Scientific Advisory Committee on Nutrition

Draft report:

Saturated fats and health

Scientific consultation: 8 May to 3 July 2018

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This is a draft report and does not necessarily represent the final views of the Scientific Advisory Committee on Nutrition, or the advice/policy of Public Health England and UK Health Departments.

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1   Introduction

Background

1.1   In June 2014, the Scientific Advisory Committee on Nutrition (SACN) agreed to conduct a review of the evidence on the role of fats, including monounsaturated, polyunsaturated and particularly, saturated fats, in health. This had been prioritised as part of the horizon scanning process and requested by Food Standards Agency (Scotland) (now Food Standards Scotland (FSS)). Following a scoping exercise, which highlighted the large evidence base, it was agreed that a review of the evidence on saturated fats and health was most pressing due to the on-going scientific and media debate which focuses on the relationship between saturated fats and cardiovascular disease (CVD). Therefore, this review covers only saturated fats and/or substitution of saturated fats and health and does not specifically consider the role of unsaturated, trans or total fats.

1.2   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). COMA recommended that the average contribution of saturated fatty acids to total dietary energy be reduced to no more than 10% (11% food and drink energy, excluding alcohol) for adults and children aged 5 years and older[1]. This recommendation is set at a population level, does not apply before two years of age, and applies in full from the age of five years. A flexible approach is recommended to the timing and extent of dietary change for individual children between two and five 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) cholesterol and in the

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[1] 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. Also see Table 16.1 in Chapter 16.

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 type 2 diabetes risk, dementias and various cancers (including colorectal, pancreatic, lung, breast and prostate) (see Table 4.1).

Terms of reference

1.3   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 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, 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, 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 or oversight. They are becoming the expected and required standard for assessing evidence, and the only form of evidence used by some regulatory and health authorities.

2.3   Additional eligibility criteria included: English language publications, with no geographical restriction, published in peer-reviewed scientific or medical journals between 1991 and March 2016. 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. Studies 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. SACN also invited interested parties to highlight relevant evidence which satisfied the inclusion criteria for the review. The call for evidence, which was placed on the SACN website, opened on the 25 May 2016 and closed on the 15 June 2016. Reference lists of all included publications (identified through the online database search or highlighted by interested parties, up to March 2017) were hand searched. Reference lists of relevant reviews by international organisations were also considered. Publications identified after March 2016 will be considered as part of the draft report consultation (these will only be

included if they add substantial nuance or/ update to existing work or change 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, 33 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 6 of these publications met the inclusion criteria. Three publications were identified through hand searching of reference lists with an additional 5 identified through other sources; 2 by members of the Saturated Fats Working Group during drafting and 3 which were published after the closing date for the call for evidence, by an interested party. In total, 47 systematic reviews, meta-analyses and pooled analyses were included. Figure 2.1 displays the flow diagram for inclusion of studies.

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┌─────────────────────────────┐
│  Records identified through │
│  online searching after     │
│  duplicates removed         │
│                             │
│         n = 996             │
└─────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐
│  Title and abstract screening│
│                             │
│         n = 996             │
└─────────────────────────────┘
              │
              ▼
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┌─────────────────────────────┐
│ Additional records   │
│ identified through   │
│ call for evidence   │
│   │
│   n = 40   │
│   │
│ Hand searching   │
│   │
│   n = 3   │
│   │
│ by members of the   │
│ Working Group   │
│ during drafting   │
│   │
│   n = 2   │
│   │
│ by an interested   │
│ party after the   │
│ closing date for the   │
│ call for evidence   │
│   │
│   n = 3   │
└─────────────────────────────┘   →

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┌─────────────────────────────┐        ┌──────────────────────┐
│ Total references for title  │   →    │ Publications excluded │
│ and abstract screening      │        │                      │
│                             │        │      n = 963         │
│        n = 1044             │        └──────────────────────┘
└─────────────────────────────┘
              │
              ▼
┌─────────────────────────────┐        ┌──────────────────────┐
│ Full text articles assessed │   →    │ Full text articles   │
│ for eligibility             │        │ excluded             │
│                             │        │                      │
│        n = 81               │        │      n = 35          │
└─────────────────────────────┘        └──────────────────────┘
              │
              ▼
┌─────────────────────────────┐
│ Publications included in    │
│ qualitative synthesis       │
│                             │
│        n = 46               │
└─────────────────────────────┘
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Figure 2.1. Flow diagram showing the number of publications assessed for eligibility and included in the review.

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, was also extracted into the table.

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 was 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)](). The quality assessment tool for systematic reviews and meta-analyses was selected by comparing the results of the analysis of 5 publications identified through a literature search. Limitations were identified across all tools but AMSTAR was selected because it is more widely recognised and used by other organisations (e.g. the US Dietary Guidelines Advisory Committee and Nordic Council of Ministers) than other tools. AMSTAR consists of 11 questions. 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 from the Saturated Fats Working Group was sought.

Methods for reviewing and grading evidence

2.10 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 groups' discussions with the final text, conclusions and recommendations, discussed and agreed with the SACN main Committee. This draft report has been made available for public consultation and the comments received from interested parties will be taken into consideration before the report is finalised.

Grouping of evidence by research question

2.11 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 2.17); therefore, publications providing evidence for each of the health outcomes, intermediate markers or risk factors were subdivided according to the research questions considered in the publication.

Evaluation of the quality of identified evidence

2.12 The quality of included systematic reviews, meta-analyses and pooled analyses was assessed by:

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

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 registered protocol.

Primary studies considered within systematic reviews/meta-analyses

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- 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 (e.g. dietary fat intakes, presence of disease, relevant medication usage, smoking habits, physical activity levels, 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.

2.13   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

2.14 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 2 models, and therefore the types of data that it is recommended are combined within them. In the presence of heterogeneity, random-effects models weight studies more equally than fixed-effect models. SACN noted that fixed-effect models typically give more weight to larger primary studies and may offer a number of advantages over random-effects models. However, it should be noted that the choice of models and their interpretation remains an area of debate among statisticians.

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

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

a) Where the results of only 1 model (i.e. fixed-effect or random-effects) were reported in a publication, the results of this meta-analysis were reported in SACN's review, and used to draw conclusions.

b) Where the results of both models were reported in a publication, these were reported in SACN's review. 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 was considered in the final grading of the evidence (see Grading of evidence below).

Grading of evidence

2.17   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.

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 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,

Strength of evidence	Explanatory notes
	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.

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, |

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Strength of evidence	Explanatory notes
	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. 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 3-4 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

Strength of evidence	Explanatory notes
	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, <3-4 eligible randomised controlled trials or cohort studies were identified. Therefore, it is not possible to draw conclusions.

Limitations of evidence

2.18   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, this may be a consideration when interpreting analyses which report no effect or association.

- Studies that substituted saturated fats with carbohydrate generally did not specify or undertake analyses which considered the type of carbohydrate. Different types of

carbohydrate could have different effects/associations (for example, those with low compared to high glycaemic index; whole grains compared to refined starch)[2].

- Studies that substituted saturated fats with polyunsaturated fats (PUFA) generally did not consider the possible effects of different classes of PUFA (e.g. n-3 and n-6 PUFAs).

- 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 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 review.

- 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 7.7). 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 5% 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 fat included trials where there were reductions in the intakes of both saturated and total fats, which limits the ability to attribute the observed effects solely to a change in saturated fat intakes.

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[2] More detailed information is available at
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf

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- The dietary interventions in the trials considered were often complex, resulting in changes in more than just saturated fat intake. 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 saturated fat intake may also be relevant to PCS and other epidemiological evidence.

- 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.

- The homeostasis model assessment (HOMA) assays are not standardised and glycated haemoglobin (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 (e.g. statins) in the studies published after 1990 due to a sharp increase in prescriptions of statins in the 1990s.

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 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.
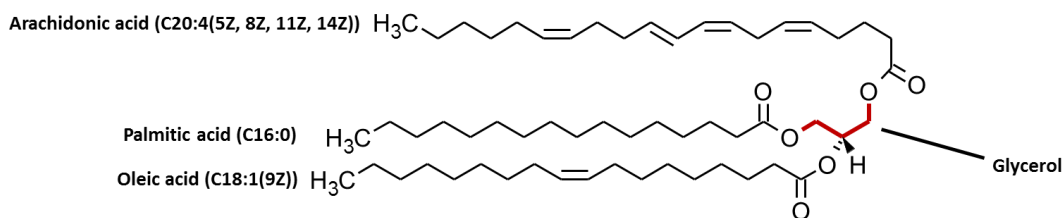
Figure 3.1. Chemical structure of a typical triacylglycerol. Triacylglycerols consist of 3 fatty acids each forming an ester bond with glycerol (shown in red). A triacylglycerol formed by esterification with the 3 different fatty acids palmitic acid, oleic acid and arachidonic acid is shown in the example above, 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.
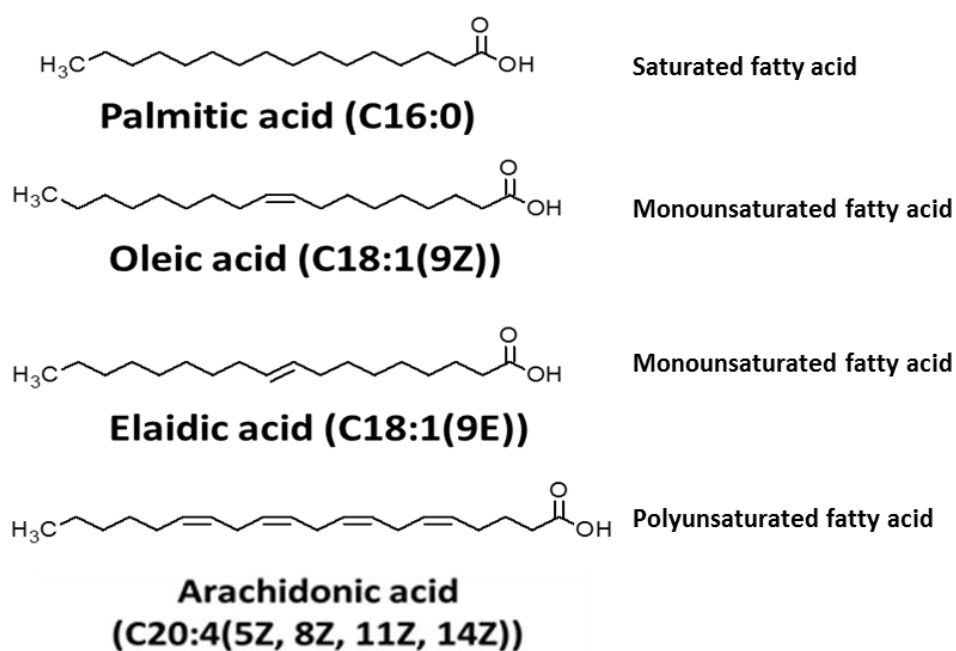
Figure 3.2. The structure of some different types of fatty acids. Double bonds influence the geometry of fatty acids, cis double bonds have the carbon chain on the same side of the double bond, while trans fatty acids are on opposite sides of the double bond. The double bonds have profound effects on the physicochemical properties of fats such as membrane fluidity.

3.5   Humans cannot synthesise the n-3 or n-6 double bond structure, therefore fats with this structure have to be ingested. Only two fatty acids are considered to be essential in the

diet: linoleic (18:2 n-6) and *a*-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 the compound and its derivatives are commonly found in fat-containing foods. 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 an important 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 500-900 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 9th and 10th 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, e.g. 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	icosanoic 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) 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.

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 atheroma 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).
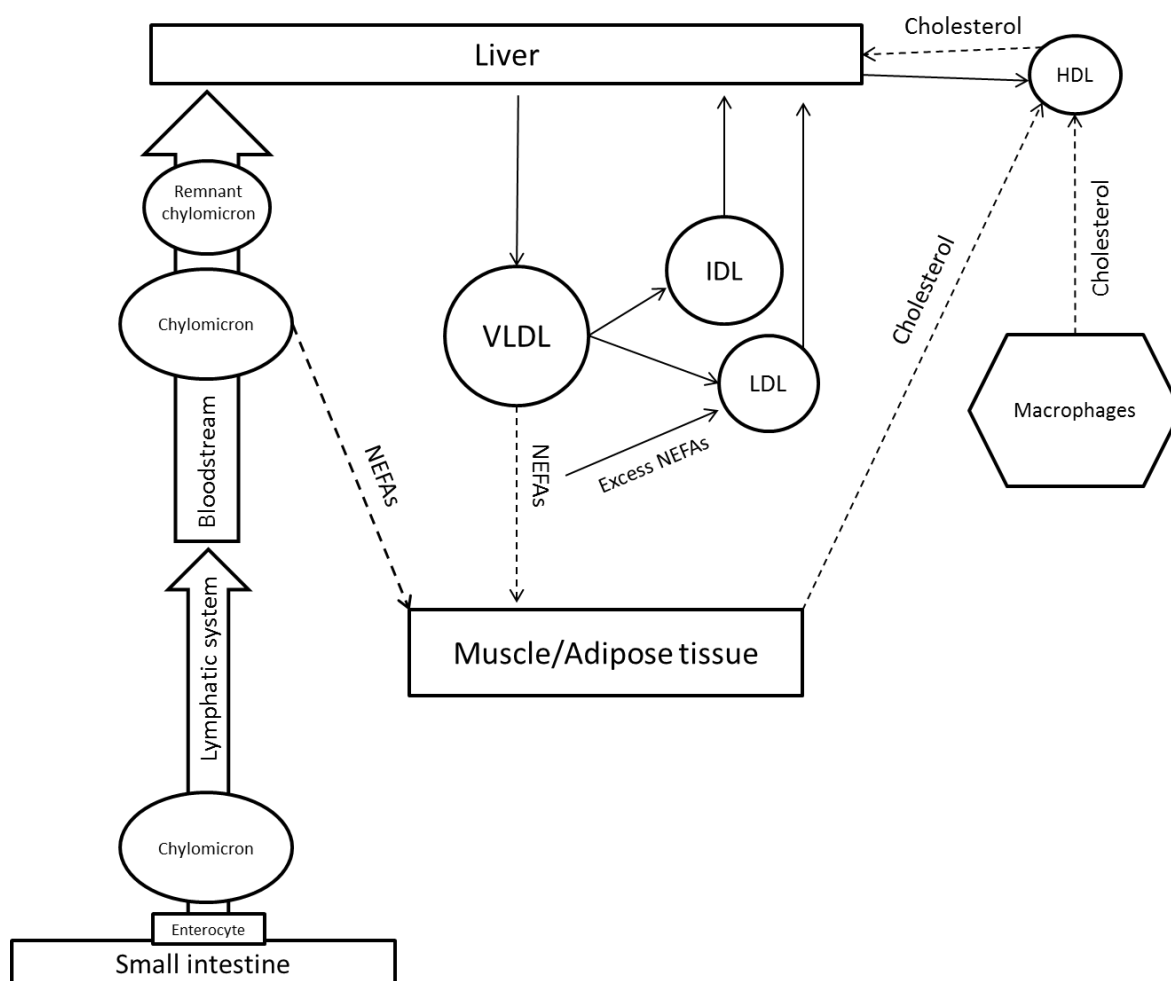
Figure 3.3. Schematic of some of the processes involved in the transport of cholesterol, non-esterified fatty acids (NEFAs) and lipoprotein particles across the body. Fats are absorbed from the intestine and form chylomicron particles. These are transported through the lymph system before emptying into 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 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.

Metabolism

3.19   One gram of dietary fat provides approximately 37kJ (9 kcal) of energy compared with 17kJ (4 kcal) per gram for carbohydrates and protein (Berg et al., 2012a). Fatty acids, stored as triacylglycerols in the body, form anhydrous droplets, while carbohydrate stored as glycogen, requires water. Thus, fats store approximately 6 times more energy than carbohydrate by weight.

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 adipose cells activate an enzyme called lipase which breaks down triacylglycerols to monoacylglycerols and free fatty acids. Free fatty acids are released from the cell into the blood stream 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 the 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 CoAs and then transported via the carnitine shuttle (Berg et al., 2012b).

3.23   Fatty acids (in the form of fatty acyl CoAs) 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 (e.g. 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 used in organs which do not metabolise fatty acids directly, such as the brain.

3.27   The liver can also convert carbohydrate 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, myristate (C14:0), palmitate (C16:0) and stearate (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-gamma linolenic (DGLA) [18:3 n-6], arachidonic acid (AA) [20:4 n-6], eicosapentaenoic (EPA) [20:5 n-3] and docosahexaenoic acid (DHA) [22:6 n-3] (Sprecher, 2002).

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

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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 (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.

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, 1991; COMA, 1994). COMA recommended that adults and children aged 5 years and older should consume on average no more than 10% of their total dietary energy (11% food and drink energy, excluding alcohol) as saturated fats[3]. 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 US Dietary Guidelines Advisory Committee (DGAC) (2015), the Australian Government Department of Health and New Zealand Ministry of Health (2014), the Nordic Council of Ministers (2012), the European Food Safety Authority (EFSA) (2010) and the Food and Agriculture Organization/World Health Organization (FAO/WHO) (2008) 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 8-10% 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 fat 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 it with polyunsaturated fatty acids, reduces total- and LDL-cholesterol levels and the risk of cardiovascular disease (CVD).

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[3] This recommendation does not apply before two years of age, and applies in full from the age of five years. A flexible approach is recommended to the timing and extent of dietary change for individual children between two and five years (COMA, 1994).

4.3   The French Food Safety Agency (AFSSA) reviewed the evidence on dietary fats in 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 observation 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.

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

Organisation	Recommendations for saturated fats	Level of recommendation (population/ unstated)
COMA (1991); (COMA, 1994) (UK)	No more than 10% total dietary energy (11% food and drink energy, excluding alcohol) 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 unsaturated fatty acids	Population
(Australian Government Department of Health and the New Zealand Ministry of Health, 2013) (Australia and New Zealand)	8-10% 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 2-18 years	Population

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

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4.4   The 2015 recommendations of the Health Council of the Netherlands (HCN) 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, diabetes, colorectal cancer and lung 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 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 diet and nutrition in adults and children aged 18 months upwards. Intakes presented in this chapter are based on a UK representative sample of 4738 adults aged 19 years and over and 4636 children aged 1.5-18 years, collected over 6 years between 2008 and 2014[4] (Bates et al., 2016; Bates et al., 2014b). Data are also available for Scotland (Bates et al., 2014a) and Northern Ireland (Bates et al., 2015a) covering the 2008 to 2012 period, and 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 four-day diary. Participants (or a parent/carer for children) were asked to keep a detailed diary of all foods and drinks consumed for four 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, however, in the final data there is a slight over-representation of Fridays and weekend days compared to other days. The LIDNS used an interviewer-led 24 hour recall repeated on four non-consecutive days (Nelson et al., 2007).

5.4 Dietary surveys are reliant on self-reported measures of intake. Misreporting of food consumption, generally under reporting, 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 16-64 years was on average 34% lower than total energy expenditure (TEE) measured by doubly labelled water. The difference for other age groups was similar

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[4] Please note the information will be updated with the NDNS Years 7 and 8 data post-consultation.

except for children aged 4-10 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. 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 saturated fat intakes applies equally to all sources of saturated fats.

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 (the population average intake of saturated fatty acids should not exceed 10% of total dietary energy intake (11% of food and drink energy, excluding alcohol)) for those aged 5 years and over. Mean intakes of saturated fats as a percentage of total dietary energy were 13.3% and 12.5% in children aged 4-10 years (89.3% exceed the DRV) and 11-18 years (84.7% exceed the DRV), respectively. Mean intakes of saturated fats among adults aged 19-64 years were 12.1% (74.5%

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exceed the DRV) and 12.9% (83.3% exceed the DRV) among older adults aged 65 years and over. The actual distribution of intake of saturated fats among adults (19-64 years) is shown in Figure 5.1.
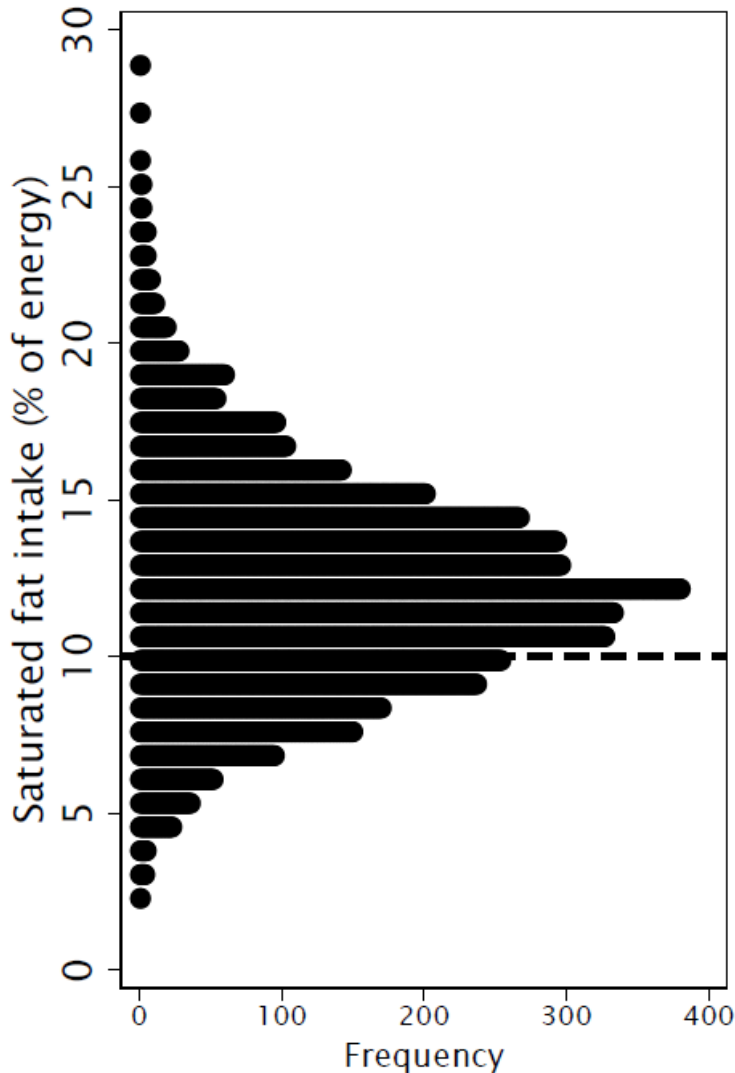
Figure 5.1 The distribution of intake of saturated fats among adults (19-64 years). Data obtained from the NDNS (2008/09 to2013/14).
The horizontal dashed line (--) is the dietary reference value for saturated fats is 10% of total dietary energy (11% of energy from food and drinks excluding alcohol) (COMA, 1994).

