the scientific quality of the included studies used appropriately in formulating conclusions?**	**Were the methods used to combine the findings of studies appropriate?**	**1) Was the likelihood of publication bias assessed? 2) how was it assessed?**	**1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?**
de Souza et al (2015) (Systematic review with meta-analysis)	Yes	1) No 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes - in supplement. 5) Yes - in supplement. 6) Yes	No	1) Yes 2) No	Yes - in supplement.	1) Yes 2) Yes	Yes	Risk ratios (highest and lowest intakes). ≥ 2 studies random effects meta-analysis performed. ≤ 3 studies fixed effect estimates also considered. Heterogeneity: Cochran's Q test (significant at $P<0.10$), and I^2 statistic. If ≥ 10 studies and $I^2 > 60\%$ or $P_Q < 0.10$, meta-regression used.	1) only if ≥ 10 studies 2) Funnel plots Egger's and Begg's tests.	1) Yes 2) Yes 3) World Health Organization

Study	**Was an 'a priori' design provided?**	**Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?**	**Was a comprehensive literature search performed?** **1) ≥2 electronic databases searched** **Reported:** **2) Search period** **3) Databases searched** **4) Key words / MESH terms** **5) Search strategy** **6) Reference lists searched**	**Was the status of publication (i.e. grey literature) used as an inclusion criterion?**	**Was a list of 1) included studies and 2) excluded studies provided?**	**Were the characteristics of the included studies provided?**	**Was the scientific quality of the included studies 1) assessed and 2) documented?**	**Was the scientific quality of the included studies used appropriately in formulating conclusions?**	**Were the methods used to combine the findings of studies appropriate?**	**1) Was the likelihood of publication bias assessed? 2) how was it assessed?**	**1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?**
Hooper et al (2015) (Systematic review with meta-analysis)	Yes	1) **Two authors** for search dates 06/2010 – 03/2014. **One author** for studies in Hooper et al, 2012 2) **Two authors** for latest search. **One author** for studies in Hooper et al, 2012. 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	Yes	1) Yes 2) Yes	Yes	1) Yes 2) Yes	Yes	Risk ratios: random-effects meta-analysis. Heterogeneity: I^2 statistic.	1)Yes 2) Funnel plot	1) Yes 2) No 3) Institute of Child Health, University of London, UK – to support the first systematic review.
Xia et al (2015) (Meta-analysis)	Yes	1) Yes 2) No 3) No	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) No 6) Yes	No	1)Yes 2) No	Yes	1) Yes 2) Yes-Newcastle-Ottawa scale.	Yes	Random and fixed effect model meta-analysis. Heterogeneity: I^2.	1) Yes 2) Begg funnel-plot and Egger test.	1) Yes 2) No 3) National Natural Science Foundation.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Xu et al, (2015a) (Systematic review with meta-analysis)	Yes	1) Yes 2) Yes 3) Yes	1) Yes 2) yes 3) Yes 4) Yes 5) Yes 6) Yes	No	1) Yes 2) No	Yes	1) Yes 2) Yes – Newcastle Ottawa Scale	N/A	Dose-response meta-analysis calculated by generalised least-squares method, and then random-effect model. Fixed effect model used to pool subgroups before inclusion in overall analysis. Heterogeneity: I^2 statistic. Random-effects meta-analysis assessed influence of subgroup covariates on intervention effect.	1) Yes 2) Egger's test	1) Yes 2) No 3) No support of funding to report

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Xu et al, (2015b) (Meta-analysis)	No	1) Can't answer 2) Can't answer 3) Can't answer	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	Yes	1) Yes 2) Yes	Yes – in supplement	1) Yes 2) No	Yes	Where an exposure of interest was reported by 2 studies in a consistent way, these were combined. Pooled effect size calculated and 95% CI. Heterogeneity between studies: I^2 statistic. Where significant ($p<0.05$) it was further analysed. When heterogeneity could not be explained, random effect model used.	1) Yes 2) Egger test – where significant trim and fill method used.	1) Yes 2) No 3) Not reported

