Guidelines: Saturated fatty acid and *trans*-fatty acid intake for adults and children

Contents

Acknowledgements

(To be completed)

Abbreviations and acronyms

BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
CLA	conjugated linoleic acid
CVDs	cardiovascular diseases
eLENA	WHO e-Library of Evidence for Nutrition Actions
FAO	Food and Agriculture Organization of the United Nations
GINA	WHO Global Database on the Implementation of Nutrition Action
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL	high-density lipoprotein
HOMA-IR	homeostasis model of insulin resistance
kcal	kilocalorie
kJ	kilojoules
LDL	low-density lipoprotein
MD	mean difference
MUFA	monounsaturated fatty acids
NCDs	noncommunicable diseases
NUGAG	WHO Nutrition Guidance Expert Advisory Group
PICO	population, intervention, comparator and outcome
PUFA	polyunsaturated fatty acids
RCT	randomized controlled trial
RR	risk ratio
SFA	saturated fatty acids
SMD	standardized mean difference
TFA	*trans*-fatty acids
USA	United States of America
WHO	World Health Organization

Executive summary

Background

Noncommunicable diseases (NCDs) are the world's leading cause of death: they were responsible for an estimated 39.5 million (72%) of the 54.7 million deaths in 2016 *(1)*. Many of those deaths were premature (i.e. under the age of 70 years) and occurred in low- and middle-income countries. Of the major NCDs, cardiovascular diseases (CVDs)[1] were the leading cause of NCD mortality in 2016, being responsible for nearly half (45%) of all NCD deaths. Modifiable risk factors such as unhealthy diet, physical inactivity, tobacco use, and harmful use of alcohol are major causes of CVDs. Dietary saturated fatty acids and *trans*-fatty acids are of particular concern because high levels of intake are correlated with increased risk of CVDs *(2)*.

Saturated fatty acids are fatty acids containing only single carbon–carbon bonds (i.e. no double bonds). Saturated fatty acids are found in foods from animal sources such as butter, cow's milk, meat, salmon and egg yolks, and in some plant-derived products such as chocolate and cocoa butter, and coconut, palm and palm kernel oils. *Trans*-fatty acids are unsaturated fatty acids with at least one double carbon–carbon bond in the *trans* configuration. *Trans*-fatty acids can be produced industrially by the partial hydrogenation of vegetable and fish oils, but also occur naturally in meat and dairy products from ruminant animals (e.g. cattle, sheep, goats, camels). Industrially-produced *trans*-fatty acids can be found in baked and fried foods, pre-packaged snacks and food, and partially hydrogenated cooking oils and fats which are often used at home, in restaurants, or in the informal food sector (such as street vendors), and are the predominant source of *trans*-fatty acid intake in many populations.

Reduced intake of saturated fatty acids has been associated with a significant reduction in risk of coronary heart disease (CHD) when replaced with polyunsaturated fatty acids (PUFA) or carbohydrates from whole grains *(3-6)*. Similarly, studies have demonstrated that high intakes of industrially-produced *trans*-fatty acids are strongly associated with increased risk of CHD and related mortality *(7, 8)*. Few studies have identified an association between intake of ruminant *trans*-fatty acids and CVDs; however, to date, ruminant *trans*-fatty acid intake in most study populations has been very low *(9)*. The reduction in risk of CVDs seen with decreased intake of saturated fatty acids and *trans*-fatty acids is believed to occur primarily through an effect on blood lipids, because intakes of both are positively correlated

[1] Cardiovascular diseases include coronary heart disease, cerebrovascular disease (e.g. stroke), structural abnormalities of the heart at birth or damage resulting from rheumatic fever, peripheral arterial disease, and deep vein thrombosis and pulmonary embolism.

with total and low-density lipoprotein (LDL) cholesterol[1] levels *(10, 11)*. Total cholesterol has been shown to be positively associated with CHD *(12)*, and LDL cholesterol is a well-established biomarker for measuring the effects of interventions on CVD risk *(13-15)*.

Although there have been few studies of *trans*-fatty acid intake in children, results of dietary intervention studies conducted in children have demonstrated significant reductions in total cholesterol, LDL cholesterol, or both, when saturated fatty acids were replaced with PUFA *(16-21)*.

Objective

The objective of these guidelines are to provide recommendations on the intake of saturated fatty acids and *trans*-fatty acids to reduce the risk of NCDs in adults and children, particularly CVDs which are a leading cause of NCD mortality. The recommendations in these guidelines can be used by policy-makers and programme managers to assess current intake levels of these fatty acids in their populations relative to a benchmark with a view to develop measures to decrease intake of saturated fatty acids and *trans*-fatty acids, where necessary, through a range of policy actions and public health interventions.

Methods

WHO developed the present evidence-informed guidelines using the procedures outlined in the *WHO handbook for guideline development (22)*. The steps in this process included:

- identification of priority questions and outcomes;
- retrieval of the evidence;
- assessment and synthesis of the evidence;
- formulation of recommendations;
- identification of research gaps; and
- planning for dissemination, implementation, impact evaluation and updating of the guideline.

Grading of Recommendations Assessment, Development and Evaluation (GRADE)[2] methodology was used to assess the quality of evidence identified through recent systematic reviews of the scientific literature on preselected topics related to intake of saturated fatty acids and *trans*-fatty acids. An international, multidisciplinary group of experts including

[1] In these guidelines, mention of all forms of cholesterol and triglycerides refers to concentrations of these lipids in blood.
[2] http://www.gradeworkinggroup.org/

methods experts – the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health – participated in the WHO guideline development meetings. The experts reviewed and assessed the quality of evidence, drafted recommendations and reached consensus on the strength of the recommendations. The group also took into consideration desirable and undesirable effects of the recommendations, the quality of the available evidence, priority of the problem that the recommendations address, values and preferences related to the recommendations in different settings, the cost of the options available to public health officials and programme managers in different settings, feasibility and acceptability of implementing the recommendations in different settings, and the potential impact on equity and human rights. All members of the NUGAG Subgroup on Diet and Health, as well as external resource persons including additional subject-matter experts and systematic review teams, completed a declaration of interest form before each meeting. Declaration of interest forms were then reviewed by the WHO Secretariat in consultation with the WHO Legal Office previously, but since 2014 with the Department of Compliance and Risk Management and Ethics, as part of the preparatory process for holding the NUGAG meetings. In addition, each NUGAG member verbally declared his or her interests at the start of each NUGAG meeting. The procedures for management of interests outlined in the WHO *Guidelines for declaration of interests for WHO experts (23)* were strictly followed.

The evidence

Saturated fatty acids

Meta-analysis of randomized controlled trials (RCTs or 'trials') conducted in adults found that reducing saturated fatty acid intake reduced the risk of cardiovascular events (*moderate*[1] quality evidence). The effect appeared to be strongest when serum cholesterol concentrations were significantly reduced or when saturated fatty acids were replaced with PUFA (*low* quality evidence). Non-significant reductions in risk of CHD events (*low* quality evidence) and myocardial infarction (*moderate* quality evidence) were also observed with reduced saturated fatty acid intake. No significant effect of reducing saturated fatty acid

[1] Based on the grades of evidence set by the GRADE Working Group: *high* quality, we are very confident that the true effect lies close to that of the estimate of the effect; *moderate* quality, we are moderately confident in the effect estimate – the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; *low* quality, our confidence in the effect estimate is limited – the true effect may be substantially different from the estimate of the effect; and *very low* quality, we have very little confidence in the effect estimate – the true effect is likely to be substantially different from the estimate of the effect *(22)*.

intake on mortality,[1] non-fatal myocardial infarction alone or stroke was observed (*moderate* quality evidence).

A second systematic review and multiple regression of RCTs conducted in adults found that isocalorically[2] replacing saturated fatty acids with PUFA, monounsaturated fatty acids (MUFA) or carbohydrates lowered total and LDL cholesterol across a wide range of saturated fatty acid intakes, including intakes below 10% of total energy intake. Replacing saturated fatty acids with PUFA, MUFA or carbohydrates also lowered high-density lipoprotein (HDL) cholesterol slightly; replacing with PUFA or MUFA additionally lowered triglycerides, the total cholesterol to HDL cholesterol ratio, and the LDL cholesterol to HDL cholesterol ratio, with PUFA replacement demonstrating the largest effect on all outcomes, except HDL cholesterol, where replacement with carbohydrates resulted in the greatest decrease. A small increase in triglycerides was observed when saturated fatty acids were replaced with carbohydrates. Increasing saturated fatty acid intake through the isocaloric replacement of PUFA, MUFA or carbohydrates with saturated fatty acids had the opposite effect to replacing saturated fatty acids with PUFA, MUFA or carbohydrates, including raising LDL cholesterol. The overall quality of available evidence for an association between saturated fatty acid intake and all blood lipid outcomes was considered to be *high,* except for the total cholesterol to HDL cholesterol ratio outcome when exchanging saturated fatty acids and carbohydrates, the quality of which was considered to be *moderate*.

Meta-analysis of RCTs conducted in children found that reducing saturated fatty acid intake reduced total cholesterol, LDL cholesterol and diastolic blood pressure. A small number of trials suggest that the effect was strongest when saturated fatty acids were replaced primarily with PUFA or a mixture of PUFA and MUFA, and when saturated fatty acid intake was reduced to a level less than 10% of total energy intake. No significant effects were observed for HDL cholesterol, triglycerides and systolic blood pressure, or for anthropometric measures such as height, weight, body mass index (BMI) and waist circumference. There were no adverse effects reported with reduced saturated fatty acid intake. The overall quality of available evidence for an association between a reduction in saturated fatty acid intake and all outcomes in children was considered to be *high,* except for systolic blood pressure, triglycerides, waist circumference and insulin resistance, for all of which the quality was considered to be *moderate*.

[1] From any cause (i.e. all-cause) or specifically from CVDs or CHD.
[2] The amount of PUFA, MUFA or carbohydrates used as replacement for saturated fatty acids was identical to that of the saturated fatty acids being replaced, *in terms of calories*.

Trans-fatty acids

Meta-analysis of prospective cohort studies found an association between lower *trans*-fatty acid intake and reduced risk of all-cause mortality, CHD mortality and CHD events in adults. Significant associations were not observed between lower *trans*-fatty acid intake and stroke and type 2 diabetes. *Trans*-fatty acid intakes of less than 1% of total energy intake were associated with reduced risk of CHD mortality and events, whereas intakes greater than 1% of total energy intake were associated with increased risk of CHD mortality and events. The overall quality of available evidence for an association between *trans*-fatty acid intake and all outcomes was considered to be *moderate,* except for all-cause mortality and stroke, where the quality was considered to be *low* (for reduction in *trans*-fatty acid intake only) and *very low*, respectively.

Meta-regression analysis of RCTs conducted in adults found that isocalorically replacing *trans*-fatty acids with PUFA, MUFA or carbohydrates decreased total and LDL cholesterol across a wide range of *trans*-fatty acid intakes, including intakes below 1% of total energy intake, whereas replacing *trans*-fatty acids with saturated fatty acids resulted in raised total and LDL cholesterol. Replacing *trans*-fatty acids with PUFA or MUFA also lowered triglycerides; replacing with PUFA, MUFA, or carbohydrates lowered the total cholesterol to HDL cholesterol ratio and the LDL cholesterol to HDL cholesterol ratio, and raised HDL cholesterol, with PUFA replacement demonstrating the largest effect on all outcomes. Increasing *trans*-fatty acid intake through the isocaloric replacement of PUFA, MUFA or carbohydrates with *trans*-fatty acids had the opposite effect to replacing *trans*-fatty acids with PUFA, MUFA or carbohydrates, including raising LDL cholesterol. The overall quality of available evidence for an association between *trans*-fatty acid intake and all blood lipid outcomes was considered to be *high*, except for HDL and triglycerides when *trans*-fatty acids were replaced with MUFA, and for triglycerides when *trans*-fatty acids were replaced with saturated fatty acids, for all of which the quality was considered to be *moderate*.

No studies were identified that met the inclusion criteria established for the systematic review of studies conducted in children.

Based on the body of evidence, WHO generated the following recommendations for saturated fatty acid and *trans*-fatty acid intake for adults and children.

Recommendations and remarks

Saturated fatty acids

Recommendations

- In adults and children whose saturated fatty acid intake is greater than 10% of total energy intake[1], WHO recommends reducing saturated fatty acid intake (*strong recommendation*[2]).

- In adults and children, WHO suggests reducing the intake of saturated fatty acids to less than 10% of total energy intake (*conditional recommendation*[3]).

- WHO suggests using polyunsaturated fatty acids as a source of replacement energy, if needed, when reducing saturated fatty acid intake (*conditional recommendation*).

- In adults and children whose saturated fatty acid intake is less than 10% of total energy intake, WHO suggests no increase in saturated fatty acid intake (*conditional recommendation*).

Remarks

- 'Children' in these recommendations refer to individuals 2–19 years of age inclusive.

- The recommendations for saturated fatty acid intake in children are based on the totality of evidence reviewed, including surrogate endpoints and intermediate outcome markers for cardiovascular diseases (i.e. blood lipids and blood pressure) assessed directly in children, and extrapolation of adult data on risk of cardiovascular diseases and

[1] Total energy intake is the sum of all daily calories/kilojoules consumed from food and drink. Energy comes from macronutrients, such as fat (9 kcal/37.7 kJ per gram), carbohydrate (4 kcal/16.7 kJ per gram) including total sugars (free sugars + intrinsic sugars + milk sugars) and dietary fibre, protein (4 kcal/16.7 kJ per gram) and ethanol (i.e. alcohol) (7 kcal/29.3 kJ per gram). Total energy intake is calculated by multiplying these energy factors by the number of grams of each type of food and drink consumed and then adding all values together. A percentage of total energy intake is therefore a percentage of total calories/kilojoules consumed per day.

[2] *Strong* recommendations are those recommendations for which the WHO guideline development group is confident that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. Strong recommendations can be adopted as policy in most situations. *(22)*.

[3] *Conditional* recommendations are those recommendations for which the WHO guideline development group is uncertain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. Policy-making related to conditional recommendations therefore may require substantial debate and involvement of various stakeholders *(22)*.

surrogate endpoints and intermediate outcome markers for cardiovascular diseases (i.e. blood lipids).

- The evidence indicates that children's growth is not compromised by reduction of saturated fatty acid intake. Evidence for effects on cognitive development and iron status in children is limited but does not suggest that these outcomes are adversely affected.

- In RCTs that assessed cardiovascular outcomes and mortality outcomes *(24),* in which saturated fatty acids were largely replaced with polyunsaturated fatty acids, the polyunsaturated fatty acids were primarily from plant-based oils, rich in linoleic acid.

- In RCTs that assessed blood lipid outcomes, the LDL cholesterol-lowering effect of reducing saturated fatty acid intake appears linear across the range of 2% to 24% of total energy intake, suggesting benefit in terms of lowering LDL cholesterol at levels of saturated fatty acid intake already below 10% of total energy intake. Benefit in terms of not raising LDL cholesterol is also suggested for not increasing saturated fatty acid intake if it is already less than 10% of total energy intake.

- The recommendation to reduce saturated fatty acid intake in those whose saturated fatty acid intake is above 10% of total energy intake (first recommendation) is based on the totality of evidence reviewed, including *moderate* quality evidence for reduced risk of cardiovascular events in adults, *high* quality evidence for reduced LDL cholesterol in adults, and *high* quality evidence for reduced LDL cholesterol and diastolic blood pressure in children. The first recommendation was considered to be strong, based on the quality of evidence, together with consideration of the other factors[1] that impact the strength of a recommendation as described in Annex 7.

- The recommendation to reduce saturated fatty acid intake to less than 10% of total energy intake (second recommendation) is based on the totality of evidence reviewed, including *high* quality evidence for reduced LDL cholesterol in adults and children. Although LDL cholesterol is a well-established surrogate endpoint for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore,

[1] Values and preferences, balance of benefits and harms, resource implications, priority of the problem, equity and human rights, acceptability and feasibility (22).

although the evidence for LDL cholesterol reduction was of high quality, a conservative approach was taken and the second recommendation was considered to be conditional.

- The recommendation to replace saturated fatty acids with polyunsaturated fatty acids, when a replacement is needed (third recommendation), is based on the totality of evidence reviewed, including *moderate* quality evidence for reduced risk of cardiovascular events in adults, and *high* quality evidence for reduced LDL cholesterol in adults and children. Although there was moderate to high quality evidence for benefit in replacing saturated fatty acids with polyunsaturated fatty acids, none of the RCTs included in the analyses of cardiovascular and mortality outcomes directly compared different replacement nutrients to one another. Therefore, a conservative approach was taken, and the third recommendation was considered to be conditional.

- The recommendation to replace saturated fatty acids with polyunsaturated fatty acids, when a replacement is needed (third recommendation), does not preclude replacing saturated fatty acids with monounsaturated fatty acids, as replacement with monounsaturated fatty acids significantly lowered LDL cholesterol in the analysis of RCTs that assessed blood lipids (but had no effect on cardiovascular or mortality outcomes). However, polyunsaturated fatty acids were the primary replacement source in the RCTs that demonstrated a reduction in risk of cardiovascular events and demonstrated the largest effect on LDL cholesterol when used as replacement for saturated fatty acids in RCTs that assessed blood lipid outcomes. Although replacement with carbohydrates resulted in a small reduction in LDL cholesterol (but had no effect on cardiovascular or mortality outcomes), the composition of the carbohydrates used as replacement in these RCTs was largely unknown. Therefore, a conclusive interpretation of the results for carbohydrate replacement of saturated fatty acids in the analyses supporting the recommendations in these guidelines was considered not possible.

- The recommendation to not increase saturated fatty acid intake if intake is already below 10% of total energy intake (fourth recommendation) is based on the totality of evidence reviewed, including *high* quality evidence for increased LDL cholesterol with increased intake of saturated fatty acids in adults. Although LDL cholesterol is a well-established surrogate endpoint for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore, although the evidence for LDL cholesterol reduction was of high quality, a conservative approach was taken with

respect to assessing the impact of values and preferences on the strength of this recommendation, and the fourth recommendation was considered to be conditional.

- These recommendations should be considered in the context of other WHO guidelines on healthy diets, including those on the intake of free sugars *(25)*, sodium *(26)*, potassium *(27)*, and *trans*-fatty acids in this guideline document, as well as total fat, polyunsaturated fatty acids and carbohydrates which are all currently being updated. Public health interventions should aim to reduce saturated fatty acid intake, while reducing total fat intake where necessary, and without increasing free sugars intake.

Trans-fatty acids

Recommendations

- In adults and children whose *trans*-fatty acid intake is greater than 1% of total energy intake, WHO recommends reducing *trans*-fatty acid intake (*strong recommendation*).

- In adults and children, WHO suggests reducing the intake of *trans*-fatty acids to less than 1% of total energy intake (*conditional recommendation*).

- WHO suggests using polyunsaturated fatty acids as a replacement for *trans*-fatty acids (*conditional recommendation*).

- In adults and children, whose *trans*-fatty acid intake is less than 1% of total energy intake, WHO suggests no increase in *trans*-fatty acid intake (*conditional recommendation*).

Remarks

- *Trans*-fatty acids include all fatty acids with a double bond in the *trans* configuration regardless of whether they come from ruminant sources or are produced industrially.[1]

[1] This definition includes conjugated linoleic acid (CLA). The number of trials included in the meta-regression of RCTs *(10)* that specifically assessed the effects of naturally-occurring CLA on blood lipids were limited and intakes of CLA were very low, however, results of these trials provided no indication that they had an effect on blood lipids that was significantly different from other *trans*-fatty acids when consumed at similar levels. This was further supported by a separate meta-analysis of studies in which CLA was provided as supplements *(28)*, which found that supplemental CLA raised LDL cholesterol and lowered HDL cholesterol in a manner similar to that observed for other *trans*-fatty acids.

- 'Children' in these recommendations refer to individuals 2–19 years of age inclusive.

- The recommendations for *trans*-fatty acid intake in children are based on extrapolation of adult data on risk of cardiovascular diseases and surrogate endpoints and intermediate outcome markers for cardiovascular diseases (i.e. blood lipids).

- In RCTs that assessed blood lipid outcomes, the LDL cholesterol-lowering effect of reducing *trans*-fatty acid intake appears linear across the range of 0% to 10.9% of total energy intake and effects on coronary heart disease and mortality outcomes in prospective cohort studies were observed across a range of intakes, from approximately 0.7% to 3.8% of total energy intake. Together, this suggests benefit in terms of lowering LDL cholesterol at levels of *trans*-fatty acid intake already below 1% of total energy intake, as well as benefit in terms of not raising LDL cholesterol by not increasing *trans*-fatty acid intake if it is already less than 1% of total energy intake.

- The recommendation to reduce *trans*-fatty acid intake in those whose *trans*-fatty acid intake is above 1% of total energy intake (first recommendation) is based on the totality of evidence reviewed, including *low* quality evidence of an association with lower all-cause mortality, *moderate* quality evidence of an association with fewer coronary heart disease events and lower coronary heart disease mortality in adults, and *high* quality evidence for reduced LDL cholesterol in adults. The first recommendation was considered to be strong based on the quality of evidence, together with consideration of the other factors that impact the strength of a recommendation as described in Annex 7.

- The recommendation to reduce *trans*-fatty acid intake to less than 1% of total energy intake (second recommendation) is based on the totality of evidence reviewed, including *moderate* quality evidence of an association with fewer coronary heart disease events and lower coronary heart disease mortality in adults, and *high* quality evidence for reduced LDL cholesterol in adults. Although the evidence for coronary heart disease events and coronary heart disease mortality is of *moderate* quality, confidence regarding the absolute effects of reducing *trans*-fatty acid intake on these outcomes was diminished because of the few events occurring in studies with up to 21 years of follow-up. In addition, the association with all-cause mortality observed in the evidence for the first recommendation, with a large number of events in one study with 7 years of follow-up, is not included in the evidence for the second recommendation as it was not relevant to specifically looking at effects of reducing *trans*-fatty acid intake to less than 1% of total energy intake. Furthermore, although LDL cholesterol is a well-established

surrogate endpoint for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore, although the evidence for an association with fewer coronary heart disease events and lower coronary heart disease mortality was of *moderate* quality, and evidence for LDL cholesterol reduction of *high* quality, a conservative approach was taken and the second recommendation was considered to be conditional.

- The recommendation to replace *trans*-fatty acids with polyunsaturated fatty acids (third recommendation), is based on the totality of evidence reviewed, including *high* quality evidence for reduced LDL cholesterol in adults. Although LDL cholesterol is a well-established surrogate endpoint for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore, although the evidence for LDL cholesterol reduction was of high quality, a conservative approach was taken and the third recommendation was considered to be conditional.

- The recommendation to replace *trans*-fatty acids with polyunsaturated fatty acids (third recommendation), does not preclude replacing *trans*-fatty acids with monounsaturated fatty acids, as replacement with monounsaturated fatty acids significantly lowered LDL cholesterol in the analysis of RCTs that assessed blood lipids. However, polyunsaturated fatty acids demonstrated the largest effect on LDL cholesterol when used as replacement for *trans*-fatty acids in RCTs that assessed blood lipid outcomes. Although replacement with carbohydrates resulted in a small reduction in LDL cholesterol, the composition of the carbohydrates used as replacement in these RCTs was largely unknown. Therefore, a conclusive interpretation of the results for carbohydrate replacement of *trans*-fatty acids in the analyses supporting the recommendations in these guidelines was considered not possible.

- The recommendation to not increase *trans*-fatty acid intake if intake is already below 1% of total energy intake (fourth recommendation) is based on the totality of evidence reviewed, including *moderate* quality evidence of an association with a greater number of coronary heart disease events and higher coronary heart disease mortality in adults, and *high* quality evidence for increased LDL cholesterol in adults. Although the evidence for coronary heart disease events and coronary heart disease mortality is of *moderate* quality, confidence regarding the absolute effects of increasing *trans*-fatty acid intake on these outcomes was diminished because of the few events occurring studies with up to 21 years of follow-up. In addition, the association with all-cause mortality observed in the

evidence for the first recommendation, with a large number of events in one study with 7 years of follow-up, is not included in the evidence for the fourth recommendation as it was not relevant to specifically looking at effects of increasing *trans*-fatty acid intake if intake is already below 1% of total energy intake. Furthermore, although LDL cholesterol is a well-established biomarker for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore, although the evidence for an association with a greater number of coronary heart disease events and higher coronary heart disease mortality was of *moderate* quality, and evidence for an increase in LDL cholesterol of *high* quality, a conservative approach was taken and the fourth recommendation was considered to be conditional.

- These recommendations should be considered in the context of other WHO guidelines on healthy diets, including those on the intake of free sugars *(25)*, sodium *(26)*, potassium *(27)*, and saturated fatty acids in this guideline document, as well as total fat, polyunsaturated fatty acids and carbohydrates which are all currently being updated. Public health interventions should aim to reduce *trans*-fatty acid intake, while reducing total fat intake where necessary, and without increasing saturated fatty acids and free sugars intake.

Introduction

Scope and purpose

Following the work of the 1989 WHO Study Group on Diet, Nutrition and Prevention of Noncommunicable Diseases *(29)*, the 2002 Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases *(2)* updated the guidance on saturated fatty acid and *trans*-fatty acid intake as part of the guidance on population nutrient intake goals for the prevention of noncommunicable diseases (NCDs). Since then, numerous studies and analyses of saturated fatty acid intake have been published, and different interpretations of the results have led some to question the role of saturated fatty acid intake in the development of NCDs. Consequently, the debate has continued as to whether the available evidence for adverse health effects related to consumption of saturated fatty acids warrants appreciable reduction in intake. Also, while there is increasing scientific consensus about the adverse health effects of industrially-produced *trans*-fatty acid intake, discussion continues regarding the role consumption of ruminant *trans*-fatty acids may play in the development of NCDs. Therefore, it was considered important to review the evidence in a systematic manner, and update WHO's guidance on saturated fatty acid and *trans*-fatty acid intake through the current WHO guideline development process.