5.7   As for the UK as a whole, mean intakes in Scotland, Wales and Northern Ireland exceed the DRV for all age groups.

Contributors to saturated fats intake

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

5.9   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 biscuits, buns, cakes, pastries, fruit pies and puddings), with each food group providing 22% of total saturated fat intake. Fat spreads provided a further 10% of total saturated fat intake (14% in those aged 65 years and over). The main contributors in Scotland, Northern Ireland and Wales were very similar to those in the UK as a whole.

5.10   In children aged 4 to 10 years, milk and milk products (31%) (about half from whole milk and cheese) were the largest contributors to saturated fat intake. Cereals and cereal products (26%) (mainly pasta, rice, pizza, biscuits, buns, cakes, pastries and fruit pies) and meat and meat products (17%) were the other main contributors. For those aged 11 to 18 years, the main contributors to saturated fat intake were cereals and cereal products (27%), milk and milk products (22%) (about half from cheese and semi-skimmed milk) 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 intakes by equivalised household income quintile in the NDNS did not show a consistent pattern across the quintiles. Where differences were seen they were generally in the direction of slightly lower intakes of saturated fats as a percentage of energy in the lowest income quintile. The mean intakes in all income quintiles exceeded the DRV for saturated fat (Bates et al., 2014b).

5.12   In the UK LIDNS (2003 to2005), 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 2008-2012 reported intakes s in the

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general population. It is possible that these differences may be more related to temporal changes in saturated fat intake than socio-economic status.

5.13   Analysis of intakes by equivalised household income quintile and by index of multiple deprivation in Scotland, Northern Ireland and Wales, also show no consistent pattern.

Polyunsaturated fats (n-3 and n-6) intakes in the UK

5.14   Mean intakes of 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 n-6 PUFA 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). The DRV for PUFA (a mixture of n-3 PUFA and n-6 PUFA) is 6% of total dietary energy.

Monounsaturated fats intakes in the UK

5.15   Mean intakes of monounsaturated fats (MUFA) provided 12% of total energy for children aged 4 to 10 years and 12% for adults aged 19 to 64 years (Annex 3, Table A3.4). The DRV for MUFA is 12% of total dietary energy as a population average (COMA, 1991).

Summary

5.16   Available survey data indicated 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) were the leading contributors. There was no consistent pattern in saturated fat intake by household income.

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6   Temporal trends

Average daily intake of saturated fats among adults

6.1   The long term trends of saturated fats intakes among adults are shown in Annex 3, Tables A3.5 and A3.6. Between 1986/87 and 2008/14 mean daily saturated fat intake among adults decreased from approximately 16% to 12% of total energy.

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

6.2   There has been little change between 1986/87[5] and 2008/14 in the main sources of saturated fats. Cereal and cereal products (half from biscuits, buns, cakes, pastries and fruit pies), milk and milk products (less than half from cheese) and meat and meat products being the main contributors across all survey years, each providing around 22% (Annex 3, Tables A3.7 and A3.8). Although there was a marked decline in the contribution of whole milk (from approximately 11% to 2% of average daily saturated fats 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 mainly due to a decreased intake of butter, especially among adults aged 19-64 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 saturated fat content of food purchases at household level is available from the Family Food module of Defra's (Department of Environment, Food and Rural Affairs) 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 nutrient content as a proxy for nutrient intake. Although less detailed than the NDNS,

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

and with different methodology, the reported estimates and trends are broadly consistent.

6.4   Data from household purchases or household and eating out food and drink confirm a long term decline in saturated fats as percentage of energy, from 18.6% in 1974 to 14.1% in 2014 (Defra, 2014b; Defra, 2014a) (Annex 3, Figures A3.1 and A3.2).

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 1986/7 to 0.5% to 2012/14 (in line with the dietary reference value (DRV) that intakes should not exceed 2% of food energy) (Annex 3, Tables A3.9 and A3.10).

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 2012/14. This reflects the reduction in the content of manufactured trans fats of the food supply over this period (Annex 3, Table A3.11).

6.7   In the early to mid-1990s, the analysis of composite samples of fat spreads, including products based on unsaturated fat, found that samples typically contained 2-8g trans fat per 100g product. More recent data (2009/10) indicate that reduced and low fat spreads had much lower trans fat levels (Annex 3, Table A3.12.

Average daily intake of dietary cholesterol among adults

6.8   In adults aged 19-64 years mean dietary cholesterol intake decreased from 390mg/day in men and 280mg/day in women in 1986/87 to 263mg/day in men and 219mg/day in 2012/14 (Annex 3, Table A3.13).

Blood lipids analysis among adults by sex and age

6.9   Trends in blood lipids between 1986/87 and 2008/14 among adults are shown in Annex 3, Tables A3.14 and A3.15 There has been virtually no change in mean serum total

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cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol among adults (19 to 64 years) and older adults (aged 65 years and over). The NDNS data between 2008 and 2014 showed that recommendations for mean serum total cholesterol (5mmol/L or less for healthy adults)[6], mean serum LDL cholesterol (3mmol/L or less for healthy adults)[6] and mean serum HDL cholesterol (1mmol/L or above)[6] were almost met among adults (19 to 64 years) and men aged 65 years and over. Females aged 65 years and over exceeded the recommendation for serum total cholesterol (mean 5.32mmol/L) and serum LDL cholesterol (mean 3.2mmol/L). To note, mean serum 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 2008/14 surveys. In earlier surveys, non-fasting blood samples were used and values for serum LDL cholesterol were not corrected for plasma triglycerides.

Summary

6.10   Between 1986/87 and 2008/12 saturated fat intakes as a percent of energy has decreased in adults but still remained above the DRV. The main sources of saturated fats showed little change over time. Cereal and cereal products (about half from biscuits, buns, cakes, pastries and fruit pies), milk and milk products (about half from cheese) and meat and meat products have remained the top contributors 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. The intake of trans fats and cholesterol has decreased among adults.

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

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7   Background on health outcomes, intermediate markers and risk factors

Background

7.1   Outcomes were considered if there was an adequate evidence base, a significant disease burden, and a plausible potential link with saturated fats. The relationships between saturated fat intake and cardio-metabolic outcomes, body weight change, cancers 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 review 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 has been reviewed.

Dietary fats and blood lipids

7.3   Serum (or plasma) cholesterol is measured in millimoles per litre, often shortened to mmol/L. As a general guide, 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 lipoproteins (LDL) concentration should be 3mmol/L or less for healthy adults and 2mmol/L or less for those at high risk of CVD. An ideal concentration of high density lipoproteins (HDL) should be above 1mmol/L. A lower concentration of HDL can increase the risk of heart disease[7]. 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

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

in this tool is the ratio of total cholesterol:HDL cholesterol from a non-fasting blood sample[8].

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

7.5   Higher concentrations of cholesterol in LDL particles are associated with increased risk of developing CVD including atherosclerosis, myocardial infarction (MI) and stroke. Dietary treatments and pharmaceutical intervention (for example, statins) which reduce the LDL cholesterol have been consistently shown to reduce CVD. NICE recommends that people with a 10% chance of developing CVD in the next 10 years should be offered lipid-lowering drugs (e.g. statins)[8]. 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).

7.6   Increased concentration of cholesterol in HDL particles has been associated with reduced risk of CVD. The hypothesised mechanism relates to the role of HDL in transporting cholesterol from blood to the liver. However, this association has not been found in all studies.

7.7   Trans fats are associated with increased risk of developing CVD. This is in part mediated by increased consumption of trans fats being associated with increased concentrations of LDL and reduced concentrations of HDL cholesterol in blood.

7.8   COMA based their recommendations for saturated fat intakes on the effect on LDL cholesterol concentrations. At the time the recommendations were made, the

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

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This is a draft report and does not necessarily represent the final views of the Scientific Advisory Committee on Nutrition, or the advice/policy of Public Health England and UK Health Departments.

importance of HDL cholesterol was not fully understood. The ratio of total cholesterol:HDL cholesterol has subsequently become more widely used in clinical practice and is the primary lipid parameter in the QRISK2 assessment to predict CVD risk[9].

Cardiovascular diseases

7.9   Cardiovascular diseases are generally categorised into 3 types: coronary heart disease (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 69,000 deaths each year (BHF, 2015). The number of people dying from CHD has decreased from approximately 180,000 deaths per year in 1981 to 56,493 in 2015 (BHF, 2017; BHF, 2011). Between 1981 and 2015, the number of deaths from stroke in men and women declined from 80,000 to 32,627 deaths per year (BHF, 2017; BHF, 2011).

7.10   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

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

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

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) which it can support and is conventionally recorded as systolic pressure over diastolic pressure (SACN, 2003). Ideal blood pressure is considered to be between 90/60 mmHg and 120/80mmHg. High blood pressure is considered to be 140/90 mmHg or higher.

7.13 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).

Type 2 diabetes and markers of glycaemic control

7.14 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).

7.15 Plasma glucose concentration or measurement of glycated haemoglobin (HbA1c) may be 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 (American Diabetes Association and National Institute of Diabetes Digestive and Kidney Diseases, 2002; Pi-Sunyer et al., 2007).

7.16 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

7.17 The prevalence of obesity (body mass index (BMI) 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 27% in 2015 (Health and Social Care Information Centre, 2016). Obesity is associated with a range of health problems including type 2 diabetes, CVD and cancer.

7.18 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).

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

7.20   BMI, both underweight and obesity, is an independent predictor of many adverse perinatal outcomes including preeclampsia, 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

7.21   Cancer is a leading cause of death in many populations. In the UK, 352,197 cases of cancer were diagnosed in 2013, equating to 605 people per 100,000 of the population. Breast, prostate, lung and bowel cancers together accounted for over half (53%) of all new cancer cases. In 2014 there were around 163,000 cancer deaths in the UK, of which lung, bowel, 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).

7.22   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.

7.23   It has been estimated that over 40% of cancers in the UK would be preventable through risk factor modification, with the most important modifiable risk factors being smoking, viruses, obesity, diet, alcohol, physical activity and sunlight exposure (Cancer Research UK, 2016).

Cognitive impairment and dementias

7.24   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 WHO disease groupings, ahead of ischemic heart disease (11.5%) (ONS, 2016).

7.25   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[10]; frontotemporal dementia and mixed dementia. Alzheimer's disease accounts for an estimated 60% of cases (Qiu et al., 2007).

7.26   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.

7.27   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.

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[10] 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 Intermediate markers and risk factors, and their associated health outcomes

Risk factors and intermediate markers	Health outcomes
Fasting blood lipid concentrations: Increased serum total cholesterol Increased serum LDL cholesterol Reduced HDL cholesterol Increased total cholesterol:HDL cholesterol Increased serum triacylglycerol	Cardiovascular diseases, cognitive impairment and dementias
Blood pressure: Increased blood pressure Increased systolic blood pressure Increased diastolic blood pressure	Cardiovascular diseases and renal impairment
Glycaemic control: Increased fasting glucose Increased fasting insulin Increased HbA1c Impaired glucose tolerance Increased insulin resistance	Type 2 diabetes and cardiovascular diseases
Anthropometrics: Increased body weight Increased BMI Increased 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 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   Seventeen systematic reviews, 11 with meta-analyses and 6 without meta-analyses examined the relationship between saturated fats and cardiovascular diseases (Harcombe et al., 2016b; Harcombe et al., 2016a; Ramsden et al., 2016; de Souza et al., 2015; Harcombe et al., 2015; Hooper et al., 2015; Chowdhury et al., 2014; Farvid et al., 2014; Schwab et al., 2014; Ramsden et al., 2013; Micha & Mozaffarian, 2010; Mozaffarian et al., 2010; Siri-Tarino et al., 2010; Jakobsen et al., 2009; Mente et al., 2009; Skeaff & Miller, 2009; Van Horn et al., 2008). The Hooper et al. (2015) review included virtually all randomised controlled trials (RCTs) included in other studies. 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.

Total cardiovascular diseases (CVD)

Saturated fat intake and CVD

8.3   Five systematic reviews, 3 with meta-analyses (de Souza et al., 2015; Hooper et al., 2015; Siri-Tarino et al., 2010) and 2 without meta-analyses (Schwab et al., 2014; Van Horn et al., 2008) examined the relationship between reduced intake of saturated fat 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 2 assessed the results from both RCTs and PCS (Schwab et al., 2014; Van Horn et al., 2008).

Randomised controlled trials

8.4   One comprehensive Cochrane systematic review and meta-analysis of RCTs (Hooper et al., 2015) and 1 systematic review without meta-analysis (Van Horn et al., 2008) assessed the effect of saturated fat intake on CVD mortality and CVD events.

8.5   On CVD mortality, Hooper et al. (2015) analysed 10 RCTs and found no effect of saturated fat reduction compared with usual diet after a mean follow-up of 53 months using a random-effects model (RR[11] 0.95, 95% CI 0.80 to 1.12; p=0.51; I^2 =30%; 10 RCTs; 53,421 participants, 1096 CVD deaths). This was also the case for fixed-effect models: Mantel-Haenszel (RR 0.95, 95% CI 0.85 to 1.07; p>0.05; I^2 =30%; 10 RCTs; 53,421 participants, 1096 CVD deaths) and Peto (RR 0.95, 95% CI 0.84 to 1.08; p>0.05; I^2 =41%; 10 RCTs; 53,421 participants, 1096 CVD deaths). 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 saturated fat intake compared with usual diet, using a random-effects model (RR 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

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[11] Relative risk

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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). Mean intakes of saturated fats reported in each RCT are summarised in Annex 2, Figure A2.2.

8.7   Van Horn et al. (2008) in a systematic review of 83 primary studies and 19 review articles concluded that low intake of saturated fats (<7% of total energy) resulted in reduced risk of CVD, although no meta-analysis was performed in this paper and discussion was based predominantly on the impact of diets on circulating lipids.

Prospective cohort studies

8.8   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).

8.9   Siri-Tarino et al. (2010), in a systematic review and meta-analysis of 21 PCS found no association between saturated fats and CVD mortality when comparing the highest with the lowest quartiles of saturated fat intake, using a random-effects model (RR 1.00, 95% CI 0.89 to 1.11; p=0.95; I^2 =56%; 21 PCS; 347,747 participants, 11,006 CVD events). Fifteen of the 21 included PCS adjusted for energy intake. The findings were similar between genders and age (under and over 60 years of age) (Siri-Tarino et al., 2010).

8.10   de Souza et al. (2015) in a systematic review and meta-analysis compared 3 PCS with lower saturated fat intakes (<14% of energy) with 2 PCS with higher saturated fat intakes (≥14% of energy). They found no association between saturated fat intake and CVD mortality using a random-effects model (RR 0.97, 95% CI 0.84 to 1.12; p=0.69; I^2 =19%; 3 PCS; 90,501 participants, 3,792 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, Japan Collaborative Cohort (JACC), which included 58,672 men and women, living in Japan who consumed relatively low saturated fat (7.3% of energy in the highest quintile compared to 3.0% of energy in the lowest quintile).

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8.11   Similar conclusions of no association between saturated fats and CVD mortality were given in a systematic review of 5 PCS (Schwab et al., 2014).

8.12   In summary, Hooper et al. (2015) concluded that there was no effect of saturated fats on CVD mortality using both random-effects and fixed-effect models. This evidence was considered as *adequate* due to the high number of studies and reported CVD cases. However, a significant reduction in CVD events was reported using both random-effects and fixed-effect models (Hooper et al., 2015). This evidence was considered as *adequate* due to the high number of studies and reported CVD events. No association between saturated fat intake and CVD mortality was reported in the most comprehensive meta-analysis of PCS, which included 21 studies and 53,300 participants (Siri-Tarino et al., 2010). In addition, no association was reported in the most up to date analysis (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). This evidence was considered as *adequate*. *Insufficient* evidence was identified from PCS on saturated fat intake and CVD events.

Saturated fat intake 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
- *Insufficient* evidence

Substitution of saturated fats with polyunsaturated fats (PUFA) (or unsaturated fats) and CVD

8.13 Four systematic reviews, 2 with meta-analyses (Hooper et al., 2015; Ramsden et al., 2013) and 2 without meta-analyses (Schwab et al., 2014; Van Horn et al., 2008) examined the relationship between substitution of saturated fats with PUFA or unsaturated fats (combination 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 2 assessed the results from both RCTs and PCS (Schwab et al., 2014; Van Horn et al., 2008).

Randomised controlled trials

8.14 The comprehensive Cochrane systematic review and meta-analysis of 7 RCTs (Hooper et al., 2015) found no effect of saturated fats substitution with PUFA on CVD mortality using a random-effects meta-regression (RR 0.95, 95% CI 0.73 to 1.25; p>0.05; I^2 =55%; 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-

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effects meta-regression (RR 0.73, 95% CI 0.58 to 0.92; p<0.05; I^2 =69%; 7 RCTs; 3895 participants, 884 CVD events) (Hooper et al., 2015).These analyses did not separate the effects of different types of PUFA (i.e. n-3 and n-6 PUFA).

8.15　Ramsden et al. (2013) analysed 7 RCTs published between 1965 and 1994. It was reported that substitution of PUFA for saturated fats had no effect on CVD mortality (HR 0.97, 95% CI 0.82 to 1.15; p=0.74; I^2 =45%; 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 (HR 1.27, 95% CI 0.98 to 1.65; p=0.07; I^2 =22%; 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 replaced with n-6 and n-3 PUFA (combined) or n-3 PUFA alone (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).

8.16　 Schwab et al. (2014), in their systematic review without meta-analysis, reported on 24 RCTs, focusing on evidence published after 2000. This reported on the effect of saturated fats substitution with unsaturated fats (PUFA or MUFA) on CVD events. The authors reported a 14% reduction in RR of CVD events (RR 0.86, 95% CI 0.77 to 0.96; p=0.07; I^2 =50%; 24 RCTs; 65,508 participants, 4586 CVD events). There was no effect of saturated fat change on CVD mortality (RR 0.94, 95% CI 0.85 to 1.04; p=0.23; I^2 =0%; 16 RCTs; 65,978 participants, 1407 CVD deaths).

8.17　A systematic review by Van Horn et al. (2008) reported a reduced risk of CVD when saturated fats were substituted with unsaturated fats including MUFA (<20% of energy) and PUFA (<10% of energy). However, it was unclear on which of the included RCTs this statement was based and no meta-analysis was performed.

Prospective cohort studies

8.18 Evidence from systematic reviews of PCS indicate a reduction in CVD mortality when saturated fats were substituted with PUFA (Schwab et al., 2014; Van Horn et al., 2008) or a combination of MUFA and PUFA (Schwab et al., 2014), however there was no formal meta-analysis of these data which limits their quality.

8.19 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.

8.20 In summary, the comprehensive Cochrane systematic review and meta-analysis (Hooper et al., 2015) reported a 27% lower risk of CVD events following substitution of saturated fats with PUFA. There was no effect on CVD mortality. These findings were consistent with the results of other systematic reviews of RCTs and the evidence was considered *adequate*. 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 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 PUFA and MUFA on CVD mortality
- *Limited* evidence
- The direction of the association indicates that substitution of saturated fats with PUFA or PUFA and MUFA lowers CVD mortality

CVD events
- No evidence

Substitution of saturated fats with MUFA and CVD

8.21   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

8.22   Hooper et al. (2015) identified one trial (n=52 participants) that investigated the effect of saturated fats substitution with MUFA on CVD outcomes. The trial reported no effect on CVD mortality but this was based on 4 CVD deaths (RR 3.0, 95% CI 0.33 to 26.99; p>0.05; I^2 NA; 1 RCT; 52 participants, 4 CVD deaths). The trial also reported no effect on CVD events (RR 1.00, 95% CI 0.53 to 1.89; p>0.05; I^2 NA; 1 RCT; 52 participants, 22 CVD events).

8.23   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 carbohydrate and CVD

8.24   Three systematic reviews, 1 with meta-analysis (Hooper et al., 2015) and 2 without meta-analyses (Schwab et al., 2014; Van Horn et al., 2008) examined the relationship between substitution of saturated fats with carbohydrate and CVD. One systematic review analysed the results from RCTs (Hooper et al., 2015) and 2 evaluated the results from both RCTs and PCS (Schwab et al., 2014; Van Horn et al., 2008).

Randomised controlled trials

8.25   Hooper et al. (2015) found in a systematic review and meta-analysis of 6 RCTs, no effect on CVD mortality following substitution of saturated fats with carbohydrate at a mean follow-up of 46 months using a random-effects model (RR 0.99, 95% CI 0.86 to 1.14; $p>0.05$; $I^2 =0\%$; 6 RCTs; 51,232 participants, 745 CVD deaths). They also reported no effect on CVD events using a random-effects model (RR 0.93, 95% CI 0.79 to 1.08; $p>0.05$; $I^2 =57\%$; 6 RCTs; >51,000 participants, 3785 events) (Hooper et al., 2015). The analysis did not stratify by carbohydrate type and the analysis heavily relied on data from the Women's Health Initiative, which did not explicitly test the effect of substitution of saturated fats with carbohydrate.

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Prospective cohort studies

8.26   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 carbohydrate 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 carbohydrate (defined in paper as high glycaemic index), but not complex carbohydrate (low glycaemic index) (1 PCS). These outcomes were supported by comments in a systematic review by Van Horn et al. (2008).

8.27   In summary, the data from RCTs included in a systematic review and meta-analysis by Hooper et al. (2015) indicated no effect of saturated fats substitution with carbohydrate on CVD mortality or CVD events. The evidence was classed as *limited* as it heavily relied on the Women's Health Initiative, which did not explicitly test the effect of substitution of saturated fats with carbohydrate. There was also no information on carbohydrate 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 carbohydrate 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 protein and CVD

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

Randomised controlled trials

8.29   Hooper et al. (2015) considered the effect of substituting saturated fats with protein, based on 5 RCTs with a mean 48 month follow-up. They found no effect on CVD mortality using a random-effects model (RR 0.99, 95% CI 0.86 to 1.14; p>0.05; I^2 =0%; 5 RCTs; 51,177 participants, 741 CVD deaths). They also found no effect on CVD events using a random-effects model (RR 0.98, 95% CI 0.90 to 1.06; p>0.05; I^2 =15%; 5 RCTs; 51,177 participants, 3757 CVD events). The results relied heavily on a study on the Women's Health Initiative, which did not explicitly test the effect of saturated fats substitution with protein.

8.30   In summary, the data from RCTs showed no effect of saturated fats substitution with protein on CVD mortality or CVD events. The evidence was classed as *limited* due 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 protein.