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Yao & Tian (2015) (Meta-analysis)	No	1) Yes 2) Yes 3) No	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	No	1) Yes - in supplement 2) No	Yes – in supplement.	1) Yes - Newcastle Ottawa Scale 2) Yes - in supplement.	Yes	Random or fixed effects models (RRs and 95% CI). Heterogeneity: I^2.	1) Yes 2) Egger's and Begg's method and visual inspection of funnel plots.	1) Yes 2) No 3) Not reported.
Barnard et al (2014) (Narrative systematic review)	Yes	1) Yes 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	No	1) Yes 2) No	Yes	1) Yes 2) No	N/A	Narrative systematic review- data not combined. Heterogeneity not assessed.	1) No 2) N/A	1) Yes 2) Yes - authors affiliated with the Physicians Committee for Responsible Medicine. 3) Not reported.
Chowdhury et al (2014) (Systematic review and meta-analysis)	Yes	1) No 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	No	1) Yes 2) No	Yes	1) Yes 2) Yes	Yes	Random-effects model and parallel analysis - fixed effects models (RR). Heterogeneity: Within studies - X^2 and I^2 statistic; between studies – meta-regression.	1) Yes 2) Funnel plots and Egger tests	1) Yes 2) Yes 3) British Heart Foundation, MRC, Cambridge National Institute for Health Research Biomedical Research Centre, Gates Cambridge.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Farvid et al (2014) (Systematic review and meta-analysis)	No	1) Yes 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	Fixed-effects models (RR). Random-effects models: sensitivity analysis. Heterogeneity: I^2 statistic, stratified analysis and meta-regression.	1) Yes 2) Visual inspection of funnel plot; Begg's test.	1) Yes 2) Yes 3) National Institute of Health grant.
Schwab et al (2014) (Systematic narrative review)	Yes	1) Yes 2) Not reported 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes - in Appendix 1. 5) Yes - in Appendix 1. 6) Yes	No	1) Yes - in appendix 3. 2) Yes - in appendix 2.	Yes - In appendix 3	1) Yes 2) Yes in appendix's 3-6.	Yes	N/A – narrative review.	1) No 2) N/A	1) Yes 2) No 3) Yes- Nordic Council on Ministers.
Makarem et al (2013) (Systematic review)	No	1) No 2) No 3) N/A	No 1) No 2) Yes 3) Yes 4) Yes 5) Yes 6) yes	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	Narrative review.	1) No 2) No	1) Yes 2) No 3) American Cancer Society; The National cancer Institute.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) >2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Ramsden et al, (2013) (Meta-analysis) (information provided in the supplementary material and Ramsden et al, 2010[37])	Yes	1) No 2) No 3) Can't answer	Yes 1) Yes 2) No 3) Yes 4) Yes 5) No 6) Yes	No	1) Yes 2) No	Yes - *limited data provided in the supplementary material; more comprehensive data available in Ramsden 2010.*	1) No 2) N/A	N/A	Fixed effects meta-analysis performed for linoleic acid-selective and mixed n-3/n-6 PUFA intervention datasets for CHD death, CVD death and total deaths. Heterogeneity: Q-statistic to determine whether effects of linoleic acid-selective and mixed n-3/n-6 PUFA intervention datasets should be evaluated separately.	1)Yes 2) Funnel plot	1) Yes 2) No 3) Life Insurance Medical Research Fund of Australia and New Zealand and Intramural Program of the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health.