The objective of these guidelines is to provide recommendations on the intake of saturated fatty acids and *trans*-fatty acids to reduce the risk of NCDs in adults and children, with a particular focus on the prevention of cardiovascular diseases (CVDs).[1] This is in recognition of the fact that CVDs are the leading cause of death globally. The recommendations in these guidelines can be used by policy-makers and programme managers to assess current levels of saturated fatty acid and *trans*-fatty acid intake in their populations relative to a benchmark. They can also be used to develop measures to decrease the intake of saturated fatty acids and *trans*-fatty acids, where necessary, through a range of public health policy actions and intervention programmes.

It is hoped that the guidelines will also help to accelerate the implementation of actions to promote healthy diets, improve health and nutritional status of all people, and ultimately reduce the burden of NCDs to help accelerate achievement of the Sustainable Development Goals. The guidelines are intended for a wide audience including government officials, scientists, health and nutrition-related nongovernmental organizations (NGOs), and other

[1] Cardiovascular diseases include coronary heart disease, cerebrovascular disease (e.g. stroke), structural abnormalities of the heart at birth or damage resulting from rheumatic fever, peripheral arterial disease, and deep vein thrombosis and pulmonary embolism.

partners and stakeholders involved in the development, design and implementation of policies and programmes in nutrition and public health.

This guideline document presents the key recommendations and a summary of the supporting evidence. Further details of the evidence base are provided in Annex 1 and in other documents listed in the references.

Background

NCDs are the world's leading cause of death: they were responsible for 39.5 million (72%) of the 54.7 million deaths in 2016 *(1)*. Many of those deaths were premature (i.e. under the age of 70 years) and occurred in low- and middle-income countries. Of the major NCDs, CVDs were the leading cause of NCD mortality in 2016, being responsible for nearly half (45%) of all NCD deaths. Modifiable risk factors such as unhealthy diet, physical inactivity, tobacco use and harmful use of alcohol are major causes of CVDs. Dietary saturated fatty acids and *trans*-fatty acids are of particular concern because high levels of intake are correlated with increased risk of CVDs *(2)*.

Saturated fatty acids are fatty acids containing only single carbon–carbon bonds (i.e. no double bonds). Saturated fatty acids are found in foods from animal sources such as butter, cow's milk, meat, salmon and egg yolks, and some plant-derived products such as chocolate and cocoa butter, and coconut, palm and palm kernel oils.

Trans-fatty acids are unsaturated fatty acids with at least one double carbon–carbon bond in the *trans* configuration. *Trans*-fatty acids can be produced industrially by the partial hydrogenation of vegetable and fish oils, but also occur naturally in meat and dairy products from ruminant animals (e.g. cattle, sheep, goats, camels, etc.) as a result of the conversion of *cis* double bonds in unsaturated fatty acids to the *trans* position by bacterial enzymes in the stomach (i.e. rumen) of the animals. Though the sources are different, the individual isomers in industrially-produced and ruminant *trans*-fatty acids are largely the same, but present in differing proportions *(30-32)*. Industrially-produced *trans*-fatty acids are the predominant source of dietary *trans*-fatty acids in many populations and can be found in baked and fried foods (e.g. doughnuts, cookies, crackers and pies), pre-packaged snacks and food, and partially hydrogenated cooking oils and fats which are often used at home, in restaurants, or in the informal sector, such as street vendors. While current intakes are generally low, ruminant *trans*-fatty acids may become a more important dietary source of *trans*-fatty acids in populations where industrially-produced *trans*-fatty acids are being phased out of the food supply *(33-35)*.

Reduced intake of saturated fatty acids has been associated with a significant reduction in risk of coronary heart disease (CHD) when replaced with polyunsaturated fatty acids or carbohydrates from whole grains *(3-6)*. However, an apparent lack of effect is often observed in studies where the macronutrients replacing saturated fatty acids are unknown, not accounted for, or consist largely of refined carbohydrates *(3, 6, 36, 37)*. Studies have also demonstrated that high intakes of industrially-produced *trans*-fatty acids are strongly associated with increased risk of CHD and related mortality *(7, 8)*. Few studies have identified an association between intake of ruminant *trans*-fatty acids and CVD; however, to date, ruminant *trans*-fatty acid intake in most study populations has been very low *(9)*. Efforts to understand the effects of saturated fatty acid intake in greater detail have shown that individual saturated fatty acids may have differing effects on blood lipids *(11)*, and emerging evidence has led to the suggestion that different saturated fatty acid-containing foods, such as dairy foods, may have different effects on risk of cardiovascular diseases and type 2 diabetes, either as a result of differing composition of saturated fatty acids across foods, other constituents of the foods, or a combination of the two *(38-42)*. However, many questions remain to be answered before a clear understanding can be reached and firm conclusions drawn.

The reduction in risk of CVDs observed with decreased intake of saturated fatty acids and *trans*-fatty acids is believed to occur primarily through an effect on blood lipids, because intakes of both are positively correlated with total and low-density lipoprotein (LDL) cholesterol[1] levels *(10, 11)*, and are negatively correlated with high-density lipoprotein (HDL) cholesterol in the case of *trans*-fatty acids *(10)*, though other physiological mechanisms, such as inflammation, may also play a role *(43, 44)*. Total cholesterol has been shown to be positively associated with CHD *(12)*, and LDL cholesterol is a well-established surrogate endpoint for measuring the effects of interventions on CVD risk *(13, 14)*. Other lipid measures – such as non-HDL cholesterol,[2] triglycerides, cholesterol ratios and cholesterol particle number – have also been suggested as possible predictors of CVD risk.

Although CVDs typically present later in life, preclinical signs of atherosclerosis in the form of atherosclerotic lesions in the aorta and coronary arteries can begin to appear in childhood *(45, 46)*, and are positively associated with abnormal blood lipid levels and other CVD risk factors *(47, 48)*. Elevated total and LDL cholesterol in childhood are, in turn, associated with an increase in CVD risk factors in adulthood *(49)*, including thickening of the carotid artery

[1] As used in this guideline, mention of all forms of cholesterol and triglycerides refers to concentrations of these lipids in blood.
[2] Non-HDL cholesterol is obtained by subtracting HDL cholesterol from total cholesterol.

intima-media *(50-52)*, which is a marker of subclinical atherosclerosis and a predictor of future cardiovascular events *(53)*. Results of dietary intervention studies conducted in children have demonstrated significant reductions in total or LDL cholesterol when saturated fatty acids were replaced with polyunsaturated fatty acids *(16-21)*. Despite the positive effect on blood lipids, concern has been raised about the possible negative impact of a reduced-fat diet or diets intended to reduce blood lipids on normal growth and development in children *(54, 55)*, although the primary concern has generally been the potential for inadequate caloric intake rather than any effects related to changes in saturated fat *per se*.

Studies of *trans*-fatty acid intake in children are limited; nevertheless, there is no evidence to suggest that the effects on blood lipids would be different from those observed in adults, and intake may therefore lead to preclinical signs of atherosclerosis *(45-48)*, as described in the preceding paragraph.

Despite longstanding dietary advice to limit saturated fatty acid intake, and a limited number of focused efforts to reduce intake at the population level through fiscal policy measures, saturated fatty acid intake remains high in many parts of the world *(56)*. And while more consistent efforts to reduce the level of industrially-produced *trans*-fatty acids in the food supply at the local to national level have led to decreased intake in some countries *(57)*, the global average intake of *trans*-fatty acids in 2010 *(56)* was estimated to exceed the population nutrient intake goal of 1% of total energy intake established by the 1989 WHO Study Group on Diet, Nutrition and Prevention of Noncommunicable Diseases *(29)* and updated by the WHO 2002 Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases *(2)*.

Guideline development process

These guidelines were developed in accordance with the WHO evidence-informed guideline development process outlined in the *WHO handbook for guideline development (22)*.

Advisory groups

Development of these guidelines was undertaken by the WHO Department of Nutrition for Health and Development (NHD), in partnership with the members of the WHO Secretariat (Annex 2). The work was guided by the WHO Steering Committee for Nutrition Guideline Development (Annex 3) which provided overall supervision of the guideline development process. The WHO Secretariat and the Steering Committee included representatives from all departments in WHO with an interest in the provision of scientific advice on nutrition. Two

additional groups were formed – a guideline development group and an external peer-review group – as outlined below.

Guideline development group

The guideline development group – entitled the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health – was convened to support the development of these guidelines (Annex 4). This group included experts who had previously participated in various WHO expert consultations or were members of the WHO expert advisory panels, and others identified through open calls for experts. In forming this group, the WHO Secretariat took into consideration the need for expertise from multiple disciplinary areas, representation from all WHO regions and a balanced gender mix. Efforts were made to include subject-matter experts (e.g. in nutrition, epidemiology, paediatrics and physiology); experts in systematic review, programme evaluation and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologies; and representatives of potential stakeholders (e.g. programme managers, policy advisers and other health professionals involved in the health-care process). The names, institutional affiliations and summary background information of the members of the NUGAG Subgroup on Diet and Health have been posted on the guideline development webpages within the NHD website, which includes all relevant information regarding the nutrition guideline development process, including the scope and purpose of each NUGAG meeting.

External resource persons – including additional subject-matter experts and systematic review teams and GRADE methodologists – were also invited to the NUGAG meetings, as required, to provide technical inputs and to present systematic reviews. These individuals did not participate in the decision-making processes. Representatives of commercial organizations were not invited to participate as the inclusion of such individuals is considered to be inappropriate for membership of any WHO guideline development group because of actual, potential and perceived conflicts of interest.

The role of the NUGAG Subgroup on Diet and Health was to advise WHO on the scope of the guidelines and priority questions for which systematic reviews of evidence would be undertaken; the choice of important outcomes for decision-making and developing recommendations; the interpretation of the evidence with explicit consideration of the overall balance of risks and benefits; and the final formulation of recommendations, taking into consideration the evidence reviewed and assessed by the NUGAG Subgroup on Diet and Health, as well as diverse values and preferences, balance of benefits and harms, resource implications, priority of the problem, equity and human rights, acceptability and feasibility.

External peer-review group

(To be completed before finalization)

Public consultation

(To be completed before finalization)

Scoping of the guideline, evidence appraisal and decision-making

(To be added before finalization)

Management of conflicts of interest

According to the rules in the WHO *Basic documents (58)*, whenever an expert or an individual provides independent advice to WHO, including participating in WHO meetings, a declaration of interest form must be submitted and an analysis of all declarations must be performed. In the case of guideline development, this means that all members of the NUGAG Subgroup on Diet and Health, individuals who prepare systematic reviews and evidence profiles and any other experts (including external peer-reviewers) who participate in the process of guideline development in an individual capacity. Declaration of interest forms were reviewed by the WHO Secretariat in consultation with the WHO Legal Office when finalizing the composition of the NUGAG Subgroup on Diet and Health. Prior to every NUGAG meeting, the members of the NUGAG Subgroup on Diet and Health, systematic review team and other experts who would be participating in the meeting, were requested to submit their updated declaration of interest forms which were assessed by the WHO Secretariat in consultation with the WHO Legal Office previously, but since 2014 with the Department of Compliance and Risk Management and Ethics, as part of the preparatory process for holding the NUGAG meetings. In addition, each NUGAG member verbally declared his or her interests at the start of each NUGAG meeting. The procedures for management of interests outlined in the WHO *Guidelines for declaration of interests for WHO experts (23)* were strictly followed. The potential interests declared by members of the NUGAG Subgroup on Diet and Health and experts who participated in NUGAG meetings as external resource persons are summarized in Annex 8.

Similarly, declaration of interest forms from external peer-reviewers were assessed by the WHO Secretariat, also following the procedures for management of interests outlined in the WHO *Guidelines for declaration of interests for WHO experts (23).*The summaries of those declared interests are also provided in Annex 8.

Summary of evidence

Saturated fatty acids

Three systematic reviews of randomized controlled trials (RCTs or 'trials') were conducted to assess the effects of modifying intake of saturated fatty acids on health outcomes; two that included trials conducted in adults *(24, 59)* and one that included trials conducted exclusively in children *(60)*.[1]

Priority health outcomes considered for adults were all-cause mortality, coronary heart disease (incidence, mortality and morbidity), cardiovascular diseases (incidence, mortality and morbidity), stroke (incidence, mortality and morbidity) and blood lipids.[2] Priority health outcomes considered for children were blood lipids, height, weight and other measures of adiposity, blood pressure, type 2 diabetes incidence and insulin resistance, linear growth and potential adverse effects.

The key research questions guiding the systematic reviews undertaken were as shown below.

What is the effect on risk of NCDs in adults and children of:

- lower intake of saturated fatty acids relative to higher intake;
- a decrease in saturated fatty acid intake to below 10% of total energy intake[3];
- replacement of saturated fatty acids in the diet with polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), carbohydrates or protein; and
- lower intake of individual saturated fatty acids[1] relative to higher intake?

[1] A fourth review of prospective cohort studies in adults was also conducted *(61)*; however, the quality of evidence for relevant outcomes in the analyses of cohort studies was lower than that for the analyses of RCTs. Furthermore, it was not possible to assess potential differential effects of replacing saturated fatty acids with different nutrients in the meta-analysis of the cohort studies. Because evidence from meta-analyses of RCTs with mortality and morbidity outcomes was available and of higher quality, and results of the meta-analysis of cohort studies were not inconsistent with the results observed for the RCTs (i.e. results from the meta-analysis of cohort studies did not indicate an effect in the opposite direction to that from the RCTs), the systematic review of cohort studies was not considered in the formulation of the recommendations on saturated fatty acid intake.

[2] Blood lipids are indirect measures of patient-important CVD outcomes. However, total cholesterol is a relevant indicator of CVD risk *(12)*, and LDL cholesterol is a well-established biomarker for measuring the effects of interventions on CVD risk *(13, 14)*. Therefore, LDL was included as a *critical* outcome *(22)* in the formulation of recommendations on saturated and trans-fatty acid intake, and was not downgraded for indirectness when determining the quality of evidence within the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Total cholesterol, HDL cholesterol, triglycerides and blood lipid ratios were also considered when formulating the recommendations; however, in noting that the evidence supporting their use to measure effects of interventions on CVD risk was less certain, they were classified as *important* outcomes.

[3] The population nutrient intake goal for saturated fatty acids recommended by the joint WHO/FAO expert consultation is less than 10% of total energy intake *(2)*.

Adults

Reducing saturated fatty acid intake

A systematic review of RCTs that assessed the effects of reducing the intake of saturated fatty acids on risk of CVDs and mortality in adults identified 15 trials (17 comparisons) with over 59 000 participants *(24)*.[2] The review included:

- trials with a stated intention to reduce intake of saturated fatty acids; and
- trials that provided a general dietary aim (e.g. improving heart health or reducing total fat intake), and also achieved a statistically significant reduction in saturated fatty acid intake ($P<0.05$) in the intervention group compared with the control group.

Interventions included dietary advice or provision of food (either supplementation of fats, oils or modified or low-fat foods, or a complete diet), or a combination of the two. Outcomes assessed included all-cause mortality, CVD mortality, cardiovascular events, coronary heart disease (CHD) mortality, CHD events, myocardial infarction, and stroke. Only trials in which the dietary intervention lasted at least 2 years were included in the review (trial duration ranged from 2 to >8 years, with a mean duration of 4.7 years).[3] Trials were conducted in Australia, the Netherlands, New Zealand, Norway, the United Kingdom of Great Britain and Northern Ireland (United Kingdom) and the United States of America (USA). Of the 17 comparisons, six included only people at high risk of CVDs, four at moderate risk and five at low risk. Saturated fatty acid intake ranged from 6% to 18.5% of total energy intake across intervention and control groups.

Meta-analysis of RCTs that included a control group with saturated fatty acid intake greater than 10% of total energy intake found that reducing saturated fatty acid intake reduced risk

[1] Saturated fatty acids are comprised of many different, individual saturated fatty acid molecules that vary in chain length (i.e. the number of carbon atoms in the carbon backbone of fatty acids). Common saturated fatty acids found in the diet of humans, include lauric acid (12 carbons), myristic acid (14 carbons), palmitic acid (16 carbons), and stearic acid (18 carbons).

[2] This systematic review is part of an update of a previously published, comprehensive systematic review on dietary fat intake and CVDs *(62)*, which has been split into smaller reviews (of which this review is one) for the purpose of updating.

[3] The selection of a minimum study duration of 2 years as a criterion for study inclusion was based on recognition that the effects of changes in diet on the development of many NCDS (including CVDs) may not be observed with short-term follow up. In selecting a minimum study duration, consideration was given to what is known regarding statin use as an example of an intervention that is known to have a significant effect on LDL cholesterol levels and cardiovascular outcomes. An ongoing meta-analysis of statin efficacy trials including a large number of participants has established a minimum treatment duration of 2 years as an inclusion criterion *(13, 63, 64)*. Dietary changes are generally anticipated to have a less robust physiological impact than statins; therefore, 2 years was selected as a conservative estimate for physiological effects of dietary changes in the review of Hooper et al *(24)*.

of cardiovascular events[1] by 17% (relative risk [RR] 0.83; 95% confidence interval [CI]: 0.72, 0.96; 13 trials with 53 300 participants). Non-significant decreases in risk of CHD events[2] (RR 0.87; 95% CI: 0.74, 1.03; 12 trials with 53 199 participants) and fatal and non-fatal myocardial infarction (RR 0.90; 95% CI: 0.80, 1.01; 11 trials with 53 167 participants) were also observed with reduced intake of saturated fatty acids, but no effect on non-fatal myocardial infarction was observed when considered alone (RR 0.95; 95% CI: 0.80, 1.13; nine trials with 52 834 participants). Reducing saturated fatty acid intake did not appear to have an effect on risk of all-cause mortality (RR 0.97; 95% CI: 0.90, 1.05; 12 trials with 55 858 participants), CVD mortality (RR 0.95; 95% CI: 0.80, 1.12; 12 trials with 53 421 participants), CHD mortality (RR 0.98; 95% CI: 0.84, 1.15; 10 trials with 53 159 participants) or stroke (RR 1.00; 95% CI: 0.89, 1.12; eight trials with 50 952 participants).

Subgroup and meta-regression analyses suggested that the degree of reduction in risk of cardiovascular events was positively correlated to the degree of reduction in serum total cholesterol, with greater reductions in total cholesterol being associated with greater reduction in risk *(24)*. Subgroup analysis further suggested a greater reduction in risk of cardiovascular events with larger reductions in saturated fatty acid intake.

A second systematic review of RCTs that assessed the effects of modifying intake of fatty acids on blood lipids[3] identified 84 trials with 2363 participants *(59)*.[4] Of these, 74 trials provided 177 data points[5] that were used to assess the effects of different classes of fatty acids on blood lipids, and 52 trials provided 134 data points that were used to assess the effects of individual saturated fatty acids on blood lipids. Saturated fatty acid intake ranged from 1.6% to 24.4% of total energy intake across the included trials. The RCTs included in this review were all strictly controlled dietary trials, of 13–91 days duration, in which cholesterol,[6] protein and alcohol intake were held constant and dietary fat or carbohydrate intake was varied. Outcomes assessed included total cholesterol, LDL cholesterol, high-

[1] Cardiovascular events include cardiovascular deaths, cardiovascular morbidity (non-fatal myocardial infarction, angina, stroke, heart failure, peripheral vascular events or atrial fibrillation) and unplanned cardiovascular interventions (coronary artery bypass surgery or angioplasty).

[2] CHD events include fatal or non-fatal myocardial infarction, angina and sudden death.

[3] All data from the meta-regression analysis of saturated fatty acid intake refers to lipid levels in serum, which is the liquid portion of coagulated (clotted) blood containing lipids, proteins and other factors that are not part of red and white blood cells.

[4] This review is an update of a previously published review on the effects of dietary fatty acids and carbohydrates on serum lipids and lipoproteins *(11)*.

[5] Data points consisted of the fatty acid (i.e. saturated fatty acids, PUFA and MUFA) and carbohydrate composition of a particular diet, and the mean serum lipid concentration of intervention and control groups, as measured at the end of the intervention period in all included trials.

[6] The difference in daily cholesterol intake between treatment groups within a study had to be no more than 100 mg.

density lipoprotein (HDL) cholesterol, triglyceride, LDL cholesterol to HDL cholesterol ratio, total cholesterol to HDL cholesterol ratio, triglyceride to HDL cholesterol ratio, apolipoprotein A-I (ApoA-I) and apolipoprotein B (ApoB). Trials were primarily conducted in the USA, but also in Austria, Canada, Denmark, Finland, Germany, Israel, Italy, Malaysia, the Netherlands, New Zealand, Norway, Spain, Sweden and the United Kingdom. Using multiple regression analysis – in which the intake of saturated fatty acids, PUFA, MUFA and carbohydrates as a percentage of total energy intake served as the independent variables and the mean concentration of a given blood lipid or lipid ratio as the dependent variable – four models were developed that provide an estimate of the effect (i.e. regression coefficient) on a given blood lipid when 1% of total energy intake as saturated fatty acids was isocalorically[1] exchanged with PUFA, MUFA or carbohydrates. A fifth model was developed to estimate the effects of individual saturated fatty acids.

Multiple regression analysis found that, for every 1% of total energy intake as saturated fatty acid replaced with PUFA, MUFA or carbohydrates, LDL cholesterol was significantly lowered by 0.055 mmol/L (95% CI: –0.061, –0.050), 0.042 mmol/L (95% CI: –0.047, –0.037) and 0.033 mmol/L (95% CI: –0.039, –0.027), respectively *(59)*. Replacing saturated fatty acids with PUFA, MUFA or carbohydrates also lowered total cholesterol; replacing with PUFA or MUFA additionally lowered triglycerides, and the total cholesterol to HDL cholesterol ratio and the LDL cholesterol to HDL cholesterol ratio, with PUFA replacement demonstrating the largest effect on all outcomes. HDL cholesterol was slightly reduced with all replacements, and a small increase in triglycerides was observed when saturated fatty acids were replaced with carbohydrates.

The quality of available evidence for an effect of reducing saturated fatty acid intake in adults whose intake is greater than 10% of energy intake, on all cardiovascular and mortality outcomes was considered to be *moderate,* except for CHD events, where the quality was considered to be *low;* and on all blood lipid outcomes was considered to be *high,* except for the total cholesterol to HDL cholesterol ratio outcome when replacing carbohydrates with saturated fatty acids, for which the quality was considered to be *moderate* (Annex 1; GRADE evidence profile 1).

Saturated fatty acid intake of less than 10% of total energy intake

To assess the effect of different levels of saturated fatty acid intake on cardiovascular and mortality outcomes, trials that assessed these outcomes were grouped by saturated fatty

[1] The amount of PUFA, MUFA or carbohydrates used as replacement for saturated fatty acids was identical to that of the saturated fatty acids being replaced, *in terms of calories*.

acid intake achieved in the intervention group. The threshold for saturated fatty acid intake achieved was stepped down in increments of 1% of total energy intake, from 13% to 7%,[1] and each group was assessed for possible effect on outcomes via meta-analysis *(24)*. Results of this analysis were difficult to interpret, and confidence intervals for pooled effect estimates were wide. No clear effect on any cardiovascular or mortality outcome was observed when reducing saturated fatty acid intake to less than 10% of total energy intake (*low* to *moderate* quality evidence). However, significant reductions in risk of CVD mortality (RR 0.69; 95% CI: 0.51, 0.94) and cardiovascular events (RR 0.79; 95% CI: 0.62, 0.99) were observed in meta-analysis of two trials with 979 participants in which saturated fatty acid intake was reduced to less than 9% of total energy intake *(24).*

Effects of modifying saturated fatty acid intake on blood lipids in multiple regression were observed across a wide range of saturated fatty acid intakes (1.6 to 24.4% of total energy intake) *(59)*. Of the 177 data points used in the multiple regression, 113 included a saturated fatty acid intake component of 10% of total energy intake or less, including 65 data points with intakes of less than 8%. Analysis of the residuals of the regression line for LDL cholesterol indicates that the relationship between reducing or increasing saturated fatty acid intake and effects on blood lipids is consistent across the entire range of saturated fatty acid intakes reported in the included trials, and therefore suggests benefit in reducing intake to below 10% of total energy intake.

The quality of available evidence for an effect of reducing saturated fatty acid intake to less than 10% of total energy intake on all-cause mortality, myocardial infarction and stroke was considered to be *moderate*; on CVD mortality, cardiovascular events and CHD events was considered to be *low*; and on all blood lipid outcomes was considered to be *high,* except for the total cholesterol to HDL cholesterol ratio outcome when replacing carbohydrates with saturated fatty acids, for which the quality was considered to be *moderate* (Annex 1; GRADE evidence profile 3).

Replacement macronutrients for saturated fatty acids

Subgroup analysis was used to assess effects of replacing saturated fatty acids with PUFA, MUFA, carbohydrates or protein on cardiovascular and mortality outcomes *(24)*. Trials were grouped based on whether the difference in saturated fatty acid intake and replacement macronutrient between the intervention and control groups achieved statistical significance

[1] For example, trials were included in the 10% group if they had an intervention group that achieved a saturated fatty acid intake of less than 10% of total energy intake and a control group with intake greater than 10%. Thus, the 10% group would also contain all trials included in the 9%, 8% and 7% groups.