Saturated fats substitution with protein 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)

Saturated fat intake and CHD outcomes

8.31   Nine systematic reviews, 7 with meta-analyses (Harcombe et al., 2016b; de Souza et al., 2015; Harcombe et al., 2015; Hooper 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. Three systematic reviews analysed the results from RCTs (Harcombe et al., 2016b; Harcombe et al., 2015; Hooper et al., 2015) and 6 evaluated the results from PCS (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

8.32   Of the identified reviews, 3 included data on CHD outcomes from 6 to 12 RCTs (Hooper et al., 2015; Harcombe et al., 2015; Harcombe et al., 2016b).

8.33   Harcombe et al. (2015) included data from 6 RCTs; 5 secondary prevention trials and 1 including healthy participants, with between 2 and 11 years follow-up. It was reported

that there was no difference between lower saturated fats (intervention) groups compared with higher saturated fats (control) groups on CHD mortality using a random-effects model (RR 0.99, 95% CI 0.78 to 1.25; p>0.05; I^2 =31%; 6 RCTs; 2467 participants, 423 CHD deaths). However, the included papers were all published before 1978, excluding more recent data.

8.34   A follow-up paper by 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 published between 1965 and 2006. These included all of the studies in the review discussed in paragraph 8.33. There was no effect of saturated fats on CHD mortality using a random-effects model (RR 0.98, 95% CI 0.88 to 1.08; p>0.05; I^2 =0%; 10 RCTs; 62,421 participants, 1218 CHD deaths).

8.35   In the Cochrane systematic review and 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 consumption on MI (fatal and non-fatal) after a mean 52 month follow-up using a random-effects model (RR 0.90, 95% CI 0.80 to 1.01; p=0.09; I^2 =10%; 11 RCTs; 53,167 participants, 1714 cases). Similar results were reported when using a Mantel-Haenszel fixed-effect model (RR 0.92, 95% CI 0.84 to 1.01; p>0.05; I^2 =10%; 11 RCTs; 53,167 participants, 1714 cases) and Peto fixed-effect model (RR 0.92, 95% CI 0.83 to 1.01; p>0.05; I^2 =31%; 11 RCTs; 53,167 participants, 1714 cases). Results were unchanged by sensitivity analysis.

8.36   Hooper et al. (2015) reported no effect of reduced consumption of saturated fats compared with usual intakes on non-fatal MI after a mean 55 month follow-up using a random-effects model (RR 0.95, 95% CI 0.80 to 1.13; p=0.57; I^2 =27%; 9 RCTs; 52,834 participants, 1348 cases). Similar results were reported when using a Mantel-Haenszel fixed-effect model (RR 0.94, 95% CI 0.85 to 1.05; p>0.05; I^2 =27%; 9 RCTs; 52,834 participants, 1348 cases) and a Peto fixed-effect model (RR 0.94, 95% CI 0.84 to 1.05; p>0.05; I^2 =27%; 9 RCTs; 52,834 participants, 1348 cases). Results were not changed by sensitivity analysis.

8.37   Hooper et al. (2015) reported no effect of reduced consumption of saturated fats compared with usual intakes on CHD mortality after a mean 65 month follow-up using a random-effects model (RR 0.98, 95% CI 0.84 to 1.15; p=0.78; I^2 =21%; 10 RCTs; 53,159 participants, 886 cases). Similar results were reported when using a Mantel-Haenszel fixed-effect model (RR 0.98, 95% CI 0.86 to 1.12; p>0.05; I^2 =21%; 10 RCTs; 53,159 participants, 886 MI cases) and a Peto fixed-effect model (RR 0.98, 95% CI 0.85 to 1.13; p>0.05; I^2 =21%; 10 RCTs; 53,159 participants, 886 MI cases). Results were not changed by sensitivity analysis. Mean intakes of saturated fats from individual RCTs are summarised in Annex 2, Figure A2.3.

8.38   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 sensitivity analysis. However, analysis using fixed-effect models indicated that reducing saturated fats compared with usual intake resulted in a 7-8% 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). 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 the random-effects model. Mean intakes of saturated fats from individual RCTs are summarised in Annex 2, Figure A2.4.

Prospective cohort studies

8.39   There were 6 systematic reviews that included data on CHD outcomes from 3 to 20 PCS (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).

8.40   de Souza et al. (2015) performed the most recently published systematic review and meta-analysis of 11 PCS with 15 comparisons and reported no association between the

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highest and lowest intakes of saturated fats and CHD mortality for the most adjusted multivariable ratio[12] using a random-effects model (RR 1.15, 95% CI 0.97 to 1.36; p=0.10; I^2 =70%; 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 (RR 1.06, 95% CI 0.95 to 1.17; p=0.29; I^2 =47%; 12/17 (PCS/comparisons); 267,416 participants, 6383 CHD deaths).

8.41   Chowdhury et al. (2014) performed the most comprehensive systematic review and meta-analysis on 20 PCS, comparing tertiles of saturated fat intake with a follow-up of 5 to 20 years. No association was found with CHD outcomes when comparing the top tertile of saturated fat intakes with the bottom tertile using a random-effects model (RR 1.02, 95% CI 0.97 to 1.07; p=0.058; I^2 =35.5%; 20 PCS; 283,963 participants, 10,518 cases). However, a significantly increased risk of CHD outcomes with higher saturated fat intake was found when using a fixed-effect model (RR 1.04, 95% CI 1.01 to 1.07; p<0.05; 20 PCS; 283,963 participants, 10,518 cases).

8.42   Siri-Tarino et al. (2010) performed a systematic review and meta-analysis on 16 PCS with follow-ups of 6 to 23 years. No association was found between upper and lower quartiles of saturated fats intake and CHD using a random-effects model (RR 1.07, 95% CI 0.96 to 1.19; p=0.22; I^2 =41%; 16 PCS; 214,182 participants). There was also no association when saturated fat intakes were adjusted for total energy intake, energy from protein, energy from carbohydrate, and energy from fats.

8.43   Skeaff & Miller (2009) performed a systematic review and meta-analysis on associations with low (7-11 % total energy) versus high (14-18 % total energy) intakes of saturated fats, using random-effects models. There was no association with CHD mortality at 5 to 16 years follow-up (RR 1.14, 95% CI 0.82 to 1.60; p=0.431; I^2 =72%; 6 PCS; 80,655 participants, 1313 CHD deaths) or CHD events at 5 to 20 years follow-up (RR 0.93, 95% CI

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

0.83 to 1.05; p=0.269; I^2 =0.1%; 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 (RR 1.11, 95% CI 0.75 to 1.65; p=0.593; I^2 =63%; 2 PCS; 46,695 participants, 367 CHD deaths) or CHD events (RR 1.03, 95% CI 0.87 to 1.22; p=0.723; I^2 =34%; 3 PCS; 126,221 participants, 2826 CHD events).

8.44   Harcombe et al. (2016a) included data from 6 PCS, all published before 1982, involving 31,445 participants and 360 CHD deaths with a mean follow-up of 6.2 to 7.5 years. No meta-analysis was performed and it was reported that none of the studies found an association between CHD death and intakes of saturated fats.

8.45   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 (RR 1.06, 95% CI 0.96 to 1.15; p>0.05; 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).

8.46   In summary, evidence from the most recent systematic review and 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 and meta-analysis performed according to the Cochrane protocol, Hooper et al. (2015) reported on both CHD mortality and events. In agreement with Harcombe et al. (2015), there was no significant effect on CHD deaths when using a random-effects model. The committee considered the evidence on CHD mortality *adequate* for no effect. However, it was noted that, for this type of outcome, the study design may have been confounded due to short follow-up and low numbers of CHD deaths. Hooper et al. (2015) also found no effect on CHD events when using a random-effects model. However, when Hooper et al. (2015) performed sensitivity analysis and repeated the meta-analysis using two fixed-effect models (Peto and Mantel-Haenszel), this indicated a statistically significant effect on CHD events. In addition, Hooper et al.

(2015) performed a number of sensitivity analyses, including removing the largest study (Women's Health Initiative), and this resulted in no difference in reported effects. The committee noted that the random-effects and fixed-effect models gave the same direction of effect, but different P-values (random >0.05, fixed <0.05). The committee, on balance, therefore considered these data on reduced saturated fat intake and lower RR for CHD events to be *moderate* evidence. Despite the large number of studies and large numbers of events, the committee did not consider the evidence *adequate* due to the differing P values from random-effects and fixed-effect models.

8.47   Regarding observational data, both the most recent de Souza et al. (2015) and most comprehensive systematic review and meta-analysis 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 saturated fat intake (Chowdhury et al., 2014). The committee noted that the random-effects and fixed-effect models were in the same direction of effect, it was only their significance that differed (random >0.05, fixed <0.05). The committee, on balance, therefore considered these data to be *moderate* evidence. 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.

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

8.48   Seven systematic reviews, 4 with meta-analyses (Ramsden et al., 2016; Hooper et al., 2015; Farvid et al., 2014; Skeaff & Miller, 2009), 1 without meta-analysis (Micha & Mozaffarian, 2010) 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. Five systematic reviews analysed the results from RCTs (Ramsden et al., 2016; Hooper et al., 2015; Micha & Mozaffarian, 2010; 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

8.49   Five 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; Micha & Mozaffarian, 2010; Mozaffarian et al., 2010; Skeaff & Miller, 2009).

8.50   Hooper et al. (2015) reported on the most comprehensive systematic review and 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 (RR 0.83, 95% CI 0.67 to 1.02; >3000 participants, 591 events). There was also no effect on CHD mortality (RR 0.98, 95% CI 0.74 to 1.28; 4000 participants, 491 cases). However, there was a 24% reduction in CHD events (RR 0.76, 95% CI 0.57 to 1.00; >3000 participants, 737 events).

8.51   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 (RR 0.84, 95% CI 0.62 to 1.12; p=0.867; I^2=12.4%; 5 RCTs; 4528 participants, 284 deaths) but reduced the risk for CHD events (RR 0.83, 95% CI 0.69 to 1.00; p=0.05; I^2=44.2%; 8 RCTs; 4528 participants, 284 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 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 events).

8.52   Mozaffarian et al. (2010) reported on a pooled analysis of 8 RCTs (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 consumption 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. There was no evidence for statistical heterogeneity (Q-statistic p =0.13; I^2=37%).

8.53 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.

8.54 In a systematic review without meta-analysis, Micha & Mozaffarian (2010) concluded that substitution of saturated fats with PUFA modestly decreased CHD risk, with around 10% reduction in risk with a 5% energy substitution (RR 0.90, 95% CI 0.83 to 0.97).

Prospective cohort studies

8.55 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

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

8.57 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 carbohydrate. 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).

8.58 Farvid et al. (2014), in a systematic review with meta-analysis of 13 PCS with 310,602 participants, reported on the substitution of saturated fats with dietary linoleic acid (n-6 PUFA). Increasing percent of energy from linoleic acid (by 5%) instead of saturated fats 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 similar using a random-effects model (RR 0.86, 95% CI 0.76 to 0.97). There was a 9%

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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 non-significant using a random-effects model (RR 0.90, 95% CI 0.80 to 1.01).

8.59   In summary, the evidence from the most recent meta-analysis of RCTs (Hooper et al., 2015) found no effect of saturated fats substitution with PUFA on CHD mortality, but did find a significant effect on CHD events. The evidence was deemed as *adequate* for CHD mortality and *limited* for CHD events, based on an adequate number of studies and events, consistency with the outcome of Mozaffarian et al. (2010), but an upper confidence interval from Hooper et al. (2015) of exactly 1.00.

8.60   There was *adequate* data from PCS indicating reduced CHD outcomes when substituting saturated fats with PUFA. The modelling by Jakobsen et al. (2009) in particular showed a significant decrease in CHD events and mortality.

Saturated fats substitution with PUFA and CHD outcomes

Randomised controlled trials

CHD mortality
- No effect
- *Adequate* evidence

CHD events
- Effect
- *Limited* evidence
- The direction of the effect indicates that substitution of saturated fats with PUFA lowers CHD events

Prospective cohort studies

CHD mortality
- Association
- *Adequate* evidence
- The direction of the association indicates that substitution of saturated fats with PUFA lowers CHD mortality

CHD events
- Association
- *Adequate* 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

8.61   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

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

8.63   Hooper et al. (2015) reported that in 1 RCT, substitution of saturated fats with MUFA did not affect fatal or non-fatal MI (RR 1.40, 95% CI 0.51 to 3.85; 52 participants, 12 events). There was also no effect on non-fatal MI alone (RR 1.20, 95% CI 0.42 to 3.45; 52 participants, 11 events) or CHD mortality (RR 3.33, 95% CI 0.33 to 26.99; 52 participants, 11 events). There was no reduction in CHD events (RR 0.55, 95% CI 0.62 to 3.61; 52 participants, 15 events).

8.64   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

8.65   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.

8.66   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 carbohydrate. 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 (HR 1.01, 95% CI 0.73 to 1.41). Jakobsen et al. (2009) noted that there may have been confounding by trans fats intakes, as the major sources of MUFA in the studies considered were dairy, meat, and partially hydrogenated oils.

8.67   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 fat 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 carbohydrate and CHD outcomes

8.68   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 carbohydrate 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

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

8.70   Hooper et al. (2015) reported that in 10 RCTs, subgrouping based on substitution of saturated fats with carbohydrate did not suggest any effect on fatal and non-fatal MI (RR 0.96, 95% CI 0.86 to 1.06; 10 RCTs; >51,000 participants, 1392 events). There was also no effect on non-fatal MI alone (RR 0.99, 95% CI 0.73 to 1.35; >51,000 participants, 1188

events) or CHD mortality (RR 1.01, 95% CI 0.86 to 1.18; >51,000 participants, 586 deaths). There was no reduction in CHD events (RR 0.98, 95% CI 0.83 to 1.14; >51,000 participants, 2846 events).

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

Prospective cohort studies

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

8.73 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 carbohydrate. The models used are described in detail in their paper. A 5% reduction in saturated fats as a percentage of energy and an equivalent increase in energy from carbohydrate was associated with an increase in CHD events (HR 1.07, 95% CI 1.01 to 1.14) but not CHD deaths (HR 0.96, 95% CI 0.82 to 1.13).

8.74 In summary, evidence from RCTs suggests that there was no effect from substituting saturated fats with carbohydrate on CHD outcomes (Hooper et al., 2015). However, substitution with different types of carbohydrate may have differential effects. The evidence was classed as *limited* due to the inclusion of 3 RCTs for CHD mortality. The evidence was classed as *moderate* for CHD events due to the inclusion of 5 RCTs, one of which was the Women's Health Initiative, which did not explicitly test the effect of substitution of saturated fats with carbohydrate.

8.75 For PCS, conclusions rely on the modelling of Jakobsen et al. (2009), which demonstrates that substitution of saturated fats with carbohydrate 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 carbohydrate 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 carbohydrate increases CHD events

Substitution of saturated fats with protein and CHD outcomes

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

Randomised controlled trials

8.77 Hooper et al. (2015) reported that 4 RCTs of substitution of saturated fats with protein did not indicate any effect on fatal and non-fatal MI using a random-effects model (RR 0.96, 95% CI 0.86 to 1.07; >51 000 participants, 1389 events). There was also no effect on non-fatal MI alone using a random-effects model (RR 0.99, 95% CI 0.73 to 1.35; >51 000 participants, 1188 events) or CHD mortality using a random-effects model (RR 1.01, 95% CI 0.86 to 1.18; >51 000 participants, 586 deaths). There was no reduction in CHD events using a random-effects model (RR 0.99, 95% CI 0.88 to 1.12; >51 000 participants, 2833 events).

8.78   In summary, there was no effect of saturated fats substitution with protein on CHD outcomes. The evidence was deemed to be *limited,* due to the inclusion of only 3 studies in the analysis, one of which was the Women's Health Initiative, which did not explicitly test the effect of saturated fats substitution with protein.

Saturated fats substitution with protein and CHD outcomes

Randomised controlled trials
 	
CHD mortality
    • No effect
    • *Limited* evidence
CHD events
    • No effect
    • *Limited* evidence
 	
Prospective cohort studies
 	
CHD mortality/events
    • No evidence

Strokes

Saturated fat intake and strokes

8.79   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-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 3 evaluated the results from PCS (de Souza et al., 2015; Micha & Mozaffarian, 2010; Siri-Tarino et al., 2010).

8.80   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 (e.g. haemorrhagic or ischaemic), although 1 systematic review and meta-analysis of PCS reported on ischemic stroke only (de Souza et al., 2015).

Randomised controlled trials

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

8.82   A Cochrane systematic review with meta-analysis found no effect of reduction of saturated fats on all fatal or non-fatal strokes when the lowest intakes of saturated fats were compared with usual intake using a random-effects model (RR 1.00, 95% CI 0.89 to 1.12; p>0.05; I^2=0%; 7 RCTs; 50,952 participants, 1125 strokes). This was also the case for fixed-effect analysis (Mantel-Haenszel: RR 0.99, 95% CI 0.89 to 1.11; p>0.05; I^2=0%; 7 RCTs; 50,952 participants, 1125 strokes; Peto: RR 0.99, 95% CI 0.88 to 1.13; p>0.05; I^2 =18%; 7 RCTs; 50,952 participants, 1125 strokes). This did not change with sensitivity analysis (Hooper et al., 2015). Mean intakes of saturated fats from individual RCTs are summarised in Annex 2, Figure A2.5.

Prospective cohort studies

8.83   de Souza et al. (2015) performed the most comprehensive systematic review and meta-analysis on 12 PCS with 15 comparisons. They reported no association between intakes of saturated fats and ischemic stroke mortality for the most adjusted random-effects model (RR 1.02, 95% CI 0.90 to 1.15; p=0.79; I^2 =59%; 12/15 (PCS/comparisons); 339,090 participants, 6226 CVD deaths) and least adjusted models (RR 1.03, 95% CI 0.91 to 1.16; p=0.65; I^2 =66%; 12/15 (PCS/comparisons); 339,090 participants, 6226 CVD deaths). No study was an influential outlier (de Souza et al., 2015).

8.84   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 strokes was observed using a random-effects model (RR 0.81, 95% CI 0.62 to 1.05; p=0.11; I^2 =61%; 8 PCS; 179,436 participants, 2362 strokes). This was the case when extreme quartiles of saturated fat intakes were compared or when saturated fats adjusted for total energy intake, energy from protein, carbohydrate and fats, but not PUFA, were compared.

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

8.86   In summary, no association or effect was identified between the intake of saturated fats and strokes in both RCTs and PCS. The evidence was considered *adequate* as sufficient studies were assessed in the 2 most comprehensive meta-analyses for both RCTs (n=7) (Hooper et al., 2015) and PCS (n=12) (de Souza et al., 2015).

Saturated fat intake and strokes (fatal, non-fatal, all types)
Randomised controlled trials • No effect • *Adequate* evidence *Prospective cohort studies* • No association • *Adequate* evidence

Substitution of saturated fats with PUFA and strokes

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 and meta-analysis of 4 RCTs, no effect of saturated fats substitution with PUFA on strokes (any time and outcome) was identified after a mean follow-up of 63 months using a random-effects model (RR 0.68, 95% CI 0.37 to 1.27; $p > 0.05$; $I^2 = 0\%$; 4 RCTs; 1706 participants, 41 stroke deaths) (Hooper et al., 2015).

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

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 carbohydrate and strokes

8.91   One systematic review with meta-analysis of RCTs (Hooper et al., 2015) examined the effect of substitution of saturated fats with carbohydrate 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 and 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 carbohydrate on strokes using a random-effects model (any time or outcome) (RR 1.01, 95% CI 0.90 to 1.13; $p>0.05$; I^2 =0%; 4 RCTs; 49,066 participants, 1083 strokes).

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

Saturated fat substitution with carbohydrate 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 protein and strokes

8.94 One systematic review with meta-analysis of RCTs (Hooper et al., 2015) examined the effect of substitution of saturated fats with protein 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 protein on strokes using a random-effects model (any time and outcome) (RR 1.01, 95% CI 0.90 to 1.13; p>0.05; I^2 =11%; 3 RCTs; 49,011 participants, 1082 strokes).

8.96 In summary, a meta-analysis of 3 RCTs found no effect of saturated fats substitution with protein on strokes (Hooper et al., 2015). This Cochrane analysis was comprehensive, however relied heavily on the Women's Health Initiative, which did not explicitly test the effect of substitution of saturated fats with protein, therefore the evidence was classed as *limited*.

Saturated fats substitution with protein 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 a robust meta-analysis of 11 RCTs for a 7-17% reduction in CVD events with lower intake of saturated fats compared with usual intake. This effect is observed using both fixed-effect and random-effects models (17% random-effects, 7% Mantel-Haenszel and 8% Peto fixed-effect statistical models).

8.98   There was *moderate* evidence from RCTs for at least an 8% lower risk for CHD events with lower intake of saturated fats compared with usual intake. The direction of effect was consistent for both random-effects and fixed-effect models. However, while the effect size was greater using the random-effects model (RR 0.87, 95% CI 0.74 to 1.03; p=0.07), due to the larger uncertainty in effect size, statistical significance was only reached following fixed-effect analysis (RR 0.92, 95% CI 0.86 to 0.99; p<0.05). 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 a 2 -4% increased risk of CHD outcomes with higher compared with lower saturated fat intake. This was the case using both fixed-effect (RR 1.04) and random-effects (RR 1.02) models.

8.99   There was *adequate* evidence from RCTs and PCS for no effect or association of reducing saturated fats on CHD and CVD mortality and all strokes.

8.100   There was evidence for a differential impact on risk when the macronutrient that substitutes saturated fats is considered. *Adequate* evidence was identified for an effect of

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saturated fats substitution with PUFA on the reduction in risk for CVD events, from RCTs and PCS. In addition, evidence from PCS for a reduction in risk of CVD mortality (*limited*) and CHD mortality (*adequate*) was reported, although this was not supported by data from RCTs. *Insufficient* evidence was available for the effect of saturated fats substitution with PUFA on stroke.

8.101 *Insufficient* evidence 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 carbohydrate on CVD or stroke. However, *adequate* evidence for higher CHD events when saturated fats were substituted with carbohydrate was identified from modelling of PCS. The effect may depend on the type of carbohydrate consumed, but it was not possible to comment further on this due to lack of evidence. Substitution of saturated fats with carbohydrate 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 protein 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 and 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

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extracting information. Mean intakes of saturated fats from individual RCTs that assessed the effect on cardiovascular outcomes are summarised in Annex 3, Figures A2.1 to A2.5.