[37] Ramsden CE, Hibbeln JR, Majchrzak SF, Davis JM (2010) n-6 fatty acid-specific and mixed polyunsaturated dietary interventions have different effects on CHD risk: a meta-analysis of randomised controlled trials. *Br J Nutr* **104;** 1586-600.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Alhazmi et al (2012) (Systematic review with meta-analysis)	Yes	1) Yes 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	Yes	1) Yes 2) No	Yes	1) Yes - JBI checklist 2) Yes	Yes	RRs (95% CI) comparing type 2 diabetes risk between highest and lowest quintiles of macronutrient intake. Random effects meta-analysis, (within- and between-study variations taken into account). Subgroup analysis conducted by length of follow-up, sex and follow-up or baseline only FFQ. Heterogeneity (between studies): I^2 statistic.	1) Yes 2) Visual inspection of funnel plots and Egger's test	1) Yes 2) No 3) One author has a scholarship from the government of Saudi Arabia.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Fogelholm et al, (2012) (Systematic narrative review)	No	1) Yes 2) Yes 3) No	Yes 1) Yes 2) Yes 3)Yes 4) Yes – in Appendix 1 5) Yes 6)No	No	1) Yes 2) Yes – in Appendix 2	Yes	1) Yes 2) Yes – in Appendices	Yes	N/A – narrative review	1) No 2) N/A	1) None declared 2) N/A 3) Nordic Council of Ministers
Liu et al (2011) (Meta-analysis)	No	1) No 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) No 6) Yes	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	Random effects model: RR (95% CI). Heterogeneity: Q-test and I^2 statistic.	1) Yes 2) Inspection of funnel plots, Begger rank correlation and Egger weighted regression model.	1) Yes 2) No 3) Not reported.
Turner (2011) (Meta-analysis)	No	1) No 2) No 3) N/A	Yes 1) Yes 2) Yes 3) Yes 4) No 5) No 6) Yes	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	Random effects meta-analysis. Heterogeneity assessment not reported.	1) No 2) N/A	1) No 2) N/A 3) Not reported.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Lee et al (2010) (Narrative systematic review)	No	1) Yes 2) Not reported 3) Not reported	No 1) Yes 2) Yes 3) Yes 4) Yes 5) No 6) No	No	1) Yes 2) No	Yes	1) Yes 2) No	N/A	N/a - narrative review.	1) No 2) N/A	1) Yes 2) No 3) Health Promotion Fund and Clinical Research Centre for Dementia; both Ministry for Health, Welfare and Family Affairs, Republic of Korea.
Micha & Mozaffarian (2010) (Systematic review)	No	1) Yes 2) Yes 3) Yes	No 1) No 2) Yes 3) Yes 4) Yes 5) No 6) Yes	No	1) No 2) No	No	1) No 2) N/A	N/A	N/A – narrative review.	1) No 2) N/A	1) Yes 2) Yes 3) Searle Funds, Bill and Melinda Gates Foundation/ World Health Organisation Global Burden of Diseases, Injuries and Risk Factors Study.
Mozaffarian et al (2010) (Systematic review and meta-analysis)	Yes - *protocol in supplementary material*	1) Yes 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	Yes	1) Yes 2) Yes	Yes	1) Yes 2) Yes	Yes	Pooled effect calculated using random effects meta-analysis. Heterogeneity (between studies):Q-statistic, I^2 statistic, and meta-regression.	1) Yes 2) Visual inspection of funnel plot and Begg's test.	1) Yes 2) Yes 3) National Heart, Lung and Blood Institute, National Institute of Health and Searle Funds at the Chicago Community Trust.