(*P*<0.05), regardless of whether or not that macronutrient constituted the main replacement for saturated fatty acids.[1]

Subgroup analysis found that replacing saturated fatty acids with PUFA reduced the risk of combined cardiovascular events by 27% (RR 0.73; 95% CI: 0.58, 0.92; seven trials with 3895 participants). Non-significant decreases in risk of CHD events (RR 0.76; 95% CI: 0.57, 1.00; seven trials with 3900 participants), fatal and non-fatal myocardial infarction (RR 0.83; 95% CI: 0.67, 1.02; seven trials with 3895 participants) and non-fatal myocardial infarction when considered alone (RR 0.80; 95% CI: 0.63, 1.03; five trials with 3738 participants), were also observed. Replacing saturated fatty acids with PUFA did not appear to have an effect on risk of all-cause mortality, CVD mortality, CHD mortality or stroke. No significant effect on any cardiovascular or mortality outcome was observed when replacing saturated fatty acids with MUFA, carbohydrates or protein; however, only one small trial was included in the MUFA subgroup. Furthermore, there was insufficient information regarding the composition of carbohydrates used as replacement in the trials included in the carbohydrate subgroup to assess whether different types of carbohydrates might have differentially affected pooled effect estimates for cardiovascular or mortality outcomes.

Multiple regression analysis found that, for every 1% of total energy intake as saturated fatty acid replaced with PUFA, MUFA or carbohydrates, LDL cholesterol was significantly lowered by 0.055 mmol/L (95% CI: –0.061, –0.050), 0.042 mmol/L (95% CI: –0.047, –0.037) and 0.033 mmol/L (95% CI: –0.039, –0.027), respectively *(59)*. Replacing saturated fatty acids with PUFA, MUFA or carbohydrates also lowered total cholesterol; replacing with PUFA or MUFA additionally lowered triglycerides, and the total cholesterol to HDL cholesterol ratio and the LDL cholesterol to HDL cholesterol ratio, with PUFA replacement demonstrating the largest effect on all outcomes. HDL cholesterol was slightly reduced with all replacements, and a small increase in triglycerides was observed when saturated fatty acids were replaced with carbohydrates.

The quality of available evidence for the effect of replacing saturated fatty acids with polyunsaturated fatty acids on all-cause mortality, cardiovascular events and myocardial infarction was considered to be *moderate*; on CVD mortality and CHD events was considered to be *low*; and on stroke was considered to be *very low*. The quality of available evidence for the effect of replacing saturated fatty acids with monounsaturated fatty acids on all cardiovascular and mortality outcomes was *very low*. The quality of available evidence for

[1] Trials in which saturated fatty acids were replaced by more than one nutrient at statistically significant levels are therefore included in more than one subgroup.

an effect of replacing saturated fatty acids with carbohydrates on all cardiovascular and mortality outcomes was considered to be *moderate,* except for cardiovascular events and CHD events, where the quality was considered to be *low.* The quality of available evidence for the effect of replacing saturated fatty acids with protein on all cardiovascular and mortality outcomes was considered to be *moderate.* The quality of available evidence for the effect of replacing saturated fatty acids with polyunsaturated fatty acids, monounsaturated fatty acids or carbohydrates on all blood lipid outcomes was considered to be *high,* except for the total cholesterol to HDL cholesterol ratio outcome when replacing saturated fatty acids with carbohydrates, for which the quality was considered to be *moderate* (Annex 1; GRADE evidence profiles 5, 7, 9, 11).

Increasing saturated fatty acid intake

Regression analysis allows for the calculation of effects of both increases and decreases in saturated fatty acid intake from the same set of trials, and results for increasing saturated fatty acid intake are opposite to those obtained for decreasing intake.[1] Results of multiple regression analysis found that, for every 1% of total energy intake as PUFA, MUFA or carbohydrates replaced with saturated fatty acids, LDL cholesterol was significantly raised by 0.058 mmol/L (95% CI: 0.052, 0.064), 0.045 mmol/L (95% CI: 0.039, 0.051) and 0.036 mmol/L (95% CI: 0.030, 0.043), respectively *(59)*. Replacing PUFA, MUFA or carbohydrates with saturated fatty acids also increased total cholesterol and replacing PUFA or MUFA with saturated fatty acids additionally increased triglycerides, the total cholesterol to HDL cholesterol ratio, and the LDL cholesterol to HDL cholesterol ratio. HDL cholesterol was slightly increased when all nutrients were replaced with saturated fatty acids, and a small decrease in triglycerides was observed when carbohydrates were replaced with saturated fatty acids.

The quality of available evidence for an effect of increasing saturated fatty acid intake on all blood lipid outcomes was considered to be *high,* except for the total cholesterol to HDL cholesterol ratio outcome when replacing carbohydrates with saturated fatty acids, for which the quality was considered to be *moderate* (Annex 1; GRADE evidence profile 13).

Individual saturated fatty acid intake

To assess the effects of individual saturated fatty acids on blood lipids, multiple regression analysis was conducted to estimate the effects of isocalorically replacing a mixture of

[1] The numerical values are opposite in sign and are similar in magnitude, but not identical. The slight variation is a result of the separate multivariable calculations made for increasing or decreasing saturated fatty acid intake.

carbohydrates with lauric acid, myristic acid, palmitic acid or stearic acid *(59)*. Replacement of carbohydrates with lauric, myristic or palmitic acids significantly raised total, LDL and HDL cholesterol, and lowered triglyceride levels and the triglyceride to HDL cholesterol ratio. Lauric acid lowered the total cholesterol to HDL cholesterol ratio and the LDL cholesterol to HDL cholesterol ratio. Stearic acid did not have a significant effect on any outcome assessed. Although differences in effects of the individual saturated fatty acids on the lipid profile were observed, reported intakes of lauric and myristic acids in the individual trials included in the regression analysis were low (mean of 1.2% of total energy intake) and trials that assessed cardiovascular or mortality outcomes were not reviewed by the NUGAG Subgroup on Diet and Health. It was therefore concluded that further research is needed before recommendations on the intake of individual saturated fatty acids can be made.

Children

Reducing saturated fatty acid intake

A systematic review of RCTs that assessed the effects of reducing intake of saturated fatty acids on CVD risk factors and growth and development in children identified a total of eight trials with 2430 participants *(60)*. The trials included children and adolescents aged from 2 to 19 years[1], with either normal or elevated cholesterol levels. Interventions included dietary advice or provision of food in which the fatty acid content had been modified, or a combination of the two. Outcomes assessed included total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, and associated blood lipid ratios; height; body weight, body mass index (BMI) and other measures of adiposity; systolic blood pressure; diastolic blood pressure; insulin resistance and incidence of impaired glucose tolerance, impaired fasting glycaemia or type 2 diabetes; and potential adverse effects. Trials were conducted in Australia, China, Finland, Spain and the USA. Trial duration ranged from 5 weeks to approximately 19 years. Saturated fatty acid intake ranged from 9% to 16.6% of total energy intake across intervention and control groups.

Meta-analysis of RCTs that included a control group with saturated fatty acid intake greater than 10% of total energy intake found that reducing saturated fatty acid intake lowered total cholesterol by 0.18 mmol/L (95% CI: –0.28, –0.09; six trials, 1990 participants), LDL cholesterol by 0.16 mmol/L (95% CI: –0.25, –0.08; six trials, 1622 participants), and diastolic blood pressure by 1.45 mmHg (95% CI: –2.34, –0.56; two trials, 1106 participants). Significant effects of reducing saturated fatty acid intake were not observed for HDL cholesterol, triglycerides or systolic blood pressure. Additionally, reduced saturated fatty acid

[1] One trial recruited infants at 7 months of age and followed up the participants for approximately 19 years.

intake had no effect on anthropometric measures, including height (standardized mean difference [SMD] 0.09; 95% CI: –0.03, 0.21; three trials, 1287 participants), body weight (SMD –0.03; 95% CI: –0.13, 0.07; four trials, 1419 participants), body mass index (BMI) (MD –0.10 kg/m^2; 95% CI: –0.32, 0.12; three trials, 1189 participants) or waist circumference (MD –0.20 cm; 95% CI: –1.38, 0.98; two trials, 576 participants). One study reported improvements in insulin sensitivity as measured by the homeostasis model of insulin resistance (HOMA-IR)[1] at 9 years of age *(65)*, and again between 15 and 20 years of age, during which HOMA-IR was on average 7.5% lower in the intervention group than in the control group *(66)*. Two trials reported on micronutrient intake and cognitive development in children with reduced saturated fatty acid intake *(67-71)*, and one further reported on sexual maturation *(72)*; however, data were not suitable for pooling. Neither study reported any significant difference in any of these outcomes between those children with reduced saturated fatty acid intake and those consuming usual levels of saturated fatty acids.

The quality of available evidence for an effect of reducing saturated fatty acid intake on all outcomes in children was considered to be *high,* except for systolic blood pressure, triglycerides, waist circumference and insulin resistance, for all of which the quality was considered to be *moderate* (Annex 1; GRADE evidence profile 2).

Saturated fatty acid intake of less than 10% of total energy intake

The intervention group in one trial achieved a reduction in saturated fatty acid intake to 9% of total energy intake, and demonstrated larger reductions in in total cholesterol (MD –0.29 mmol/L; 95% CI: –0.40, –0.18) (*high* quality evidence) and LDL cholesterol (MD –0.29 mmol/L; 95% CI: –0.38, –0.20) (*high* quality evidence) than in the remaining trials, in which the achieved intake was greater than 10% of total energy intake, and which showed mean reductions in total cholesterol of –0.15 mmol/L (95% CI: –0.23, –0.06) and LDL cholesterol of –0.13 mmol/L (95% CI: –0.19, –0.06). A non-significant effect was observed for body weight (*moderate* quality evidence) (Annex 1; GRADE evidence profile 4).

Replacement macronutrients for saturated fatty acids

Complete dietary information was not available for all RCTs, but two trials reported replacement of saturated fatty acids with unsaturated fatty acids. In one trial in which saturated fatty acids were replaced almost entirely with PUFA, total cholesterol was reduced by 0.29 mmol/L (95% CI: –0.40, –0.18) (*high* quality evidence) and LDL cholesterol was reduced by 0.29 mmol/L (95% CI: –0.38, –0.20) (*high* quality evidence) and there was a non-

[1] HOMA-IR is the combined outcome of serum insulin and glucose levels and is a proxy measure of insulin sensitivity that is often used in epidemiological studies.

significant effect on body weight (*moderate* quality evidence). In the second trial in which saturated fatty acids were replaced predominantly with MUFA (MUFA 80%, PUFA 20%), total cholesterol was reduced by 0.33 mmol/L (95% CI: –0.52, –0.14) (*high* quality evidence) and LDL cholesterol was reduced by 0.26 mmol/L (95% CI: –0.41, –0.11) (*high* quality evidence) (Annex 1; GRADE evidence profiles 6, 8). In subgroup analysis, these two trials when combined showed stronger reductions in total cholesterol (MD –0.30 mmol/L; 95% CI: –0.39, –0.21) (*high* quality evidence) and LDL cholesterol (MD –0.28 mmol/L; 95% CI: –0.36, –0.20]) (*high* quality evidence) than in the remaining trials, which, when pooled, showed mean reductions in in total cholesterol of –0.10 mmol/L (95% CI: –0.15, –0.04)LDL cholesterol of –0.07 mmol/L (95% CI: –0.15, 0.01) *(60)*.

In addition to the evidence reviewed from trials conducted in children, evidence for cardiovascular, mortality and blood lipid outcomes from adults was also considered when formulating the recommendations for children, without downgrading for indirectness. Although clinical cardiovascular outcomes are rarely observed in children, abnormal changes in blood lipids are associated with early stages of CVDs in children *(45-48)* and are linked to future cardiovascular events *(50-53)*.

Trans-fatty acids

Three systematic reviews were conducted to assess the effects of modifying intake of *trans*-fatty acids on health outcomes. One of these reviews included prospective cohort studies conducted in adults *(61)* and two included RCTs conducted in adults *(73)* and children *(60)*.

Priority health outcomes considered for adults were: all-cause mortality, CHD (incidence, mortality and morbidity), CVDs (incidence, mortality and morbidity), stroke (incidence, mortality and morbidity), blood lipids, type 2 diabetes incidence and insulin sensitivity. Priority health outcomes considered for children were blood lipids, height, weight and other measures of adiposity, blood pressure, type 2 diabetes incidence and insulin resistance, linear growth and potential adverse effects.

The key research questions guiding the systematic reviews undertaken were as follows:

- What is the effect of lower intake of *trans*-fatty acids relative to higher intake on risk of NCDs in adults and children?

- What is the effect of a decrease in *trans*-fatty acid intake to below 1% of total energy[1] on risk of NCDs in adults and children?
- What is the effect of replacing *trans*-fatty acids with other macronutrients on risk of NCDs in adults and children?

Adults

A systematic review of prospective cohort studies that assessed the effects of higher intake of *trans*-fatty acids compared with lower intake on risk of CVDs and mortality in adults identified 20 studies (28 comparisons) with over 450 000 participants *(61)*. Eighteen studies contributed to an analysis of the effects of total *trans*-fatty acids (i.e. *trans*-fatty acids from all sources), four studies to an analysis of the effects of industrially-produced *trans*-fatty acids, and eight studies to an analysis of the effects of ruminant *trans*-fatty acids. Studies were conducted in China, Denmark, Finland, the Netherlands, Norway and the USA. Intake of total *trans*-fatty acids across studies ranged from 0.6% to 4.7% of total energy intake. Outcomes assessed included all-cause mortality, coronary heart disease (CHD) mortality, CHD events, myocardial infarction, stroke and type 2 diabetes.

A second systematic review of RCTs that assessed the effects of modifying intake of *trans*-fatty acids on blood lipids in adults identified 16 RCTs with 680 participants *(73)*.[2] Sixteen trials contributed to an analysis of the effects of *trans*-fatty acids, 13 to the effects of industrially-produced *trans*-fatty acids, and four to the effects of ruminant *trans*-fatty acids.[3] The RCTs included in this review were all strictly controlled dietary trials, 14–56 days in duration, in which protein and cholesterol intake were held constant, and intervention groups received either industrial or ruminant *trans*-fatty acid-enriched food compared to a control group with low *trans*-fatty acid intake. Outcomes assessed included total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, LDL cholesterol to HDL cholesterol ratio, total cholesterol to HDL cholesterol ratio, ApoB and ApoA-I. Trials were conducted in Canada, Denmark, Finland, the Netherlands, Norway, the United Kingdom and the USA. Intake of *trans*-fatty acids ranged from 0% to 10.9% of total energy intake across the included trials. Using meta-regression analysis – in which the change in *trans*-fatty acid intake served as the independent variable and the change in a given blood lipid or lipid ratio as the dependent variable – a model was developed that provides an estimate of the effect (i.e. regression

[1] The population nutrient intake goal for *trans*-fatty acids recommended by the joint WHO/FAO expert consultation is less than 1% of total energy intake *(2)*.
[2] This review is an update of a previously published review on the effects of *trans*-fatty acids on blood lipids *(10)*.
[3] One trial assessed the effects of both industrial and ruminant *trans*-fatty acids.

coefficient) on a given blood lipid when 1% of total energy intake as total, industrial or ruminant *trans*-fatty acids is isocalorically exchanged with PUFA, MUFA, carbohydrates or saturated fatty acids.

Results were generated for total *trans*-fatty acid intake, and separately for industrial and ruminant *trans*-fatty acid intake for both analyses.[1] In the meta-analyses of prospective cohort studies, results for total and industrially-produced *trans*-fatty acid intake were similar in their effects on risk of CHD events and mortality.[2] Significant associations were not observed for the analysis of studies reporting effects of ruminant *trans*-fatty acid intake.[3] In the meta-regression of RCTs, reduced intake of total *trans*-fatty acids or industrially-produced *trans*-fatty acids was associated with a beneficial effect on the blood lipid profile, regardless of which nutrient was used as a replacement. A significant effect of reducing ruminant *trans*-fatty acid intake on lowering LDL cholesterol was only observed when ruminant *trans*-fatty acids were replaced with PUFA. For all other blood lipid outcomes, results were not statistically significant; however, they were similar to those for total and industrially-produced *trans*-fatty acids, both in direction and magnitude.[4] Intake of ruminant *trans*-fatty acids in the studies included in the analyses of both prospective cohort studies and RCTs was very low relative to intakes of industrially-produced *trans*-fatty acids. The evidence reviewed suggests that differences in effect on health outcomes between ruminant and industrially-produced *trans*-fatty acids observed in many studies are most likely to be due to differences in dose of *trans*-fatty acids rather than differences in type of *trans*-fatty acids.[5] It was therefore determined that the available evidence did not support making a

[1] For the meta-analysis of prospective cohort studies, separate analyses were performed for total, industrial and ruminant *trans*-fatty acids, because some studies did not differentiate between industrial and ruminant *trans*-fatty acids and only reported results for total *trans*-fatty acid intake. For the meta-regression analysis of total *trans*-fatty acids, all trials that assessed either industrial or ruminant *trans*-fatty acid intake were included in a single analysis.

[2] Only total *trans*-fatty acid intake was significantly associated with all-cause mortality.

[3] A significant association was observed between lower intake of a single ruminant *trans*-fatty acid isomer, t*rans*-palmitoleic acid and increased risk of type 2 diabetes (RR 1.72; 95% CI: 1.35, 2.08) *(61)*; however, it is unclear whether the effect observed was due to t*rans*-palmitoleic acid itself or to other components of dairy. Although there is evidence linking dairy intake to reduced risk of type 2 diabetes *(41)*, the effect observed for t*rans*-palmitoleic acid does not allow for any conclusions to be made regarding possible associations between intake of ruminant *trans*-fatty acids as a class of molecules and risk of type 2 diabetes. This evidence was therefore not considered in formulating the recommendations for *trans*-fatty intake.

[4] The two trials that reported ruminant *trans*-fatty acid intakes at levels more similar to the intakes reported for industrially-produced *trans*-fatty acids (i.e. >2% of total energy intake), reported larger reductions in LDL cholesterol *(74, 75)*.

[5] Post-hoc meta-analysis of total *trans*-fatty acids showed that intake was no longer associated with CHD mortality when limited only to studies in which total *trans*-fatty acid intake was at similar levels to those reported in studies included in the analysis of ruminant *trans*-fatty acid intake, although a significant association remained for CHD events *(61)*.

distinction between industrial and ruminant *trans*-fatty acids,[1] and data solely from analyses of total *trans*-fatty acids were considered when formulating the recommendations on *trans*-fatty acid intake.

Reducing trans-fatty acid intake

Meta-analysis of prospective cohort studies that included a comparison group with *trans*-fatty acid intake greater than 1% of total energy intake found a significant association between lower *trans*-fatty acid intake and decreased all-cause mortality (RR 0.81; 95% CI: 0.68, 0.96; one study with one comparison and 18 513 participants), CHD mortality (RR 0.78; 95% CI: 0.67, 0.92; five studies with six comparisons and 70 864 participants) and CHD events[2] (RR 0.83; 95% CI: 0.75, 0.91; six studies with seven comparisons and 145 922 participants) *(61)*. Significant associations were not observed between lower *trans*-fatty acid intake and stroke (RR 0.93; 95% CI: 0.78, 1.14; three studies with four comparisons and 190 284 participants) or type 2 diabetes (RR 0.91; 95% CI: 0.79, 1.05; six studies with six comparisons and 230 135 participants).

Meta-regression analysis of RCTs found that, for every 1% of total energy intake as *trans*-fatty acids replaced with PUFA, MUFA or carbohydrates, LDL cholesterol was significantly lowered by 0.048 mmol/L (95% CI: –0.055, –0.041), 0.035 mmol/L (95% CI: –0.042, –0.028) and 0.026 mmol/L (95% CI: –0.033, –0.019), respectively. Replacing *trans*-fatty acids with PUFA, MUFA or carbohydrates also lowered total cholesterol. Replacing *trans*-fatty acids with saturated fatty acids resulted in raised LDL cholesterol (0.010 mmol/L; 95% CI: 0.003, 0.017) and total cholesterol. Replacing *trans*-fatty acids with PUFA or MUFA also lowered triglycerides; replacing with PUFA, MUFA, carbohydrates or saturated fatty acids also lowered the total cholesterol to HDL cholesterol ratio and the LDL cholesterol to HDL cholesterol ratio, and raised HDL cholesterol, with PUFA replacement demonstrating the largest effect on all outcomes *(73)*.

The quality of available evidence for an effect of reducing *trans*-acid intake in adults whose intake is greater than 1% of energy intake, on CHD mortality and CHD events was considered to be *moderate*; on all-cause mortality was considered to be *low*; on stroke and type 2 diabetes was considered to be *very low;* and on all blood lipid outcomes was

[1] This approach is further supported by results of a study that was unpublished at the time the evidence was reviewed for this guideline (and thus has not been included in the systematic review of RCTs with blood lipid outcomes), in which a diet enriched with the predominant ruminant trans-fatty acid isomer, vaccenic acid, was shown not only to raise LDL cholesterol significantly compared to a control diet, but also in comparison to a diet high in industrially-produced *trans*-fatty acids *(76)*.

[2] CHD events include fatal myocardial infarction or death with CHD listed as the cause. Studies that had sudden cardiac death as a sole outcome were not included.

considered to be *high*, except for HDL cholesterol and triglycerides when *trans*-fatty acids were replaced with MUFA, and for triglycerides when *trans*-fatty acids were replaced with saturated fatty acids, for all of which the quality was considered to be *moderate* (Annex 1; GRADE evidence profile 15).

Trans-fatty acid intake of less than 1% of total energy intake

Meta-analysis of prospective cohort studies that included a group with *trans*-fatty acid intake below 1% of total energy intake found a significant association between *trans*-fatty acid intakes of less than 1% of total energy intake (compared to higher intakes) and decreased CHD mortality (RR 0.77; 95% CI: 0.67, 0.93; four studies with four comparisons and 68 957 participants) (*moderate* quality evidence) and CHD events (RR 0.86; 95% CI: 0.78, 0.96; four studies with four comparisons and 101 499 participants) (*moderate* quality evidence) *(61)*. A non-significant association was observed between *trans*-fatty acid intake of less than 1% of total energy intake and stroke (RR 1.25; 95% CI: 0.85, 1.85; one study with one comparison and 86 152 participants) (*very low* quality evidence) and type 2 diabetes (RR 0.93; 95% CI: 0.78, 1.09; four studies with four comparisons and 109 963 participants) (*very low* quality evidence). No studies were identified that included a group with *trans*-fatty acid intake below 1% of total energy intake and reported all-cause mortality as an outcome.

Effects of modifying *trans*-fatty acid intake on blood lipids in meta-regression were observed across a wide range of *trans*-fatty acid intakes (0–10.9% of total energy intake) *(73)*. Analysis of the residuals of the regression line for LDL cholesterol indicates that the relationship between reducing or increasing *trans*-fatty acid intake and effects on blood lipids is consistent across the entire range of *trans*-fatty acid intakes reported in the included studies, and therefore suggests benefit in reducing intake to below 1% of total energy intake.

The quality of available evidence for an effect of reducing *trans*-fatty acid intake to less than 1% of total energy intake on CHD mortality and CHD events was considered to be *moderate*; on stroke and type 2 diabetes was considered to be *very low;* and on all blood lipid outcomes was considered to be *high*, except for HDL and triglycerides when MUFA were replaced with *trans*-fatty acids, and for triglycerides when saturated fatty acids were replaced with *trans*-fatty acids, for all of which the quality of the evidence was considered to be *moderate* (Annex 1; GRADE evidence profile 16).

Replacement macronutrients for trans-fatty acids

Meta-regression analysis of RCTs found that, for every 1% of total energy intake as *trans*-fatty acids replaced with PUFA, MUFA or carbohydrates, LDL cholesterol was significantly lowered by 0.048 mmol/L (95% CI: –0.055, –0.041), 0.035 mmol/L (95% CI: –0.042, –0.028)

and 0.026 mmol/L (95% CI: –0.033, –0.019), respectively. Replacing *trans*-fatty acids with PUFA, MUFA or carbohydrates also lowered total cholesterol. Replacing *trans*-fatty acids with saturated fatty acids resulted in raised LDL cholesterol (0.010 mmol/L; 95% CI: 0.003, 0.017) and total cholesterol. Replacing *trans*-fatty acids with PUFA or MUFA also lowered triglycerides; replacing with PUFA, MUFA, carbohydrates or saturated fatty acids also lowered the total cholesterol to HDL cholesterol ratio and the LDL cholesterol to HDL cholesterol ratio, and raised HDL cholesterol, with PUFA replacement demonstrating the largest effect on all outcomes *(73)*.

The quality of available evidence for an effect of replacing *trans*-fatty acids with polyunsaturated fatty acids, monounsaturated fatty acids, carbohydrates or saturated fatty acids on all blood lipid outcomes was considered to be *high*, except for HDL cholesterol and triglycerides when *trans*-fatty acids were replaced with MUFA, and for triglycerides when *trans*-fatty acids were replaced with saturated fatty acids, for all of which the quality was considered to be *moderate* (Annex 1; GRADE evidence profiles 17-20).

Increasing trans-fatty acid intake

Meta-analysis of prospective cohort studies that included a group with *trans*-fatty acid intake below 1% of total energy intake found a significant association between higher *trans*-fatty acid intake and increased CHD mortality (RR 1.28; 95% CI: 1.09, 1.50; four studies with four comparisons and 68 957 participants) (*moderate* quality evidence) and CHD events (RR 1.16; 95% CI: 1.04, 1.29; four studies with four comparisons and 101 499 participants) (*moderate* quality evidence) *(61)*. Significant associations were not observed between higher *trans*-fatty acid intake and stroke (RR 0.80; 95% CI: 0.54, 1.18; one study with one comparison and 86 152 participants) (*very low* quality evidence) or type 2 diabetes (RR 1.08; 95% CI: 0.92, 1.28; four studies with four comparisons and 109 963 participants) (*very low* quality evidence). No studies were identified that included a group with *trans*-fatty acid intake below 1% of total energy intake and reported all-cause mortality as an outcome.