8.106   Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrate or protein, and cardiovascular outcomes is summarised below in Table 8.1.
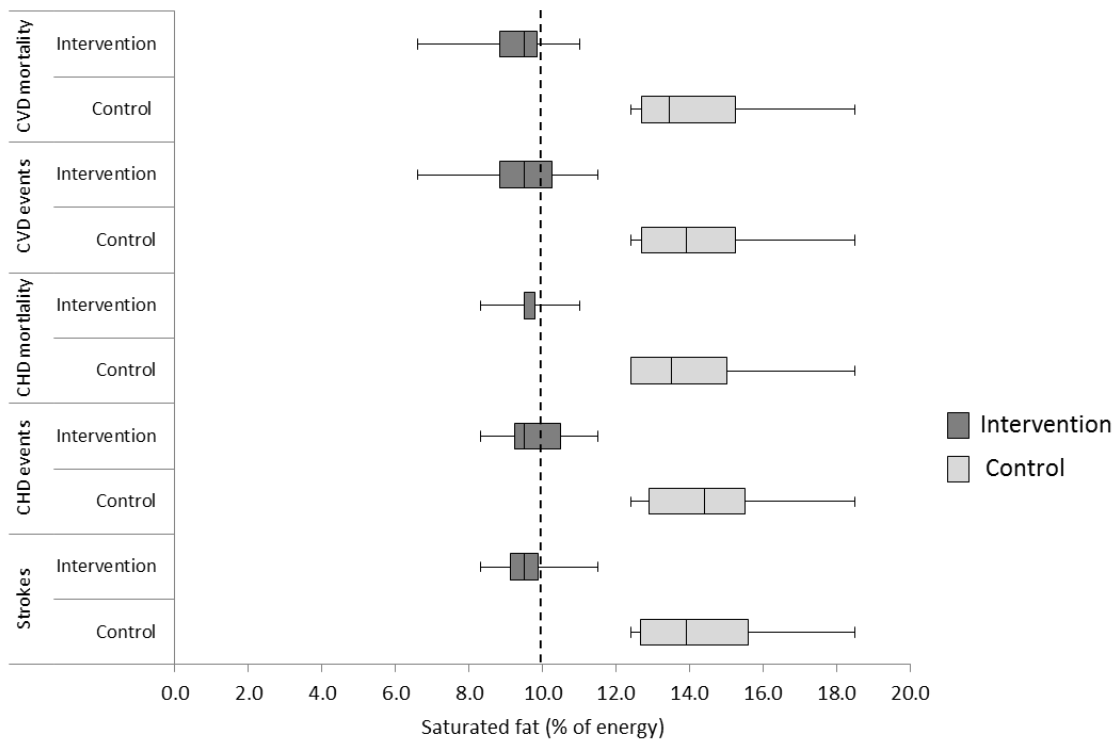
Figure 8.1 Box plots of intakes of saturated fat as percent of total energy intake in control and intervention arms for individual outcomes (Hooper et al., 2015).
The vertical dashed line (---) represents the dietary reference value for saturated fats is 10% of dietary energy (COMA, 1994).

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

Outcome	Saturated fats intake		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrate		Saturated fats substitution with protein	
	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	↓	Limited	n/a	Insufficient	-	Moderate	-	Limited
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	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CVD events	n/a	Insufficient	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CHD mortality	↓	Moderate	↓	Adequate	-	Limited	-	Adequate	n/a	No evidence
CHD events	↓	Moderate	↓	Adequate	↑	Limited	↑	Adequate	n/a	No evidence
Strokes	-	Adequate	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%).

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9   Blood lipids

9.1   Ten systematic reviews, 6 with meta-analyses and 4 without meta-analyses examined the relationship between saturated fats and blood lipids (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; Brunner et al., 1997; 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 carbohydrate) and/or diets where the total calorie intake was decreased. The characteristics of these publications are summarised in Annex 2, Table A2.3. The quality of the meta-analyses and systematic reviews is summarised in Annex 4.

9.2   None of the systematic reviews, meta-analyses or pooled analyses included randomised controlled trials (RCTs) or prospective cohort studies (PCS) where saturated fats in the diet were substituted with protein. Thus, protein supplementation is not considered in this chapter due to an absence of studies that met the inclusion criteria. While the OmniHeart study (Appel et al., 2005) was included in Van Horn et al. (2008) this concerns protein supplementation for carbohydrate, and thus it is difficult to interpret in terms of saturated fats (Appel et al., 2005).

Serum total cholesterol

Saturated fats intake and serum total cholesterol

9.3   Four systematic reviews, 3 with meta-analyses (Hooper et al., 2015; Yu-Poth et al., 1999; Tang et al., 1998) and 1 without meta-analysis (Van Horn et al., 2008) examined the relationship between reduced intake of saturated fats and serum total cholesterol. Three systematic reviews analysed the results from RCTs (Hooper et al., 2015; Yu-Poth et al., 1999; Tang et al., 1998) and 1 evaluated the results from both RCTs and PCS (Van Horn et al., 2008).

Randomised controlled trials

9.4 The most recent 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 saturated fat intake or altering saturated fats. Interventions were at least 24 months in duration. As secondary outcomes they examined the effects of reduced saturated fat intake on serum blood lipids (serum total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride). Hooper et al. (2015) concluded that serum total cholesterol was reduced by a reduction in saturated fat intake 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).

9.5 Tang et al. (1998) examined the effect of dietary advice on lowering serum total cholesterol in a systematic review and meta-analysis of 19 RCTs published before 1996. Interventions were classified according to the American Heart Association National Cholesterol Education Programme (NCEP) Step 1 diet[13] (where saturated fat intake is 8 to 10% of dietary energy) and Step 2 diet[14] (where saturated fat intake 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.

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[13] <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
[14] <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

9.6   Yu-Poth et al. (1999) conducted a systematic review and meta-analysis of 37 RCTs published between 1981 and 1997, to investigate the effects of the American Heart Association 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 decreased serum total cholesterol (mean difference -0.63 ± 0.06 mmol/L (10%), p<0.01 for Step 1 diet (where saturated fat intake is 8 to 10% of dietary energy); mean difference 0.81 ± 0.12 mmol/L (13%), p<0.01 for Step 2 diet (where saturated fat intake is <7% of dietary energy)). Results were the same for males and females. 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[15]=0.59; 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.

9.7   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 provided in the paper).

Prospective cohort studies

9.8   Evidence from PCS was limited to 1 systematic review without meta-analysis considering evidence from PCS alongside results from RCTs (Van Horn et al., 2008). However, the

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[15] Regression coefficient

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main conclusions from the systematic review by Van Horn et al. (2008) focused on RCTs. Thus, the evidence was classed as *insufficient*.

9.9   In summary, *adequate* evidence from RCTs from 3 systematic reviews indicated that reducing saturated fat intake reduces serum total cholesterol. The results of meta-analyses across the publications were statistically significant and a systematic review without meta-analysis came to the same conclusion. The most recent systemic review (Hooper et al., 2015) included 13 RCTs (with 7115 participants), however, in this study serum total cholesterol was a secondary outcome. Taken in their entirety the identified publications were considered to be of good quality. 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 saturated fat intake is ≤7% of dietary energy) reduced serum total cholesterol by 6.1% compared with 3% for the Step 1 diet (where saturated fat intake is 8 to 10% of dietary energy) (Tang et al., 1998). However, a reduction in serum total cholesterol was also significantly associated with weight loss, particularly for studies described by Tang et al. (1998). Evidence from PCS was limited to 1 systematic review without meta-analysis considering evidence from PCS alongside results from RCTs (Van Horn et al., 2008). Thus, the evidence was classed as *insufficient*.

Saturated fats intake 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 and serum total cholesterol

9.10   Five systematic reviews, 3 with meta-analyses (Hooper et al., 2015; Brunner et al., 1997; Clarke et al., 1997) and 2 without meta-analyses (Schwab et al., 2014; Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with PUFA and serum total cholesterol. Three systematic reviews analysed the results from RCTs (Hooper et al., 2015; Micha & Mozaffarian, 2010; Brunner et al., 1997), 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

9.11   In a systematic review and meta-analysis Hooper et al. (2015) reported that serum total cholesterol was reduced by a reduction in saturated fat intake using a random-effects model (mean difference -0.24 mmol/L, 95% CI -0.36 to -0.13; p<0.0001, I² =60%, 13 RCTs, 7115 participants) and the effect of reduction in saturated fats was statistically significant regardless of dietary substitution with PUFA, MUFA or carbohydrate. However, serum total cholesterol was a secondary outcome.

9.12   Brunner et al. (1997) undertook a systematic review and meta-analysis examining how dietary advice to change consumption of total fat, salt and fibre affected serum total cholesterol in 17 RCTs, with trial durations of at least 3 months and comprising of 6893 participants. Only 4 of the 17 included RCTs (588 participants across the 4 RCTs) directly involved a change in saturated fat intake; 1 RCT examined reduced saturated fat intake and 3 RCTs investigated substitution of saturated fats with PUFA. Brunner et al. (1997) reported a reduction in serum total cholesterol following reduction in total fat at 3-6 months using a random-effects model (mean difference -0.28 mmol/L, 95% CI -0.42 to -0.15; p<0.001; 8 RCTs) and at 9-18 months using a random-effects model (mean difference -0.22 mmol/L, 95% CI -0.39 to -0.05; p<0.01; 5 RCTs). However, there was significant heterogeneity across the included RCTs both in terms of effect size and study design.

9.13   In a systematic review and 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 dietary studies ('metabolic ward' experiments where diet was modified in volunteers under clinically controlled conditions) representing 5901 participants/diet measurements. Clarke et al. (1997) concluded that isoenergetic substitution of saturated fats with PUFA produced a decrease in serum total cholesterol (mean difference -0.65 mmol/L, 95% CI -0.73 to -0.57; $p<0.001$).

9.14   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 reduced serum total cholesterol (9 out of 9 RCTs demonstrated this effect, 476 participants, no statistics provided in the paper).

9.15   The systematic review without meta-analysis of Micha & Mozaffarian (2010) studying RCTs reported that increased consumption of PUFA in the diet as a substitution for saturated fats reduced serum total cholesterol (no statistics provided in the paper).

Prospective cohort studies

9.16   Evidence from PCS was limited to 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.

9.17   In summary, *adequate* evidence from systematic reviews of RCTs indicated that substitution of saturated fats with PUFA reduced serum total cholesterol. This was further exemplified in metabolic ward experiments where the effects of saturated fats substitution with PUFA were examined under highly controlled conditions. The results of meta-analyses across the publications were statistically significant and systematic reviews without meta-analyses agreed with this outcome. The most recent systemic review (Hooper et al., 2015) consisted of 13 RCTs with 7115 participants, however, in this

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study serum total cholesterol was a secondary outcome. Taken in their entirety the identified publications were considered to be of good quality. Data from PCS were *insufficient* to draw any clear conclusions due to the limited number of PCS considered.

Saturated fats substitution with PUFA and serum total cholesterol

Randomised controlled trials
- Effect
- *Adequate* evidence
- The direction of the effect indicates that substituting saturated fats with PUFA lowers serum total cholesterol

Prospective cohort studies
- *Insufficient* evidence

Substitution of saturated fats with MUFA and serum total cholesterol

9.18   Four systematic reviews, 2 with meta-analyses (Hooper et al., 2015; Clarke et al., 1997) and 2 without meta-analyses (Schwab et al., 2014; Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with MUFA and serum total cholesterol. Two systematic reviews analysed the results from RCTs (Hooper et al., 2015; Micha & Mozaffarian, 2010), 1 examined the results from clinically controlled metabolic ward experiments (Clarke et al., 1997), and 1 evaluated the results from both RCTs and PCS (Schwab et al., 2014).

Randomised controlled trials

9.19   In a systematic review and meta-analysis, Hooper et al. (2015) reported that serum total cholesterol was reduced by lower saturated fat intake (mean difference -0.24 mmol/L, 95% CI -0.36 to -0.13; $p < 0.001$; $I^2 = 60\%$; 13 RCTs, 7115 participants), and this reduction was similar for interventions where PUFA, MUFA, carbohydrate or mixed diets substituted saturated fats. However, in the Hooper et al. (2015) review serum total cholesterol was a secondary outcome.

9.20   In the systematic review and meta-analysis by Clarke et al. (1997) of metabolic ward experiments (where diet was modified in volunteers under clinically controlled conditions), multivariate analysis across 395 dietary experiments representing 5901 subject/diet measurements demonstrated that isoenergetic substitution of saturated fats with MUFA produced a decrease in serum total cholesterol (mean difference - 0.52 mmol/L, 95% CI 0.58 to 0.46; p<0.001).

9.21   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 reduced serum total cholesterol (9 out of 9 RCTs demonstrated this effect, 476 participants, no statistics provided in the paper).

9.22   Micha & Mozaffarian (2010) performed a systematic review without meta-analysis of RCTs that considered the effect of diet on blood lipid outcomes. Substituting saturated fats with MUFA reduced serum total cholesterol (no statistics provided in the paper).

Prospective cohort studies

9.23   Evidence from PCS was limited to 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.

9.24   In summary, *adequate* evidence from RCTs indicates that substitution of saturated fats with MUFA reduced serum total cholesterol. This was further exemplified in metabolic ward experiments reported by Clarke et al. (1997) where the effects of saturated fats substitution with MUFA were examined under highly controlled conditions. The results of meta-analyses across the publications were statistically significant and systematic reviews without meta-analyses agreed with this outcome. The most recent systemic review (Hooper et al., 2015) consisted of 13 RCTs with 7115 participants, however, in this study serum total cholesterol was a secondary outcome. Taken in their entirety the

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identified publications were considered to be of good quality. For PCS the evidence was considered to be *insufficient* due to the limited number of PCS considered.

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

Substitution of saturated fats with carbohydrate and serum total cholesterol

9.25   Three systematic reviews, 2 with meta-analyses (Hooper et al., 2015; Clarke et al., 1997) and 1 without meta-analysis (Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with carbohydrate and serum total cholesterol. One systematic review analysed the results from RCTs (Hooper et al., 2015), 1 examined the results from clinically controlled metabolic ward experiments (Clarke et al., 1997) and 1 evaluated the results from RCTs and PCS (Micha & Mozaffarian, 2010).

Randomised controlled trials

9.26   In a systematic review with meta-analysis, Hooper et al. (2015) reported that serum total cholesterol (a secondary outcome in this study) was reduced by lower saturated fat intake 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 effect of reduction in saturated fats was statistically significant regardless of dietary substitution with PUFA, MUFA or carbohydrate.

9.27   The systematic review and meta-analysis of 227 solid food metabolic ward experiments by Clarke et al. (1997) reported that isoenergetic substitution of saturated fats with complex carbohydrates equivalent to 10% of total calories resulted in a decrease in

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serum total cholesterol (mean difference 0.52 mmol/L, 95% CI 0.58 to 0.43, p<0.001). While results were considered from RCTs and cross-over designs, conclusions were the same when considering only RCTs.

9.28 Micha & Mozaffarian (2010) performed a systematic review without meta-analysis of RCTs that considered the effect of diet on blood lipid outcomes. Substituting saturated fats with carbohydrate, reduced serum total cholesterol but to a lesser extent than substitution with PUFA or MUFA (no statistics provided in the paper).

Prospective cohort studies

9.29 Evidence from PCS was limited to 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).

9.30 In summary, *adequate* evidence from RCTs indicates that substitution of saturated fats with carbohydrate decreased serum total cholesterol. This was further exemplified in metabolic ward experiments reported by Clarke et al. (1997) where the effects of saturated fats substitution with carbohydrate were examined under highly controlled conditions. Meta-analyses were statistically significant and systematic reviews came to the same conclusion. The most recent systemic review (Hooper et al., 2015) consisted of 13 RCTs with 7115 participants, however, in this study serum total cholesterol was a secondary outcome. Taken in their entirety the identified publications were considered to be of good quality. For PCS, the evidence was classed as *insufficient* due to the low number of PCS.

<table>
<tr><td>**Saturated fats substitution with carbohydrate and serum total cholesterol**</td></tr>
</table>

Randomised controlled trials
- Effect
- *Adequate* evidence
- The direction of the effect indicates that substituting saturated fats with carbohydrate lowers serum total cholesterol

Prospective cohort studies
- *Insufficient* evidence

Serum LDL cholesterol

Saturated fats intake and serum LDL cholesterol

9.31   Four systematic reviews, 3 with meta-analyses (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 LDL cholesterol. Three systematic reviews analysed the results from RCTs (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

9.32   In a systematic review with meta-analysis Hooper et al. (2015) reported that lower saturated fats intake reduced LDL cholesterol using a random-effects model (mean difference -0.19 mmol/L, 95% CI -0.33 to -0.05; p<0.05; I² =37%; 5 RCTs, 3291 participants). The effect of reduction in saturated fats was statistically significant regardless of whether the dietary intervention was substitution with PUFA, MUFA, carbohydrate or mixed diets. However, in the Hooper et al. (2015) review LDL cholesterol was a secondary outcome.

9.33   Yu-Poth et al. (1999) conducted a systematic review and meta-analysis of 37 RCTs published between 1981 and 1997, focusing on the American Heart Association NCEP Step 1 diet (where saturated fat intake is 8 to 10% of dietary energy) and Step 2 diet

(where saturated fat intake 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 decreased 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 LDL cholesterol of 0.056 mmol/L. As noted in paragraph 9.6 these dietary interventions were complex and resulted in changes in more than just saturated fat intake.

9.34   Howell et al. (1997) performed a systematic review and meta-analysis on 224 RCTs including 8143 participants to examine primarily how reduced saturated fat intake affects serum total cholesterol and triglyceride content, but as a secondary outcome they also considered the effect on LDL cholesterol. On the basis of this data, authors estimated that reducing saturated fat intake to American Heart Association NCEP Step 1 diet (where saturated fat intake is 8 to 10% of dietary energy) and Step 2 diet (where saturated fat intake is ≤7% of dietary energy) would lead to a reduction of 4.5-7.7% in LDL cholesterol for patients within the high risk range of LDL cholesterol (> 4.14mmol/L). However, as noted previously, these dietary interventions were complex, resulting in changes in more than just saturated fat intake.

9.35   Van Horn et al. (2008) performed a systematic review without meta-analysis of the effect of saturated fat intake on 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 reduced 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 provided in the paper).

Prospective cohort studies

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

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9.37   In summary, while LDL cholesterol has been considered as an outcome in fewer meta-analyses than serum total cholesterol, there is *adequate* evidence that reducing saturated fat intake reduces LDL cholesterol in RCTs (Hooper et al., 2015; Van Horn et al., 2008; Clarke et al., 1997; Howell et al., 1997). As with serum total cholesterol, diets associated with larger weight loss had the biggest effect. The most recent systematic review (Hooper et al., 2015) consisted of 5 RCTS with 3291 participants, however, in this study LDL cholesterol was a secondary outcome. For PCS, the evidence was classed as *insufficient* due to the low number of PCS.

Saturated fats intake 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

9.38   Four systematic reviews, 2 with meta-analyses (Hooper et al., 2015; Clarke et al., 1997) and 2 without meta-analyses (Schwab et al., 2014; Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with PUFA and LDL cholesterol. One systematic review analysed the results from RCTs (Hooper et al., 2015), 1 evaluated the results from clinically controlled metabolic ward experiments (Clarke et al., 1997) and 2 analysed the results from both RCTs and PCS (Schwab et al., 2014; Micha & Mozaffarian, 2010).

Randomised controlled trials

9.39   In a systematic review with meta-analysis, Hooper et al. (2015) reported that lower saturated fat intake reduced 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

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participants). The effect of reduction in saturated fats was statistically significant regardless of whether the dietary intervention was substitution with PUFA, MUFA, carbohydrate or mixed diets. However, in the Hooper et al. (2015) review LDL cholesterol was a secondary outcome.

9.40   In a systematic review and meta-analysis Clarke et al. (1997) described 227 solid food metabolic ward experiments (where diet was modified in volunteers under clinically controlled conditions) that examined the effects of saturated fat intake on LDL cholesterol. Isoenergetic substitution of saturated fats with PUFA resulted in a decrease in LDL cholesterol (mean difference -0.058 ± 0.005 mmol/L, per percentage decrease in total calories from saturated fats, 95% CI 0.068 to 0.048; $p <0.001$; based on multilevel regression analysis).

9.41   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 LDL cholesterol compared with diets higher in saturated fats (8 out of 9 RCTs demonstrated this effect, no statistics provided in the paper).

9.42   Micha & Mozaffarian (2010) described in their systematic review of RCTs without meta-analysis that where saturated fats were substituted with PUFA there was a decrease in LDL cholesterol (further characteristics of studies not summarised, no statistics provided in the paper).

Prospective cohort studies

9.43   Evidence from PCS was limited to 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 LDL cholesterol.

9.44   In summary, there was *adequate* evidence that reducing saturated fat intake by substitution with PUFA reduces LDL cholesterol in RCTs. This was further exemplified in metabolic ward experiments reported by Clarke et al. (1997) where the effects of

saturated fats substitution with PUFA were examined under highly controlled conditions. The most recent systematic review (Hooper et al., 2015) consisted of 5 RCTS with 3291 participants; however, in this study LDL cholesterol was a secondary outcome. For PCS the evidence was considered to be *insufficient* due to limited number of PCS considered and potential confounding in diets which also reduced dietary cholesterol or caused weight loss.

Saturated fats substitution with PUFA and LDL cholesterol

Randomised controlled trials
- Effect
- *Adequate* evidence
- The direction of the effect indicates that substituting saturated fats with PUFA lowers LDL cholesterol

Prospective cohort studies
- *Insufficient* evidence

Substitution of saturated fats with MUFA and serum LDL cholesterol

9.45 Four systematic reviews, 2 with meta-analyses (Hooper et al., 2015; Clarke et al., 1997) and 2 without meta-analyses (Schwab et al., 2014; Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with MUFA and LDL cholesterol. One systematic review analysed the results from RCTs (Hooper et al., 2015), 1 evaluated the results from clinically controlled metabolic ward experiments (Clarke et al., 1997) and 2 examined the results from both RCTs and PCS (Schwab et al., 2014; Micha & Mozaffarian, 2010).

Randomised controlled trials

9.46 Hooper et al. (2015) in a systematic review and meta-analysis of 13 RCTs reported that substitution of saturated fats with MUFA reduced 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 effect of reduction in saturated fats was statistically

significant regardless of whether the dietary intervention was substitution of PUFA, MUFA or carbohydrate.

9.47   In a systematic review and meta-analysis Clarke et al. (1997) described 227 solid food metabolic ward experiments (where diet was modified in volunteers under clinically controlled conditions) that examined the effects of substituting saturated fat intake with MUFA on LDL cholesterol. Across 227 dietary experiments, it was reported that isoenergetic substitution of saturated fats with MUFA resulted in a decrease in LDL cholesterol (mean difference -0.044 mmol/L, 95% CI -0.0638 to -0.0242 for a 1% replacement of saturated fat by MUFA; p<0.001; based on multivariate regression analysis).