Study	**Was an 'a priori' design provided?**	**Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?**	**Was a comprehensive literature search performed?** **1) ≥2 electronic databases searched** **Reported:** **2) Search period** **3) Databases searched** **4) Key words / MESH terms** **5) Search strategy** **6) Reference lists searched**	**Was the status of publication (i.e. grey literature) used as an inclusion criterion?**	**Was a list of 1) included studies and 2) excluded studies provided?**	**Were the characteristics of the included studies provided?**	**Was the scientific quality of the included studies 1) assessed and 2) documented?**	**Was the scientific quality of the included studies used appropriately in formulating conclusions?**	**Were the methods used to combine the findings of studies appropriate?**	**1) Was the likelihood of publication bias assessed? 2) how was it assessed?**	**1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?**
Siri-Tarino et al (2010) (Meta-analysis)	Can't answer	1) Yes 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) No 6) Yes	No	1) Yes 2) No	Yes	1) Yes 2) Yes - in supplement.	Yes	RR (95% CI) log transformed to derive corresponding SEs for β-coefficients using Greenland's formula. Otherwise used p-values to drive SE where possible. Random effects meta-analysis: pooled RR.	1) Yes 2) Funnel plots	1) Yes 2) Yes – *one author supported by postdoctoral fellowship from Uniliver Corporate Research* 3) National Dairy Council; grant from National Centre for Research Resources.
Jakobsen et al (2009) (Pooled analysis)	Can't answer	1) No 2) No 3) No	No 1) No 2) No 3) No 4) No 5) No 6) No	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	Study-specific logs of hazard ratios weighted by inverse of variances and pooled estimate of hazard ratios computed using random-effects model. Heterogeneity (between-studies): Q statistic.	1) No 2) N/A	1) Yes 2) No 3) National Heart, Lung and Blood Institute, National Institute of Health and the Danish Heart Foundation.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Mente et al (2009) (Systematic review)	Can't answer	1) Yes 2) Can't answer 3) Yes	No 1) No 2) Yes 3) Yes 4) No 5) No 6) Yes	No	1) No 2) No	Yes - in supplement.	1) Yes 2) Yes	No	Bradford Hill criteria used to evaluate evidence of causal relationship between dietary exposures and CHD. Heterogeneity (between studies): Q statistic. Random effects-effects model: summary statistics.	1) No 2) N/A	1) Yes 2) No 3) None
Skeaff & Miller (2009) (Meta-analysis)	Can't answer	1) No 2) No 3) No	Can't answer 1) Yes 2) No 3) Yes 4) No 5) No 6) Yes	No	1) No 2) No	Yes	1) No 2) N/A	N/A	Random effects meta-analysis: summary estimates of CHD RR high vs low exposure to dietary fat or fat classes. Heterogeneity: I^2 statistic.	1) Yes 2) Funnel plots	1) Yes 2) Yes - Dr Skeaff has conducted clinical research trials funded through the University of Unilever and Fonterra. 3) Not reported.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Van Horn et al (2008) (Systematic narrative review)	No	1) No 2) No 3) No	Yes 1) Yes 2) Yes 3) Yes 4) No 5) No 6) Yes	No	1) Yes 2) No	Yes	1) Yes 2) Yes	Yes	N/A – narrative review.	1) No 2) N/A	1) No 2) Can't answer 3) Can't answer
Patterson et al (2007) (Narrative systematic review)	No	1) Yes 2) Yes 3) Yes	No 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes (in appendix) 6) Yes	No	1) No 2) No	No	1) Yes 2) No	N/A	Narrative review: Risk factors and RR. Heterogeneity not assessed.	1) No 2) N/A	1) Yes 2) Yes (Authors received support from Pfizer, Lundbeck, Novartis, Voyage Pharmaceuticals, Neurochem, Myriad) 3) Institute of Advanced studies, Uni of Bologna, CIHR.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Dennis et al (2004) (Meta-analysis)	No	1) No 2) No 3) N/A	No 1) No 2) Yes 3) Yes 4) Yes 5) No 6) Yes	No	1) Yes 2) No	Yes- in online supplement	1) No 2) N/A	N/A	RR examined, selecting those with the greatest number of potential confounders. Pooled estimates of risk from random effects obtained. Heterogeneity: Cochran's X^2 and I^2 statistic.	1) No 2) N/A	1) No 2) N/A 3) National Cancer Institute grant.
Boyd et al (2003) (Meta-analysis)	No	1) No 2) No 3) N/A	Yes 1) Yes 2) Yes 3) Yes 4) No 5) No 6) Yes	No	1) Yes 2) No	Yes	1) Yes 2)Yes	Yes	Random effects model of DerSimonian and Laird. Also employed subgroup and regression analysis.	1) No 2) N/A	1) No 2) N/A 3) University of Toronto.
Mensink et al (2003) (Meta-analysis)	No	1) No 2) No 3) No	No 1) Can't answer 2) Yes 3) No 4) No 5) No 6) Yes	No	1) Yes 2) No	Yes	1) No 2) No	N/A	Estimated regression coefficients calculated.	1) No 2) N/A	1) Yes 2) No 3) Maastricht University, Wageningen University and Wageningen Centre for Food Sciences.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Smith-Warner et al (2002) (Pooled analysis)	No	1) No 2) No 3) N/A	No 1) No 2) No 3) No 4) No 5) No 6) No	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	Cox proportional hazards model: RRs (adjusted for smoking history, education, BMI, alcohol consumption, fruit and vegetable consumption, E intake). Two sided 95% CIs calculated. Random effects model: pooled RR. Heterogeneity (between studies): asymptotic DerSimonian and Laird Q statistics.	1) No 2) N/A	1) No 2) No 3) Supported by Grants NIH CA55075 and CA78548. Article considered an advertisement as defrayed in part by payment of page charges.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Smith-Warner et al (2001) (Pooled analysis)	No	1) No 2) No 3) N/A	No 1) No 2) No 3) No 4) No 5) No 6) No	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	Analysed primary data using a standardized approach. Holding total energy intake constant, RR calculated for increments of 5% of energy for each type of fat compared with an equivalent amount of energy from carbohydrates or other types of fat. Random effects model: study-specific RR combined. Heterogeneity (between studies): asymptotic DerSimonian and Laird Q Statistic.	1) No 2) N/A	1) No 2) N/A 3) National Institutes of health, Cancer Research foundation of America/America Society of Preventive Oncology, American Cancer Society.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Ernst (1999) (Narrative systematic review)	No	1) No 2) No 3) No	Yes 1) Yes 2) Yes 3) Yes 4) No 5) No 6) Yes	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	N/A - narrative review.	1) No 2) N/A	1) No 2) N/A. 3) Not reported.
Yu-Poth et al (1999) (Meta-analysis)	No	1) No 2) No 3) No	No 1) No 2) Yes 3) Yes 4) No 5) No 6) Yes	No	1) Yes 2) No	Yes	1) No 2) No	N/A	Analysis of variance compared effects of Step I with Step II dietary interventions. Changes in plasma TC, LDL-C, HDL-C and TAG in response to ΔSFA evaluated by regression analysis.	1) No 2) N/A	1) No 2) No 3) Not reported.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Tang et al (1998) (Systematic review)	No	1) No 2) Yes 3) Yes	Yes 1) Yes 2) Yes 3) Yes 4) No 5) No 6) Yes	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	Percentage reduction in cholesterol concentrations in each trial calculated and compared. SE of difference for each comparison calculated. Same methods applied to changes in dietary intakes. Heterogeneity: comparing observed results in different categories of trials grouped according to type of diet, intensity of advice, and type of patients.	1) No – although it is considered 2) The authors comment on it in the discussion	1) Yes 2) No 3) Department of Health and Medical Research Council.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Brunner et al (1997) (Meta-analysis)	No	1) One author screened abstracts, four authors screened full publications. 2) No 3) No	No 1) No 2) Yes 3) No 4) No 5) No 6) No	No	1) Yes 2) No	Yes	1) No 2) N/A	N/A	Intervention effects: mean changes intervention and control (and SE). Most and least intensive interventions compared where >3 randomised groups. Random effects meta-analysis: weighted by inverse of sum of between-studies variance and study intervention effect. Heterogeneity - Q statistic.	1) Yes 2) Funnel plots (data not shown).	2) No 3) Health Education Authority and North Thames Regional Health Authority.