The quality of available evidence for an effect of replacing *trans*-fatty acids with polyunsaturated fatty acids, monounsaturated fatty acids, carbohydrates or saturated fatty acids on all blood lipid outcomes was considered to be *high*, except for HDL cholesterol and triglycerides when *trans*-fatty acids were replaced with MUFA, and for triglycerides when *trans*-fatty acids were replaced with saturated fatty acids, for all of which the quality was considered to be *moderate* (Annex 1; GRADE evidence profiles 21).

Regression analysis allows for the calculation of effects of both increases and decreases in *trans*-fatty acid intake from the same set of studies, and results for increasing *trans*-fatty acid

intake are opposite to those obtained for decreasing intake.[1] Meta-regression analysis of RCTs found that, for every 1% of total energy intake as PUFA, MUFA or carbohydrates replaced with *trans*-fatty acids, LDL cholesterol was significantly raised by 0.047 mmol/L (95% CI: 0.040, 0.055), 0.027 mmol/L (95% CI: 0.019, 0.035) and 0.026 mmol/L (95% CI: 0.019, 0.033), respectively *(73)*. Total cholesterol was also raised. Replacing saturated fatty acids with *trans*-fatty acids resulted in lower LDL cholesterol (–0.010 mmol/L; 95% CI: –0.017, –0.003) and total cholesterol. Replacing PUFA or MUFA with *trans*-fatty acids also raised triglycerides, and replacing PUFA, MUFA, carbohydrates or saturated fatty acids with *trans*-fatty acids raised the total cholesterol to HDL cholesterol ratio and the LDL cholesterol to HDL cholesterol ratio, and lowered HDL cholesterol.

The overall quality of available evidence for an effect of increasing *trans*-fatty acid intake on all blood lipid outcomes was considered to be *high*, except for HDL and triglycerides when MUFA were replaced with *trans*-fatty acids, and for triglycerides when saturated fatty acids were replaced with *trans*-fatty acids, for all of which the quality of the evidence was considered to be *moderate* (Annex 1; GRADE evidence profile 21).

Children

No studies meeting the inclusion criteria established for the systematic review of studies conducted in children were identified *(60)*.

Evidence for clinical and blood lipid outcomes from adults were considered when formulating the recommendations for children, without downgrading for indirectness. *Trans*-fatty intake is expected to have the same effect on blood lipids in children as observed in adults, and although clinical cardiovascular outcomes are rarely observed early in life, abnormal changes in blood lipids are associated with early stages of CVDs in children *(45-48)* and are linked to future cardiovascular events *(50-53)*.

[1] The numerical values are opposite in sign and are identical in magnitude. This is a result of a single set of calculations made for linear regression analysis, which captures both increasing and decreasing *trans*-fatty acid intake.

Recommendations and remarks

Saturated fatty acids

Recommendations

- In adults and children whose saturated fatty acid intake is greater than 10% of total energy intake[1], WHO recommends reducing saturated fatty acid intake (*strong recommendation*[2]).

- In adults and children, WHO suggests reducing the intake of saturated fatty acids to less than 10% of total energy intake (*conditional recommendation*[3]).

- WHO suggests using polyunsaturated fatty acids as a source of replacement energy, if needed, when reducing saturated fatty acid intake (*conditional recommendation*).

- In adults and children whose saturated fatty acid intake is less than 10% of total energy intake, WHO suggests no increase in saturated fatty acid intake (*conditional recommendation*).

Remarks

- 'Children' in these recommendations refer to individuals 2–19 years of age inclusive.

- The recommendations for saturated fatty acid intake in children are based on the totality of evidence reviewed, including surrogate endpoints and intermediate outcome markers for cardiovascular diseases (i.e. blood lipids and blood pressure) assessed directly in children, and extrapolation of adult data on risk of cardiovascular diseases and surrogate endpoints and intermediate outcome markers for cardiovascular diseases (i.e. blood lipids).

[1] Total energy intake is the sum of all daily calories/kilojoules consumed from food and drink. Energy comes from macronutrients, such as fat (9 kcal/37.7 kJ per gram), carbohydrate (4 kcal/16.7 kJ per gram) including total sugars (free sugars + intrinsic sugars + milk sugars) and dietary fibre, protein (4 kcal/16.7 kJ per gram) and ethanol (i.e. alcohol) (7 kcal/29.3 kJ per gram). Total energy intake is calculated by multiplying these energy factors by the number of grams of each type of food and drink consumed and then adding all values together. A percentage of total energy intake is therefore a percentage of total calories/kilojoules consumed per day.

[2] *Strong* recommendations are those recommendations for which the WHO guideline development group is confident that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. Strong recommendations can be adopted as policy in most situations. *(22)*.

[3] *Conditional* recommendations are those recommendations for which the WHO guideline development group is uncertain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. Policy-making related to conditional recommendations therefore may require substantial debate and involvement of various stakeholders *(22)*.

- The evidence indicates that children's growth is not compromised by reduction of saturated fatty acid intake. Evidence for effects on cognitive development and iron status in children is limited, but does not suggest that these outcomes are adversely affected.

- In RCTs that assessed cardiovascular outcomes and mortality outcomes *(24),* in which saturated fatty acids were largely replaced with polyunsaturated fatty acids, the polyunsaturated fatty acids were primarily from plant-based oils, rich in linoleic acid.

- In RCTs that assessed blood lipid outcomes, the LDL cholesterol-lowering effect of reducing saturated fatty acid intake appears linear across the range of 2% to 24% of total energy intake, suggesting benefit in terms of lowering LDL cholesterol at levels of saturated fatty acid intake already below 10% of total energy intake. Benefit in terms of not raising LDL cholesterol is also suggested for not increasing saturated fatty acid intake if it is already less than 10% of total energy intake.

- The recommendation to reduce saturated fatty acid intake in those whose saturated fatty acid intake is above 10% of total energy intake (first recommendation) is based on the totality of evidence reviewed, including *moderate* quality evidence for reduced risk of cardiovascular events in adults, *high* quality evidence for reduced LDL cholesterol in adults, and *high* quality evidence for reduced LDL cholesterol and diastolic blood pressure in children. The first recommendation was considered to be strong, based on the quality of evidence, together with consideration of the other factors[1] that impact the strength of a recommendation as described in Annex 7.

- The recommendation to reduce saturated fatty acid intake to less than 10% of total energy intake (second recommendation) is based on the totality of evidence reviewed, including *high* quality evidence for reduced LDL cholesterol in adults and children. Although LDL cholesterol is a well-established surrogate endpoint for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore, although the evidence for LDL cholesterol reduction was of high quality, a conservative approach was taken and the second recommendation was considered to be conditional.

[1] Values and preferences, balance of benefits and harms, resource implications, priority of the problem, equity and human rights, acceptability and feasibility (22).

- The recommendation to replace saturated fatty acids with polyunsaturated fatty acids, when a replacement is needed (third recommendation), is based on the totality of evidence reviewed, including *moderate* quality evidence for reduced risk of cardiovascular events in adults, and *high* quality evidence for reduced LDL cholesterol in adults and children. Although there was moderate to high quality evidence for benefit in replacing saturated fatty acids with polyunsaturated fatty acids, none of the RCTs included in the analyses of cardiovascular and mortality outcomes directly compared different replacement nutrients to one another. Therefore, a conservative approach was taken, and the third recommendation was considered to be conditional.

- The recommendation to replace saturated fatty acids with polyunsaturated fatty acids, when a replacement is needed (third recommendation), does not preclude replacing saturated fatty acids with monounsaturated fatty acids, as replacement with monounsaturated fatty acids significantly lowered LDL cholesterol in the analysis of RCTs that assessed blood lipids (but had no effect on cardiovascular or mortality outcomes). However, polyunsaturated fatty acids were the primary replacement source in the RCTs that demonstrated a reduction in risk of cardiovascular events and demonstrated the largest effect on LDL cholesterol when used as replacement for saturated fatty acids in RCTs that assessed blood lipid outcomes. Although replacement with carbohydrates resulted in a small reduction in LDL cholesterol (but had no effect on cardiovascular or mortality outcomes), the composition of the carbohydrates used as replacement in these RCTs was largely unknown. Therefore, a conclusive interpretation of the results for carbohydrate replacement of saturated fatty acids in the analyses supporting the recommendations in these guidelines was considered not possible.

- The recommendation to not increase saturated fatty acid intake if intake is already below 10% of total energy intake (fourth recommendation) is based on the totality of evidence reviewed, including *high* quality evidence for increased LDL cholesterol with increased intake of saturated fatty acids in adults. Although LDL cholesterol is a well-established surrogate endpoint for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore, although the evidence for LDL cholesterol reduction was of high quality, a conservative approach was taken with respect to assessing the impact of values and preferences on the strength of this recommendation, and the fourth recommendation was considered to be conditional.

- These recommendations should be considered in the context of other WHO guidelines on healthy diets, including those on the intake of free sugars *(25)*, sodium *(26)*, potassium *(27)*, and*trans*-fatty acids in this guideline document, as well as total fat, polyunsaturated fatty acids and carbohydrates which are all currently being updated. Public health interventions should aim to reduce saturated fatty acid intake, while reducing total fat intake where necessary, and without increasing free sugars intake.

Trans-fatty acids

Recommendations

- In adults and children whose *trans*-fatty acid intake is greater than 1% of total energy intake, WHO recommends reducing *trans*-fatty acid intake (*strong recommendation*).

- In adults and children, WHO suggests reducing the intake of *trans*-fatty acids to less than 1% of total energy intake (*conditional recommendation*).

- WHO suggests using polyunsaturated fatty acids as a replacement for *trans*-fatty acids (*conditional recommendation*).

- In adults and children, whose *trans*-fatty acid intake is less than 1% of total energy intake, WHO suggests no increase in *trans*-fatty acid intake (*conditional recommendation*).

Remarks

- *Trans*-fatty acids include all fatty acids with a double bond in the *trans* configuration regardless of whether they come from ruminant sources or are produced industrially.[1]
- 'Children' in these recommendations refer to individuals 2–19 years of age inclusive.

[1] This definition includes conjugated linoleic acid (CLA). The number of trials included in the meta-regression of RCTs *(10)* that specifically assessed the effects of naturally-occurring CLA on blood lipids were limited and intakes of CLA were very low, however, results of these trials provided no indication that they had an effect on blood lipids that was significantly different from other *trans*-fatty acids when consumed at similar levels. This was further supported by a separate meta-analysis of studies in which CLA was provided as supplements *(28)*, which found that supplemental CLA raised LDL cholesterol and lowered HDL cholesterol in a manner similar to that observed for other *trans*-fatty acids.

- The recommendations for *trans*-fatty acid intake in children are based on extrapolation of adult data on risk of cardiovascular diseases and intermediate outcome markers for cardiovascular diseases (i.e. blood lipids).

- In RCTs that assessed blood lipid outcomes, the LDL cholesterol-lowering effect of reducing *trans*-fatty acid intake appears linear across the range of 0% to 10.9% of total energy intake and effects on coronary heart disease and mortality outcomes in prospective cohort studies were observed across a range of intakes, from approximately 0.7% to 3.8% of total energy intake. Together, this suggests benefit in terms of lowering LDL cholesterol at levels of *trans*-fatty acid intake already below 1% of total energy intake, as well as benefit in terms of not raising LDL cholesterol by not increasing *trans*-fatty acid intake if it is already less than 1% of total energy intake.

- The recommendation to reduce *trans*-fatty acid intake in those whose *trans*-fatty acid intake is above 1% of total energy intake (first recommendation) is based on the totality of evidence reviewed, including *low* quality evidence of an association with lower all-cause mortality, *moderate* quality evidence of an association with fewer coronary heart disease events and lower coronary heart disease mortality in adults, and *high* quality evidence for reduced LDL cholesterol in adults. The first recommendation was considered to be strong based on the quality of evidence, together with consideration of the other factors that impact the strength of a recommendation as described in Annex 7.

- The recommendation to reduce *trans*-fatty acid intake to less than 1% of total energy intake (second recommendation) is based on the totality of evidence reviewed, including *moderate* quality evidence of an association with fewer coronary heart disease events and lower coronary heart disease mortality in adults, and *high* quality evidence for reduced LDL cholesterol in adults. Although the evidence for coronary heart disease events and coronary heart disease mortality is of *moderate* quality, confidence regarding the absolute effects of reducing *trans*-fatty acid intake on these outcomes was diminished because of the few events occurring in studies with up to 21 years of follow-up. In addition, the association with all-cause mortality observed in the evidence for the first recommendation, with a large number of events in one study with 7 years of follow-up, is not included in the evidence for the second recommendation as it was not relevant to specifically looking at effects of reducing *trans*-fatty acid intake to less than 1% of total energy intake. Furthermore, although LDL cholesterol is a well-established surrogate endpoint for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore, although the evidence for an association with fewer

coronary heart disease events and lower coronary heart disease mortality was of *moderate* quality, and evidence for LDL cholesterol reduction of *high* quality, a conservative approach was taken and the second recommendation was considered to be conditional.

- The recommendation to replace *trans*-fatty acids with polyunsaturated fatty acids (third recommendation), is based on the totality of evidence reviewed, including *high* quality evidence for reduced LDL cholesterol in adults. Although LDL cholesterol is a well-established biomarker for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore, although the evidence for LDL cholesterol reduction was of high quality, a conservative approach was taken and the third recommendation was considered to be conditional.

- The recommendation to replace *trans*-fatty acids with polyunsaturated fatty acids (third recommendation), does not preclude replacing *trans*-fatty acids with monounsaturated fatty acids, as replacement with monounsaturated fatty acids significantly lowered LDL cholesterol in the analysis of RCTs that assessed blood lipids. However, polyunsaturated fatty acids demonstrated the largest effect on LDL cholesterol when used as replacement for *trans*-fatty acids in RCTs that assessed blood lipid outcomes. Although replacement with carbohydrates resulted in a small reduction in LDL cholesterol, the composition of the carbohydrates used as replacement in these RCTs was largely unknown. Therefore, a conclusive interpretation of the results for carbohydrate replacement of *trans*-fatty acids in the analyses supporting the recommendations in these guidelines was considered not possible.

- The recommendation to not increase *trans*-fatty acid intake if intake is already below 1% of total energy intake (fourth recommendation) is based on the totality of evidence reviewed, including *moderate* quality evidence of an association with a greater number of coronary heart disease events and higher coronary heart disease mortality in adults, and *high* quality evidence for increased LDL cholesterol in adults. Although the evidence for coronary heart disease events and coronary heart disease mortality is of *moderate* quality, confidence regarding the absolute effects of increasing *trans*-fatty acid intake on these outcomes was diminished because of the few events occurring studies with up to 21 years of follow-up. In addition, the association with all-cause mortality observed in the evidence for the first recommendation, with a large number of events in one study with 7 years of follow-up, is not included in the evidence for the fourth recommendation as it

was not relevant to specifically looking at effects of increasing *trans*-fatty acid intake if intake is already below 1% of total energy intake. Furthermore, although LDL cholesterol is a well-established surrogate endpoint for cardiovascular diseases, it is not a physical manifestation or confirmation of disease. Therefore, although the evidence for an association with a greater number of coronary heart disease events and higher coronary heart disease mortality was of *moderate* quality, and evidence for an increase in LDL cholesterol of *high* quality, a conservative approach was taken and the fourth recommendation was considered to be conditional.

- These recommendations should be considered in the context of other WHO guidelines on healthy diets, including those on the intake of free sugars *(25)*, sodium *(26)*, potassium *(27)*, and saturated fatty acids in this guideline document, as well as total fat, polyunsaturated fatty acids and carbohydrates which are all currently being updated. Public health interventions should aim to reduce *trans*-fatty acid intake, while reducing total fat intake where necessary, and without increasing saturated fatty acids and free sugars intake.

Dissemination, translation and implementation, and monitoring and evaluation

Dissemination

The guidelines will be disseminated through:

- the WHO e-Library of Evidence for Nutrition Actions (eLENA),[1] which is an online library of evidence-informed guidance for nutrition interventions that provides policy-makers, programme managers, health workers, partners, stakeholders and other interested actors with access to the latest nutrition guidelines and recommendations, as well as complementary documents, such as systematic reviews, and biological, behavioural and contextual rationales for the effectiveness of nutrition actions;
- the eLENA mobile phone application, eLENA*mobile,* which provides offline access to eLENA content;
- the WHO Department of Nutrition for Health and Development (NHD) website,[2] along with the Executive summary in all six official WHO languages;

[1] http://www.who.int/elena/en/
[2] http://www.who.int/nutrition/en/

- the mailing lists of NHD (>6000 addressees) and the United Nations Standing Committee on Nutrition (approximately 2500 addressees);
- the network of the six WHO Regional Offices and Country Offices;
- the WHO Collaborating Centres; and
- the Global Network of Institution for Scientific Advice on Nutrition.

The guidelines will also be disseminated at various related WHO meetings as well as at global and regional scientific meetings.

Translation and implementation

These guidelines should be used in conjunction with other guidance on dietary goals and nutrition guidelines, in particular those related to free sugars *(25)*, sodium *(26)* and potassium *(27)*, as well as total fat, polyunsaturated fatty acids and carbohydrates which are all currently being updated, to guide effective policy actions and intervention programmes to promote healthy diets and nutrition, and prevent diet-related NCDs. The recommendations in these guidelines can be:

- used by policy-makers and programme managers to:
  - assess current intake of saturated fatty acids and *trans*-fatty acids of their populations relative to a benchmark; and
  - develop policy measures to reduce intake of saturated fatty acids and *trans*-fatty acids, where necessary, through a range of public health interventions; measures and interventions that are already being implemented by countries include:
    - nutrition labelling (i.e. mandatory nutrient declaration), including front-of-pack labelling systems;
    - regulation of marketing food and non-alcoholic beverages that are high in saturated fatty acids and *trans*-fatty acids, including bans on marketing of food which contains industrially-produced *trans*-fatty acids;
    - restricting the sales and promotion of food and beverages that are high in saturated fatty acids and *trans*-fatty acids in schools, including bans on the sales and promotion of food which contains industrially-produced *trans*-fatty acids;
    - fiscal policies targeting foods and beverages that are high in saturated fatty acids and *trans*-fatty acids; and
    - consumer education.

- used to develop a strategy to reformulate food products; in particular, processed foods that are high in saturated fatty acids and *trans*-fatty acids; and

- translated at the country-level into culturally and contextually specific food-based dietary guidelines that take into account locally available food and dietary customs.

Regarding *trans*-fatty acids, it should be noted that elimination of industrially-produced *trans*-fatty acids is among the priority actions identified by WHO in its 13th General Programme of Work which will guide the work of the Organization in 2019 – 2023. Industrially-produced *trans*-fatty acids are the predominant source of dietary *trans*-fatty acids in many populations and can be found in baked and fried foods (e.g. doughnuts, cookies, crackers and pies), pre-packaged snacks and food, and partially-hydrogenated cooking oils and fats which are often used at home, in restaurants or in the informal sector, such as street vendors. Therefore, removing industrially-produced *trans*-fatty acids from the food supply through legislation or regulatory action represents a well-defined mechanism for translating the recommendations into action and achieving significant reductions in *trans*-fatty intake at the population level. Industrially-produced *trans*-fatty acids have already largely been removed or are in the process of being removed from the food supply at the national and subnational level in many countries *(35, 77, 78)*, demonstrating that this is an achievable goal.

Providing overall dietary guidance is beyond the scope of these guidelines, because such guidance should be based on overall dietary goals that consider all required nutrients. However, it is feasible to achieve the recommendations in these guidelines because a wide variety of fresh foods are naturally low in saturated fatty acids and *trans*-fatty acids.

Monitoring and evaluation of guideline implementation

The impact of these guidelines can be evaluated by assessing its adoption and adaptation across countries. Evaluation at the global level will be through the WHO Global Database on the Implementation of Nutrition Action (GINA)[1] – a centralized platform developed by NHD for sharing information on nutrition actions in public health practice implemented around the world. GINA currently contains information on nearly 2000 policies (including laws and legislations) and 3000 nutrition actions and programmes in 196 countries. GINA is being updated with the data and information from the 2nd Global Nutrition Policy Review 2016 – 2017 *(79)*. This includes information on various actions and regulatory measures to reduce intake of saturated fatty acids and *trans*-fatty acids, such as *trans*-fat bans and reformulation.

[1] http://www.who.int/nutrition/gina/en/index.html

Through providing programmatic implementation details, specific country adaptations and lessons learnt, GINA serves as a platform for monitoring and evaluating how guidelines are being translated into various policy actions and intervention programmes to address the issues related to the consumption of saturated fatty acids and *trans*-fatty acids in various countries.

Research gaps and future initiatives

Implications for future research

Based on the results of the systematic reviews and discussions with the NUGAG Subgroup on Diet and Health, a number of pending questions and implications for future research were identified, as outlined below.

Research needed on saturated fatty acids:

- large RCTs that include populations from different geographical regions and assess the effects on risk of cardiovascular diseases and mortality of replacing saturated fatty acids with MUFA and different types of carbohydrates (e.g. refined and unrefined) and PUFA (e.g. n-3 PUFA, n-6 PUFA);
- RCTs comparing the effects of saturated fatty acids from different food sources (e.g. plant, animal and dairy) on cardiovascular diseases and mortality; and
- RCTs in settings with low saturated fatty acid intake (i.e. less than 10% of total energy intake) to assess lower thresholds, above which saturated fatty acid intake increases the risk of CVD and mortality.

Research needed on *trans*-fatty acids:

- observational studies in children, with long-term follow-up to assess the effects of *trans*-fatty acid intake on CVD risk and inflammation;
- basic research and epidemiological studies to better understand the physiological pathways through which *trans*-fatty acid intake affects mortality and cardiovascular outcomes, including effects on inflammation and the immune response; and
- assessment of the current levels of *trans*-fatty acid intake in different countries, particularly in developing countries.

Research needed relevant to both saturated fatty acids and *trans*-fatty acids:

- RCTs to assess the effects on risk of cardiovascular diseases and mortality of reducing saturated fatty acid or *trans*-fatty acid intake (or both) in those at high risk of CVDs who are on lipid-lowering medication; and

- improved methods of analysis for assessing fatty acid intakes in individuals, including development of robust biomarkers.

Updating the guideline

WHO regularly updates its guidelines and recommendations to reflect the latest scientific and medical knowledge; hence, updating of these guidelines is part of the ongoing efforts of WHO to update existing dietary goals and nutrition guidance for promoting healthy diets, nutrition and the prevention of NCDs. It is planned that the recommendations in these guidelines will be reviewed when new data and information becomes available. At that time, a guideline review group will be convened to evaluate the new evidence and revise the recommendations. NHD, together with partners in other departments within the WHO Secretariat, will be responsible for coordinating the updating of the guidelines, following the formal procedure described in the *WHO handbook for guideline development (22)*. At the time the guidelines are due for review, WHO will welcome suggestions for additional questions that could be addressed in the guidelines.

Annex 1: GRADE evidence profiles

GRADE evidence profile 1
Question: What is the effect of a reduction in saturated fatty acid intake in adults with intakes greater than 10% of total energy intake?[1]
Population: General adult population

Quality assessment							No. of events/participants (study event rate)		Relative effect (95% CI)	Absolute effects[3] (per 10 000)	Quality[4]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other	Reduced SFA intake	Usual SFA intake			
All-cause mortality (follow-up mean 56 months)											
12	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	1377/22819 (6%)	1899/33039 (5.7%)	**RR 0.97** (0.9 to 1.05)	**17 fewer** (from 57 fewer to 29 more)	⊕⊕⊕O MODERATE
Cardiovascular disease mortality (follow-up mean 53 months)[9]											
12	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	483/21844 (2.2%)	613/31577 (1.9%)	**RR 0.95** (0.8 to 1.12)	**10 fewer** (from 39 fewer to 23 more)	⊕⊕⊕O MODERATE
Cardiovascular events (follow-up mean 52 months)											
13	RCTs	No serious risk of bias[5]	Serious inconsistency[10]	No serious indirectness	No serious imprecision[11]	None[12]	1774/21791 (8.1%)	2603/31509 (8.3%)	**RR 0.83** (0.72 to 0.96)	**138 fewer** (from 33 fewer to 228 fewer)	⊕⊕⊕O MODERATE
Coronary heart disease events (follow-up mean 59 months)											
12	RCTs	No serious risk of bias[5]	Serious inconsistency[13]	No serious indirectness	Serious imprecision[7]	None[8]	1346/21746 (6.2%)	1961/31458 (6.2%)	**RR 0.87** (0.74 to 1.03)	**80 fewer** (from 160 fewer to 19 more)	⊕⊕OO LOW
Fatal and nonfatal myocardial infarction (follow-up mean 55 months)[14]											
11	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	717/21725 (3.3%)	997/31442 (3.2%)	**RR 0.90** (0.8 to 1.01)	**32 fewer** (from 63 fewer to 3 more)	⊕⊕⊕O MODERATE
Stroke (follow-up mean 59 months)											
8	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[15]	451/20403 (2.2%)	672/30156 (2.2%)	**RR 1.00** (0.89 to 1.11)	**0 fewer** (from 25 fewer to 25 more)	⊕⊕⊕O MODERATE
LDL cholesterol (follow-up 13 to 91 days; units mmol/L per 1% energy exchange; better indicated by lower values)											
69 (165)[16]	RCTs	No serious risk of bias[17]	No serious inconsistency[18]	No serious indirectness[19]	No serious imprecision[20]	None[21]	1973[22]	--	**–0.055** (–0.061 to –0.050)[23]	--	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCT, randomized controlled trial; RR, relative risk; SFA, saturated fatty acids

[1] For outcomes other than LDL cholesterol, only studies that included a control group with SFA intake greater than 10% of total energy intake were included in the analysis. For the LDL cholesterol outcome, effects of decreasing SFA intake on blood lipids by replacement with polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA) or carbohydrates, as obtained from regression analysis, were observed across a wide range of SFA intakes, from 1.6% to 24.4% of total energy intake. Of the 177 total data points used in the multiple regression, 61 included an SFA intake component of more than 10% of total energy intake. Residuals analysis indicates that the relationship between SFA intake and effect on blood lipids is linear across the entire range of SFA intakes.