9.48   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 LDL cholesterol compared with diets rich in saturated fats (8 out of 9 RCTs demonstrated this effect, no statistics provided in the paper).

9.49   Micha & Mozaffarian (2010) described in their systematic review of RCTs without meta-analysis that where saturated fats were substituted with MUFA this led to a decrease in serum LDL cholesterol (further characteristics of studies not summarised, no statistics provided in the paper).

Prospective cohort studies

9.50   Evidence from PCS was limited to 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 LDL cholesterol.

9.51   In summary, there is *adequate* evidence that reducing saturated fat intake by substitution with MUFA reduces LDL cholesterol in RCTs. This was further exemplified in metabolic ward experiments reported by Clarke et al. (1997) where the effects of saturated fats substitution with MUFA were examined under highly controlled

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conditions. The most recent systematic review (Hooper et al., 2015) consisted of 5 RCTS with 3291 participants; however, in this study LDL cholesterol was a secondary outcome. For PCS the evidence was considered to be *insufficient* due to limited number of PCS considered and potential confounding in diets which also reduced dietary cholesterol or caused weight loss.

Saturated fats substitution with MUFA and LDL cholesterol

Randomised controlled trials
- Effect
- *Adequate* evidence
- The direction of the effect indicates that substituting saturated fats with MUFA lowers LDL cholesterol

Prospective cohort studies
- *Insufficient* evidence

Substitution of saturated fats with carbohydrate and serum LDL cholesterol

9.52   Three systematic reviews, 2 with meta-analyses (Hooper et al., 2015; Clarke et al., 1997) and 1 without meta-analysis (Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with carbohydrate and LDL cholesterol. One systematic review analysed the results from RCTs (Hooper et al., 2015) and 1 analysed the results from metabolic ward experiments (Clarke et al., 1997) and 1 examined the results from both RCTs and PCS (Micha & Mozaffarian, 2010).

Randomised controlled trials

9.53   Hooper et al. (2015) reported that lower saturated fat intake reduced LDL cholesterol (mean difference -0.19 mmol/L, 95% CI -0.33 to -0.05; $p<0.05$; $I^2 =37\%$; 5 RCTs; 3291 participants). The effect of reduction in saturated fats was statistically significant regardless of whether the dietary intervention was substitution with PUFA, MUFA or carbohydrate. However, in the Hooper et al. (2015) review LDL cholesterol was a secondary outcome.

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9.54   In a systematic review and meta-analysis Clarke et al. (1997) described 227 solid food metabolic ward experiments (where diet was modified in volunteers under clinically controlled conditions) that examined the effects of saturated fat intake on LDL cholesterol. Isoenergetic substitution of saturated fats with complex carbohydrate resulted in a decrease in 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); based on multivariate and univariate regression analysis).

9.55   Micha & Mozaffarian (2010) described in their systematic review of RCTs without meta-analysis that substitution of saturated fats with carbohydrate increased LDL cholesterol (no statistics provided in the paper).

Prospective cohort studies

9.56   Evidence from PCS was limited to 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.

9.57   In summary, while LDL cholesterol has been considered as an outcome in fewer meta-analyses than serum total cholesterol there is *adequate* evidence that substituting saturated fats with carbohydrate reduces LDL cholesterol in RCTs (Hooper et al., 2015; Clarke et al., 1997). The reductions in LDL cholesterol were less for isoenergetic diets when comparing diets where saturated fats were decreased without substitution and/or there was weight loss. For PCS the evidence was considered to be *insufficient* due to the low number of PCS.

Saturated fats substitution with carbohydrate and serum LDL cholesterol

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

Serum HDL cholesterol

Saturated fats intake and serum HDL cholesterol

9.58   Two systematic reviews with meta-analyses of RCTs (Yu-Poth et al., 1999; Howell et al., 1997) analysed the effect of reduced intake of saturated fats on HDL cholesterol. No systematic reviews, meta-analyses, pooled analyses that evaluated PCS were identified.

Randomised controlled trials

9.59   Yu-Poth et al. (1999) conducted a systematic review and 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 saturated fat intake is 8 to 10% of dietary energy) and Step 2 (where saturated fat intake is ≤7% of dietary energy) diets. The correlation between change in saturated fats and 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 HDL cholesterol by 0.012 mmol/L.

9.60   Howell et al. (1997) conducted a systematic review and regression meta-analysis of 224 RCTs on 8143 participants to investigate as a secondary outcome, how changes in saturated fat intake influenced concentrations of HDL cholesterol. HDL cholesterol was best modelled (i.e. the models that best predicted HDL cholesterol) using regression with respect to change in saturated fats and total fat. The relationship accounted for 41% of the variance associated with HDL cholesterol (r=7.42 ± 1.68, 95% CI 4.06 to 10.78;

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p<0.00005). A 1% decrease in total energy from saturated fats was associated with a 7.4 μmol/L decrease in HDL cholesterol.

9.61   In summary, there was *adequate* evidence that reduction of saturated fat intake decreased HDL cholesterol (Yu-Poth et al., 1999; Howell et al., 1997), although many of these interventions were associated with weight loss and/or reduced dietary cholesterol intake.

Saturated fats intake and serum HDL cholesterol

Randomised controlled trials
- Effect
- *Adequate* evidence
- The direction of the effect indicates that a reduced intake of saturated fats lowers serum HDL cholesterol

Prospective cohort studies
- No evidence

Substitution of saturated fats with PUFA and serum HDL cholesterol

9.62   Four systematic reviews, 3 with meta-analyses (Hooper et al., 2015; Mensink et al., 2003; Clarke et al., 1997) and 1 without meta-analysis (Micha & Mozaffarian, 2010) analysed the relationship between substitution of saturated fats with PUFA and serum HDL cholesterol. Three systematic reviews analysed the results from RCTs (Hooper et al., 2015; Micha & Mozaffarian, 2010; Mensink et al., 2003) and 1 evaluated the results from clinically controlled 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

9.63   Hooper et al. (2015) examined 15 RCTs covering 17 comparisons and involving approximately 59,000 participants. RCTs either aimed to assess the effect on total mortality and cardiovascular mortality of reducing saturated fat intake or altering dietary fats to achieve a reduction in saturated fats. As a secondary outcome, they also examined

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HDL cholesterol. There was no statistically significant effect of reducing saturated fat intake on HDL cholesterol (mean difference -0.01 mmol/L, 95% CI -0.02 to 0.01; p=0.21; I^2 =0%; 7 RCTs; 5147 participants), including dietary modifications where intake of saturated fats were substituted with PUFA.

9.64 Mensink et al. (2003) performed a systematic review and meta-analysis across 60 RCTs (1672 volunteers) to estimate the regression coefficient for mean changes in total HDL cholesterol when carbohydrate constituting 1% of dietary energy is substituted isoenergetically with PUFA. The results indicated that HDL cholesterol increased when carbohydrate was substituted with PUFA (r=0.006, 95% CI 0.003 to 0.009; p<0.001). It was estimated that the substitution of 1% of energy from saturated fats with an equal percentage of PUFA was predicted to lower HDL cholesterol concentrations by 0.002 mmol/L indicating that saturated fats substitution with PUFA had a marginal impact on HDL cholesterol.

9.65 In a systematic review and meta-analysis Clarke et al. (1997) described 227 solid food metabolic ward experiments (where diet was modified in volunteers under clinically controlled conditions) to examine the impact of the substitution of carbohydrate with PUFA on HDL cholesterol. Substitution of carbohydrate with PUFA resulted in an increase in HDL cholesterol (r =0.005 ±0.002 change in HDL cholesterol per unit of isoenergetic change in carbohydrate adjusted for age, weight, and all other dietary factors). Given this was a smaller increase than that caused by a substitution of saturated fats with carbohydrate (see paragraph 9.77) this indicates that substitution of saturated fats with PUFA resulted in a smaller decrease in HDL cholesterol than substitution with carbohydrate.

9.66   Micha & Mozaffarian (2010) described in their systematic review without meta-analysis that substitution of saturated fats with PUFA slightly lowered HDL cholesterol (further characteristics of studies not summarised, no statistics provided in the paper).

9.67 In summary, there was evidence that substitution of saturated fats with PUFA results in a slight lowering of HDL cholesterol. However, these changes were not detected in all systematic reviews (Hooper et al., 2015) and thus, the evidence was graded as *moderate*.

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

Substitution of saturated fats with MUFA and serum HDL cholesterol

9.68 Four systematic reviews, 3 with meta-analyses (Hooper et al., 2015; Mensink et al., 2003; Clarke et al., 1997) and 1 without meta-analyses (Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with MUFA and HDL cholesterol. Three systematic reviews analysed the results from RCTs (Hooper et al., 2015; Micha & Mozaffarian, 2010; Mensink et al., 2003) and 1 evaluated the results from clinically controlled 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

9.69 Hooper et al. (2015) examined 15 RCTs covering 17 comparisons involving approximately 59,000 participants where the studies either aimed to assess the impact on total mortality and cardiovascular mortality of reducing saturated fat intake or altering saturated fats. As secondary outcomes they also examined HDL cholesterol. There was no statistically significant effect of reducing saturated fat intake on HDL cholesterol (7 RCTs, 5147 participants), including dietary modifications where saturated fats were substituted with MUFA.

9.70   Mensink et al. (2003) performed a meta-analysis across 60 RCTs (1672 participants) to estimate the regression coefficient for mean changes in total HDL cholesterol when carbohydrate constituting 1% of dietary energy is isoenergetically substituted with MUFA. Using regression analysis the results indicated that HDL cholesterol increased when carbohydrate was substituted with MUFA (r=-0.008, 95% CI -0.005 to -0.011; p<0.001). It was estimated that the substitution of 1% of energy from saturated fats with an equal percentage of MUFA is predicted to lower HDL cholesterol concentrations by 0.002 mmol/L, indicating that substituting saturated fats with MUFA had a marginal impact on HDL cholesterol.

9.71   In a systematic review and meta-analysis Clarke et al. (1997) described 227 solid food metabolic ward experiments (where diet was modified in volunteers under clinically controlled conditions) to examine the impact of the substitution of carbohydrate with MUFA on HDL cholesterol. Substitution of carbohydrate with MUFA resulted in an increase in HDL cholesterol (r=0.006 ±0.002 change in blood cholesterol per unit of isoenergetic change in carbohydrate adjusted for age, weight, and all other dietary factors). Given this was a smaller increase than that caused by a substitution of saturated fats with carbohydrate (see paragraph 9.77), this indicates that substitution of saturated fats with MUFA produced a smaller decrease in HDL cholesterol than substitution with carbohydrate.

9.72   Micha & Mozaffarian (2010) described in their systematic review of RCTs without meta-analysis that substitution of saturated fats with MUFA decreased HDL cholesterol (further characteristics of studies not summarised, no statistics provided in the paper).

9.73   In summary, there is *moderate* evidence that substituting MUFA for saturated fats reduces HDL cholesterol (Micha & Mozaffarian, 2010; Mensink et al., 2003; Clarke et al., 1997). However, these changes were not detected in all systematic reviews (Hooper et al., 2015) and thus, the evidence was graded as *moderate*.

Saturated fats substitution with MUFA and serum HDL cholesterol

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

Substitution of saturated fats with carbohydrate and serum HDL cholesterol

9.74   Four systematic reviews, 3 with meta-analyses (Hooper et al., 2015; Mensink et al., 2003; Clarke et al., 1997) and 1 without meta-analyses (Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with carbohydrate and HDL cholesterol. Three systematic reviews analysed the results from RCTs (Hooper et al., 2015; Micha & Mozaffarian, 2010; Mensink et al., 2003) and 1 evaluated the results from clinically controlled 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

9.75   Hooper et al. (2015) considered 15 RCTs covering 17 comparisons involving approximately 59,000 participants to examine how a reduction in saturated fats impacted on total mortality and cardiovascular mortality. The included studies aimed to either (i) reduce saturated fat intake or (ii) change total fat intake more generally to achieve a significant ($p<0.05$) reduction in saturated fats. As secondary outcomes, they also examined HDL cholesterol. There was no statistically significant effect of reducing saturated fat intake on HDL cholesterol (7 RCTs, 5147 participants).

9.76   Mensink et al. (2003) performed a meta-analysis across 60 RCTs (1672 participants) to estimate the regression coefficient for mean changes in HDL cholesterol when carbohydrate constituting 1% of dietary energy was substituted isoenergetically with

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saturated fats. Using regression analysis, the results indicated that HDL cholesterol increased with higher saturated fat intake (r=0.010, 95% CI 0.007 to 0.013; p<0.001).

9.77   In a systematic review and meta-analysis Clarke et al. (1997) described 227 solid food metabolic ward experiments (where diet was modified in volunteers under clinically controlled conditions) to examine the impact of the substitution of saturated fats with carbohydrate on HDL cholesterol concentrations. Substitution of saturated fats with carbohydrate resulted in a decrease in HDL cholesterol (r=-0.013, 95% CI -0.017 to -0.009; p<0.001 change in blood HDL cholesterol per unit of isoenergetic change in carbohydrate adjusted for age, weight, and all other dietary factors).

9.78   Micha & Mozaffarian (2010) described in their systematic review without meta-analysis that substitution of saturated fats with carbohydrate decreased HDL cholesterol (further characteristics of studies not summarised; no statistics provided in the paper).

9.79   In summary, there was evidence that substitution of saturated fats with carbohydrate decreased HDL cholesterol (Micha & Mozaffarian, 2010; Mensink et al., 2003; Clarke et al., 1997), although not all systematic reviews agreed with this conclusion, with Hooper et al. (2015) reporting no difference. The committee, on balance, considered this evidence to be *moderate.*

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

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Serum total cholesterol:HDL cholesterol ratio

Saturated fats intake and serum total cholesterol:HDL cholesterol ratio

Randomised controlled trials

9.80   The three systematic reviews that reported on total cholesterol:HDL cholesterol ratio in RCTs (Hooper et al., 2015; Micha & Mozaffarian, 2010; Mensink et al., 2003) all considered isoenergetic substitution of saturated fats in terms of their meta-analyses. Thus, there was no evidence reviewed for reduction, without substitution, of saturated fats.

Saturated fats intake and serum total cholesterol:HDL cholesterol ratio

Randomised controlled trials
    • No evidence
Prospective cohort studies
    • No evidence

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

9.81   Three systematic reviews, 2 with meta-analyses (Hooper et al., 2015; Mensink et al., 2003) and 1 without meta-analysis (Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with PUFA and 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

9.82   Hooper et al. (2015) examined 3 RCTs (2985 participants) where the studies either aimed to (i) reduce saturated fat intake, or (ii) change total fat intake more generally to achieve a significant ($p<0.05$) reduction in saturated fats. They also examined total cholesterol:HDL cholesterol ratio as a secondary outcome. Substitution of saturated fats with PUFA had no effect on the ratio.

9.83   Mensink et al. (2003) performed a systematic review and meta-analysis of 60 RCTs (1672 volunteers) where carbohydrate was substituted with different classes of fatty acids. Substitution of carbohydrate with PUFA reduced the total cholesterol:HDL cholesterol ratio (estimated regression coefficients for mean changes in total cholesterol:HDL cholesterol ratio when carbohydrate constituting 1% energy is substituted isoenergetically with PUFA; r= -0.032, 95% CI -0.042 to -0.022; p<0.001). Given the direction of change induced by substitution of carbohydrate with saturated fats described in paragraph 9.93, this indicates that a substitution of saturated fats with PUFA would produce a decrease in total cholesterol:HDL cholesterol ratio.

9.84   Micha & Mozaffarian (2010) performed a systematic review of RCTs without meta-analysis of the evidence of saturated fats contributing to CVD risk. Diets where saturated fats were substituted with PUFA decreased the ratio of total cholesterol:HDL cholesterol (further characteristics of studies not summarised, no statistics provided in the paper).

9.85   In summary, there was evidence that substitution of saturated fats with PUFA produces a slight lowering of the ratio of total cholesterol:HDL cholesterol (Micha & Mozaffarian, 2010; Mensink et al., 2003). However, these changes were not detected in all systematic reviews (Hooper et al., 2015) and thus, the evidence was graded as *moderate*.

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

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

9.86   Three systematic reviews, 2 with meta-analyses (Hooper et al., 2015; Mensink et al., 2003) and 1 without meta-analysis (Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with MUFA and 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

9.87   Hooper et al. (2015) examined 3 RCTs (2985 participants) where the studies aimed to either (i) reduce saturated fat intake, or (ii) change total fat intake more generally to achieve a significant ($p<0.05$) reduction in saturated fats. They also assessed total cholesterol:HDL cholesterol ratio as a secondary outcome. Substitution of saturated fats with MUFA had no effect on the ratio.

9.88   Mensink et al. (2003) performed a systematic review with meta-analysis of 60 RCTs (1672 volunteers) where carbohydrate was substituted with different classes of fatty acids. Substitution of carbohydrate with MUFA reduced total cholesterol:HDL cholesterol ratio (estimated regression coefficients for mean changes in total cholesterol:HDL cholesterol ratio when carbohydrate constituting 1% is substituted isoenergetically with MUFA; r= -0.026 (95% CI -0.035 to -0.017; $p<0.001$). Given the direction of change induced by substitution with saturated fats described in paragraph 9.93, this indicates that a replacement of saturated fats with MUFA produced a decrease in total cholesterol:HDL cholesterol ratio.

9.89   Micha & Mozaffarian (2010) performed a systematic review of RCTs without meta-analysis of the evidence of saturated fats contributing to CVD risk. Diets where saturated fats were substituted with MUFA decreased the ratio of total cholesterol:HDL cholesterol (further characteristics of studies not summarised, no statistics provided in the paper).

9.90   In summary, there was evidence that substitution of saturated fats with MUFA produced a slight lowering of the ratio of total cholesterol:HDL cholesterol ratio (Micha & Mozaffarian, 2010; Mensink et al., 2003). However, these changes were not detected in all systematic reviews (Hooper et al., 2015) and thus, the evidence was graded as *moderate*.

Saturated fats substitution with MUFA and serum total cholesterol:HDL cholesterol ratio

Randomised controlled trials
- Effect
- *Moderate* evidence
- The direction of the effect indicated that substituting saturated fats with MUFA lowers the ratio of serum total cholesterol:HDL cholesterol

Prospective cohort studies
- No evidence

Substitution of saturated fats with carbohydrate and total cholesterol:HDL cholesterol ratio

9.91   Three systematic reviews, 2 with meta-analyses (Hooper et al., 2015; Mensink et al., 2003) and 1 without meta-analysis (Micha & Mozaffarian, 2010) examined the relationship between substitution of saturated fats with carbohydrate and 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

9.92   Hooper et al. (2015), in their systematic review of 3 RCTs with meta-analysis, reported that there was no statistically significant effect of reducing saturated fat intake on total cholesterol:HDL cholesterol ratio regardless of what was substituted for saturated fats (PUFA, MUFA or carbohydrate) (mean difference -0.10, 95% CI -0.33 to 0.13; p>0.05, I^2=24%, 2985 participants). However, in the Hooper et al. (2015) review total cholesterol:HDL cholesterol ratio was a secondary outcome.

9.93 Mensink et al. (2003) performed a systematic review and meta-analysis of 60 RCTs (1672 volunteers) where fatty acid composition was varied while maintaining other components of the diet constant including dietary cholesterol. Regression analysis across the studies demonstrated that total cholesterol:HDL cholesterol ratio did not change when saturated fats were substituted with carbohydrate, as total cholesterol and HDL cholesterol decreased to a similar extent (estimated regression coefficients for mean changes in total cholesterol:HDL cholesterol ratio when carbohydrate constituting 1% is substituted isoenergetically with saturated fats; r=0.003 (95% CI -0.008 to 0.013, no effect).

9.94 Micha & Mozaffarian (2010) performed a systematic review of RCTs without meta-analysis of the evidence of saturated fats contributing to CVD risk. Diets where carbohydrate was substituted with saturated fats had a minimal effect on the ratio of total cholesterol:HDL cholesterol (further characteristics of studies not summarised, no statistics provided in the paper).

9.95 In summary, *adequate* evidence from RCTs demonstrated that there was no effect on the ratio of total cholesterol:HDL cholesterol for diets where saturated fats were substituted with carbohydrate.

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

Serum triacylglycerol

Saturated fats intake and serum triacylglycerol

Randomised controlled trials

9.96   One systematic review with meta-analysis of RCTs (Yu-Poth et al., 1999) analysed the effect of reduced intake of saturated fats on serum triacylglycerol.

9.97   Yu-Poth et al. (1999) conducted a systematic review and 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 decreased 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 and dietary cholesterol intake in the multiple regression, there was no effect of total fat intake on serum triacylglycerol. This questions whether the effects associated with saturated fat intake were direct or mediated through weight loss or dietary cholesterol.

9.98   In summary, there was *adequate* evidence that a reduction in saturated fat intake lowered serum triacylglycerol (Yu-Poth et al., 1999), although when the analysis was corrected for weight loss there was no relationship, questioning whether the reduction in serum triacylglycerol was associated with saturated fat intake or weight loss.

Saturated fats intake and serum triacylglycerol

Randomised controlled trials
     • Effect
     • *Adequate* evidence
     • The direction of the effect indicates that reduced intake of saturated fats lowers serum triacylglycerol
 	
 Prospective cohort studies
     • No evidence

Substitution of saturated fats with PUFA and serum triacylglycerol

9.99 Four systematic reviews, 1 with meta-analysis (Hooper et al., 2015) and 3 without meta-analyses (Schwab et al., 2014; Micha & Mozaffarian, 2010; 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

9.100 Hooper et al. (2015), in their systematic review of 7 RCTs with meta-analysis, reported that there was no statistically significant effect of reducing saturated fat intake on triacylglycerol regardless of what substituted saturated fats (PUFA, MUFA or carbohydrate) (mean difference -0.08 mmol/L, 95% CI -0.21 to 0.04; p>0.05; I^2=51%; 7 RCTs; 3845 participants). However, in the Hooper et al. (2015) review serum triacylglycerol was a secondary outcome.

9.101 Schwab et al. (2014), in their systematic review of 8 RCTs published between 2000 and 2010 (648 individuals) 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, reported that an effect was 'unlikely' (no statistics provided in the paper).

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9.102 Micha & Mozaffarian (2010) performed a systematic review without meta-analysis of RCTs of the evidence of saturated fats contributing to CVD risk. Substitution of saturated fats with PUFA or MUFA had little effect on blood triacylglycerol level (based on 1254 publications; further characteristics of studies not summarised, no statistics provided in the paper).