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Clarke et al (1997) (Meta-analysis)	No	1) No 2) No 3) N/A	No 1) No 2) No 3) Yes 4) No 5) Available on request. 6) Yes	No	1) No 2) No	No	1) No 2) N/A	N/A	Multilevel regression analyses (age, weight and nutrient dietary intake, 1 unique term/study to ensure people within one study were compared directly only with each other). Assessed sources of variability: within group, between experiments; within study, between matched groups; within study, between unmatched groups; between studies.	1) No 2) N/A	1) Yes 2) No 3) British Heart Foundation and Medical Research Council

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
Howell et al (1997) (Meta-analysis)	No	1) No 2) No 3) No	Yes 1) Yes 2) Yes 3) Yes 4) Yes 5) Yes 6) Yes	No	1) No 2) No	Yes	1) Yes 2) Yes	Yes	Dietary change variables: difference final and initial dietary TC and TF, PUFA, MUFA, SFA (% of energy). Bivariate Pearson correlations - between dietary variables and between dietary variables and response variables. Stepwise-multiple-regression: linear prediction equations for each response measures, evaluating combined and independent contributions of specified dietary variables. Modified linear predication model into a nonlinear, used for effects of	1) No 2) N/A	1) No 2) N/A 3) Yes- American Egg Board and Agricultural Experiment station (University of Arizona).