[2] All studies were conducted in the population of interest and employed appropriate interventions to assess the effect of lower compared to higher SFA intake on priority health outcomes decided upon prior to initiating the reviews. For outcomes other than LDL cholesterol, a small number of the RCTs included in the corresponding systematic review *(24)* employed one or more dietary interventions in addition to SFA reduction (i.e. multifactorial dietary interventions), however, all studies either explicitly or implicitly aimed to reduce SFA intake, achieved a reduction in SFA intake, or both.

[3] Based on the control event rate (CER), which is the number of people with events in the control group divided by the total number of people in the control group. The absolute effect (per 10 000 people) is calculated with the following equation: absolute effect =10 000 x [CER x (1-RR)]. The magnitude of absolute effect depends on baseline risk, which can vary across different populations.
[4] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*.
Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(59)*.
[5] These large RCTs of relatively long duration (minimum duration of 24 months) all appeared to use appropriate methods of random sequence generation, and about half had good allocation concealment (allocation concealment in the remaining studies was unclear). Incomplete outcome reporting was variable across studies, and most included studies had systematic differences in care (i.e. intervention group had more time or attention than the control group). No other biases were noted. Not downgraded for bias, but it is noted that the level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null. Most studies were not blinded, as blinding in dietary trials is generally very difficult.
[6] I^2 < 50%, indicating a low level of heterogeneity.
[7] The 95% CI crosses a threshold of important benefit or harm.
[8] Visual inspection of the funnel plot did not suggest any publication bias.
[9] Additional evidence on the relationship between reduced SFA intake and cardiovascular and mortality outcomes comes from meta-analysis of 10 studies with coronary heart disease mortality as an outcome (RR 0.98; 95% CI: 0.84, 1.15) (*moderate*-quality evidence).
[10] I^2 > 50%, indicating a significant level of heterogeneity. The heterogeneity was partly explained by the degree of SFA reduction and cholesterol lowering achieved, as assessed by subgroup analysis and meta-regression. The outcome was conservatively downgraded.
[11] The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[12] Visual inspection of the funnel plot did not suggest any publication bias. A dose–response relationship was observed via both subgroup and meta-regression analyses, but the outcome was not upgraded as it had already been downgraded for inconsistency.
[13] I^2 > 50%, indicating a significant level of heterogeneity.
[14] Additional evidence on the relationship between reduced SFA intake and cardiovascular outcomes comes from meta-analysis of nine studies with nonfatal myocardial infarction as an outcome (RR 0.95; 95% CI: 0.8, 1.13) (*moderate*-quality evidence).
[15] Publication bias was not formally assessed due to the small number of studies, but studies included for this outcome are a subset of the complete set of studies, for which no publication bias was detected.
[16] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, PUFA, MUFA and carbohydrate intake, as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period. Each data point was extracted for all treatment groups within studies included in the multiple regression analysis of blood lipids.
[17] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization, whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments, and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it is possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.
[18] This analysis was conducted as a multiple regression in which data points (see footnote 16) were directly extracted from each study, rather than mean differences extracted between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.
[19] LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[20] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect. The rationale for this was that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[21] Publication bias was not formally assessed but, given the large number and nature of the studies included in the analysis (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified), risk of publication bias is likely to be low.
[22] Data points (see footnote 16) were directly extracted from all treatment groups within included studies, without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.

[23] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as SFA is replaced with an isocaloric amount of PUFA. Reductions in LDL cholesterol were also observed when SFA were replaced with MUFA (–0.042 mmol/L; 95% CI: –0.047, –0.037) (*high*-quality evidence) or carbohydrates (–0.033 mmol/L; 95% CI:–0.039, –0.027) (*high*-quality evidence).

For details of the studies included in the reviews, see references *(24)* and *(59)*.

GRADE evidence profile 2
Question: What is the effect of a reduction in saturated fatty acid intake in children with intakes greater than 10% of total energy intake?[1]
Population: General child population

Quality assessment							No. of participants[2]		Relative effect (95% CI)	Quality[3]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reduced SFA intake	Usual SFA intake		
Cardiovascular events (*as assessed in adults*) (follow-up mean 52 months)										
13	RCTs	No serious risk of bias[4]	Serious inconsistency[5]	No serious indirectness[6]	No serious imprecision[7]	None[8]	21 791	31 509	**RR 0.83** (0.72 to 0.96)	⊕⊕⊕O MODERATE
LDL cholesterol (follow-up 5 weeks – 19 years; units mmol/L; better indicated by lower values)[9]										
6	RCTs	No serious risk of bias[10]	No serious inconsistency[11]	No serious indirectness[12]	No serious imprecision[7]	None[13]	939	905	**MD 0.16 lower** (0.25 lower to 0.08 lower)	⊕⊕⊕⊕ HIGH
Diastolic blood pressure (follow-up 12 weeks – 14 years; units mmHg; better indicated by lower values)[14]										
2	RCTs	No serious risk of bias[10]	No serious inconsistency[15]	No serious indirectness[12]	No serious imprecision[7]	None	549	557	**MD 1.45 lower** (2.34 lower to 0.56 lower)	⊕⊕⊕⊕ HIGH
BMI (follow-up 24 weeks – 19 years; units kg/m^2; better indicated by lower values)[16]										
3	RCTs	No serious risk of bias[10]	No serious inconsistency[15]	No serious indirectness[12]	No serious imprecision[17]	None	590	599	**MD 0.10 lower** (0.32 lower to 0.12 higher)	⊕⊕⊕⊕ HIGH
Height (follow-up 12 weeks – 14 years; units SD; better indicated by higher values)										
3	RCTs	No serious risk of bias[10]	No serious inconsistency[15]	No serious indirectness[12]	No serious imprecision[17]	None	664	623	**SMD 0.09 higher** (0.03 lower to 0.21 higher)	⊕⊕⊕⊕ HIGH
Insulin resistance (follow-up 18 years; unitless, measured as HOMA-IR;[18] better indicated by lower values)										
1	RCTs	Serious risk of bias[19]	No serious inconsistency[20]	No serious indirectness[12]	No serious imprecision[20]	None	245	275	**MD 7.5% lower** p = 0.0051	⊕⊕⊕O MODERATE
Adverse effects										
2	Outcomes reported varied across studies that reported adverse events; not suitable for pooling[21]									

BMI, body mass index; CI, confidence interval; HOMA-IR, homeostasis model of insulin resistance; LDL, low-density lipoprotein; RCTs, randomized controlled trials; MD, mean difference; SD, standard deviation; SFA, saturated fatty acids; SMD, standardized mean difference

[1] Only studies that included a control group consuming greater than 10% of total energy intake as SFA were included in this analysis. In addition to the outcomes directly assessed in children and the cardiovascular events outcome for adults included in this evidence profile, the remaining evidence for adults was also considered for children, without downgrading for indirectness as noted in footnote 6.
[2] Participants in crossover trials are counted in both the *Reduced SFA intake and Usual SFA intake* columns.
[3] All outcomes in this evidence profile are *critical* outcomes except *Height* and *Adverse effects* which are *important* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for additional *important* outcomes can be found in the systematic review of studies conducted in children *(60)*.
[4] These large RCTs of relatively long duration (minimum duration of 24 months) all appeared to use appropriate methods of random sequence generation and about half had good allocation concealment (allocation concealment in the remaining studies was unclear). Incomplete outcome reporting was variable across studies, and most included studies had systematic differences in care

(i.e. intervention group had more time or attention than the control group). No other biases were noted. Not downgraded for bias, but it is noted that the level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[5] I^2 > 50%, indicating a significant level of heterogeneity. The heterogeneity was partly explained by the degree of SFA reduction and cholesterol lowering achieved, as assessed by subgroup analysis and meta-regression. The outcome was conservatively downgraded.
[6] All studies were conducted in adults and, although adverse clinical cardiovascular outcomes in children are rare, there is no evidence to indicate that the physiological response to a change in SFA intake would be significantly different between adults and children *(47-53)*. Therefore, this outcome has not been downgraded for indirectness.
[7] The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[8] Visual inspection of the funnel plot did not suggest any publication bias. A dose–response relationship was observed via both subgroup and meta-regression analyses, but the outcome was not upgraded because it had already been downgraded for inconsistency.
[9] Additional evidence on the relationship between SFA intake and blood lipids came from meta-analysis of six studies conducted in children with total cholesterol as an outcome (MD –0.18 mmol/L; 95% CI: –0.28, –0.09) (*high*-quality evidence) and meta-regression analysis of 69 studies conducted in adults with LDL cholesterol as an outcome (–0.055 mmol/L; 95% CI: –0.061, –0.050; SFA replaced with polyunsaturated fatty acids) (*high*-quality evidence), (–0.042 mmol/L; 95% CI: –0.047, –0.037; SFA replaced with monounsaturated fatty acids) (*high*-quality evidence) and (–0.033 mmol/L; 95% CI: –0.039, –0.027; SFA replaced with carbohydrates) (*high*-quality evidence).
[10] Potential sources of bias were identified in some of the studies included in this analysis, but none of the studies was assessed as having serious risk of bias overall. The following potential sources of bias were noted: two studies had systematic differences in care in terms of frequency of participant interaction with study personnel (i.e. dietary counselling sessions), one study did not report effects for all pre-defined outcomes and one study employed cluster randomization based on ability of study centres to implement the intervention (food modification).
[11] I^2 > 50%, indicating a significant level of heterogeneity, but point estimates were similar and virtually all the heterogeneity could be explained by study design and/or nature of nutrient-replacing SFA in the studies, as assessed by subgroup analysis. Two crossover studies, in which SFA were replaced primarily with polyunsaturated fatty acids and/or monounsaturated fatty acids, achieved greater reductions in total and LDL cholesterol than in studies in which the nature of the replacement nutrients was less clear. The outcome was therefore not downgraded for serious inconsistency.
[12] All studies were conducted in the population of interest, all comparisons were made directly to an appropriate control group and all outcomes were priority outcomes that were decided on before initiating the review. LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[13] Too few studies to conduct funnel plot analysis.
[14] Additional evidence on the relationship between SFA intake and blood pressure comes from meta-analysis of two studies with systolic blood pressure as an outcome (MD 0.68 mmHg; 95% CI: –1.71, 0.35) (*moderate*-quality evidence).
[15] I^2 < 50%, indicating a low level of heterogeneity.
[16] Additional evidence on the relationship between reduced SFA intake and adiposity comes from meta-analysis of four studies with body weight as an outcome (SMD 0.03; 95% CI: –0.13, 0.07) (*high*-quality evidence) and two studies with waist circumference as an outcome (MD –0.20 cm; 95% CI: –1.38, 0.98) (*moderate*-quality evidence).
[17] The 95% CI crosses zero but does not cross a threshold of important benefit or harm and is therefore an accurate estimate of no effect, and was not downgraded for imprecision.
[18] HOMA-IR is a composite measure of insulin resistance incorporating both glucose and insulin and is calculated as follows: HOMA-IR = fasting glucose (mmol/L) x fasting insulin (mU/L) / 22.5.
[19] Possible confounding by dietary fibre intakes which were higher in intervention children than in control children. Dietary fibre was significantly associated with HOMA-IR in girls.
[20] Only one study included, reporting a small *P* value for effect on HOMA-IR.
[21] In addition to no observed effects on growth (i.e. height and weight), there was no evidence of adverse effects of reducing SFA intake in children on micronutrient intakes, cognitive development or sexual maturation in the two studies reporting these outcomes.
For details of the studies included in the reviews, see references *(24)* and *(60)*.

GRADE evidence profile 3
Question: What is the effect of a reduction in saturated fatty acid intake in adults to less than 10% of total energy intake?[1]
Population: General adult population

Quality assessment							No. of events/participants (study event rate)		Relative effect (95% CI)	Absolute effects[3] (per 10 000)	Quality[4]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other	Reduced SFA intake	Usual SFA intake			
All-cause mortality (follow-up mean 56 months)											
5	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	1165/20279 (5.7%)	1664/30048 (5.5%)	**RR 0.99** (0.90 to 1.09)	**6 fewer** (from 55 fewer to 50 more)	⊕⊕⊕O MODERATE
Cardiovascular disease mortality (follow-up mean 53 months)[9]											
5	RCTs	No serious risk of bias[5]	Serious inconsistency[10]	No serious indirectness	Serious imprecision[7]	None[8]	308/20279 (1.5%)	431/30048 (1.4%)	**RR 0.97** (0.74 to 1.26)	**4 fewer** (from 37 fewer to 37 more)	⊕⊕OO LOW
Cardiovascular events (follow-up mean 52 months)											
4	RCTs	No serious risk of bias[5]	Serious inconsistency[10]	No serious indirectness	Serious imprecision[7]	None[8]	1462/20058 (7.3%)	2232/29811 (7.5%)	**RR 0.89** (0.74 to 1.07)	**82 fewer** (from 195 fewer to 52 more)	⊕⊕OO LOW
Coronary heart disease events (follow-up mean 59 months)											
3	RCTs	No serious risk of bias[5]	Serious inconsistency[10]	No serious indirectness	Serious imprecision[7]	None[8]	1063/19992 (5.3%)	1637/29744 (5.5%)	**RR 0.93** (0.76 to 1.14)	**39 fewer** (from 132 fewer to 77 more)	⊕⊕OO LOW
Fatal and nonfatal myocardial infarction (follow-up mean 55 months)[11]											
3	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	490/19992 (2.5%)	744/29744 (2.5%)	**RR 0.93** (0.80 to 1.08)	**18 fewer** (from 50 fewer to 20 more)	⊕⊕⊕O MODERATE
Stroke (follow-up mean 59 months)											
3	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	447/19992 (2.2%)	665/29744 (2.2%)	**RR 1.00** (0.89 to 1.12)	**0 fewer** (from 25 fewer to 27 more)	⊕⊕⊕O MODERATE
LDL cholesterol (follow-up 13 to 91 days; units mmol/L per 1% energy exchange; better indicated by lower values)											
69 (165)[12]	RCTs	No serious risk of bias[13]	No serious inconsistency[14]	No serious indirectness[15]	No serious imprecision[16]	None[17]	1973[18]	--	**–0.055** (–0.061 to –0.050)[19]	--	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; RR, relative risk; SFA, saturated fatty acids

[1] For outcomes other than LDL cholesterol, only studies that included an intervention group achieving SFA intake of less than 10% of total energy intake were included in the analysis. For the LDL cholesterol outcome, effects of decreasing SFA intake on blood lipids by replacement with polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA) or carbohydrates, as obtained from regression analysis, were observed across a wide range of SFA intakes, from 1.6 to 24.4% of total energy intake. Of the 177 total data points used in the multiple regression, 113 included an SFA intake component of less than 10% of total energy intake; 65 data points included intakes of less than 8%. Residuals analysis indicates that the relationship between SFA intake and effect on blood lipids is linear across the entire range of SFA intakes.
[2] All studies were conducted in the population of interest and employed appropriate interventions to assess the effect of lower compared to higher SFA intake on priority health outcomes decided upon prior to initiating the reviews. For outcomes other than LDL cholesterol, a small number of the RCTs included in the corresponding systematic review *(24)*employed one or more dietary interventions in addition to SFA reduction (i.e. multifactorial dietary interventions), however, all studies either explicitly or implicitly aimed to reduce SFA intake, achieved a reduction in SFA intake, or both.

[3] Based on the control event rate (CER), which is the number of people with events in the control group divided by the total number of people in the control group. The absolute effect (per 10 000 people) is calculated with the following equation: absolute effect =10 000 x [CER x (1-RR)]. The magnitude of absolute effect depends on baseline risk, which can vary across different populations.
[4] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(59)*.
[5] These large RCTs of relatively long duration (minimum duration of 24 months) all appeared to use appropriate methods of random sequence generation and about half had good allocation concealment (allocation concealment in the remaining studies was unclear). Blinding was only well-conducted in one study. Incomplete outcome reporting was variable across studies, and most included studies had systematic differences in care (i.e. intervention group had more time or attention than the control group) but sensitivity analyses removing studies with systematic differences in care did not alter effect sizes. No other biases were noted. Not downgraded for bias; however, it is noted that the level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[6] I^2 < 50%, indicating a low level of heterogeneity.
[7] The 95% CI crosses a threshold of important benefit or harm.
[8] Publication bias not formally assessed due to small number of studies, but studies included for this outcome are a subset of the complete set of studies, for which no publication bias was detected.
[9] Additional evidence on the relationship between reduced SFA intake and cardiovascular and mortality outcomes comes from meta-analysis of three studies with coronary heart disease mortality as an outcome (RR 1.05; 95% CI: 0.83, 1.32) (*moderate*-quality evidence).
[10] I^2 > 50%, indicating a significant level of heterogeneity.
[11] Additional evidence on the relationship between reduced SFA intake and cardiovascular outcomes comes from meta-analysis of two studies with nonfatal myocardial infarction as an outcome (RR 0.99 [95% CI: 0.69, 1.41]) (*low*-quality evidence).
[12] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, PUFA, MUFA and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of blood lipids.
[13] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.
[14] This analysis was conducted as a multiple regression in which data points (see footnote 12) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.
[15] LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[16] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[17] Publication bias was not formally assessed but, given the large number and nature of the studies included in the analysis (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified), risk of publication bias is likely to be low.
[18] Data points (see footnote 12) were directly extracted from all treatment groups within included studies without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.
[19] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as SFA is replaced with an isocaloric amount of PUFA. Reductions in LDL cholesterol were also observed when SFA were replaced with MUFA (–0.042 mmol/L; 95% CI: –0.047, –0.037) (*high*-quality evidence) or carbohydrates (–0.033 mmol/L; 95% CI:–0.039, –0.027) (*high*-quality evidence).

For details of the studies included in the reviews, see references *(24)* and *(59)*.

GRADE evidence profile 4
Question: What is the effect of a reduction in saturated fatty acid intake in children to less than 10% of total energy intake?[1]
Setting: General child population

Quality assessment							No. of participants[2]		Relative effect (95% CI)	Quality[3]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Reduced SFA intake	Usual SFA intake		
LDL cholesterol (follow-up 5 weeks; units mmol/L; better indicated by lower values)[4]										
1	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness[7]	No serious imprecision[8]	None[9]	134	134	**MD 0.29 lower** (0.38 to 0.20 lower)	⊕⊕⊕⊕ HIGH
LDL cholesterol (*as assessed in adults*) (follow-up 13 – 91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)[10]	RCTs	No serious risk of bias[11]	No serious inconsistency[12]	No serious indirectness[13]	No serious imprecision[14]	None[15]	1973	--	**–0.055** (–0.061 to –0.050)[16]	⊕⊕⊕⊕ HIGH
Systolic blood pressure[17]										
0	No studies identified reporting this outcome									
Body weight (follow-up 5 weeks; units kg; better indicated by lower values)										
1	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness[7]	Serious imprecision[18]	None	134	134	**MD 0.20 lower** (0.63 lower to 0.23 higher)	⊕⊕⊕O MODERATE

CI, confidence interval; LDL, low-density lipoprotein; MD, mean difference; RCTs, randomized controlled trials; SFA, saturated fatty acids

[1] For the LDL cholesterol outcome assessed directly in children, only studies that included an intervention group achieving SFA intake of less than 10% of total energy intake were included in the analysis. For the LDL cholesterol outcome, effects of decreasing SFA intake on blood lipids by replacement with polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA) or carbohydrates, as obtained from regression analysis, were observed across a wide range of SFA intakes, from 1.6 to 24.4% of total energy intake. Of the 177 total data points used in the multiple regression, 113 included an SFA intake component of less than 10% of total energy intake; 65 data points included intakes of less than 8%. Residuals analysis indicates that the relationship between SFA intake and effect on blood lipids is linear across the entire range of SFA intakes. In addition to the outcomes directly assessed in children and the LDL cholesterol outcome for adults included in this evidence profile, the remaining evidence for adults was also considered for children, without downgrading for indirectness as noted in footnote 13.
[2] For the LDL cholesterol outcome measured directly in children, participants in the crossover trial are counted in both the *Reduced SFA intake and Usual SFA intake* columns. For the LDL cholesterol outcome measured in adults, data points (see footnote 10) were directly extracted from all treatment groups within included studies without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.
[3] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for *important* lipid outcomes as measured in adults and children can be found in the respective systematic reviews *(59)* and *(60)*.
[4] Additional evidence on the relationship between SFA intake and blood lipids comes from results of one study in children with total cholesterol as an outcome (MD –0.29 mmol/L; 95% CI: –0.40, –0.18) (*high*-quality evidence).
[5] No serious risk of bias in the included study.
[6] Only one study included.
[7] The studies were conducted in the population of interest, all comparisons were made directly to an appropriate control group and all outcomes are priority outcomes that were decided on before initiating the review. LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[8] The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[9] Too few studies to conduct funnel plot analysis.
[10] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, PUFA, MUFA and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of blood lipids.

[11] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.

[12] This analysis was conducted as a multiple regression in which data points (see footnote 10) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.

[13] Although studies were conducted in adults, there was no evidence to indicate that the effect on LDL cholesterol resulting from a change in SFA intake would be significantly different between adults and children. LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*. Therefore, this outcome was not downgraded for indirectness.

[14] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.

[15] Publication bias was not formally assessed but, given the large number and nature of the studies included in the analysis (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified), risk of publication bias is likely to be low.

[16] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as SFA is replaced with an isocaloric amount of PUFA. Reductions in LDL cholesterol were also observed when SFA were replaced with MUFA (–0.042 mmol/L; 95% CI: –0.047, –0.037) (*high*-quality evidence) or carbohydrates (–0.033 mmol/L; 95% CI:–0.039, –0.027) (*high*-quality evidence).

[17] In addition to systolic blood pressure, no studies were identified reporting diastolic blood pressure, height, BMI, waist circumference, insulin resistance or adverse effects.

[18] The 95% CI crosses a threshold of important benefit or harm.

For details of the studies included in the reviews, see references *(59)* and *(60)*.

GRADE evidence profile 5
Question: What is the effect of replacing some saturated fatty acids in the diet of adults with polyunsaturated fatty acids?[1]
Population: General adult population

Quality assessment							No. of events/participants (study event rate)		Relative effect (95% CI)	Absolute effects[3] (per 10 000)	Quality[4]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other	Reduced SFA intake	Usual SFA intake			
All-cause mortality (follow-up mean 56 months)											
7	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	406/2123 (19.1%)	418/2115 (19.8%)	**RR 0.96** (0.82 to 1.13)	**79 fewer** (from 360 fewer to 256 more)	⊕⊕⊕O MODERATE
Cardiovascular disease mortality (follow-up mean 55 months)[9]											
7	RCTs	No serious risk of bias[5]	Serious inconsistency[10]	No serious indirectness	Serious imprecision[7]	None[8]	266/2123 (12.5%)	287/2128 (13.5%)	**RR 0.95** (0.73 to 1.25)	**67 fewer** (from 364 fewer to 337 more)	⊕⊕OO LOW
Cardiovascular events (follow-up mean 53 months)											
7	RCTs	No serious risk of bias[5]	Serious inconsistency[10]	No serious indirectness	No serious imprecision[11]	None[8]	390/1953 (20%)	494/1942 (25.4%)	**RR 0.73** (0.58 to 0.92)	**687 fewer** (from 204 fewer to 1068 fewer)	⊕⊕⊕O MODERATE
Coronary heart disease events (follow-up mean 53 months)											
7	RCTs	No serious risk of bias[5]	Serious inconsistency[10]	No serious indirectness	Serious imprecision[7]	None[8]	329/1956 (16.8%)	408/1944 (21%)	**RR 0.76** (0.57 to 1.0)	**504 fewer** (from 902 fewer to 0 more)	⊕⊕OO LOW
Fatal and nonfatal myocardial infarction (follow-up mean 53 months)[12]											
7	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	269/1953 (13.8%)	322/1942 (16.6%)	**RR 0.83** (0.67 to 1.02)	**282 fewer** (from 547 fewer to 33 more)	⊕⊕⊕O MODERATE
Stroke (follow-up mean 63 months)											
4	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Very serious imprecision[13]	None[8]	17/856 (2%)	24/850 (2.8%)	**RR 0.68** (0.37 to 1.27)	**90 fewer** (from 178 fewer to 76 more)	⊕OOO VERY LOW
LDL cholesterol (follow-up 13 to 91 days; units mmol/L per 1% energy exchange; better indicated by lower values)											
69 (165)[14]	RCTs	No serious risk of bias[15]	No serious inconsistency[16]	No serious indirectness[17]	No serious imprecision[18]	None[19]	1973[20]	--	**–0.055** (–0.061 to –0.050)[21]	--	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; RR, relative risk; SFA, saturated fatty acids

[1] For outcomes other than LDL cholesterol, the polyunsaturated fatty acids (PUFA) used as replacement for SFA in the studies included in the analysis were predominantly of plant origin. Studies were included in this analysis if the difference in PUFA intakes between intervention and control groups were statistically significant ($P<0.05$), regardless of whether or not PUFA constituted the main replacement for SFA. For the LDL cholesterol outcome, the PUFA used as replacement for SFA in the studies included in the regression analysis were predominantly linoleic acid and α-linolenic acid.
[2] All studies were conducted in the population of interest and employed appropriate interventions to assess the effect of lower compared to higher SFA intake on priority health outcomes decided upon prior to initiating the reviews. For outcomes other than LDL cholesterol, a small number of the RCTs included in the corresponding systematic review *(24)* employed one or more dietary interventions in addition to SFA reduction (i.e. multifactorial dietary interventions), however, all studies either explicitly or implicitly aimed to reduce SFA intake, achieved a reduction in SFA intake, or both.
[3] Based on the control event rate (CER), which is the number of people with events in the control group divided by the total number of people in the control group. The absolute effect (per 10 000 people) is calculated with the following equation: absolute effect =10 000 x [CER x (1-RR)]. The magnitude of absolute effect depends on baseline risk, which can vary across different populations.