9.103 Van Horn et al. (2008), in the systematic review of RCTs without meta-analysis, reported that substitution of saturated fats with a combination of PUFA and MUFA produced a small decrease in serum triacylglycerol (-16.4 mg/dL) but this was based on a single RCT (the OminiHeart Randomised trial (Appel et al. (2005); 164 individuals randomised to three diets, no statistics provided in the paper).

9.104 In summary, *moderate* evidence suggested no effect of reducing saturated fat intake by substitution with PUFA on serum triacylglycerol, with most systematic reviews reporting no effect. The evidence was graded as *moderate* due to the disagreement across the studies.

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

Substitution of saturated fats with MUFA and serum triacylglycerol

9.105 Four systematic reviews, 1 with meta-analysis (Hooper et al., 2015) and 3 without meta-analyses (Schwab et al., 2014; Micha & Mozaffarian, 2010; 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

9.106   In a systematic review and meta-analysis Hooper et al. (2015) reported that there was no statistically significant effect of reducing saturated fat intake on triacylglycerol regardless of what substituted saturated fats (MUFA, PUFA or carbohydrate) (mean difference -0.08 mmol/L, 95% CI -0.21 to 0.04; p>0.05, I^2 51%, 7 RCTs, 3845 participants, random-effects model). However, in the Hooper et al. (2015) review serum triacylglycerol was a secondary outcome.

9.107   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 provided in the paper).

9.108   Micha & Mozaffarian (2010) performed a systematic review of RCTs without meta-analysis of the evidence of saturated fats contributing to CVD risk. Substitution of saturated fats with PUFA or MUFA had little effect on blood triacylglycerol level (further characteristics of studies not summarised, no statistics provided in the paper).

9.109   Van Horn et al. (2008), in their systematic reviews of 1 RCT without meta-analysis, reported that substitution of saturated fats with a combination of PUFA and MUFA produced a small decrease in serum triacylglycerol (-16.4 mg/dL[16]) but this was based on a single RCT (the OmniHeart Randomised trial (Appel et al., 2005), 164 individuals randomised to 3 diets, no statistics provided in the paper).

9.110   In summary, *moderate* evidence suggested no effect of reducing saturated fat intake by substitution with MUFA on serum triacylglycerol, with most systematic reviews reporting no effect. The evidence was graded as *moderate* due to the disagreement across the studies.

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[16] 1mmol/L=18mg/dL

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Saturated fats substitution with MUFA and serum triacylglycerol

Randomised controlled trials
- No effect
- *Moderate* evidence

Prospective cohort studies
- No evidence

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Substitution of saturated fats with carbohydrate and serum triacylglycerol

9.111   Three systematic reviews, 1 with meta-analysis (Hooper et al., 2015) and 2 without meta-analyses (Micha & Mozaffarian, 2010; Van Horn et al., 2008) of RCTs examined the relationship between substitution of saturated fats with carbohydrate and serum triacylglycerol. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

9.112   Hooper et al. (2015), in the systematic review of 7 RCTs with meta-analysis, reported that there was no statistically significant effect of reducing saturated fat intake on triacylglycerol regardless of what substituted saturated fats (PUFA, MUFA or carbohydrate) (mean difference -0.08 mmol/L, 95% CI -0.21 to 0.04; p>0.05; I^2 =51%, 7 RCTs, 3845 participants). However, in the Hooper et al. (2015) review serum triacylglycerol was a secondary outcome.

9.113   Micha & Mozaffarian (2010) performed a systematic review of RCTs without meta-analysis of the evidence of saturated fats contributing to CVD risk. Diets where carbohydrate was substituted for saturated fats had a slight triacylglycerol lowering effect (further characteristics of studies not summarised, no statistics provided in the paper).

9.114   Van Horn et al. (2008) reported that substitution of saturated fats with carbohydrate produced a small increase in serum triacylglycerol (0.1 mg/dL) but this was based on a

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single RCT (the OmniHeart Randomised trial (Appel et al., 2005), 164 individuals randomised to 3 diets, no statistics provided in the paper).

9.115 In summary, there was conflicting evidence from RCTs as to whether lower saturated fat intake had an effect on total triacylglycerol, and whether the observed effects depended on what diets were being compared. Diets where saturated fats were substituted with carbohydrate tended to report either no effect or small changes. The evidence was considered to be *inconsistent* for RCTs.

Saturated fats substitution with carbohydrate and serum triacylglycerol
Randomised controlled trials • *Inconsistent* evidence *Prospective cohort studies* • No evidence

Summary

9.116 Across the systematic reviews considered, including a number that scored highly on the AMSTAR rating of systematic reviews, there was good agreement that reducing saturated fat intake lowered total cholesterol, LDL cholesterol and HDL cholesterol across RCTs regardless of dietary intervention (reduction in saturated fats and substitution with PUFA, MUFA or carbohydrate). There was some evidence that diets lowering saturated fat intake by substitution with PUFA or MUFA lowered the total cholesterol:HDL cholesterol ratio, but substitutions with carbohydrate had no effect. There was no effect or evidence was *inconsistent* across the individual RCTs for changes in serum triacylglycerol concentrations when saturated fats were substituted with PUFA, MUFA or carbohydrate.

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

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

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

Outcome	Saturated fats intake		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrate		Saturated fats substitution with protein	
	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										
Serum total cholesterol	↓	Adequate	↓	Adequate	↓	Adequate	↓	Adequate	n/a	No evidence
Serum LDL cholesterol	↓	Adequate	↓	Adequate	↓	Adequate	↓	Adequate	n/a	No evidence
Serum HDL cholesterol	↓	Adequate	↓	Moderate	↓	Moderate	↓	Moderate	n/a	No evidence
Serum total/HDL cholesterol ratio	n/a	No evidence	↓	Moderate	↓	Moderate	-	Adequate	n/a	No evidence
Serum lipid triacylglycerol	↓	Adequate	-	Moderate	-	Moderate	n/a	Inconsistent	n/a	No evidence
PCS										
Serum total cholesterol	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	No evidence
Serum LDL cholesterol	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	Insufficient	n/a	No evidence
Serum HDL cholesterol	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Serum total/HDL cholesterol ratio	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Serum lipid triacylglycerol	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

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10 Blood pressure

10.1 Three systematic reviews, 1 with meta-analysis (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 protein 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), carbohydrate or protein and blood pressure.

10.3 Although the Hooper et al. (2015) review was considered to be of high quality, and the number of included subjects was relatively large, blood pressure was not a primary outcome and it was not included as in the search terms (see the AMSTAR assessment in Annex 4). Data on blood pressure was only included if reported in papers selected for consideration in relation to other primary outcomes, such as cardiovascular disease (CVD).

Blood pressure

Saturated fat intake and blood pressure

10.4 One systematic review and meta-analysis of RCTs (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 Hooper et al. (2015) found no effect of reducing intakes of saturated fats on systolic blood pressure (mean difference -0.19 mmHg, 95% CI -1.36 to 0.97; I^2 =0%; 5 RCTs; 3812 participants) or diastolic blood pressure (mean difference -0.36 mmHg, 95% CI -1.03 to

0.32; I^2 =0%, 5 RCTs; 3812 participants). Three out of 5 of the RCTs included in the meta-analysis reported a significant reduction in intakes of saturated fats in the intervention group. In the other 2 RCTs, intakes of saturated fats were not reported or were unclear. Saturated fats were mainly substituted with PUFA in 3 of the 5 RCTs and carbohydrate in the other 2 RCTs. As well as altering the intake of saturated fats, total fat intake was significantly reduced in 2 of the 5 RCTs and significantly increased in 1 RCT, there was no significant difference in fat intake in another trial and in the final trial fat intake was reported as being 'unclear'.

10.6   In summary, there was *limited* evidence from 1 systematic review and meta-analysis of RCTs (Hooper et al., 2015) that reduced intake of saturated fats had no effect on blood pressure. The evidence was graded as *limited* because the systematic review had not included blood pressure as a primary outcome and had not included it as a key term in the literature search. Therefore, the extent to which this can be considered to be a formal review of the effect of saturated fats on blood pressure is questionable.

Saturated fat intake and blood pressure
Randomised controlled trials   • No effect   • *Limited* evidence   *Prospective cohort studies*   • No evidence

Substitution of saturated fats with PUFA and blood pressure

10.7   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

10.8   A systematic review without meta-analysis of 5 RCTs (360 participants, with follow-up to 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.

10.9   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.

10.10   In summary, there was *limited* evidence from systematic reviews of RCTs (Schwab et al., 2014; Micha & Mozaffarian, 2010) 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

10.11   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 &

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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

10.12 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 resulted in a reduction in blood pressure while the smaller study (60 participants) reported no significant effect of MUFA relative to saturated fats on blood pressure.

10.13 In a systematic review without meta-analysis Micha and Mozaffarian (2010) analysed 5 RCTs (481 participants) with follow-up to 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

10.14 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).

10.15 In summary, there was no effect of saturated fats substitution with MUFA on blood pressure. The evidence was graded as *limited* because there was 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 carbohydrate and blood pressure

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

Randomised controlled trials

10.17 There was no effect on blood pressure in any of the 4 RCTs that evaluated substitution of saturated fats with carbohydrate (Micha & Mozaffarian, 2010).

10.18 In summary, there was no effect of substituting saturated fats with carbohydrate on blood pressure. The evidence was deemed 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 carbohydrate and blood pressure

Randomised controlled trials
    • No effect
    • *Limited* evidence
 	
Prospective cohort studies
    • No evidence

Summary

10.19 Evidence from systematic reviews and meta-analyses of RCTs was identified which reported on blood pressure and saturated fat intakes. There was *limited* evidence from RCTs that reduced intake of saturated fats or substituting saturated fats with PUFA, MUFA or carbohydrate 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 the modelled substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and blood pressure.

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

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

Outcome	Saturated fats intake		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrate		Saturated fats substitution with protein	
	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   Six systematic reviews of which 4 included meta-analyses were identified that examined the relationship between saturated fats and risk of type 2 diabetes, and markers of glycaemic control (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 A2.7. 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 on 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 protein and risk of type 2 diabetes and markers of glycaemic control.

Saturated fat intake 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   Four 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   de Souza et al. (2015) performed the most recently published systematic review and meta-analysis of 8 PCS with data on 237,454 participants (8739 cases) aged 34 years and

over. There was no association between the highest versus lowest intakes of saturated fats and risk of type 2 diabetes for the most adjusted multivariable ratio using random-effects model (RR 0.95, 95% CI 0.88 to 1.03; p=0.20; I^2 =0%; 8/8 (PCS/comparisons)).

11.6   Alhazmi et al. (2012) performed a systematic review and meta-analysis on 7 PCS with data on 352,262 participants (5442 cases) aged ≥34 years. 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). There was 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 (RR 0.99, 95% CI 0.91 to 1.07; p=0.75; I^2 = 0%).

11.7   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). Using a fixed-effect model Micha & Mozaffarian (2010) reported that none of the 4 PCS found an association between saturated fats and risk of type 2 diabetes (RR 0.98, 95% CI 0.87 to 1.10; p-value not reported).

11.8   Schwab et al. (2014) carried out a systematic review without meta-analysis. They reported on 2 PCS that both found no statistically significant associations between saturated fat intake and risk of type 2 diabetes.

11.9   In summary, there was no evidence from RCTs on the effect of saturated fats and risk of type 2 diabetes. The meta-analysis of PCS by de Souza et al. (2015) has been used to draw conclusions on the evidence from PCS, as it is the most up-to-date review and includes the largest number of studies. de Souza et al. (2015) found no association between saturated fat intake 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*.

Saturated fat intake 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. 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 statistically significant association of changing the PUFA: saturated fats ratio (OR 0.91, 95% CI 0.81 to 1.03), 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 was *insufficient* to draw any conclusions on substitution of saturated fats with PUFA and risk of type 2 diabetes.

Saturated fat substitution with PUFA and type 2 diabetes

Randomised controlled trials
    • No evidence
 	
Prospective cohort studies
    • *Insufficient* evidence

Substitution of saturated fats with MUFA or protein 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 protein and risk of type 2 diabetes.

Substitution of saturated fats with carbohydrate 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 carbohydrate and risk of type 2 diabetes. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.15 Two systematic reviews, 1 with meta-analysis (Hooper et al., 2015) and 1 without meta-analysis (Micha & Mozaffarian, 2010) considered evidence from RCTs. Both reviews identified and reported on the same single RCT, the Woman's Health Initiative, which included data on 45,887 post-menopausal women. Reducing saturated fat intake from 12.7 to 9.5% energy intake over 8 years was reported to have no statistically significant effect on the risk of type 2 diabetes (RR 0.96, 95% CI 0.90 to 1.02; p=0.21). However, the Women's Health Initiative did not explicitly test the effect of substitution of saturated fats with carbohydrate. Both reviews reported that saturated fats were substituted mainly with carbohydrate but did not differentiate between the different types of carbohydrate.

11.16 In summary, there was *insufficient* evidence from RCTs on the effect of saturated fats substitution with carbohydrate on risk of type 2 diabetes. Although the Woman's Health

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Initiative trial (the only trial identified by Micha & Mozaffarian (2010) and Hooper et al. (2015)) was a large RCT that included more than 45000 people, the participants were all female. Another limitation of this RCT was that as well as reducing saturated fat intake, 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 carbohydrate and type 2 diabetes
Randomised controlled trials •   *Insufficient* evidence *Prospective cohort studies* •   No evidence

Markers of glycaemic control

11.17 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 changes in saturated fat intake with 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.

11.18 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). Therefore the extent to which Hooper et al. (2015) can be considered to be a formal review of the effect of saturated fats on these outcomes is questionable. 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

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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 11.19-11.99, 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

Saturated fat intake and fasting glucose

11.19 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on the relationship between saturated fat intake and fasting glucose.

Substitution of saturated fats with PUFA and fasting glucose

11.20 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

11.21 Imamura et al. (2016) carried out a meta-regression analysis of data from 99 RCTs with 4144 participants. There was a significant beneficial effect (i.e. 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; $p<0.05$). 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.

11.22 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

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participants with type 2 diabetes and the rest were healthy or at-risk (e.g. overweight) populations. One RCT evaluated the effect of saturated fats compared with PUFA on fasting glucose and reported that no effect was identified.

11.23 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 which 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.

11.24 In summary*, adequate* evidence 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

11.25 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

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This is a draft report and does not necessarily represent the final views of the Scientific Advisory Committee on Nutrition, or the advice/policy of Public Health England and UK Health Departments.

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

Randomised controlled trials

11.26 Imamura et al. (2016) carried out a systematic review with meta-regression analysis of data from 99 RCTs with 4144 participants. There was no statistically significant effect on fasting glucose when saturated fats were substituted with MUFA (mean difference -0.02 mmol/L, 95% CI -0.04 to 0.00). 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.

11.27 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 (e.g. 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.

11.28 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 which 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, $p<0.05$).

11.29 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 carbohydrate and fasting glucose

11.30   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 carbohydrate on measures of fasting glucose. No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.31   Imamura et al. (2016) carried out a systematic review with meta-regression analysis of data from 99 RCTs with 4144 participants. This showed no statistically significant effect on fasting glucose when 5% energy as saturated fats was isoenergetically substituted with carbohydrate (type not reported in paper) (mean difference 0.02 mmol/L, 95% CI -0.01 to 0.04).

11.32   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 (e.g. overweight) populations. Four RCTs evaluated the effect of saturated fats compared to carbohydrate on fasting glucose and reported that no effect was identified.

11.33   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 carbohydrate on fasting glucose. One RCT reported that saturated fats increased fasting blood glucose compared to carbohydrate (11 participants, 28 days intervention duration p<0.05), whereas the 2 RCTs in healthy participants reported no significant difference.

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

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

Fasting Insulin

Saturated fat intake and fasting insulin

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

Substitution of saturated fats with PUFA and fasting insulin

11.36 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 reported on that evaluated PCS were identified.

Randomised controlled trials

11.37 Imamura et al. (2016) carried out a systematic review with meta-regression analysis of data from 90 RCTs with 3774 participants. These show no statistically significant effect

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when saturated fats were substituted with PUFA. 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.

11.38 Schwab et al. (2014) reported on 8 RCTs with varying specificity of saturated fats substitution in a systematic review without meta-analysis. One RCT (17 participants) evaluated the effect of saturated fats compared with PUFA on fasting insulin and reported that no statistically significant effect was identified.

11.39 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.

11.40 In summary, *adequate* evidence for no effect on fasting blood 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 an 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

11.41   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

11.42   Imamura et al. (2016) carried out a systematic review with meta-regression analysis of data from 90 trials with 3774 participants. These showed a statistically significantly higher fasting insulin when saturated fats were substituted with MUFA (mean difference 1.17 pmol/L[17], 95% CI 0.57 to 1.78; p<0.001). 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.

11.43   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.

11.44   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.

11.45   In summary*, adequate* evidence for a potentially detrimental increase in fasting insulin when saturated fats are substituted with MUFA is supported by the statistical significance

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[17] 1 pmol/L= 0.14 μIU/mL

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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 an 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 carbohydrate and fasting insulin

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

Randomised controlled trials

11.47   Imamura et al. (2016) carried out a systematic review with meta-regression analysis of data from 90 trials with 3774 participants. These show a statistically significantly lower fasting insulin when 5% energy as saturated fats was isoenergetically substituted with carbohydrate (mean difference -1.12 pmol/L[18], 95% CI -1.72 to -0.53 p<0.01) 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.

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[18] 1 pmol/L= 0.14 µIU/mL

11.48 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 carbohydrate on fasting insulin. Both RCTs reported fasting insulin to be higher with saturated fats compared with carbohydrate.

11.49 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. Four 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 carbohydrate on fasting insulin. One RCT including healthy participants reported saturated fats significantly increased fasting insulin in comparison with carbohydrate (59 participants, intervention duration 28 days, $p<0.001$). There was no significant effect of saturated fats in the other 2 RCTs with carbohydrate.

11.50 In summary, *adequate* evidence for a potentially detrimental increase in fasting insulin when saturated fats are substituted with carbohydrate 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 an 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 carbohydrate and fasting insulin
Randomised controlled trials • Effect • *Adequate* evidence • The direction of the effect indicates that substitution of saturated fats with carbohydrate increases fasting insulin. *Prospective cohort studies* • No evidence

Glycated haemoglobin (HbA1c)

Saturated fat intake and glycated haemoglobin (HbA1c)

11.51   No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on the relationship between saturated fat intake and glyclated haemoglobin (HbA1c).

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

11.52   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

11.53   Imamura et al. (2016) carried out a systematic review with meta-regression analysis of data from 23 RCTs with 618 participants. 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; $p < 0.001$). 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 saturated fat intakes.

11.54   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)

11.55 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 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

11.56 Imamura et al. (2016) carried out a systematic review with meta-regression analysis of data from 23 RCTs with 618 participants. 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). 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 saturated fat intakes.

11.57 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.

11.58 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, $p<0.01$).

11.59 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 carbohydrate and glycated haemoglobin (HbA1c)

11.60 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 carbohydrate 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

11.61 Imamura et al. (2016) carried out a meta-analysis with meta-regression analysis of data from 23 RCTs with 618 participants. These show that HbA1c was not significantly

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different when 5% energy as saturated fats was isoenergetically substituted with carbohydrate (mean difference 0.03%, 95% CI -0.02 to 0.09). 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 saturated fat intakes.

11.62 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 carbohydrate.

11.63 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 carbohydrate (11 participants, 28 days intervention duration, p<0.01).

11.64 In summary, *adequate* evidence for no effect of substitution of saturated fats with carbohydrate on 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 carbohydrate and HbA1c

Randomised controlled trials
- No effect
- *Adequate* evidence

Prospective cohort studies
- No evidence

Glucose tolerance

Saturated fat intake and glucose tolerance

11.65 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

11.66 A systematic review and meta-analysis of RCTs (Hooper et al., 2015) included data from 3 RCTs with 249 participants, reporting changes in 2 hour oral glucose tolerance tests (OGTT) following reductions in saturated fat intakes. Interventions reducing saturated fat intake significantly reduced OGTT glucose values at 2 hour (i.e. improved glucose tolerance) (mean difference -1.69 mmol/L, 95% CI -2.55 to -0.82, p =0.0001; I^2 =45%). 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.

11.67 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 a secondary outcome measure, 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.

Saturated fat intake and glucose tolerance

Randomised controlled trials
   • *Insufficient* evidence
Prospective cohort studies
   • No evidence

Substitution of saturated fats with PUFA and glucose tolerance

11.68 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 (e.g. OGTT). No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.69 Imamura et al. (2016) carried out a systematic review with meta-regression analysis on data from 11 RCTs with 615 participants. 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). 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.

11.70 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.

11.71 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

11.72 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 (e.g. 2 hour

OGTT). No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.73   Imamura et al. (2016) carried out a systematic review with meta-regression analysis on data from 11 RCTs with 615 participants. These show that glucose tolerance derived from a 2 hour OGTT was not significantly different when saturated fats were substituted with MUFA (mean difference -0.10 mmol/L, 95% CI -0.91 to 0.70). 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.

11.74   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.

11.75   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 carbohydrate and glucose tolerance

11.76   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 carbohydrate on measures of glucose tolerance (e.g. 2

hour OGTT). No systematic reviews, meta-analyses or pooled analyses that evaluated PCS were identified.

Randomised controlled trials

11.77   Imamura et al. (2016) carried out a systematic review with meta-regression analysis on data from 11 RCTs with 615 participants. 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 carbohydrate (mean difference -0.04 mmol/L, 95% CI -0.39 to 0.31). 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.

11.78   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 carbohydrate on glucose tolerance. No significant effect was reported.

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

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

Insulin resistance

Saturated fat intake and insulin resistance

11.80 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on the relationship between saturated fat intakes and insulin resistance.

Substitution of saturated fats with PUFA and insulin resistance

11.81 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 homeostatic model assessment (HOMA) or infusion tests (e.g. 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

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

11.83 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) with 1292 participants, all without type 2 diabetes. This showed no statistically significant differences when saturated fats were substituted with PUFA (mean difference 0.24 10^{-5}/ (pmol/L)/min, 95% CI -0.13 to 0.61).

11.84 In a systematic review without meta-analysis Schwab et al. (2014) reported on 9 RCTs with varying specificity of saturated fats substitution (i.e. 5 RCTs reported on substitution of saturated fats with MUFA or PUFA; 4 RCTs reported on substitution of saturated fats with MUFA and carbohydrate). 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.