Study	Was an 'a priori' design provided?	Was there 1) duplicate study selection 2) duplicate data extraction? 3) was a consensus procedure for disagreement in place?	Was a comprehensive literature search performed? 1) ≥2 electronic databases searched Reported: 2) Search period 3) Databases searched 4) Key words / MESH terms 5) Search strategy 6) Reference lists searched	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of 1) included studies and 2) excluded studies provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies 1) assessed and 2) documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	1) Was the likelihood of publication bias assessed? 2) how was it assessed?	1) Was the conflict of interest included? 2) Was there a conflict or potential conflict of interest? 3) Funding source?
									dietary manipulation. Heterogeneity testing not reported.		

ANNEX 5: Glossary

Alzheimer's Disease	The most common type of dementia, characterised by a slow, progressive deterioration in cognitive function. Problems with day-to-day memory are often noticed first, but other symptoms may include difficulties with word finding, problem solving, decision making or visual perception.
National Cholesterol Education Programme (NCEP)	Is a program managed by the US National Heart, Lung and Blood Institute, a division of the National Institute of Health. Its goal is to reduce increased CVD rates due to hypercholesterolemia in the US.
Atherosclerosis	A potentially serious condition where arteries become clogged with fatty deposits called plaques, or atheroma. These deposits are made up of cholesterol, fatty substances, cellular waste products, calcium and fibrin. It can build up in the artery walls and, over time, narrowing them and reducing blood flow.
Beta (β)	Type 2 error or a regression slope.
Body mass index (BMI)	BMI is used to standardise body weight for different heights. BMI is calculated by weight in kilograms divided by height in metres squared (weight (kg)/height (m^2)). BMI ranges: • below 18.5 – underweight range • between 18.5 and 24.9 – healthy weight range • between 25 and 29.9 – overweight range • between 30 and 39.9 – obese range. (For children and young people aged 2 to 18, the BMI calculation takes into account age and sex as well as height and weight)
Cardiovascular disease	A general term for conditions affecting the heart or blood vessels. It can be categorised into 3 types: coronary heart disease, cerebrovascular disease or peripheral vascular disease.
Cerebrovascular disease	Includes ischaemic and haemorrhagic stroke, which occurs when the arterial supply to parts of the brain is blocked, or blood escapes from a ruptured blood vessel (cerebral haemorrhage).

Cognitive impairment	Mild cognitive impairment (MCI) is defined as a slight decline in cognitive abilities, including memory and thinking skills, but not to such an extent that it hinders activities of daily living. MCI is not a form of dementia, but a person with MCI is at an increased risk of developing dementia (including Alzheimer's disease).
Coronary heart disease	A complete or partial narrowing of the coronary arteries which supply the heart muscle. Includes myocardial infarction (MI) and other manifestations of coronary atherosclerosis.
Dementias	Dementia is caused by a variety of diseases and injuries that primarily or secondarily affect the brain. The most common types of dementia are: Alzheimer's disease (AD) (including early-onset AD); vascular dementia; dementia with Lewy bodies; frontotemporal dementia or mixed dementia.
Diabetes	A metabolic disorder involving impaired metabolism of glucose due to either failure of secretion of the hormone insulin, insulin-dependent or type 1 diabetes, OR impaired responses of tissues to insulin, non-insulin-dependent or type 2 diabetes.
Dietary reference values (DRVs)	DRVs describe the distribution of nutrient and energy requirements in a population. They comprise: **Estimated Average Requirement (EAR)**: half of a group in a population will need more than this amount and half will need less; **Reference Nutrient Intake (RNI)**: the intake that will be adequate to meet the needs of 97.5% of the population; **Lower Reference Nutrient Intake (LRNI)**: the intake which will meet the needs of only 2.5% of the population.
Dyslipidaemia	An abnormal amount of lipids (triacylglycerols, cholesterol or phospholipids) in the blood.