[4] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(59)*.
[5] These large RCTs of relatively long duration (minimum duration of 24 months) all appeared to use appropriate methods of random sequence generation and about half had good allocation concealment (allocation concealment in the remaining studies was unclear). Blinding was only well-conducted in one study. Incomplete outcome reporting was variable across studies, and most included studies had systematic differences in care (i.e. intervention group had more time or attention than the control group) but sensitivity analyses removing studies with systematic differences in care did not alter effect sizes. No other biases were noted. Not downgraded for bias; however it is noted that the level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[6] $I^2 < 50\%$, indicating a low level of heterogeneity.
[7] The 95% CI crosses a threshold of important benefit or harm.
[8] Publication bias not formally assessed due to small number of studies, but studies included for this outcome are a subset of the complete set of studies, for which no publication bias was detected.
[9] Additional evidence on the relationship between reduced SFA intake and cardiovascular and mortality outcomes comes from meta-analysis of seven studies with coronary heart disease mortality as an outcome (RR 0.98; 95% CI: 0.74, 1.28) (*moderate*-quality evidence).
[10] $I^2 > 50\%$, indicating a significant level of heterogeneity.
[11] The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[12] Additional evidence on the relationship between reduced SFA intake and cardiovascular outcomes comes from meta-analysis of five studies with nonfatal myocardial infarction as an outcome (RR 0.80; 95% CI: 0.63, 1.03]) (*moderate*-quality evidence).
[13] The number of events is very small and the 95% CI crosses a threshold of appreciable benefit or harm. Downgraded twice for very serious imprecision.
[14] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, MUFA, PUFA and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of serum lipids.
[15] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.
[16] This analysis was conducted as a multiple regression in which data points (see footnote 14) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.
[17] LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[18] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[19] Publication bias was not formally assessed but, given the large number and nature of the studies included in the analysis (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified), risk of publication bias is likely to be low.
[20] Data points (see footnote 14) were directly extracted from all treatment groups within included studies without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.
[21] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as SFA is replaced with an isocaloric amount of PUFA.

For details of the studies included in the reviews, see references *(24)* and *(59)*.

GRADE evidence profile 6
Question: What is the effect of replacing some saturated fatty acids in the diet of children with polyunsaturated fatty acids?[1]
Setting: General child population

Quality assessment							No. of participants[2]		Relative effect (95% CI)	Quality[3]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Reduced SFA intake	Usual SFA intake		
Cardiovascular events (*as assessed in adults*) (follow-up mean 53 months)										
7	RCTs	No serious risk of bias[4]	Serious inconsistency[5]	No serious indirectness[6]	No serious imprecision[7]	None[8]	1953	1942	**RR 0.73** (0.58 to 0.92)	⊕⊕⊕O MODERATE
LDL cholesterol (follow-up 5 weeks; units mmol/L; better indicated by lower values)[9]										
1	RCTs	No serious risk of bias[10]	No serious inconsistency[11]	No serious indirectness[12]	No serious imprecision[7]	None[8]	134	134	**MD 0.29 lower** (0.38 to 0.20 lower)	⊕⊕⊕⊕ HIGH
LDL cholesterol (*as assessed in adults*) (follow-up 13 – 91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)[13]	RCTs	No serious risk of bias[14]	No serious inconsistency[15]	No serious indirectness[16]	No serious imprecision[17]	None[18]	1973	--	**–0.055** (–0.061 to –0.050)[19]	⊕⊕⊕⊕ HIGH
Systolic blood pressure[20]										
0	No studies identified reporting this outcome									
Body weight (follow-up 5 weeks; units kg; better indicated by lower values)										
1	RCTs	No serious risk of bias[10]	No serious inconsistency[11]	No serious indirectness[12]	Serious imprecision[21]	None	134	134	**MD 0.20 lower** (0.63 lower to 0.23 higher)	⊕⊕⊕O MODERATE

CI, confidence interval; LDL, low-density lipoprotein; MD, mean difference; RCTs, randomized controlled trials; SFA, saturated fatty acids

[1] For the cardiovascular events outcome, the polyunsaturated fatty acids (PUFA) used as replacement for SFA in the studies included in the analysis were predominantly of plant origin. Studies were included in this analysis if the difference in PUFA intakes between intervention and control groups were statistically significant (P<0.05), regardless of whether or not PUFA constituted the main replacement for SFA. For the LDL cholesterol outcome assessed directly in children, only studies that included an intervention group in which dietary SFA were predominantly replaced with PUFA were included in this analysis. For the LDL cholesterol outcome assessed in adults, the PUFA used as replacement for SFA in the studies included in the regression analysis were predominantly linoleic acid and α-linolenic acid. In addition to the outcomes directly assessed in children and the cardiovascular events and LDL cholesterol outcomes for adults included in this evidence profile, the remaining evidence for adults was also considered for children, without downgrading for indirectness as noted in footnote 6.
[2] For the LDL cholesterol outcome measured directly in children, participants in the crossover trial are counted in both the *Reduced SFA intake and Usual SFA intake* columns. For the LDL cholesterol outcome measured in adults, data points (see footnote 13) were directly extracted from all treatment groups within included studies without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.
[3] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for *important* lipid outcomes as measured in adults and children can be found in the respective systematic reviews *(59)* and *(60)*.
[4] These large RCTs of relatively long duration (minimum duration of 24 months) all appeared to use appropriate methods of random sequence generation and about half had good allocation concealment (allocation concealment in the remaining studies was unclear). Blinding was only well-conducted in one study. Incomplete outcome reporting was variable across studies, and most included studies had systematic differences in care (i.e. intervention group had more time or attention than the control group) but sensitivity analyses removing studies with systematic differences in care did not alter effect sizes. No other biases were noted. Not downgraded for bias; however, it is noted that the level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[5] I^2 > 50%, indicating a significant level of heterogeneity.
[6] All studies were conducted in adults, and though clinical cardiovascular outcomes in children are rare, there was no evidence to indicate that the physiological response to a change in SFA intake would be significantly different between adults and children *(47-53)*. Therefore, this outcome was not downgraded for indirectness.
[7] The 95% CI does not cross a threshold of irrelevant benefit or important harm.

[8] There were too few studies to conduct funnel plot analysis.
[9] Additional evidence on the relationship between SFA intake and blood lipids comes from results of one study with total cholesterol as an outcome (MD –0.29 mmol/L; 95% CI: –0.40, –0.18) (*high* quality-evidence).
[10] No serious risk of bias in the included study.
[11] Only one study included.
[12] The study was conducted in the population of interest, all comparisons were made directly to an appropriate control group and all outcomes are priority outcomes that were decided on before initiating the review. LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[13] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, PUFA, monounsaturated fatty acids (MUFA) and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of serum lipids.
[14] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.
[15] This analysis was conducted as a multiple regression in which data points (see footnote 13) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.
[16] Although studies were conducted in adults, there was no evidence to indicate that the effect on LDL cholesterol resulting from a change in SFA intake would be significantly different between adults and children. LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*. Therefore, this outcome was not downgraded for indirectness.
[17] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[18] Publication bias was not formally assessed but, given the large number and nature (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified) of the studies included in the analysis, risk of publication bias is likely to be low.
[19] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as SFA is replaced with an isocaloric amount of PUFA.
[20] In addition to systolic blood pressure, no studies were identified reporting diastolic blood pressure, height, BMI, waist circumference, insulin resistance or adverse effects.
[21] The 95% CI crosses a threshold of important benefit or harm.

For details of the studies included in the reviews, see references *(24)*, *(59)* and *(60)*.

GRADE evidence profile 7
Question: What is the effect of replacing some saturated fatty acids in the diet of adults with monounsaturated fatty acids?[1]
Population: General adult population

Quality assessment							No. of events/participants (study event rate)		Relative effect (95% CI)	Absolute effects[3] (per 10 000)	Quality[4]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other	Reduced SFA intake	Usual SFA intake			
All-cause mortality (follow-up mean 24 months)											
1	RCTs	Serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Very serious imprecision[7]	None[8]	3/26 (11.5%)	1/26 (3.8%)	**RR 3.0** (0.33 to 26.99)	**769 more** (from 258 fewer to 9996 more)	⊕OOO VERY LOW
Cardiovascular disease mortality (follow-up mean 24 months)[9]											
1	RCTs	Serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Very serious imprecision[7]	None[8]	3/26 (11.5%)	1/26 (3.8%)	**RR 3.0** (0.33 to 26.99)	**769 more** (from 258 fewer to 9996 more)	⊕OOO VERY LOW
Cardiovascular events (follow-up mean 24 months)											
1	RCTs	Serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Very serious imprecision[7]	None[8]	11/26 (42.3%)	11/26 (42.3%)	**RR 1.0** (0.53 to 1.89)	**0 fewer** (from 1988 fewer to 3765 more)	⊕OOO VERY LOW
Coronary heart disease events (follow-up mean 24 months)[10]											
1	RCTs	Serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Very serious imprecision[7]	None[8]	9/26 (34.6%)	6/26 (23.1%)	**RR 1.5** (0.62 to 3.61)	**1154 more** (from 877 fewer to 6023 more)	⊕OOO VERY LOW
Fatal and nonfatal myocardial infarction (follow-up mean 24 months)											
1	RCTs	Serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Very serious imprecision[7]	None[8]	7/26 (26.9%)	5/26 (19.2%)	**RR 1.4** (0.51 to 3.85)	**769 more** (from 942 fewer to 5481 more)	⊕OOO VERY LOW
Stroke											
0	No studies identified reporting this outcome										
LDL cholesterol (follow-up 13 to 91 days; units mmol/L per 1% energy exchange; better indicated by lower values)											
69 (165)[11]	RCTs	No serious risk of bias[12]	No serious inconsistency[13]	No serious indirectness[14]	No serious imprecision[15]	None[16]	1973[17]	--	**–0.042** (–0.047 to –0.037)[18]	--	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; RR, relative risk; SFA, saturated fatty acids

[1] For outcomes other than LDL cholesterol, studies were included in the analysis if the difference in monounsaturated fatty acids (MUFA) intakes between intervention and control groups were statistically significant ($P<0.05$), regardless of whether or not MUFA constituted the main replacement for SFA. For the LDL cholesterol outcome, the MUFA used as replacement for SFA in studies included in the regression analysis was predominantly oleic acid.
[2] All studies were conducted in the population of interest and employed appropriate interventions to assess the effect of lower compared to higher SFA intake on priority health outcomes decided on before initiating the reviews.
[3] Based on the control event rate (CER), which is the number of people with events in the control group divided by the total number of people in the control group. The absolute effect (per 10 000 people) is calculated with the following equation: absolute effect =10 000 x [CER x (1-RR)]. The magnitude of absolute effect depends on baseline risk, which can vary across different populations.
[4] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(59)*.
[5] This single, very small RCT of relatively long duration was well randomized, but had an unclear risk of bias in terms of allocation concealment and incomplete outcome data, and lacked participant blinding. Downgraded for serious risk of bias.

[6] Only one study included.
[7] The number of events is very small and the 95% CI crosses a threshold of appreciable benefit or harm, and is therefore downgraded twice for very serious imprecision.
[8] Publication bias not formally assessed due to small number of studies, but the study included for this outcome is a subset of the complete set of studies, for which no publication bias was detected.
[9] Additional evidence on the relationship between reduced SFA intake and cardiovascular and mortality outcomes comes from results of one study with coronary heart disease mortality as an outcome (RR 3.0 [95% CI: 0.33, 26.99]) (*very low*-quality evidence).
[10] Additional evidence on the relationship between reduced SFA intake and cardiovascular outcomes comes from results of one study with nonfatal myocardial infarction as an outcome (RR 1.20 [95% CI: 0.42, 3.45]) (*very low*-quality evidence).
[11] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, PUFA, MUFA and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of serum lipids.
[12] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.
[13] This analysis was conducted as a multiple regression in which data points (see footnote 12) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.
[14] LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[15] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[16] Publication bias was not formally assessed but, given the large number and nature of the studies included in the analysis (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified), risk of publication bias is likely to be low.
[17] Data points (see footnote 12) were directly extracted from all treatment groups within included studies without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.
[18] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as SFA is replaced with an isocaloric amount of MUFA.

For details of the studies included in the reviews, see references *(24)* and *(59)*.

GRADE evidence profile 8
Question: What is the effect of replacing some saturated fatty acids in the diet of children with monounsaturated fatty acids?[1]
Setting: General child population

Quality assessment							No. of participants[2]		Relative effect (95% CI)	Quality[3]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Reduced SFA intake	Usual SFA intake		
LDL cholesterol (follow-up 28 weeks; units mmol/L; better indicated by lower values)[4]										
1	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness[7]	No serious imprecision[8]	None[9]	88	88	**MD 0.26 lower** (0.41 to 0.11 lower)	⊕⊕⊕⊕ HIGH
LDL cholesterol (*as assessed in adults*) (follow-up 13 to 91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)[10]	RCTs	No serious risk of bias[11]	No serious inconsistency[12]	No serious indirectness[13]	No serious imprecision[14]	None[15]	1973	--	**–0.042** (–0.047 to –0.037)[16]	⊕⊕⊕⊕ HIGH
Systolic blood pressure[17]										
0	No studies identified reporting this outcome									

CI, confidence interval; LDL, low-density lipoprotein; MD, mean difference; RCTs, randomized controlled trials; SFA, saturated fatty acids

[1] In the included study for the LDL cholesterol outcome assessed directly in children, SFA were replaced with a mixture of unsaturated fatty acids consisting of 80% monounsaturated fatty acids (MUFA) and 20% polyunsaturated fatty acids (PUFA). For the LDL cholesterol outcome assessed in adults, the MUFA used as replacement for SFA in studies included in the regression analysis was predominantly oleic acid. In addition to the outcome directly assessed in children and the LDL cholesterol outcome for adults included in this evidence profile, the remaining evidence for adults was also considered for children, without downgrading for indirectness as noted in footnote 13.
[2] For the LDL cholesterol outcome measured directly in children, participants in the crossover trial are counted in both the *Reduced SFA intake and Usual SFA intake* columns. For the LDL cholesterol outcome measured in adults, data points (see footnote 10) were directly extracted from all treatment groups within included studies without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.
[3] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for *important* lipid outcomes as measured in adults and children can be found in the respective systematic reviews *(59)* and *(60)*.
[4] Additional evidence on the relationship between SFA intake and blood lipids comes from results of one study with total cholesterol as an outcome (MD –0.33 mmol/L; 95% CI: –0.52, –0.14) (*high* quality-evidence).
[5] No serious risk of bias in the included study.
[6] Only one study included.
[7] The study was conducted in the population of interest, all comparisons were made directly to an appropriate control group and all outcomes are priority outcomes that were decided on before initiating the review. LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[8] The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[9] Too few studies to conduct funnel plot analysis.
[10] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, PUFA, MUFA and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of serum lipids.
[11] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was

considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.

[12] This analysis was conducted as a multiple regression in which data points (see footnote 12) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.

[13] Although studies were conducted in adults, there was no evidence to indicate that the effect on LDL cholesterol resulting from a change in SFA intake would be significantly different between adults and children. LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*. Therefore, this outcome was not downgraded for indirectness.

[14] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.

[15] Publication bias was not formally assessed but, given the large number and nature (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified) of the studies included in the analysis, risk of publication bias is likely to be low.

[16] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as SFA is replaced with an isocaloric amount of MUFA.

[17] In addition to systolic blood pressure, no studies were identified reporting diastolic blood pressure, height, body weight, BMI, waist circumference, insulin resistance or adverse effects.

For details of the studies included in the reviews, see references *(59)* and *(60)*.

GRADE evidence profile 9
Question: What is the effect of replacing some saturated fatty acids in the diet of adults with carbohydrates?[1]
Population: General adult population

Quality assessment							No. of events/participants (study event rate)		Relative effect (95% CI)	Absolute effects[3] (per 10 000)	Quality[4]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness[2]	Imprecision	Other	Reduced SFA intake	Usual SFA intake			
All-cause mortality (follow-up mean 48 months)											
6	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	1080/21715 (5%)	1597/31954 (5%)	**RR 0.98** (0.91 to 1.05)	**10 fewer** (from 45 fewer to 25 more)	⊕⊕⊕O MODERATE
Cardiovascular disease mortality (follow-up mean 46 months)[9]											
6	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	316/20740 (1.5%)	429/30492 (1.4%)	**RR 0.99** (0.86 to 1.14)	**1 fewer** (from 20 fewer to 20 more)	⊕⊕⊕O MODERATE
Cardiovascular events (follow-up mean 46 months)											
6	RCTs	No serious risk of bias[5]	Serious inconsistency[10]	No serious indirectness	Serious imprecision[7]	None[8]	1512/20740 (7.3%)	2273/30492 (7.5%)	**RR 0.93** (0.79 to 1.08)	**52 fewer** (from 157 fewer to 60 more)	⊕⊕OO LOW
Coronary heart disease events (follow-up mean 51 months)											
5	RCTs	No serious risk of bias[5]	Serious inconsistency[10]	No serious indirectness	Serious imprecision[7]	None[8]	1140/20677 (5.5%)	1706/30427 (5.6%)	**RR 0.98** (0.83 to 1.14)	**11 fewer** (from 95 fewer to 79 more)	⊕⊕OO LOW
Fatal and nonfatal myocardial infarction (follow-up mean 51 months)[11]											
4	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness	Serious imprecision[7]	None[8]	572/20674 (2.8%)	820/30425 (2.7%)	**RR 0.96** (0.86 to 1.06)	**11 fewer** (from 38 fewer to 16 more)	⊕⊕⊕O MODERATE
Stroke (follow-up mean 60 months)											
4	RCTs	No serious risk of bias[6]	No serious inconsistency[7]	No serious indirectness	Serious imprecision[8]	None[9]	435/19656 (2.2%)	648/29410 (2.2%)	**RR 1.01** (0.9 to 1.13)	**2 more** (from 22 fewer to 29 more)	⊕⊕⊕O MODERATE
LDL cholesterol (follow-up 13 to 91 days; units mmol/L per 1% energy exchange; better indicated by lower values)											
69 (165)[12]	RCTs	No serious risk of bias[13]	No serious inconsistency[14]	No serious indirectness[15]	No serious imprecision[16]	None[17]	1973[18]	--	**–0.033** (–0.039 to –0.027)[19]	--	⊕⊕⊕⊕ HIGH

LDL, low-density lipoprotein; CI, confidence interval; RCTs, randomized controlled trials; RR, relative risk; SFA, saturated fatty acids

[1] For outcomes other than LDL cholesterol, there was insufficient information across all studies included in the analysis to make any determination about the type of carbohydrate used as replacement for SFA. Studies were included in this analysis if the difference in carbohydrate intakes between intervention and control groups were statistically significant ($P<0.05$), regardless of whether or not carbohydrates constituted the main replacement for SFA. For the LDL cholesterol outcome, the carbohydrates used as replacement for SFA in studies included in the regression analysis were mixtures of mono-, di- and polysaccharides; however, the number of studies providing sufficient dietary information to determine, exactly, the composition of the carbohydrate used in the studies was limited.

[2] All studies were conducted in the population of interest and employed appropriate interventions to assess the effect of lower compared to higher SFA intake on priority health outcomes decided upon prior to initiating the reviews. For outcomes other than LDL cholesterol, a small number of the RCTs included in the corresponding systematic review *(24)* employed one or more dietary interventions in addition to SFA reduction (i.e. multifactorial dietary interventions), however, all studies either explicitly or implicitly aimed to reduce SFA intake, achieved a reduction in SFA intake, or both.

[3] Based on the control event rate (CER), which is the number of people with events in the control group divided by the total number of people in the control group. The absolute effect (per 10 000 people) is calculated with the following equation: absolute effect =10 000 x [CER x (1-RR)]. The magnitude of absolute effect depends on baseline risk, which can vary across different populations.

[4] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(59)*.
[5] These large RCTs of relatively long duration (minimum duration of 24 months) all appeared to use appropriate methods of random sequence generation and about half had good allocation concealment (allocation concealment in the remaining studies was unclear). Blinding was only well-conducted in one study. Incomplete outcome reporting was variable across studies, and most included studies had systematic differences in care (i.e. intervention group had more time or attention than the control group) but sensitivity analyses removing studies with systematic differences in care did not alter effect sizes. No other biases were noted. Not downgraded for bias; however, it is noted that the level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[6] I^2 < 50%, indicating a low level of heterogeneity.
[7] The 95% CI crosses a threshold of important benefit or harm and is therefore downgraded for serious imprecision.
[8] Publication bias not formally assessed due to small number of studies, but the study included for this outcome is a subset of the complete set of studies, for which no publication bias was detected.
[9] Additional evidence on the relationship between reduced SFA intake and cardiovascular and mortality outcomes comes from meta-analysis of three studies with coronary heart disease mortality as an outcome (RR 1.01 [95% CI: 0.86, 1.18]) (*moderate*-quality evidence).
[10] I^2 > 50%, indicating a significant level of heterogeneity.
[11] Additional evidence on the relationship between reduced SFA intake and cardiovascular outcomes comes from meta-analysis of three studies with nonfatal myocardial infarction as an outcome (RR 0.99 [95% CI: 0.73, 1.35]) (*low*-quality evidence).
[12] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA) and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of serum lipids.
[13] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.
[14] This analysis was conducted as a multiple regression in which data points (see footnote 12) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.
[15] LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[16] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[17] Publication bias was not formally assessed but, given the large number and nature of the studies included in the analysis (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified), risk of publication bias is likely to be low.
[18] Data points (see footnote 12) were directly extracted from all treatment groups within included studies without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.
[18] The relative effect reported for LDL cholesterol is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as SFA is replaced with an isocaloric amount of carbohydrates.

For details of the studies included in the reviews, see references *(24)* and *(59)*.

GRADE evidence profile 10
Question: What is the effect of replacing some saturated fatty acids in the diet of children with carbohydrate?[1]
Setting: General child population

Quality assessment							No. of participants		Relative effect[2] (95% CI)	Quality[3]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Reduced SFA intake	Usual SFA intake		
LDL cholesterol[4]										
0	No studies identified reporting this outcome									
LDL cholesterol (*as assessed in adults*) (follow-up 13 to 91 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
69 (165)[5]	RCTs	No serious risk of bias[6]	No serious inconsistency[7]	No serious indirectness[8]	No serious imprecision[9]	None[10]	1973[11]	--	**–0.033** (–0.039 to –0.027)	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; SFA, saturated fatty acids

[1] For the LDL cholesterol outcome assessed in adults, the carbohydrates used as replacement for SFA in studies included in the regression analysis were mixtures of mono-, di- and polysaccharides, but the number of studies providing sufficient dietary information to determine, exactly, the composition of the carbohydrate used in the studies was limited. In addition to the LDL cholesterol outcome for adults included in this evidence profile, the remaining evidence for adults was also considered for children, without downgrading for indirectness as noted in footnote 13.
[2] The relative effect reported for LDL cholesterol is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as SFA is replaced with an isocaloric amount of carbohydrates.
[3] LDL cholesterol is a *critical* outcome. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(59)*.
[4] No studies conducted in children were identified in which it was clear that a significant portion of the nutrient replacing SFA were carbohydrates.
[5] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA) and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of serum lipids.
[6] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.
[7] This analysis was conducted as a multiple regression in which data points (see footnote 5) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.
[8] Although studies were conducted in adults, there was no evidence to indicate that the effect on LDL cholesterol resulting from a change in SFA intake would be significantly different between adults and children. LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*. Therefore, this outcome was not downgraded for indirectness.
[9] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[10] Data points (see footnote 5) were directly extracted from all study groups from included trials without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.

[11] Publication bias was not formally assessed but, given the large number and nature (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified) of the studies included in the analysis, risk of publication bias is likely to be low.
For details of the studies included in the review, see reference *(59)*.