11.85 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 fat intake 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.

11.86 In summary, *adequate* evidence for a potentially beneficial 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

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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

11.87   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 (e.g. 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

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

11.89 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) with 1292 participants, all without type 2 diabetes. This showed no statistically significant differences when saturated fats were substituted with MUFA (mean difference 0.08 10^{-5}/(pmol/L)/min, 95% CI -0.01 to 0.17).

11.90 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.

11.91 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 3 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

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participants, intervention duration 3 months, p=0.05), whereas in 3 RCTs of healthy participants there was no significant difference.

11.92 In summary, *adequate* evidence for a potentially beneficial 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 carbohydrate and insulin resistance

11.93 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 carbohydrate on measures of insulin resistance (or inversely, insulin sensitivity) derived from HOMA or infusion tests (e.g. 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

11.94 The systematic review and meta-analysis of RCTs from Hooper et al. (2015) excluded studies with exposure duration <24 months, and reported data on HOMA from only a single RCT with 2832 participants. In that trial there was no significant effect of reduced saturated fats (lower fat, higher carbohydrate) compared with usual diet on HOMA insulin sensitivity (mean difference 0.00, 95% CI -0.04 to 0.04; p= 1.00). While a significance test for subgroup differences was reported, there is no further information on these differences, and that result itself had very high heterogeneity (I^2 =93%).

11.95 Imamura et al. (2016) carried out a systematic review with meta-regression analysis of data on HOMA insulin resistance from 30 RCTs with 1801 participants. This showed no significant effect when 5% energy as saturated fats was isoenergetically substituted with carbohydrate (mean difference 0.7%, 95% CI -1.6 to 3.1). These results are also reflected in sensitivity analyses of a subset of 24 trials of participants without type 2 diabetes.

11.96 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) with 1292 participants, all without type 2 diabetes. This showed no statistically significant differences when 5% energy as saturated fats was isoenergetically substituted with carbohydrate (mean differnece -0.10 10^{-5}/(pmol/L)/min, 95% CI -0.21 to 0.02).

11.97 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 carbohydrate.

11.98 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 carbohydrate on insulin resistance tested by HOMA and reported no effect. Two RCTs compared saturated fats with carbohydrate using infusions (FSIGTT and euglycaemic clamp) to measure insulin resistance in healthy participants, reporting no significant differences.

11.99 In summary, *adequate* evidence for no effect of substitution by carbohydrate 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 carbohydrate.

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

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

Summary

11.100 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.

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

11.102 Results were available from systematic reviews and 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.

11.103 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 carbohydrate 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 significant effects of saturated fats substitution with PUFA, MUFA or carbohydrate on glucose tolerance or for insulin resistance determined by infusion methods. For the latter outcome, the direction in each case was nevertheless consistent with a non-significant adverse effect of saturated fats substitution.

11.104 Taken together, these data show no detrimental health-relevant effects of saturated fats substitution with PUFA, MUFA or carbohydrate on markers of glycaemic control, and some beneficial effects of substitutions. Specifically, the effect of saturated fats substitution with carbohydrate was overall neutral for these outcomes, whereas saturated fats substitution with PUFA or MUFA had beneficial effects on a key marker of sustained glycaemic exposures (HbA1c), supported by indications of beneficial effects on insulin resistance.

11.105 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrate or protein, 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

Outcome	Saturated fats intake		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrate		Saturated fats substitution with protein	
	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	No evidence	↓	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

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12   Anthropometry

12.1   Four systematic reviews, 1 with meta-analysis (Tielemans et al., 2016; Hooper et al., 2015; Fogelholm et al., 2012; Micha & Mozaffarian, 2010) examined the relationship between the intake of saturated fats and anthropometric measurements (body weight, body mass index (BMI), waist circumference) or gestational weight gain. One systematic review analysed the results from randomised controlled trials (RCTs) (Hooper et al., 2015) and 3 evaluated the results from prospective cohort studies (PCS) (Tielemans et al., 2016; Fogelholm et al., 2012; Micha & Mozaffarian, 2010). The characteristics of these publications are summarised in Annex 2, Table A2.9. 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 PUFA, MUFA, carbohydrate or protein and anthropometric measurements.

Anthropometric measurements (body weight, BMI or waist circumference)

Saturated fat intake and anthropometric measurements (body weight, BMI or waist circumference)

Randomised controlled trials

12.3   A systematic review and meta-analysis of RCTs by Hooper et al. (2015), which included data from 9 RCTs, reported body weight or BMI changes following reductions in intakes of saturated fats. However, in the Hooper et al. (2015) systematic review and meta-analysis, body weight and BMI 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). Therefore the extent to which Hooper et al. (2015) can be considered to be a formal review of the effect of saturated fats on body weight is questionable. All interventions were under free-living conditions with no energy restriction or weight loss goals. Interventions reducing the

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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; I² =72%; 6 RCTs; 4541 participants), and BMI (mean difference -0.50 kg/m^2, 95% CI -0.82 to -0.19; I² =55%; 6 RCTs; 5553 participants). With the exception of 1 data set each for body weight (Oslo Diet-Heart, 1966) and BMI (Sydney Diet-Heart, 1978), the intervention arm in all studies involved reductions in total fat intake, with substitution of dietary fats including saturated fats mainly by carbohydrate; however, no data are presented on saturated fats substitution by specific macronutrients.

Prospective cohort studies

12.4   Two systematic reviews without meta-analyses reported results derived from PCS.

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

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

12.7   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, this evidence is graded as *limited* because 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. It was further noted that the SACN Carbohydrates and Health Report (2015) found *limited* evidence that energy restricted, higher carbohydrate, lower fat diets may be beneficial in reducing BMI. Therefore there is *limited* evidence to attribute effects to a reduction in saturated fats specifically rather than reducing saturated fats as part of total dietary fat intake.

Saturated fats intake and anthropometric measurements (body weight, BMI or waist circumference)
Randomised controlled trials   • Effect   • *Limited* evidence   • The direction of effect indicates that reduced intake of saturated fat lowers body weight and BMI   *Prospective cohort studies*   • *Insufficient* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and anthropometric measurements (body weight, BMI or waist circumference)

12.8   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), carbohydrate and protein on anthropometric measurements.

Gestational weight gain

Saturated fat intake and gestational weight gain

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

Prospective cohort studies

12.10 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 saturated fat intakes 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.

12.11 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 saturated fat intakes (per 5% of energy compared with carbohydrate); however the measured third trimester weight was compared with a self-reported pre-pregnancy weight (Stuebe et al., 2009).

12.12 Tielemans et al. (2016) stated that the remaining 6 studies ranged from very poor to moderate quality; of these, 5 reported no association with saturated fat intake 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).

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

Saturated fat intake and gestational weight gain
Randomised controlled trials   • No evidence   *Prospective cohort studies*   • *Insufficient* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and gestational weight gain

12.14   No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on saturated fat substitution with PUFA, MUFA, carbohydrate or protein on gestational weight gain.

Summary

12.15   Results were available from systematic reviews and 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 and meta-analysis. 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. Therefore the wider validity of the body weight and BMI conclusions drawn from that review is questionable.

12.16   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).

12.17   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.

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

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

Outcome	Saturated fats intake		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrate		Saturated fats substitution with protein	
	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	↓	Limited	n/a	No evidence	n/a	No evidence	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

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 A2.11. 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 RCTs were identified that reported on the effect of saturated fats on cancers. No systematic reviews, meta-analyses or pooled analyses of randomised controlled trials (RCTs) or prospective cohort studies (PCS) were identified that reported on the relationship between saturated fats substituted with polyunsaturated fats (PUFA), monounsaturated fats (MUFA), carbohydrate or protein 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 consumption of fruit, vegetables and grains. After 8.1 years there were 480 incident cases of colorectal cancer with a hazard ratio of 1.08 (95% CI 0.90 to 1.29) (Beresford et al., 2006) and 1727 incident cases of breast cancer with a hazard ratio of 0.91 (95% CI 0.83 to 1.01) (Prentice et al., 2006) in the low fat group. However, the participants were all female and they did not explicitly test for the effect of low saturated fats.

Colorectal cancer

Saturated fat intake 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 (RR 1.00, 95% CI 0.90 to 1.12, 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, there was *adequate* evidence from PCS (Liu et al., 2011) reporting no association between lower intake of saturated fats and the risk for colorectal cancer.

Saturated fat intake and colorectal cancer
Randomised controlled trials   • No evidence   *Prospective cohort studies*   • No association   • *Adequate* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and colorectal cancer

13.8   No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and colorectal cancer.

Pancreatic cancer

Saturated fat intake and pancreatic cancer

13.9   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

13.10   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 (RR 1.04, 95% CI 0.81 to 1.35; p=0.002 I^2=74%; 6 PCS; 1,130,815 participants, 3072 cases) for the highest versus the lowest category of intake (using energy-adjusted results where available).

13.11   In summary, there was *adequate* evidence from PCS reporting no association between the intake of saturated fats and the risk for pancreatic cancer.

Saturated fat intake and pancreatic cancer
Randomised controlled trials   • No evidence   *Prospective cohort studies*   • No association   • *Adequate* evidence

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Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and pancreatic cancer

13.12 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and pancreatic cancer.

Lung cancer

Saturated fat intake and lung cancer

13.13 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

13.14 Smith-Warner et al. (2002) reported a pooled analysis of individual participant data from 8 PCS, including 3188 cases mong 430,281 participants. There was no association between the intake of saturated fats and risk of lung cancer (RR 1.01 95% CI 0.89 to 1.14) for the highest versus lowest fourth (adjusted for energy), and (RR 1.03 95% CI 0.96 to 1.11) for a 5% increase in intake of energy from saturated fats.

13.15 In summary, there was *adequate* evidence from PCS reporting no association between the consumption of saturated fats and the risk for lung cancer.

Saturated fat intake and lung cancer

Randomised controlled trials
     • No evidence
 Prospective cohort studies
     • No association
     • *Adequate* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and lung cancer

13.16 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and lung cancer.

Breast cancer

Saturated fat intake and breast cancer

13.17 One systematic review with meta-analysis (Turner, 2011), 3 meta-analyses (Cao et al., 2016; Turner, 2011; Boyd et al., 2003) and 1 pooled analysis (Smith-Warner et al., 2001) 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

13.18 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 (RR 0.99, 95% CI 0.94 to 1.05; 19 PCS; 1,379,666 participants, 24,257 cases) when comparing the highest to the lowest quartile of saturated fat intake.

13.19 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 (RR 1.08, 95% CI 0.99 to 1.18; 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.

13.20 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.

13.21 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 Xia et al. (2015) meta-analysis.

13.22 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 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.

13.23 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%

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of total dietary energy) and risk of breast cancer. There was no association between saturated fats intake and risk of breast cancer (RR 1.06, 95% CI 0.92 to 1.24; 8 PCS; 351,821 women, 7329 cases) for a 5% increase in intake of energy from saturated fats.

13.24 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).

13.25 In summary, there was *adequate* evidence, based on the largest reliable meta-analysis of PCS (Cao et al., 2016), reporting no association between the consumption of saturated fats and the risk for breast cancer.

Saturated fat intake and breast cancer
Randomised controlled trials   • No evidence   *Prospective cohort studies*   • No association   • *Adequate* evidence

Substitution of saturated fats with PUFA and breast cancer

13.26 One pooled analysis of PCS (Smith-Warner et al., 2001) evaluated the association of modelled substitution of saturated fats by PUFA with 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, in which they modelled substitutions of saturated fat with PUFA. There was no association between saturated fats substitution with PUFA and the risk of breast cancer using a

random-effects model, modelling substitution of saturated fats with 5% of energy from PUFA (RR 0.98, 95% CI 0.85 to 1.12).

13.28 In summary, there was *adequate* evidence, based on the modelling of PCS by Smith-Warner et al. (2001), that substitution of saturated fats with PUFA was not associated with the risk of breast cancer. The evidence was deemed as *adequate* due to the number of studies included in the review.

Saturated fat 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

13.29 One pooled analysis of PCS (Smith-Warner et al., 2001) evaluated the association between modelled substitution of saturated fats by MUFA with 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, in which they modelled substitutions of saturated fat with MUFA. Using a random effect model, there was no association between saturated fats substitution with MUFA and risk of breast cancer, modelling substitution of saturated fats with 5% of energy from MUFA (RR 1.18, 95% CI 0.99 to 1.42).

13.31 In summary, there was *adequate* evidence, based on the modelling of PCS by (Smith-Warner et al., 2001), that substitution of saturated fats with MUFA was not associated

with the risk of breast cancer. The evidence was deemed as *adequate* due to the number of studies included in the review.

Saturated fat substitution with MUFA and breast cancer

Randomised controlled trials
    • No evidence
 	
Prospective cohort studies
    • No association
    • *Adequate* evidence

Substitution of saturated fats with carbohydrate and breast cancer

13.32 One pooled analysis of PCS (Smith-Warner et al., 2001) evaluated the association between modelled substitution of saturated fats by carbohydrate with breast cancer risk. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

13.33 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, in which they modelled substitutions of saturated fat with carbohydrate. Using random effects models, there was no association between saturated fats substitution with carbohydrate and risk of breast cancer, modelling substitution of saturated fats with 5% of energy from carbohydrate (RR 1.09, 95% CI 1.00 to 1.19).

13.34 In summary, there was *adequate* evidence, based on the modelling of PCS by Smith-Warner et al. (2001), that substitution of saturated fats with carbohydrate was not associated with the risk of breast cancer. The evidence was deemed as *adequate* due to the number of studies included in the review.

Saturated fat substitution with carbohydrate and breast cancer

Randomised controlled trials
    • No evidence
 	
Prospective cohort studies
    • No association
    • *Adequate* evidence

Substitution of saturated fats with protein and breast cancer

13.35 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that evaluated the relationship between substitution of saturated fats with protein and breast cancer.

Prostate cancer

Saturated fat intake and prostate cancer

13.36 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

13.37 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 is 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 is not considered reliable.

13.38 Dennis et al. (2004) reported a systematic review with meta-analysis of 3 PCS. They reported no association between intake of saturated fats and risk of prostate cancer (RR

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1.03, 95% CI 0.73 to1.46; 4 PCS; 130,875 participants, 2,536 cases) for a 25 g/day increment in intake of saturated fats (adjusted for energy).

13.39   The World Cancer Research Fund (WCRF) (2014) reported the results from a systematic review and meta-analysis on saturated fats intake and risk of prostate cancer using random-effects models (RR 0.99, 95% CI 0.96 to 1.03) per 10 g/day increase in intake of saturated fats (4887 cases in 9 studies, 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 (30,698 cases in 4 studies). 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).

13.40   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.

13.41   In summary, there was *adequate* evidence, based on the largest reliable meta-analysis of PCS (Dennis et al., 2004) and consideration of the WCRF report (WCRF, 2014), for no association between the intake of saturated fats and the risk for prostate cancer.

Saturated fat intake and prostate cancer
Randomised controlled trials • No evidence *Prospective cohort studies* • No association • *Adequate* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and prostate cancer

13.42 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and prostate cancer.

Summary

13.43 No systematic reviews, meta-analyses or pooled analyses of RCTs were identified that reported on saturated fats or their substitution with PUFA, MUFA, carbohydrate or protein and incident colorectal, pancreatic, lung, breast or prostate cancer.

13.44 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 saturated fat intake and risk of colorectal, pancreatic, lung, breast or prostate cancer.

13.45 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrate or protein, 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

Outcome	Saturated fats intake		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrate		Saturated fats substitution with protein	
	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

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14   Cognitive impairment and dementias

14.1   One meta-analysis (Xu et al., 2015b) and 4 systematic reviews of prospective cohort studies (PCS) (Barnard et al., 2014; Lee et al., 2010; Patterson et al., 2007; Ernst, 1999) were identified that 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 A2.13. 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), carbohydrate or protein on cognitive outcomes.

14.3   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 saturated fat intakes. 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 recognized 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[19] (OMIM 107741) has been linked to cognitive decline

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[19] 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 three major alleles: epsilon-2 (ε2), epsilon-3 (ε3), and epsilon-4 (ε4); resulting in three major protein isoforms, APOE-ε2, APOE-ε3,

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and dementia (Davies et al., 2014), and 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 risk-increasing effects of these genes to 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 be 5 years earlier, 2 copies of APOE-ε4 shift it 10 years earlier, and 1 copy of the APOE-ε2 allele shifts it 5 years later. The magnitude of this genetic effect 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

Saturated fat intake 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 a significant association between higher 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 greater 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

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and APOE-ε4, which differ from each other by one or two amino acids at positions 112 and 158 which alter APOE structure and function (Giau et al., 2015)

between saturated fats and cognitive function (9.1g/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.

Saturated fat intake and cognitive decline
Randomised controlled trials   • No evidence   *Prospective cohort studies*   • *Inconsistent* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and cognitive decline

14.8 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and cognitive decline.

Mild cognitive impairment

Saturated fat intake and mild cognitive impairment

14.9 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

14.10 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

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21.0 years. Mild cognitive impairment was diagnosed using the criteria developed by Petersen (2004)[20], 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.

14.11   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. Evidence of an association between the intake of saturated fats and the risk of mild cognitive impairment was graded as *limited*.

Saturated fat intake and mild cognitive impairment
Randomised controlled trials   • No evidence
Prospective cohort studies   • No association   • *Limited* evidence

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[20] 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.

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Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and mild cognitive impairment

14.12   No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and mild cognitive impairment.

Alzheimer's disease

Saturated fat intake and Alzheimer's disease

14.13   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

14.14   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 (RR 1.36; 95% CI -0.03 to 2.74; I^2=0%; 6201 participants, 168 cases, 2.1 to 3.9 years of follow-up). Both studies adjusted for age, sex, and education, one 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.

14.15   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; 3.9 years follow-up, 815 participants, 131 cases) and 2 studies reported no association in a comparison of the highest and lowest quartile of saturated fat intake (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 SD increase in intake, 95% CI 0.70 to 0.98; 6 years of follow-up; 5395 participants,

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146 cases). 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.

14.16 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.

14.17 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*.

Saturated fat intake and Alzheimer's disease
Randomised controlled trials   • No evidence *Prospective cohort studies*   • *Inconsistent* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and Alzheimer's disease

14.18 No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and Alzheimer's disease.

Dementias

Saturated fat intake and dementias

14.19 One systematic review without meta-analysis of PCS (Barnard et al., 2014) evaluated the association between saturated fats and dementias. No systematic reviews, meta-analyses or pooled analyses that evaluated RCTs were identified.

Prospective cohort studies

14.20 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.

14.21 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.

Saturated fat intake and dementias

Randomised controlled trials

- No evidence

Prospective cohort studies

- *Insufficient* evidence

Substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and dementias

14.22   No systematic reviews, meta-analyses or pooled analyses of RCTs or PCS were identified that reported on substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and dementias.

Summary

14.23   No systematic reviews, meta-analyses or pooled analyses of RCTs were identified that reported on the effect of saturated fats and cognitive outcomes.

14.24   A systematic review of PCS was identified which reported on saturated fat intakes 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. No association was found between mild cognitive impairment and saturated fats and there was *insufficient* evidence to draw a conclusion on the association with dementias.

14.25   Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrate or protein, 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

Outcome	Saturated fats intake		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrate		Saturated fats substitution with protein	
	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	Insuffcient	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

Background

15.1   In June 2014, the Scientific Advisory Committee on Nutrition (SACN) proposed to prioritise a review of the evidence of the role of fats in health, including monounsaturated fats, polyunsaturated fats and saturated fats. The topic had been suggested as part of the horizon scanning process and specific advice on saturated fats was requested by 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 specifically was most pressing. This review therefore only covers saturated fats and the substitution of saturated fats in the diet. The review considers the relationship between saturated fats and health outcomes, including cardiovascular disease (CVD) and intermediate markers and risk factors for which there was an adequate evidence base. This review does not consider total fat in the diet or the role of unsaturated fats other than as a replacement for saturated fats.

15.2   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 (DRV) for Food Energy and Nutrients for the United Kingdom in 1991 and Nutritional Aspects of Cardiovascular Disease in 1994. COMA recommended that the average contribution of saturated fatty acids to dietary energy be reduced to no more than 10% for adults and children aged 5 years and older[21]. This recommendation is set at a population level, does not apply before 2 years of age, and applies in full from 5 years of age. A flexible approach is 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

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[21] 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.

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by a rise or fall in low density lipoprotein (LDL)-cholesterol and in the commensurate risk of coronary heart disease'. Since then many organisations, including those from the US, France, the Netherlands and Australia, have reviewed the evidence on saturated fats and a range of health outcomes , including type 2 diabetes risk, cognitive outcomes and various cancers, with many setting similar recommendations to COMA (see Table 4.1).

Terms of reference

15.3   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.

Approach taken in consideration of the evidence

15.4   This report considers evidence from 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 events (coronary heart disease (CHD), stroke and peripheral vascular disease)
- type 2 diabetes
- selected common cancers (colorectal, pancreatic, lung, breast and prostate cancers)
- cognitive impairment and dementias (including Alzheimer's disease).

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Intermediate markers and risk factors:

- blood lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, total: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 measures such as weight change, body mass index (BMI), waist circumference andgestational weight gain

- cognitive function (cognitive decline, mild cognitive impairment).

15.5   The SACN Framework for the Evaluation of Evidence (SACN, 2012), and the methods used in the SACN Carbohydrate and Health report (2015), were adapted for use in evaluating systematic reviews, meta-analyses and pooled analyses that met the inclusion criteria. The totality of the included evidence was considered when grading the strength of the evidence for conclusion. Evidence was graded as *adequate*, *moderate*, *limited*, *inconsistent* or *insufficient*. Grades were agreed by consensus at the outset, referring to the criteria and explanatory notes described in Chapter 2. When evaluating consistency and agreement of findings between reviews, consideration was given to the degree of overlap in the included primary studies. The Committee agreed that only outcomes where the evidence base was graded as *adequate* or *moderate* would be used to inform the recommendations.

15.6   A number of limitations were identified in some of the available evidence and considered as part of the assessment of evidence. These are described in Chapter 2 (paragraph 2.18) and included:

- lack of information on statistical power

- limited length of follow-up time of RCTs and PCSs assessing disease as an outcome

- lack of information on the type of carbohydrate substituted for saturated fats

- lack of information on the type of PUFA substituted for saturated fats

- lack of consideration of the potential impact of individual saturated fatty acids (beyond the remit of this review)

- potential confounding by trans fat intakes, particularly in older data

- lack of sufficient data on the range of intakes of saturated fats

- the complexity of dietary and other changes made during interventions

- potential confounding by changes in weight in studies which did not use iso-energetic diets

- the quality of methods for measuring dietary intake

- lack of standardisation of some assays which complicates the comparability of the results between studies

- potential confounding by pharmaceutical treatments (e.g. statins) in blood lipid profile studies published after 1990

- potential confounding in PCS.