Fasting blood glucose	Level of sugar in the blood after an overnight fast. It can be used to diagnose diabetes or 'pre diabetes'. NICE[38] defines the following blood glucose levels as: Normal: Below 5.5 mmol/l (100 mg/dl) Impaired fasting glucose: Between 5.5 and 6.9 mmol/l (between 100 mg/dl and 125 mg/dl) Diabetic: 7.0 mmol/l and above (126 mg/dl and above)
Fasting insulin	Level of insulin in the blood after an overnight fast.
Fixed effects model	A model that calculates a pooled effect estimate using the assumption that all observed variation between studies is caused by the play of chance. Studies are assumed to be measuring the same overall effect.
Glucose tolerance	Ability of the body to absorb and use glucose.
Glycated haemoglobin (HbA1c)	Provides a measure of average plasma glucose concentration.
Hazard ratio (HR)	The hazard ratio is a comparison of the effect of different variables on survival or other outcomes that develop over time.
Heterogeneity	The variation in study outcomes between studies. Heterogeneity is used generically to refer to any type of significant variability between studies contributing to a meta-analysis that renders the data inappropriate for pooling. This may include heterogeneity in diagnostic procedure, intervention strategy, outcome measures, population, study samples, or study methods. The term heterogeneity can also refer to differences in study findings. Statistical tests can be applied to compare study findings to determine whether differences between the findings are statistically significant. For example, significant heterogeneity between estimates of effect from intervention studies suggests that the studies are not estimating a single common effect. In the presence of significant heterogeneity, it is more appropriate to describe the variations in study findings than to attempt to combine the findings into one overall estimate of effect.

[38] Type 2 diabetes: prevention in people at high risk | NICE Public Health Guideline 38 - NICE. Published July 12, 2012.

High density lipoprotein (HDL) cholesterol	Carries cholesterol away from the cells and back to the liver, where it's either broken down or passed out of the body as a waste product; for this reason, HDL is referred to as "good cholesterol", and higher levels are better.
Homeostasis model assessment (HOMA)	A widely applied surrogate index of insulin resistance, using fasting insulin and glucose values.
Hyperdyslipidaemia	Increased concentration of lipids in the blood and is associated with a number of metabolic diseases.
Insulin resistance	Insulin resistance occurs when cells of the body don’t respond properly to the hormone insulin.
Intermediate markers	A marker used in place of a clinical endpoint or disease that is assumed to be representative of that clinical endpoint/ disease.
Low density lipoprotein (LDL) cholesterol	Carries cholesterol to the cells that need it. If there's too much cholesterol for the cells to use, it can build up in the artery walls and, over time, narrowing them and reducing blood flow. For this reason, LDL is known as ‘bad cholesterol’.
Meta-analysis	A quantitative pooling of estimates of effect of an exposure on a given outcome, from different studies identified from a systematic review of the literature. Meta-analysis is a specific method of statistical synthesis that is used in some systematic reviews, where the results from several studies are quantitatively combined and summarised. The pooled estimate of effect from a meta-analysis is more precise (that is, has narrower confidence intervals) than the findings of each of the individual contributing studies, because of the greater statistical power of the pooled sample.
Meta-regression	Meta-regression is a tool used in meta-analysis to examine the impact of moderator variables on study effect size using regression-based techniques. Meta-regression is more effective at this task than are standard meta-analytic techniques.
Metabolic ward experiments	Intervention studies conducted under controlled conditions.
Monounsaturated fats	Unsaturated fats have some of the hydrogen atoms missing and have been replaced by a double bond between the carbon atoms. If there is one double bond, the fat is known as a monounsaturated fatty acid.

Odds ratio (OR)	A measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared with the odds of the outcome occurring in the absence of that exposure. The OR is adjusted to address potential confounding.
Peripheral vascular disease	Results from narrowing or blockage in the arteries to the limbs (usually the legs) and aortic disease, which includes conditions that affect the aorta, including aortic aneurysm and carotid arterial narrowing.
Pooled analysis	A statistical technique for combining the results of multiple epidemiological studies.
Polyunsaturated fats	Unsaturated fats have some of the hydrogen atoms missing and have been replaced by a double bond between the carbon atoms. If there is more than one double bond the fat is known as a polyunsaturated fatty acid.
Prospective cohort study	An observational study in which a defined group of people (the cohort) is followed up over time. The outcomes of people in subsets of this cohort are compared, to examine people who were exposed or not exposed (or exposed at different levels) to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future.
Random effects model	A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.
Randomised controlled trial (RCT)	An experiment in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body).
Relative Risk (RR)	The ratio of the rate of disease or death among people exposed to a factor, compared with the rate among the unexposed, usually used in cohort studies (World Cancer Research Fund & American Institute for Cancer Research, 2007).