GRADE evidence profile 11
Question: What is the effect of replacing some saturated fatty acids in the diet of adults with protein?[1]
Population: General adult population

Quality assessment							No. of events/participants (study event rate)		Relative effect (95% CI)	Absolute effects[7] (per 10 000)	Quality[8]
No. of studies	Design	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Other[6]	Reduced SFA intake	Usual SFA intake			
All-cause mortality (follow-up mean 50 months)											
5	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	None	1079/21688 (5%)	1594/31926 (5%)	**RR 0.98** (0.91 to 1.06)	**10 fewer** (from 45 fewer to 30 more)	⊕⊕⊕O MODERATE
Cardiovascular disease mortality (follow-up mean 48 months)[9]											
5	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	None	315/20713 (1.5%)	426/30464 (1.4%)	**RR 0.99** (0.86 to 1.14)	**1 fewer** (from 20 fewer to 20 more)	⊕⊕⊕O MODERATE
Cardiovascular events (follow-up mean 48 months)											
5	RCTs	No serious risk of bias	Serious inconsistency[10]	No serious indirectness	Serious imprecision	None	1504/20713 (7.3%)	2253/30464 (7.4%)	**RR 0.98** (0.9 to 1.06)	**15 fewer** (from 74 fewer to 44 more)	⊕⊕⊕O MODERATE
Coronary heart disease events (follow-up mean 56 months)											
4	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	None	1137/20647 (5.5%)	1696/30397 (5.6%)	**RR 0.99** (0.88 to 1.12)	**6 fewer** (from 67 fewer to 67 more)	⊕⊕⊕O MODERATE
Fatal and nonfatal myocardial infarction (follow-up mean 56 months)[11]											
3	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	None	571/20647 (2.8%)	818/30397 (2.7%)	**RR 0.96** (0.86 to 1.07)	**11 fewer** (from 38 fewer to 19 more)	⊕⊕⊕O MODERATE
Stroke (follow-up mean 72 months)											
3	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	None	435/19629 (2.2%)	647/29382 (2.2%)	**RR 1.01** (0.89 to 1.15)	**2 more** (from 24 fewer to 33 more)	⊕⊕⊕O MODERATE
LDL cholesterol											
0	No studies identified reporting this outcome[12]										

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; RR, relative risk; SFA, saturated fatty acids

[1] Studies were included in this analysis if the difference in protein intakes between intervention and control groups were statistically significant (P<0.05), regardless of whether or not protein constituted the main replacement for SFA.
[2] These large RCTs of relatively long duration (minimum duration of 24 months) all appeared to use appropriate methods of random sequence generation and about half had good allocation concealment (allocation concealment in the remaining studies was unclear). Blinding was only well-conducted in one study. Incomplete outcome reporting was variable across studies, and most included studies had systematic differences in care (i.e. intervention group had more time or attention than the control group) but sensitivity analyses removing studies with systematic differences in care did not alter effect sizes. No other biases were noted. Not downgraded for bias; however, it is noted that the level of compliance with interventions involving long-term behaviour change, such as those used in these studies, can vary widely. This is likely to attenuate the pooled effect and bias it towards the null.
[3] Unless otherwise noted, I^2 < 50%, indicating a low level of heterogeneity.
[4] All studies were conducted in the population of interest and employed appropriate interventions to assess the effect of lower compared to higher SFA intake on priority health outcomes decided upon prior to initiating the reviews. For outcomes other than LDL cholesterol, a small number of the RCTs included in the corresponding systematic review employed one or more dietary

interventions in addition to SFA reduction (i.e. multifactorial dietary interventions), however, all studies either explicitly or implicitly aimed to reduce SFA intake, achieved a reduction in SFA intake, or both.

[5] For all outcomes, the 95% CI crosses a threshold of important benefit or harm and is therefore downgraded for serious imprecision.

[6] Publication bias not formally assessed due to small number of studies, but the study included for this outcome is a subset of the complete set of studies, for which no publication bias was detected.

[7] Based on the control event rate (CER), which is the number of people with events in the control group divided by the total number of people in the control group. The absolute effect (per 10 000 people) is calculated with the following equation: absolute effect =10 000 x [CER x (1-RR)]. The magnitude of absolute effect depends on baseline risk, which can vary across different populations.

[8] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*.

[9] Additional evidence on the relationship between reduced SFA intake and cardiovascular and mortality outcomes comes from meta-analysis of three studies with coronary heart disease mortality as an outcome (RR 1.01 [95% CI: 0.86, 1.18]) (*moderate*-quality evidence).

[10] I^2 > 50%, indicating a significant level of heterogeneity.

[11] Additional evidence on the relationship between reduced SFA intake and cardiovascular outcomes comes from meta-analysis of three studies with nonfatal myocardial infarction as an outcome (RR 0.99 [95% CI: 0.73, 1.35]) (*low*-quality evidence).

[12] Studies were included in the blood lipids analysis only if protein intakes were held constant, thus precluding assessment of possible effects of protein intake on the lipid profile.

For details of the studies included in the review, see reference *(24)*.

GRADE evidence profile 12
Question: What is the effect of replacing some saturated fatty acids in the diet of children with protein?[1]
Setting: General child population

Quality assessment							No. of participants		Relative effect (95% CI)	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reduced SFA intake	Usual SFA intake		
LDL cholesterol[2]										
0	No studies identified reporting this outcome									
LDL cholesterol (*as assessed in adults*)[3]										
0	No studies identified reporting this outcome									

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; SFA, saturated fatty acids

[1] In addition to the LDL cholesterol outcome for adults included in this evidence profile, the remaining evidence for adults was also considered for children, without downgrading for indirectness.
[2] No studies conducted in children were identified in which it was clear that a significant portion of the nutrient replacing SFA was protein.
[3] Studies in adults were included in the serum lipids analysis only if protein intakes were held constant, thus precluding assessment of possible effects of protein on the serum lipid profile.

GRADE evidence profile 13
Question: What is the effect of an increase in saturated fatty acid intake in adults with a starting intake of less than 10% of total energy intake?[1]
Population: General adult population

Quality assessment							No. of participants		Relative effect[2] (95% CI)	Quality[3]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reduced SFA intake	Usual SFA intake		
LDL cholesterol (follow-up 5 weeks to 19 years; units mmol/L; better indicated by lower values)										
69 (165)[4]	RCTs	No serious risk of bias[5]	No serious inconsistency[6]	No serious indirectness[7]	No serious imprecision[8]	None[9]	197 310	--	**0.058** (0.052 to 0.064)	⊕⊕⊕⊕ HIGH

SFA, saturated fatty acids; CI, confidence interval; RCTs, randomized controlled trials; LDL, low-density lipoprotein

[1] Effects of increasing SFA intake on serum lipids by replacing polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA) or carbohydrates with SFA were observed across a wide range of SFA intakes, from 1.6 to 24.4% of total energy intake. Of the 177 total data points used in the multiple regression, 113 included an SFA intake component of less than 10% of total energy intake; 65 data points included intakes of less than 8%. Analysis of the residuals of the regression line indicates that the relationship between increase of SFA intake and effect on serum lipids is linear across the entire range of SFA intakes.
[2] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as PUFA is replaced with an isocaloric amount of SFA. Increases in LDL cholesterol were also observed when SFA replaced either MUFA (0.045 mmol/L; 95% CI: 0.039, 0.051) (*high*-quality evidence) or carbohydrates (0.036 mmol/L 95% CI:0.030, 0.043) (*high* quality-evidence).
[3] LDL cholesterol is a *critical* outcome. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(59)*.
[4] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, PUFA, MUFA and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of serum lipids.
[5] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.
[6] This analysis was conducted as a multiple regression in which data points (see footnote 4) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.
[7] LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[8] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[9] Publication bias was not formally assessed but, given the large number and nature of the studies included in the analysis (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified), risk of publication bias is likely to be low.
[10] Data points (see footnote 4) were directly extracted from all study groups from included trials without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.

For details of the studies included in the review, see reference *(59)*.

GRADE evidence profile 14
Question: What is the effect of an increase in saturated fatty acid intake in children with a starting intake of less than 10% of total energy intake?[1]
Population: General child population

Quality assessment							No. of participants		Relative effect[2] (95% CI)	Quality[3]
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reduced SFA intake	Usual SFA intake		
LDL cholesterol[4]										
0	No studies identified reporting this outcome									
LDL cholesterol (*as assessed in adults*) (follow-up 5 weeks to 19 years; units mmol/L; better indicated by lower values)										
69 (165)[5]	RCTs	No serious risk of bias[6]	No serious inconsistency[7]	No serious indirectness[8]	No serious imprecision[9]	None[10]	197 311	--	**0.058** (0.052 to 0.064)	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; SFA, saturated fatty acids

[1] Effects of increasing SFA intake on serum lipids by replacing polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA) or carbohydrates with SFA were observed across a wide range of SFA intakes, from 1.6 to 24.4% of total energy intake. Of the 177 total data points used in the multiple regression, 113 included an SFA intake component of less than 10% of total energy intake; 65 data points included intakes of less than 8%. Analysis of the residuals of the regression line indicates that the relationship between increase of SFA intake and effect on serum lipids is linear across the entire range of SFA intakes.
[2] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as PUFA is replaced with an isocaloric amount of SFA. Increases in LDL cholesterol were also observed when SFA replaced either MUFA (0.045 mmol/L; 95% CI: 0.039, 0.051) (*high*-quality evidence) or carbohydrates (0.036 mmol/L 95% CI:0.030, 0.043) (*high*-quality evidence).
[3] LDL cholesterol is a *critical* outcome. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(59)*.
[4] No studies conducted in children were identified in which the intervention consisted of an increase in SFA intake.
[5] The number of data points is provided in parentheses. Each data point contains dietary information on SFA, MUFA, PUFA and carbohydrate intake as well as an associated change in LDL cholesterol for each study group (i.e. intervention and control groups) at the end of a dietary treatment period, and was extracted for all treatment groups within studies included in the multiple regression analysis of serum lipids.
[6] All studies were strictly controlled dietary trials lasting from 13 to 91 days in which protein and cholesterol intakes were held constant. Some of the studies with parallel design were assessed as having unclear risk of bias in terms of randomization, because the randomization procedure was not fully described. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization whether or not it was specifically indicated if participants were randomized, because all participants were intended to receive all treatments and thus it was unlikely that any differences at baseline would have had a significant, systematic effect on study results. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means so risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were judged as having a low risk of bias.
[7] This analysis was conducted as a multiple regression in which data points (see footnote 5) were directly extracted from each study, rather than extraction of mean differences between groups within each included study. As a result, directly measuring between-study variability in a quantitative manner was not feasible. Qualitative assessment of the included studies and the strength and consistency of the results of the multiple regression, however, suggest that any inconsistency, if present, was likely to be minor and was therefore not considered to be serious.
[8] Although studies were conducted in adults, there was no evidence to indicate that the effect on LDL cholesterol resulting from a change in SFA intake would be significantly different between adults and children. LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[9] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.

[10] Publication bias was not formally assessed but, given the large number and nature of the studies included in the analysis (i.e. interventions were not limited to only those modifying saturated fat intake but also included studies in which other dietary fats were modified), risk of publication bias is likely to be low.
[11] Data points (see footnote 5) were directly extracted from all study groups from included trials without distinction between intervention and control groups, and therefore the total number of participants is indicated in the *Reduced SFA intake* column.

For details of the studies included in the review, see reference *(59)*.

GRADE evidence profile 15
Question: What is the effect of a reduction in *trans*-fatty acid[1] intake in adults and children with intakes greater than 1% of total energy intake?[2]
Population: General adult and child population

Quality assessment							No. of events/participants (study event rate)	Relative effect[5] (95% CI)	Absolute effects[6] (per 10 000)	Quality[7]
No. of studies[3]	Design	Risk of bias	Inconsistency	Indirectness[4]	Imprecision	Other				
All-cause mortality (follow-up 7 years)										
1 (1)	Cohort studies	No serious risk of bias[8]	No serious inconsistency[9]	No serious indirectness	No serious imprecision[10]	None[11]	1573/18513 (8.5%)	**RR 0.81** (0.68 to 0.96)	**217 fewer** (from 365 fewer to 46 fewer)	⊕⊕OO LOW
Coronary heart disease mortality (follow-up 6 – 21.4 years)										
5 (6)	Cohort studies	No serious risk of bias[8]	No serious inconsistency[12]	No serious indirectness	No serious imprecision[10]	Yes[13]	1234/70864 (1.7%)	**RR 0.78** (0.67 to 0.92)	**44 fewer** (from 67 fewer to 16 fewer)	⊕⊕⊕O MODERATE
Coronary heart disease events (follow-up 1 – 20 years)										
6 (7)	Cohort studies	No serious risk of bias[8]	No serious inconsistency[12]	No serious indirectness	No serious imprecision[10]	Yes[13]	4579/145922 (3.1%)	**RR 0.83** (0.75 to 0.91)	**71 fewer** (from 105 fewer to 38 fewer)	⊕⊕⊕O MODERATE
Stroke (follow-up 7 – 14 years)										
3 (4)	Cohort studies	No serious risk of bias[8]	Serious inconsistency[14]	No serious indirectness	Serious imprecision[15]	None[16]	1905/190284 (1.0%)	**RR 0.93** (0.78 to 1.14)	**5 fewer** (from 16 fewer to 10 more)	⊕OOO VERY LOW
Type 2 diabetes (follow-up 8.8 – 20 years)										
6 (6)	Cohort studies	Serious risk of bias[17]	Serious inconsistency[14]	No serious indirectness	Serious imprecision[15]	None[16]	8690/230135 (3.8%)	**RR 0.91** (0.79 to 1.05)	**50 fewer** (from 118 fewer to 28 more)	⊕OOO VERY LOW
LDL cholesterol (follow-up 14 – 56 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
13 (18)	RCTs	No serious risk of bias[18]	No serious inconsistency[19]	No serious indirectness[20]	No serious imprecision[21]	None[22]	66 923	**–0.047** (–0.055 to –0.040)[24]	--	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; RR, relative risk; TFA, *trans*-fatty acids

[1] *Trans*-fatty acids include all fatty acids with a carbon–carbon double bond in the *trans* configuration.
[2] For outcomes other than LDL cholesterol, only cohort studies that included a reference group consuming greater than 1% of total energy intake as TFA were included in the analysis. For the LDL cholesterol outcome, effects of decreasing TFA intake on blood lipids by replacement with polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), carbohydrates or saturated fatty acids (SFA), as obtained from regression analysis, were observed across a wide range of TFA intakes, from 1.6% to 24.4% of total energy intake. Residuals analysis indicates that the relationship between TFA intake and effect on blood lipids is linear across the entire range of TFA intakes.
[3] The number of comparisons is provided in parentheses.
[4] All studies were conducted in the adult population of interest and assessed the effect of lower compared to higher *trans*-fatty acid intake on priority health outcomes decided on before initiating review. No studies meeting the inclusion criteria for children were identified and therefore results for adults were extrapolated to children. Though clinical cardiovascular outcomes in children are rare, there was no evidence to indicate that the physiological response to a change in TFA intake would be significantly different between adults and children. Therefore, with respect to children, the outcomes were not downgraded for indirectness.
[5] For outcomes other than LDL cholesterol, relative effects are most-adjusted multivariate estimates (i.e. the multivariate association measure with the highest number of covariates).
[6] Absolute risk was estimated using the method of Newcombe et al. *(80)* with estimates of baseline risk obtained from the Emerging Risk Factors Consortium analysis of risk factors for vascular disease *(81)*.
[7] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(73)*.

[8] Newcastle–Ottawa scores for included studies ranged from 6 to 9. Confounding did not appear to be significant in the most-adjusted models as they yielded weaker effect estimates than the least-adjusted models (except *stroke,* for which both models yielded non-significant estimates), suggesting that some confounders had been captured.
[9] Only one study included.
[10] The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[11] Too few studies to assess publication bias. Evidence for dose response across quintiles of TFA intake, but the single study did not present data for a continuous association.
[12] I^2 < 50%, indicating a low level of heterogeneity.
[13] Too few studies to assess publication bias. Upgraded for evidence of a continuous dose–response relationship.
[14] I^2 > 50%, indicating a significant level of heterogeneity.
[15] The 95% CI crosses a threshold of important benefit or harm.
[16] Too few studies to assess publication bias.
[17] Newcastle–Ottawa scores for included studies ranged from 6 to 9. Most-adjusted models yielded weaker effect estimates than the least-adjusted models, but evidence suggests possible residual confounding by dietary fibre and/or magnesium. Therefore, the outcome has been downgraded for serious risk of bias.
[18] All studies included in this analysis were strictly controlled, relatively short-term dietary trials. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization, whether or not it was specifically indicated that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means; hence, risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were determined to have a low risk of bias.
[19] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[20] LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[21] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[22] Results of funnel plot analysis did not suggest any publication bias.
[23] Total number of participants.
[24] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as TFA is replaced with an isocaloric amount of PUFA. Effects on LDL cholesterol were also observed when TFA were replaced with MUFA (–0.027 mmol/L; 95% CI: –0.035, –0.019) (*high*-quality evidence), carbohydrates (–0.026 mmol/L; 95% CI: –0.033, –0.019) (*high* quality evidence), or SFA (0.010 mmol/L; 95% CI: 0.003, 0.017) (*high*-quality evidence).

For details of the studies included in the reviews, see references *(61)* and *(73)*.

GRADE evidence profile 16
Question: What is the effect of a reduction in *trans*-fatty acid[1] intake in adults and children to less than 1% of total energy intake?[2]
Population: General adult and child population

Quality assessment							No. of events/participants (study event rate)	Relative effect[5] (95% CI)	Absolute effects[6] (per 10 000)	Quality[7]
No. of studies[3]	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness[4]**	**Imprecision**	**Other**				
All-cause mortality										
0	No studies identified reporting this outcome									
Coronary heart disease mortality (follow-up 6 – 21.4 years)										
4 (4)	Cohort studies	No serious risk of bias[8]	No serious inconsistency[9]	No serious indirectness	No serious imprecision[10]	Yes[11]	1093/68957 (1.6%)	**RR 0.77** (0.67 to 0.93)	**46 fewer** (from 14 fewer to 67 fewer)	⊕⊕⊕O MODERATE
Coronary heart disease events (follow-up 1 – 7.2 years)										
4 (4)	Cohort studies	No serious risk of bias[8]	No serious inconsistency[9]	No serious indirectness	No serious imprecision[10]	Yes[11]	2715/101499 (2.7%)	**RR 0.86** (0.78 to 0.96)	**59 fewer** (from 93 fewer to 17 fewer)	⊕⊕⊕O MODERATE
Stroke (follow-up 14 years)										
1 (1)	Cohort studies	No serious risk of bias[8]	No serious inconsistency[12]	No serious indirectness	Serious imprecision[13]	None[14]	455/86152 (0.5%)	**RR 1.25** (0.85 to 1.85)	**18 more** (from 11 fewer to 60 more)	⊕OOO VERY LOW
Type 2 diabetes (follow-up 8.8 – 20 years)										
4 (4)	Cohort studies	Serious risk of bias[15]	Serious inconsistency[16]	No serious indirectness	Serious imprecision[13]	None[14]	4293/109963 (3.9%)	**RR 0.93** (0.78 to 1.09)	**39 fewer** (from 123 fewer to 50 more)	⊕OOO VERY LOW
LDL cholesterol (follow-up 14 – 56 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
13 (18)	RCTs	No serious risk of bias[17]	No serious inconsistency[18]	No serious indirectness[19]	No serious imprecision[20]	None[21]	66 922	**–0.047** (–0.055 to –0.040)[23]	--	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; RR, relative risk; TFA, *trans*-fatty acids

[1] *Trans*-fatty acids include all fatty acids with a carbon–carbon double bond in the *trans* configuration.
[2] For outcomes other than LDL cholesterol, only cohort studies that included a reference group consuming less than 1% of total energy intake as TFA were included in the analysis. For the LDL cholesterol outcome, effects of decreasing TFA intake on blood lipids by replacement with polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), carbohydrates or saturated fatty acids (SFA), as obtained from regression analysis, were observed across a wide range of TFA intakes, from 1.6% to 24.4% of total energy intake. Residuals analysis indicates that the relationship between TFA intake and effect on blood lipids is linear across the entire range of TFA intakes.
[3] The number of comparisons is provided in parentheses.
[4] All studies were conducted in the adult population of interest and assessed the effect of lower compared to higher *trans*-fatty acid intake on priority health outcomes decided on before initiating review. No studies meeting the inclusion criteria for children were identified and therefore results for adults were extrapolated to children. Though clinical cardiovascular outcomes in children are rare, there was no evidence to indicate that the physiological response to a change in TFA intake would be significantly different between adults and children. Therefore, with respect to children, the outcomes were not downgraded for indirectness.
[5] For outcomes other than LDL cholesterol, relative effects are most-adjusted multivariate estimates (i.e. the multivariate association measure with the highest number of covariates).
[6] Absolute risk was estimated using the method of Newcombe et al. *(80)* with estimates of baseline risk obtained from the Emerging Risk Factors Consortium analysis of risk factors for vascular disease *(81)*.
[7] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(73)*.

[8] Newcastle–Ottawa scores for included studies ranged from 7 to 9. Confounding did not appear to be significant in the most-adjusted models as they yielded weaker effect estimates than the least-adjusted models (except *stroke,* for which both models yielded non-significant estimates), suggesting that some confounders had been captured.
[9] I^2 < 50%, indicating a low level of heterogeneity.
[10] The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[11] Too few studies to assess publication bias. Upgraded for evidence of a continuous dose–response relationship.
[12] Only one study included.
[13] The 95% CI crosses a threshold of important benefit or harm.
[14] Too few studies to assess publication bias.
[15] Newcastle–Ottawa scores for included studies ranged from 7 to 9. Most-adjusted models yielded weaker effect estimates than the least-adjusted models, but evidence suggests residual confounding by dietary fibre and/or magnesium. Therefore, the outcome has been downgraded for serious risk of bias.
[16] I^2 > 50%, indicating a significant level of heterogeneity.
[17] All studies included in this analysis were strictly controlled, relatively short-term dietary trials. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization, whether or not it was specifically indicated that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means; hence, risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were determined to have a low risk of bias.
[18] Qualitative assessment of the included studies shows that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[19] LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[20] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[21] Results of funnel plot analysis did not suggest any publication bias.
[22] Total number of participants.
[23] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as TFA is replaced with an isocaloric amount of PUFA. Effects on LDL cholesterol were also observed when TFA were replaced with MUFA (–0.027 mmol/L; 95% CI: –0.035, –0.019) (*high*-quality evidence), carbohydrates (–0.026 mmol/L; 95% CI: –0.033, –0.019) (*high*-quality evidence), or SFA (0.010 mmol/L; 95% CI: 0.003, 0.017) (*high*-quality evidence).

For details of the studies included in the reviews, see references *(61)* and *(73)*.

GRADE evidence profile 17

Question: What is the effect of replacing some *trans*-fatty acids[1] in the diet of adults and children with polyunsaturated fatty acids?
Population: General adult and child population

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality[10]
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control		
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)										
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	**–0.048** (–0.055, –0.041)	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCT, randomized controlled trial; TFA, *trans*-fatty acids

[1] "*Trans*-fatty acids" include all fatty acids with a double bond in the *trans* configuration.
[2] All but two of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.
[3] The reported effect is the regression coefficient resulting from meta-regression. It is interpreted as the change in a particular blood lipid or lipoprotein when 1% of total energy intake as TFA is exchanged with an isocaloric amount of *cis*-polyunsaturated fatty acids.
[4] Number of comparisons are provided in parentheses.
[5] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization, whether or not it was specifically indicated that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although it is possible that participants in some studies may have been able to distinguish between intervention and control diets – this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means; hence, risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were determined to have a low risk of bias.
[6] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[7] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the adult population of interest, and all comparisons within studies were made directly to an appropriate control group or diet. No studies meeting the inclusion criteria for children were identified and therefore results for adults were extrapolated to children. Though clinical cardiovascular outcomes in children are rare, there was no evidence to indicate that the physiological response to a change in TFA intake would be significantly different between adults and children. Therefore, with respect to children, the outcomes were not downgraded for indirectness.
[8] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of exchanging TFA with the specified replacement nutrients on a particular blood lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and therefore the outcome has not been downgraded for serious imprecision.
[9] Results of funnel plot analysis did not suggest any publication bias.
[10] LDL cholesterol is a *critical* outcome. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important,* can be found in the systematic review of blood lipids *(73)*.

For details of the studies included in the reviews, see references *(61)* and *(73)*.

GRADE evidence profile 18

Question: What is the effect of replacing some *trans*-fatty acids[1] in the diet of adults and children with monounsaturated fatty acids?
Population: General adult and child population

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality[10]
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control		
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)										
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	**–0.035** (–0.042, –0.028)	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCT, randomized controlled trial; TFA, *trans*-fatty acids

[1] "*Trans*-fatty acids" include all fatty acids with a double bond in the *trans* configuration.
[2] All but two of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.
[3] The reported effect is the regression coefficient resulting from meta-regression. It is interpreted as the change in a particular blood lipid or lipoprotein when 1% of total energy intake as TFA is exchanged with an isocaloric amount of *cis*-monounsaturated fatty acids.
[4] Number of comparisons are provided in parentheses.
[5] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization, whether or not it was specifically indicated that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although it is possible that participants in some studies may have been able to distinguish between intervention and control diets – this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means; hence, risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were determined to have a low risk of bias.
[6] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[7] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the adult population of interest, and all comparisons within studies were made directly to an appropriate control group or diet. No studies meeting the inclusion criteria for children were identified and therefore results for adults were extrapolated to children. Though clinical cardiovascular outcomes in children are rare, there was no evidence to indicate that the physiological response to a change in TFA intake would be significantly different between adults and children. Therefore, with respect to children, the outcomes were not downgraded for indirectness.
[8] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of exchanging TFA with the specified replacement nutrients on a particular blood lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and therefore the outcome has not been downgraded for serious imprecision.
[9] Results of funnel plot analysis did not suggest any publication bias.
[10] LDL cholesterol is a *critical* outcome. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important,* can be found in the systematic review of blood lipids *(73)*.

For details of the studies included in the reviews, see references *(61)* and *(73)*.

GRADE evidence profile 19

Question: What is the effect of replacing some *trans*-fatty acids[1] in the diet of adults and children with carbohydrates[2]?
Population: General adult and child population

Quality assessment							No. of participants[3]		Effect[4] (95% CI)	Quality[11]
No. of studies[5]	Design	Risk of bias[6]	Inconsistency[7]	Indirectness[8]	Imprecision[9]	Other[10]	TFA	Control		
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)										
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	**–0.026** (–0.033, –0.019)	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCT, randomized controlled trial; TFA, *trans*-fatty acids

[1] "*Trans*-fatty acids" include all fatty acids with a double bond in the *trans* configuration.
[2] Carbohydrates were generally of unknown composition as studies providing sufficient dietary information to determine, exactly, the composition of the carbohydrate used as replacement, were limited.
[3] All but two of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.
[4] The reported effect is the regression coefficient resulting from meta-regression. It is interpreted as the change in a particular blood lipid or lipoprotein when 1% of total energy intake as TFA is exchanged with an isocaloric amount of carbohydrates.
[5] Number of comparisons are provided in parentheses.
[6] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization, whether or not it was specifically indicated that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although it is possible that participants in some studies may have been able to distinguish between intervention and control diets – this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means; hence, risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were determined to have a low risk of bias.
[7] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[8] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the adult population of interest, and all comparisons within studies were made directly to an appropriate control group or diet. No studies meeting the inclusion criteria for children were identified and therefore results for adults were extrapolated to children. Though clinical cardiovascular outcomes in children are rare, there was no evidence to indicate that the physiological response to a change in TFA intake would be significantly different between adults and children. Therefore, with respect to children, the outcomes were not downgraded for indirectness.
[9] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of exchanging TFA with the specified replacement nutrients on a particular blood lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and therefore the outcome has not been downgraded for serious imprecision.
[10] Results of funnel plot analysis did not suggest any publication bias.
[11] LDL cholesterol is a *critical* outcome. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important,* can be found in the systematic review of blood lipids *(73)*.