Classification, biochemistry and metabolism

15.7   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. The most common fats in food are triacylglycerols (also called triglycerides) where three fatty acids are esterified to glycerol. The characteristics of fats are determined by the physical and chemical properties of the fatty acids they contain. Saturated fatty acids have no double bonds. Monounsaturated fatty acids have a single double bond, while polyunsaturated fatty acids contain two or more double bonds.

15.8   Cholesterol is a sterol with a ring structure containing an alcohol unit at one end. Although it is not a fat, the compound and its derivatives are commonly found in fat-containing foods. As well as being found in the diet, cholesterol is synthesised in the body and is an important component of membranes in cells. Only around 15% of cholesterol in the blood comes from dietary sources. Therefore, the intake of dietary cholesterol has

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limited impact on cholesterol concentration in the blood or risk of disease unless dietary intakes exceed around 300 mg per day.

15.9   One gram of dietary fat has a physiological fuel value of approximately 37kJ (9 kcal) of energy compared with 17kJ (4 kcal) per gram for carbohydrate and protein. Fats are largely stored in adipose tissue, often referred to as 'body fat' or simply 'fat'. The liver has a central role in metabolising fats. Humans can also convert excess energy from other macronutrients into the non-essential fatty acids in the process of de novo lipogenesis.

Dietary intakes and trends

15.10 The most recent data from the National Diet and Nutrition Survey (NDNS) 2008 to 2014 indicated that mean intakes of saturated fats in the UK exceeded COMA (1994) recommendations in all age, sex and income groups (Bates et al., 2016; Bates et al., 2014b). Mean intakes of saturated fats as a percentage of total dietary energy were 12.5-13.3% in children (age 4-18 years), and 12.7-13.4% among adults (age 19 years and over). There was no consistent pattern in intake by household income (Bates et al., 2014b).

15.11 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 are the main contributors to saturated fat intakes in all age groups. Milk and milk products (especially whole milk) made a larger contribution for children aged 4-10 years.

15.12 Between 1986/87 and 2008/14 the intake of saturated fats as a percent of total dietary energy decreased in adults but has remained above the DRV. The main sources of saturated fats showed little change over time. There was a notable decline in whole milk consumption (leading to a reduction in the intake of saturated fat from whole milk) from approximately 11% to 2% of average daily saturated fats intake) in adults (aged 19 to 64 years) and older adults (aged 65 years and over), but the overall percentage contribution of milk and milk products to daily saturated fats intake remained unchanged at around 22%. The contribution of fat spreads to saturated fat intake as a percent of total dietary energy has declined mainly due to a decreased intake of butter, especially among adults

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(aged 19 to 64 years). There has been a substantial decline in trans fats as a percentage of total dietary energy among all age groups from 2.1% in 1986/87 to 0.5% to 2013/14. In adults (aged 19 to 64 years), mean dietary cholesterol intake decreased between 1986/87 and 2013/14, from 380mg/day to 263mg/day in men and from 280 mg/day to 219mg/day in women.

15.13 The NDNS data indicated that between 2008 and 2014 there has been virtually no change in mean serum total cholesterol, LDL cholesterol and HDL cholesterol in adults and older adults. Comparison cannot be made to findings from earlier surveys (e.g. 1986/87, 1994/5 and 2000/01) due to methodological differences in blood sample processing and analysis.

Cardiovascular diseases

15.14 Evidence on the relationship between intakes of saturated fats and their substitution with polyunsaturated fats (PUFA), monounsaturated fats (MUFA), carbohydrate or protein, and cardiovascular outcomes is summarised below and in Annex 5. 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 (e.g. stroke) and peripheral vascular disease.

Total cardiovascular diseases

15.15 There was *adequate* evidence from RCTs that reducing intake of saturated fats had no effect on CVD mortality.

15.16 There was *adequate* evidence from RCTs that reducing intake of saturated fats reduced the risk of CVD events.

15.17 There was *adequate* evidence from PCS that intake of saturated fats was not associated with CVD mortality. There was *insufficient* evidence to determine any association between intakes of saturated fats and CVD events.

15.18   There was *adequate* evidence from RCTs that substituting saturated fats with PUFA had no effect on CVD mortality.

15.19   There was *adequate* evidence from RCTs that substituting saturated fats with PUFA reduced the risk of CVD events.

15.20   There was *limited* evidence from PCS that substituting saturated fats with unsaturated fats (a combination 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.

15.21   *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.

15.22   There was *limited* evidence from RCTs that substituting saturated fats with carbohydrate or protein 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 carbohydrate or protein.

15.23   *Insufficient* evidence was available from PCS to determine any association between substituting saturated fats with carbohydrate and CVD mortality or events.

15.24   There was no evidence available from PCS to determine if there was an association between substituting saturated fats with protein and CVD mortality or events.

Coronary heart disease

15.25   There was *adequate* evidence from RCTs that reducing intake of saturated fats had no effect on CHD mortality.

15.26   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

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statistical significance between reported statistical models, although these generated similar effect estimates and the difference between the p-values were small.

15.27　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.

15.28　There was *adequate* evidence from RCTs that substituting saturated fats with PUFA had no effect on CHD mortality.

15.29　There was *limited* evidence from RCTs that substituting saturated fats with PUFA decreased risk of CHD events. The evidence was graded as *limited* based on an adequate number of studies and events, but an upper confidence interval of exactly 1.00.

15.30　There was *adequate* evidence from PCS that substituting saturated fats with PUFA was associated with a lower risk of CHD mortality and CHD events.

15.31　There was *insufficient* evidence from RCTs to determine any effect of substituting saturated fats with MUFA on CHD mortality and events.

15.32　There was *limited* evidence from PCS indicating no association between modelled substitution of saturated fats with MUFA and 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.

15.33　There was *limited* evidence from RCTs indicating that substituting saturated fats with carbohydrate or protein had no effect on CHD mortality. 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 carbohydrate or protein.

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15.34 There was *moderate* evidence from RCTs that substituting saturated fats with carbohydrate had no effect on CHD events. The evidence was graded as *moderate* because the analyses underpinning the conclusion relied heavily on a study which did not explicitly test for the effect of substituting saturated fats with carbohydrate.

15.35 There was *adequate* evidence from PCS that modelled substitution of saturated fats with carbohydrate was not associated with a change in risk of CHD mortality but was associated with an increased risk of CHD events.

15.36 There was *limited* evidence from RCTs that substituting saturated fats with protein had no effect on CHD 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 protein. There was no evidence from PCS.

Strokes

15.37 There was *adequate* evidence from RCTs and PCS that there was no relationship between lower intake of saturated fats and strokes (fatal and non-fatal).

15.38 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.

15.39 There was *limited* evidence from RCTs that substituting saturated fats with carbohydrate or protein 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 carbohydrate or protein. There was no evidence from PCS.

Blood lipids

15.40 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrate or protein, and blood lipids is summarised below and in Annex 5.

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Serum total cholesterol

15.41 There was *adequate* evidence from RCTs that reducing the intake of saturated fats decreased total serum cholesterol.

15.42 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrate decreased total serum cholesterol. There was no evidence for protein.

15.43 There was *insufficient* evidence from PCS to determine any association between modelled substitution of saturated fats with PUFA, MUFA or carbohydrate and total serum cholesterol. There was no evidence for protein.

Serum LDL and HDL cholesterol

15.44 There was *adequate* evidence from RCTs that reducing the intake of saturated fats decreased serum LDL and HDL cholesterol.

15.45 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrate decreased serum LDL cholesterol. There was no evidence for protein.

15.46 There was *moderate* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrate decreased serum HDL cholesterol. The evidence was graded as *moderate*, as the changes were small and not detected in all systematic reviews and meta-analyses. There was no evidence for protein.

15.47 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 carbohydrate and serum LDL cholesterol. No evidence from PCS was identified that reported on similar associations with HDL cholesterol. There was no evidence for protein.

Serum total cholesterol:HDL cholesterol ratio

15.48 There was *moderate* evidence from RCTs that substituting saturated fats with PUFA or MUFA resulted in a reduction in the total serum cholesterol:HDL cholesterol ratio. The evidence was graded as *moderate* as the changes were small and not detected in all the systematic reviews and meta-analyses. SACN noted that the serum total cholesterol:HDL cholesterol ratio is more widely used for risk prediction in clinical practice than serum LDL cholesterol or serum HDL cholesterol alone (it is the primary lipid parameter in the QRISK2 assessment to predict CVD risk).

15.49 There was *adequate* evidence from RCTs that substituting saturated fats with carbohydrate had no effect on total serum cholesterol:HDL cholesterol ratio. There was no evidence for protein.

15.50 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, carbohydrate or protein and total serum cholesterol:HDL cholesterol ratio.

Serum triacylglycerol

15.51 There was *adequate* evidence from RCTs that a reduction in saturated fats decreased serum triacylglycerol.

15.52 There was *moderate* evidence from RCTs that substituting saturated fats with PUFA or MUFA had no effect on serum triacylglycerol. The evidence was graded as *moderate* due to the disagreement across the studies.

15.53 The evidence from RCTs was *inconsistent* to determine any effect of substituting saturated fats with carbohydrate on serum triacylglycerol. There was no evidence for protein.

15.54 No evidence from PCS was identified that reported on the association between lower intake or substitution of saturated fats with PUFA, MUFA, carbohydrate or protein and serum triacylglycerol.

Blood pressure

15.55   Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrate or protein, and blood pressure is summarised below and in Annex 5.

15.56   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 a primary outcome in the most recent and most comprehensive review.

15.57   There was *limited* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrate had no effect on blood pressure. The evidence base was small and heterogeneous. The evidence was graded as *limited* as blood pressure was not a primary outcome in the most recent review. There was no evidence for protein.

15.58   There was *insufficient* evidence from PCS on any association between the modelled substitution of saturated fats with MUFA and blood pressure. There was no evidence on the association between reduced intake of saturated fats or the modelled substitution of saturated fats with PUFA, carbohydrate or protein and blood pressure from PCS.

Type 2 diabetes and markers of glycaemic control

15.59   Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrate or protein, and risk of type 2 diabetes and glycaemic control is summarised below and in Annex 5.

Type 2 diabetes

15.60   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.

15.61   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

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lowest. There was no or *insufficient* evidence from PCS to determine any association of specific modelled substitutions for saturated fats with risk of type 2 diabetes.

Fasting glucose

15.62　There was *adequate* evidence from RCTs that substituting saturated fats with PUFA resulted in a small beneficial decrease in fasting blood glucose.

15.63　There was *adequate* evidence from RCTs that substituting saturated fats with MUFA or carbohydrate had no effect on fasting blood glucose.

15.64　There was no evidence from PCS to draw a conclusion on the association between lower intake of saturated fats and fasting glucose, or the effect of specific modelled substitutions for saturated fats.

Fasting insulin

15.65　There was *adequate* evidence from RCTs that substituting saturated fats with PUFA had no effect on fasting insulin.

15.66　There was *adequate* evidence from RCTs that substituting saturated fats with MUFA or carbohydrate resulted in a potentially detrimental increase in fasting insulin.

15.67　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

15.68　There was *adequate* evidence from RCTs that substituting saturated fats with PUFA or MUFA resulted in a potentially beneficial decrease in HbA1c.

15.69　There was *adequate* evidence from RCTs that substituting saturated fats with carbohydrate had no effect on HbA1c.

15.70 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 modelled substitutions for saturated fats.

Glucose tolerance

15.71 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrate had no effect on glucose tolerance.

15.72 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

15.73 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA or MUFA resulted in a potentially beneficial decrease in insulin resistance (assessed by HOMA).

15.74 There was *adequate* evidence from RCTs that substituting saturated fats with carbohydrate had no effect on insulin resistance (assessed by HOMA).

15.75 There was *adequate* evidence from RCTs that substituting saturated fats with PUFA, MUFA or carbohydrate had no effect on insulin resistance (assessed by infusion tests).

15.76 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)

15.77 Evidence on the relationship between intakes of saturated fats and their substitution with PUFA, MUFA, carbohydrate or protein, and anthropometry is summarised below and in Annex 5.

15.78 There was *limited* evidence from RCTs that reduced intakes of saturated fats reduced body weight and body mass index (kg/m^2). The evidence was graded *limited,* because it was based on trials where this was a secondary outcome, and the majority of the data came from trials where there were reductions in both saturated and total fats. There was no evidence on the effect of specific substitutions for saturated fats from RCTs.

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, carbohydrate or protein, and cancers is summarised below and in Annex 5.

15.82 No RCTs were identified that reported the effect of reduced intake of saturated fats, or saturated fats substitution with PUFA, MUFA, carbohydrate or protein, 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 for no association between modelled saturated fats substitution by PUFA, MUFA or carbohydrate and 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, carbohydrate or protein, and cognitive outcomes is summarised below and in Annex 5.

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. There was no evidence for saturated fats substitutions.

15.87 The evidence from PCS on the association between saturated fats intake and Alzheimer's disease was *inconsistent* and for dementias (including Alzheimer's disease and other forms of dementias) was *insufficient*. There was no evidence from PCS for saturated fats substitutions for any cognitive outcomes.

Overall conclusion

Reduction in saturated fats

15.88 RCTs reducing saturated fats *per se* had no effect on CVD mortality, CHD mortality or strokes. However, as noted in paragraph 15.6 on study limitations, the duration of follow-up may have been too short to detect effects on mortality.

15.89 There was *adequate* or *moderate* evidence (from RCTs) that reducing the intake of saturated fats reduces the risks of CVD and CHD events respectively, and improves serum total cholesterol, LDL cholesterol and triacylglycerol.

15.90 There was no or *insufficient* evidence from RCTs to draw a conclusion on any effect of reduced intake of saturated fats on risk of type 2 diabetes or markers of glycaemic control. *Adequate* evidence from PCS indicated no association between risk of type 2 diabetes and saturated fats. Evidence on the relationship between saturated fats and

blood pressure, anthropometric measurements, and cognitive outcomes was unclear. There was no association between saturated fats and cancers.

Substitution of saturated fats with PUFA

15.91 RCTS substituting saturated fats with PUFA had no effect on CVD and CHD mortality, however, the duration of the follow-up may have been too short to detect any effect.

15.92 There was *adequate* or *limited* evidence (from RCTs) that substituting saturated fats with PUFA reduced the risk of CVD and CHD events respectively and *adequate* evidence from PCS that substituting saturated fats with PUFA reduced the risk of CHD events.

15.93 There was *adequate* or *moderate* evidence (from RCTs) that substituting saturated fats with PUFA improved total cholesterol, LDL cholesterol and total cholesterol:HDL cholesterol ratio and improved sustained glycaemic control as evidenced by HbA1c and insulin resistance (HOMA). There was no or *insufficient* evidence from PCS.

15.94 RCTs and PCS which substituted saturated fats with PUFA did not specify the type of PUFA (i.e. n-3 or n-6). Evidence on the effect of saturated fats substitution with PUFA on blood pressure was unclear. No evidence on the relationship between substitution of saturated fats with PUFA and strokes, anthropometric measurements, cancers or cognitive outcomes was identified.

Substitution of saturated fats with MUFA

15.95 There was no or *insufficient* evidence to determine any relationship between substitution of saturated fats with MUFA and total CVD from RCTs and PCS. There was *adequate* or *moderate* evidence (from RCTs) that substitution of saturated fats with MUFA improved total cholesterol, LDL cholesterol and the total cholesterol:HDL cholesterol ratio. The evidence on blood pressure was unclear. While there was *adequate* evidence from RCTs indicating that substitution of saturated fats with MUFA resulted in a potentially beneficial decrease in HbA1c and insulin resistance (assessed by HOMA), it also resulted in a potentially detrimental increase in fasting insulin. There was no evidence on the

relationship between substitution of saturated fats with MUFA and strokes, anthropometric measurements, cancers or cognitive outcomes.

Substitution of saturated fats with carbohydrate

15.96 The evidence in relation to carbohydrate substitution and CHD events was inconsistent. There was *adequate* evidence from PCS studies that modelled substitution of saturated fats with carbohydrate was associated with an increased risk of CHD events but *moderate* evidence from RCTs that the same substitution had no effect on CHD events. There was *adequate* evidence (from RCTs) that substitution of saturated fats with carbohydrate reduced total and LDL cholesterol and *moderate* evidence (from RCTs) that substitution of saturated fats with carbohydrate reduced HDL cholesterol. Evidence was also unclear for blood pressure as it was not a primary outcome in the most recent and most comprehensive review. The evidence is unclear as studies did not usually describe the type of carbohydrate. There was *adequate* evidence from RCTs that substituting saturated fats with carbohydrate had no effect on markers of glycaemic control, apart from fasting glucose for which substitution with carbohydrate resulted in a potentially detrimental increase. No evidence was identified on anthropometric measurements, gestational weight gain, cancers or cognitive outcomes.

Substitution of saturated fats with protein

15.97 There was *limited* evidence (from RCTs) that substituting saturated fats with protein had no effect on total CVD. There was no evidence (from RCTs and PCS), to determine any effect from substitution of saturated fats with protein and the other health outcomes, intermediate markers or risk factors.

16 Recommendations

Context

16.1 In 1994, COMA recommended that the average contribution of saturated fatty acids to dietary energy be reduced to no more than 10% for adults and children age 5 years and older. The COMA recommendation 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 of age (COMA, 1994).

16.2 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-1990s (when it was around 16% of total dietary energy intake). It is currently above 12% for adults and this has changed little over the last 6 years for which data are available. The most recent data show similar levels of intakes in children aged 5 years and over.

16.3 The COMA (1994) recommendation for average contribution of saturated fatty acids was primarily based on the effect of the intake of saturated fatty acids on circulating low density lipoprotein (LDL) cholesterol concentrations and its role in coronary heart disease (CHD).

16.4 Since 1994, the evidence base on saturated fats and health has grown considerably. In addition to further work 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 and this report is based on a further analysis of these, with precedence given to evidence from randomised controlled trials (RCTs).

16.5 New evidence published since 1994 supports and strengthens the original COMA conclusion that a reduction in saturated fat intakes from current population average levels would be beneficial.

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Recommendations

16.6   Based on the totality of the evidence considered, it is recommended that:

- the dietary reference value for saturated fats remains unchanged: that the population average contribution of saturated fatty acids to total dietary energy be reduced to no more than 10% (11% food and drink energy, excluding alcohol) for adults and children aged 5 years and older

- saturated fats are substituted with unsaturated fats (PUFA or MUFA).

16.7   This recommendation is made in the context of existing dietary reference values (see Table 16.1) and existing dietary advice (as depicted by the Eatwell Guide)

16.8   No evidence meeting the inclusion criteria was identified for older adults or children aged 5 years and older. However, there is no reason to assume that the recommendations should differ for these age groups.[22]

16.9   It is recommended that the government gives consideration to strategies to reduce population average intake of saturated fats to no more than 10% of dietary energy.

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[22] Information for consultation: any further evidence on children under age 5 years will be considered by a future SACN report on feeding children aged 12 to 60 months of age. Any further evidence on older adults may be considered as part of a future SACN report on this age group.

Table 16.1 Dietary Reference Values[1,2] for energy and macronutrients for males and females in the UK

Energy	2500 kcal/day for males; 2000 kcal/day for females[7]
Macronutrients	
Protein[3]	0.75g of protein per kilogram of bodyweight[8]
Total fats[4]	Reduce to about 35% of dietary energy
Of which	
Saturated fats[4]	Reduce to no more than 10% of dietary energy
Cis MUFA[4]	No specific recommendations for MUFA [9]
Cis PUFA[3]	Continue to provide on average of 6% of total dietary energy (derived from a mixture of n-3 PUFA and n-6 PUFA)[10]
Of which	
Long chain n-3 PUFA[5]	Increase from 0.2g/day to 0.45g/day[11]
Alpha linolenic acid[3]	Provide at least 0.2% of total energy
n-6 PUFA[4]	No further increase in the average intakes and the proportion of the population consuming in excess of 10% of energy should not increase
Linoleic acid[3]	Provide at least 1% of total energy
Trans fat[4]	Provide no more than about 2% of dietary energy
Carbohydrate[6]	Approximately 50% of total dietary energy
Of which	
Free sugars[6]	Less than 5% of total dietary energy
Dietary fibre[6]	30g/day[12]

[1]Values are expressed as proportions of either total (dietary) energy or dietary energy, depending on the source report.

[2] Dietary Reference Values (DRVs) are a series of estimates of the energy and nutritional requirements of different groups of healthy people in the UK population and they are not recommendations or goals for individuals.

[3] From COMA Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (1991) recommendations.

[4] From COMA Nutritional Aspects of Cardiovascular disease (1994) recommendations.

[5] 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.

[6] From SACN Carbohydrates and Health (2015) recommendations for population aged 2 years and over.

[7]These figures are based on the current government advice and they are not in line with SACN Dietary Reference Values (2011) recommendations. SACN recommended that DRVs for adult males and females 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 19-50 years. RNI varies depending on age and gender and whether pregnant or breastfeeding.

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[9]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.

[10]To note that the recommendations for PUFA were not reviewed in COMA Nutritional Aspects of Cardiovascular disease (1994). Only separate recommendations for long chain n-3 PUFA and n-6 PUFA were made.

[11]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)'.

[12]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 section 2.17). It is therefore recommended that future research:

- ensures designs are of sufficient power and duration, to test the effect of reduced saturated fat intakes or specific substitutions on chronic disease outcomes.

- makes use of opportunities for re-analysis of data from older studies (pre 1990) which substituted saturated fats with unsaturated fats, provided that confounding by the presence of trans fats is adequately addressed.

- specifies the type of carbohydrate and considers this in analyses and interpretation (for example, those with low compared to high glycaemic index; 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.

Topics

17.2   A number of gaps in the evidence were identified during the development of this report. Therefore, further research is required to:

- undertake systematic reviews and meta-analyses (and possibly further primary research) investigating the potential effect of saturated fat intakes 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 an intervention study, sufficiently powered and of longer duration, to test the effect of lower saturated fat intakes on chronic disease outcomes. Novel study designs, including the use of genetic information in mendelian randomisation, may provide useful additional information

- examine the effects of saturated fat intakes lower than currently recommended (i.e. below 10% of total dietary energy intake) on health outcomes, intermediate markers and/or risk factors. Studies will need to avoid or control for changes to energy, total fat or cholesterol intakes

- 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 complex carbohydrate

    - protein,

and health outcomes, intermediate markers and/or risk factors.

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