Risk factor	Social, economic or biological status, behaviours or environments which are associated with or cause increased susceptibility to a specific disease, ill health, or injury.
Saturated fats	A saturated fat is a fat that has as many hydrogen atoms as they can hold (i.e. they are 'saturated' with hydrogen atoms). When hydrogen atoms are missing, carbon atoms form double bonds. Generally saturated fats are solid at room temperature.
Sensitivity analysis	An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.
Statins	A group of medicines that can help lower the level of LDL cholesterol in the blood.
Stroke	A serious life-threatening medical condition that occurs when blood supply to part of the brain is cut off.
Systematic review	A systematic review is a method of identifying, appraising, and synthesising research evidence. The aim is to evaluate and interpret all the available research that is relevant to a particular review question. A systematic review differs from a traditional literature review in that the latter describes and appraises previous work, but does not specify methods by which the reviewed studies were identified, selected, or evaluated. In a systematic review, the scope (for example, the review question and any sub-questions and/or sub-group analyses) is defined in advance, and the methods to be used at each step are specified. The steps include: a comprehensive search to find all relevant studies; the use of criteria to include or exclude studies; and the application of established standards to appraise study quality. A systematic review also makes explicit the methods of extracting and synthesising study findings.
Total cholesterol : HDL cholesterol ratio	Provides more information on an individual's CHD risk by dividing total cholesterol by HDL cholesterol. A ratio above 6 is considered high risk - the lower this figure is the better.
Trans fats	Unsaturated fats exist in either *cis* or trans forms. The cis configuration is the more abundant form, but the process of hydrogenation – which occurs either in the rumen of ruminant animals or during industrial hydrogenation of unsaturated oils – leads to the conversion of some of the *cis* to trans fats.

Triacylglycerol	Fats in foods are predominantly in the form of triacylglycerol. They are formed of glycerol and 3 fatty acids.

ANNEX 6: Abbreviations

AA	Arachidonic acid
AFSSA	The French Food Safety Agency
AMSTAR	A Measurement Tool to Assess Systematic Reviews
APOE	Apolipoprotein E
BHF	British Heart Foundation
BMI	Body Mass Index
CHD	Coronary heart disease
COMA	Committee on Medical Aspects of Food and Nutrition Policy
CT	Computed tomography
CVD	Cardiovascular disease
DGAC	US Dietary Guidelines Advisory Committee
DGLA	Dihomo-gamma linolenic acid
DHA	Docosahexaenoic acid
EFSA	European Food Safety Authority
EPA	Eicosapentaenoic acid
FAO	Food and Agriculture Organization
FATP	Fatty acid transport proteins
FSIGTT	Frequently sampled intravenous glucose tolerance test
FSS	Food Standards Scotland
HbA1c	Glycated haemoglobin
HCN	Health Council of the Netherlands
HDL	High density lipoprotein cholesterol
HOMA	Homeostasis model assessment
HR	Hazard ratio
HSE	Health Survey for England
I^2	Heterogeneity
LCPUFA	Long chain polyunsaturated fatty acids
LIDNS	Low Income Diet and Nutrition Survey
LDL	Low density lipoprotein cholesterol
MRI	Magnetic resonance image
MI	Myocardial infarction

MUFA	Monounsaturated fats
NA	Not applicable
NCEP	American Heart Association National Cholesterol Education Programme
NDNS	The National Diet and Nutrition Survey
NEFA	Non-esterified fatty acids
NICE	The National Institute for Health and Care Excellence
OGTT	Oral glucose tolerance test
OR	Odds ratio
PCS	Prospective cohort study
PET	Polyethylene terephthalate
PHE	Public Health England
PUFA	Polyunsaturated fats
r	regression coefficient
RCT	Randomised controlled trial
RR	Relative risk
SACN	Scientific Advisory Committee on Nutrition
SD	Standard deviation
TEE	Total energy expenditure