For details of the studies included in the reviews, see references *(61)* and *(73)*.

GRADE evidence profile 20

Question: What is the effect of replacing some *trans*-fatty acids[1] in the diet of adults and children with saturated fatty acids?
Population: General adult and child population

Quality assessment							No. of participants[2]		Effect[3] (95% CI)	Quality[10]
No. of studies[4]	Design	Risk of bias[5]	Inconsistency[6]	Indirectness[7]	Imprecision[8]	Other[9]	TFA	Control		
LDL cholesterol (2–8 week intervention periods; units mmol/L per 1% energy exchange; better indicated by lower values)										
16 (23)	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	669	669	**0.010** (0.003, 0.017)	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCT, randomized controlled trial; TFA, *trans*-fatty acids

[1] "*Trans*-fatty acids" include all fatty acids with a double bond in the *trans* configuration.
[2] All but two of the studies included in this analysis were of crossover or Latin square design. Participants in these studies therefore received both high TFA (*TFA*) and low TFA (*Control*) diets and are counted in both the *TFA* and *Control* columns.
[3] The reported effect is the regression coefficient resulting from meta-regression. It is interpreted as the change in a particular blood lipid or lipoprotein when 1% of total energy intake as TFA is exchanged with an isocaloric amount of saturated fatty acids.
[4] Number of comparisons are provided in parentheses.
[5] All studies included in this analysis were strictly controlled, relatively short-term dietary trials lasting from 14 days to 8 weeks, in which only dietary fat was varied and the remainder of the diet was controlled. Studies with crossover and Latin square designs were deemed to be at low risk of bias for randomization, whether or not it was specifically indicated that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and – although it is possible that participants in some studies may have been able to distinguish between intervention and control diets – this was not expected to alter compliance given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means; hence, risk of detection bias (i.e. bias resulting from non-blinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were determined to have a low risk of bias.
[6] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[7] All studies directly assessed the effect of modifying TFA intake on blood lipids and lipoproteins, which were priority health outcomes decided upon prior to initiating the systematic review. All studies were conducted in the adult population of interest, and all comparisons within studies were made directly to an appropriate control group or diet. No studies meeting the inclusion criteria for children were identified and therefore results for adults were extrapolated to children. Though clinical cardiovascular outcomes in children are rare, there was no evidence to indicate that the physiological response to a change in TFA intake would be significantly different between adults and children. Therefore, with respect to children, the outcomes were not downgraded for indirectness.
[8] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient is a direct measure of the effect of exchanging TFA with the specified replacement nutrients on a particular blood lipid or lipoprotein and the 95% CI is a measure of variability of that effect. Unless otherwise noted, the 95% CI does not cross a threshold of irrelevant benefit or important harm and therefore the outcome has not been downgraded for serious imprecision.
[9] Results of funnel plot analysis did not suggest any publication bias.
[10] LDL cholesterol is a *critical* outcome. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important,* can be found in the systematic review of blood lipids *(73)*.

For details of the studies included in the reviews, see references *(61)* and *(73)*.

GRADE evidence profile 21
Question: What is the effect of an increase in *trans*-fatty acid[1] intake in adults and children with a starting intake of less than 1% of total energy intake?[2]
Population: General adult and child population

Quality assessment							No. of events/participants (study event rate)	Relative effect[5] (95% CI)	Absolute effects[6] (per 10 000)	Quality[7]
No. of studies[3]	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness[4]**	**Imprecision**	**Other**				
All-cause mortality										
0	No studies identified reporting this outcome									
Coronary heart disease mortality (follow-up 6 – 21.4 years)										
4 (4)	Cohort studies	No serious risk of bias[8]	No serious inconsistency[9]	No serious indirectness	No serious imprecision[10]	Yes[11]	1093/68957 (1.6%)	**RR 1.30** (1.07 to 1.58)	**60 more** (from 14 more to 117 more)	⊕⊕⊕O MODERATE
Coronary heart disease events (follow-up 1 – 7.2 years)										
4 (4)	Cohort studies	No serious risk of bias[8]	No serious inconsistency[9]	No serious indirectness	No serious imprecision[10]	Yes[11]	2715/101499 (2.7%)	**RR 1.16** (1.04 to 1.29)	**67 more** (from 17 more to 122 more)	⊕⊕⊕O MODERATE
Stroke (follow-up 14 years)										
1 (1)	Cohort studies	No serious risk of bias[8]	No serious inconsistency[12]	No serious indirectness	Serious imprecision[13]	None[14]	455/86152 (0.5%)	**RR 0.80** (0.54 to 1.18)	**14 fewer** (from 33 fewer to 13 more)	⊕OOO VERY LOW
Type 2 diabetes (follow-up 8.8 – 20 years)										
4 (4)	Cohort studies	Serious risk of bias[15]	Serious inconsistency[16]	No serious indirectness	Serious imprecision[13]	None[14]	4293/109963 (3.9%)	**RR 1.08** (0.92 to 1.28)	**45 more** (from 45 fewer to 157 more)	⊕OOO VERY LOW
LDL cholesterol (follow-up 14 – 56 days; units mmol/L per 1% energy exchange; better indicated by lower values)										
13 (18)	RCTs	No serious risk of bias[17]	No serious inconsistency[18]	No serious indirectness[19]	No serious imprecision[20]	None[21]	66 922	**0.047** (0.040 to 0.055)[23]	--	⊕⊕⊕⊕ HIGH

CI, confidence interval; LDL, low-density lipoprotein; RCTs, randomized controlled trials; RR, relative risk; TFA, *trans*-fatty acids

[1] *Trans*-fatty acids include all fatty acids with a carbon–carbon double bond in the *trans* configuration.
[2] For outcomes other than LDL cholesterol, only cohort studies that included a reference group consuming less than 1% of total energy intake as TFA were included in the analysis. For the LDL cholesterol outcome, effects of decreasing TFA intake on blood lipids by replacement with polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), carbohydrates or saturated fatty acids (SFA), as obtained from regression analysis, were observed across a wide range of TFA intakes, from 1.6% to 24.4% of total energy intake. Residuals analysis indicates that the relationship between TFA intake and effect on blood lipids is linear across the entire range of TFA intakes.
[3] The number of comparisons is provided in parentheses.
[4] All studies were conducted in the adult population of interest and assessed the effect of higher compared to lower *trans*-fatty acid intake on priority health outcomes decided on before initiating review. No studies meeting the inclusion criteria for children were identified and therefore results for adults were extrapolated to children. Though clinical cardiovascular outcomes in children are rare, there was no evidence to indicate that the physiological response to a change in TFA intake would be significantly different between adults and children. Therefore, with respect to children, the outcomes were not downgraded for indirectness.
[5] For outcomes other than LDL cholesterol, relative effects are most-adjusted multivariate estimates (i.e. the multivariate association measure with the highest number of covariates).
[6] Absolute risk was estimated using the method of Newcombe et al. *(80)* with estimates of baseline risk obtained from the Emerging Risk Factors Consortium analysis of risk factors for vascular disease *(81)*.
[7] All outcomes in this evidence profile are *critical* outcomes. Outcomes can be assessed as either *important* or *critical* for decision-making when formulating recommendations *(22)*. Evidence profiles for blood lipid outcomes other than LDL cholesterol, which were classified as *important*, can be found in the systematic review of blood lipids *(73)*.

[8] Newcastle–Ottawa scores for included studies ranged from 7 to 9. Confounding did not appear to be significant in the most-adjusted models as they yielded weaker effect estimates than the least-adjusted models (except *stroke,* for which both models yielded non-significant estimates), suggesting that some confounders had been captured.
[9] I^2 < 50%, indicating a low level of heterogeneity.
[10] The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[11] Too few studies to assess publication bias. Upgraded for evidence of a continuous dose–response relationship.
[12] Only one study included.
[13] The 95% CI crosses a threshold of important benefit or harm.
[14] Too few studies to assess publication bias.
[15] Newcastle–Ottawa scores for included studies ranged from 7 to 9. Most-adjusted models yielded weaker effect estimates than the least-adjusted models, but evidence suggests residual confounding by dietary fibre and/or magnesium. Therefore, the outcome has been downgraded for serious risk of bias.
[16] I^2 > 50%, indicating a significant level of heterogeneity.
[17] All studies included in this analysis were strictly controlled, relatively short-term dietary trials. Studies with crossover and Latin-square designs were deemed to be at low risk of bias for randomization, whether or not it was specifically indicated that participants were randomized, because all participants were intended to receive all treatments and it is thus unlikely that any differences at baseline would have a significant, systematic effect on study results. The two studies with parallel design were assessed as having an unclear risk of bias in terms of randomization because it was not specified whether participants were randomized. Blinding was not deemed to be a significant source of bias because all interventions consisted of food provision and, although it was possible that participants in some studies may have been able to distinguish between intervention and control diets, this was not expected to alter compliance, given the study design and conduct. All outcomes were objectively measured by chemical and mathematical means; hence, risk of detection bias (i.e. bias resulting from unblinded outcome assessment) was considered to be very low. There was no indication of widespread attrition bias or selective reporting, and other sources of bias were minimal. Overall, the studies were determined to have a low risk of bias.
[18] Qualitative assessment of the included studies show that point estimates across individual studies were similar and 95% CIs overlapped, suggesting inconsistency is not serious.
[19] LDL cholesterol is an indirect measure of patient-important CVD outcomes. However, LDL cholesterol is a well-established biomarker for assessing the effects of interventions on CVD risk *(12, 14)*, and was therefore not downgraded for indirectness.
[20] Imprecision was assessed using the 95% CI of the regression coefficient as a proxy for the 95% CI of a pooled estimate of effect, the rationale being that the regression coefficient provides an estimate of the effect of reducing SFA intake on LDL cholesterol and the 95% CI is a measure of variability of that effect. The 95% CI does not cross a threshold of irrelevant benefit or important harm.
[21] Results of funnel plot analysis did not suggest any publication bias.
[22] Total number of participants.
[23] The relative effect is a regression coefficient which is interpreted as the change in LDL cholesterol when 1% of total energy intake as TFA is replaced with an isocaloric amount of PUFA. Effects on LDL cholesterol were also observed when TFA were replaced with MUFA (0.027 mmol/L; 95% CI: 0.019, 0.035) (*high*-quality evidence), carbohydrates (0.026 mmol/L; 95% CI: 0.019, 0.033) (*high*-quality evidence), or SFA (–0.010 mmol/L; 95% CI: –0.017, –0.003) (*high*-quality evidence).

For details of the studies included in the reviews, see references *(61)* and *(73)*.

Annex 2: WHO Secretariat

(List to be inserted before finalization)

Annex 3: Members of the WHO Steering Committee for Nutrition Guideline Development

(List to be inserted before finalization)

Annex 4: Members of the guideline development group (NUGAG Subgroup on Diet and Health) and external resource persons

(List to be inserted before finalization)

Annex 5: External peer-review group

(List to be inserted before finalization)

Annex 6: Priority questions in the format of population, intervention, control and outcomes (PICO)

Saturated fatty acids

What is the effect on risk of noncommunicable diseases (NCDs) in adults and children of

- lower intake of saturated fatty acids relative to higher intake;
- a decrease in saturated fatty acid intake to below 10% of total energy intake[1],
- replacement of saturated fatty acids in the diet with polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), carbohydrates or protein; or
- lower intake of individual saturated fatty acids relative to higher intake?

Adults

Population	Apparently healthy adults in low-, middle- and high-income countries • In each, consider population characteristics, such as age, gender, ethnicity, country/region (urban/rural), socioeconomic status, demographic factors, sanitation, health background and health status, including baseline risk of cardiovascular diseases
Intervention/exposure	Definitions • Saturated fatty acids/saturated fat • % energy intake from saturated fatty acids • Dietary fatty acids/dietary fat
Control	Comparison of levels Continuous or categorical Adherence to recommendations Appropriately matched to intervention group by randomization
Confounders/effect modifiers/intermediates	• Baseline level of saturated fatty acid intake • Energy intake • Energy expenditure; fitness and physical activity • Consider other interventions in design, dietary and non-dietary (protocol to specify) • Consider influence of other aspects of diet/dietary patterns • Consider effects of nutrients used to replace saturated fatty acids <u>Intermediates</u> • Take into account effect of energy density

[1] The population nutrient intake goal for saturated fatty acids recommended by the joint WHO/FAO expert consultation is less than 10% of total energy intake *(2)*.

	• Blood lipids as an intermediate between saturated fatty acids and cardiovascular outcomes
Outcome	• All-cause mortality • Cardiovascular outcomes - Cardiovascular diseases: events, mortality - Coronary heart disease: events, mortality - Stroke • Blood lipids
Time frame	• For studies where the intervention is advisory or provision of food, and outcomes are cardiovascular disease events and mortality, minimum study duration is two years (24 months) • For controlled feeding studies with blood lipid outcomes, minimum study duration is 13 days, which is the minimum time necessary for blood lipids to reach a new steady state in response to changes in diet

Children

Population	Apparently healthy children in low-, middle- and high-income countries • In each, consider population characteristics, such as age, gender, ethnicity, country/region (urban/rural), socioeconomic status/demographic factors/sanitation health background and health status
Intervention/exposure	Definitions • Saturated fatty acids/saturated fat • % energy intake from saturated fatty acids • Dietary fatty acids/dietary fat • Dairy fat
Control	Comparison of levels Continuous or categorical Adherence to recommendations Appropriately matched to intervention group by randomization
Confounders/effect modifiers/intermediates	• Baseline level of saturated fatty acid intake • Energy intake • Energy expenditure; fitness and physical activity • Consider other interventions in design, dietary and non-dietary (protocol to specify) • Consider influence of other aspects of diet/dietary patterns • Consider effects of nutrients used to replace saturated fatty acids <u>Intermediates</u>

	• Take into account effect of energy density • Blood lipids as an intermediate between saturated fatty acids and cardiovascular outcomes
Outcome	• Blood lipids • Measures of body weight, adiposity • Measures of growth and development • Type 2 diabetes incidence, insulin resistance • Adverse effects
Time frame	• For studies where the intervention is advisory or provision of food and outcomes are blood lipids, minimum study duration is 13 days, which is the minimum time necessary for blood lipids to reach a new steady state in response to changes in diet

Trans-fatty acids

- What is the effect of lower intake of *trans*-fatty acids relative to higher intake on risk of NCDs in adults and children?
- What is the effect of a decrease in *trans*-fatty acid intake to below 1% of total energy[1] on risk of NCDs in adults and children?

Adults

Population	Apparently healthy adults in low-, middle- and high-income countries • In each, consider population characteristics, such as age, gender, ethnicity, country/region (urban/rural), socioeconomic status/demographic factors/sanitation health background and health status, including baseline risk of cardiovascular diseases
Intervention/exposure	Definitions • *Trans*-fatty acids/trans fats • Industrially-produced *trans*-fatty acids • Ruminant *trans*-fatty acids • % energy intake from *trans*-fatty acids • Dietary fatty acids/dietary fat

[1] The population nutrient intake goal for *trans*-fatty acids recommended by the joint WHO/FAO expert consultation is less than 1% of total energy intake *(2)*.

Control	Comparison of levels Continuous or categorical Adherence to recommendations Appropriately matched to intervention group by randomization
Confounders/effect modifiers/intermediates	• Baseline level of *trans*-fatty acid intake • Energy intake • Energy expenditure; fitness and physical activity • Consider other interventions in design, dietary and non-dietary (protocol to specify) • Consider influence of other aspects of diet/dietary patterns • Consider effects of nutrients used to replace *trans*-fatty acids <u>Intermediates</u> • Take into account effect of energy density • Blood lipids as an intermediate between *trans*-fatty acids and cardiovascular outcomes
Outcome	• All-cause mortality • Cardiovascular outcomes - Cardiovascular disease: events, mortality - Coronary heart disease: events, mortality - Stroke • Blood lipids
Time frame	• No minimum duration for prospective cohort studies with cardiovascular diseases events, mortality and type 2 diabetes outcomes • For controlled feeding studies with blood lipid outcomes, minimum study duration is 13 days, which is the minimum time necessary for blood lipids to reach a new steady state in response to changes in diet

Children

Population	Apparently healthy adults in low-, middle- and high-income countries • In each, consider population characteristics, such as age, gender, ethnicity, country/region (urban/rural), socioeconomic status/demographic factors/sanitation health background and health status, including baseline risk of cardiovascular diseases
Intervention/exposure	Definitions • *Trans*-fatty acids/trans fats

	• Industrially-produced *trans*-fatty acids • Ruminant *trans*-fatty acids • % energy intake from *trans*-fatty acids • Dietary fatty acids/dietary fat • Dairy fat
Control	Comparison of levels Continuous or categorical Adherence to recommendations Appropriately matched to intervention group by randomization
Confounders/effect modifiers/intermediates	• Baseline level of *trans*-fatty acid intake • Energy intake • Energy expenditure; fitness and physical activity • Consider other interventions in design, dietary and non-dietary (protocol to specify) • Consider influence of other aspects of diet/dietary patterns • Consider effects of nutrients used to replace *trans*-fatty acids <u>Intermediates</u> • Take into account effect of energy density • Blood lipids as an intermediate between *trans*-fatty acids and cardiovascular outcomes
Outcome	• All-cause mortality • Cardiovascular outcomes - Cardiovascular diseases: events, mortality - Coronary heart disease: events, mortality - Stroke • Blood lipids
Time frame	• For studies where the intervention is advisory or provision of food and outcomes are blood lipids, minimum study duration is 13 days, which is the minimum time necessary for blood lipids to reach a new steady state in response to changes in diet

Annex 7: Summary of considerations for determining the strength of the recommendations

Saturated fatty acids

Quality of evidence	**Recommendation 1** • *Moderate* quality evidence for the effect of reducing saturated fatty acid intake on cardiovascular events and *high* quality evidence for the effect on LDL cholesterol in adults (and children as measured in adults by proxy, without downgrading for indirectness) • *High* quality evidence for the effect of a reduction in saturated fatty acid intake on LDL cholesterol and diastolic blood pressure in children **Recommendation 2** • *High* quality evidence for the effect of reducing saturated fatty acid intake to less than 10% of total energy intake on LDL cholesterol in adults (and children as measured in adults by proxy, without downgrading for indirectness) • *High* quality evidence for the effect of a reduction in saturated fatty acid intake to less than 10% of total energy intake on LDL cholesterol in children **Recommendation 3** • *Moderate* quality evidence for the effect of replacing saturated fatty acids with polyunsaturated fatty acids on cardiovascular events and *high* quality evidence for the effect on LDL cholesterol in adults (and children as measured in adults by proxy, without downgrading for indirectness) • *High* quality evidence for the effect of replacing saturated fatty acids with polyunsaturated fatty acids on LDL cholesterol in children **Recommendation 4** • *High* quality evidence for the effect of an increase in saturated fatty acid intake on LDL cholesterol in adults • *High* quality evidence for the effect of an increase in saturated fatty acid intake on LDL cholesterol in children (as measured in adults by proxy, without downgrading for indirectness)
Balance of benefits and harm	• High prevalence of cardiovascular diseases show that large portions of the world population would benefit from a reduction in risk of cardiovascular diseases • Clear evidence of benefits on health • No known adverse effects on health have been documented
Values and preferences	• The recommendations place a high value on reduction of risk of noncommunicable diseases (NCDs), particularly cardiovascular diseases • Implementation of the recommendations would help improve the quality of diets among individuals

	• NCDs are the leading cause of death globally, and interventions to reduce the burden of NCDs are valuable • NCDs affect countries in all regions and all income levels, meaning that interventions to reduce the burden of NCDs are valuable in all contexts • Values and preferences among individuals affected by the recommendations may vary based on personal preferences
Resource implications	• Implementing the recommendations is likely to be associated with long-term cost saving in health care in countries • The extent of these savings and resource use depend on strategies chosen for implementation and timescale for evaluation • Implementation of the strategies and intervention programme requires a suite of policy actions accompanied by consumer education, public health communications and nutrition communication • Prevention of NCDs can significantly reduce health-care costs, and replacing saturated fatty acids with unsaturated fatty acids has been identified as a cost-effective intervention to improve diets *(82)*. • These recommendations can be incorporated into existing public health nutrition education campaigns and other existing nutrition programmes at the global, regional, national and subnational levels • Issues of sustainability need to be considered when implementing recommendations
Priority of the problem	• High priority • Cardiovascular diseases is a leading cause of death globally and responsible for a significant number of premature deaths • Global saturated fatty acid intake was estimated to be approximately 9.4% of total energy intake in 2010 *(56)*; however, significant variability was observed in intake across countries and regions, and intake in many countries is very high (up to 27.5% of total energy intake) • Priority placed on the problem by national authorities may vary depending on real or perceived magnitude of problem within the country
Equity and human rights	• Has the potential to reduce health inequity by improving the health of those of lower socioeconomic status as they are generally disproportionately affected by NCDs, but pricing issues for food lower in saturated fatty acids would need to be carefully considered (e.g. costs of switching cooking oils, switching to leaner cuts of meat, substituting plant sources of fatty acids for some animal sources, etc.) • The effect on equity and human rights might also be affected by how the recommendations are translated into policies and actions (e.g. fiscal policies, reformulation, etc.)

Acceptability	• Acceptability should generally be high as NCDs are a significant, recognized global public health problem • Recommendations are in line with many national policies; however, acceptability may vary across different countries and cultural contexts • Acceptability may also be influenced by: - how the recommendations are translated into policies and actions (e.g. fiscal policies, reformulation, etc.) as some may be more acceptable than others; - level of awareness of the health problem that NCDs pose (e.g. it may be less acceptable in settings where awareness is low); - potential impact on national economies; and - compatibility with existing policies
Feasibility	• Influenced by resources available, infrastructure • Feasibility has been demonstrated as large-scale reduction of saturated fatty acid intake has been achieved in certain settings and health benefits noted • In settings where efforts to reduce saturated fatty acid intake are planned or are already under way, feasibility should be much higher than in settings where plans are not yet in place • Widespread use and availability of certain food items high in saturated fatty acids may pose challenges in replacing with reduced saturated fatty acid alternatives

Trans-fatty acids

Quality of evidence	**Recommendation 1** • *Low* quality evidence for the effect of reducing *trans*-fatty acid intake on all-cause mortality, *moderate* quality evidence for the effect on coronary heart disease events and coronary heart disease mortality, and *high* quality evidence for the effect on LDL cholesterol in adults and children (as measured in adults by proxy, without downgrading for indirectness) **Recommendation 2** • *Moderate* quality evidence for the effect of a reduction in *trans*-fatty acid intake to less than 1% of total energy intake on coronary heart disease events and coronary heart disease mortality, and *high* quality evidence for the effect on LDL cholesterol in adults and children (as measured in adults by proxy, without downgrading for indirectness) **Recommendation 3** • *High* quality evidence for the effect on LDL cholesterol in adults and children (as measured in adults by proxy, without downgrading for indirectness) **Recommendation 4** • *Moderate* quality evidence for the effect of an increase in *trans*-fatty acid intake on coronary heart disease events and coronary heart disease mortality, and *high* quality evidence for the effect on LDL cholesterol in adults on LDL cholesterol in adults and children (as measured in adults by proxy, without downgrading for indirectness)
Trade-off between benefits and harm	• High prevalence of cardiovascular diseases shows that large portions of the world population would benefit from a reduction in risk of cardiovascular diseases • Clear evidence of benefits on health • No known adverse effects on health have been documented
Values and preferences	• The recommendations place a high value on reduction of risk of noncommunicable diseases (NCDs), particularly cardiovascular diseases • Implementation of the recommendations would help improve the quality of diets among individuals • NCDs are the leading cause of death globally, and interventions to reduce the burden of NCDs are valuable • NCDs affect countries in all regions and all income levels, meaning that interventions to reduce the burden of NCDs are valuable in all contexts • Values and preferences among individuals affected by the recommendations may vary based on personal preferences
Resource	• Implementing this recommendation is likely to be associated with long-

implications	term cost saving in health care in countries • The extent of these savings and resource use depend on strategies chosen for implementation and timescale for evaluation • Implementation of the strategies and intervention programme requires a suite of policy actions accompanied by consumer education, public health communications and nutrition communication • Prevention of NCDs can significantly reduce health-care costs, and replacing *trans*-fatty acids with unsaturated fatty acids is a very cost effective intervention that has been designated a "best-buy"[1] *(82-84)* • These recommendations can be incorporated into existing public health nutrition education campaigns and other existing nutrition programmes at the global, regional, national and subnational levels • Issues of sustainability need to be considered when implementing recommendations
Priority of the problem	• High priority • Cardiovascular diseases are a leading cause of death globally and responsible for a significant number of premature deaths • Global *trans*-fatty acid intake was estimated to be approximately 1.4% of total energy intake in 2010 *(56)*; however, significant variability was observed in intake across countries and regions, and intake in many countries is very high (up to 6.5% of total energy intake)
Equity and human rights	• Has the potential to reduce health inequity by improving the health of those of lower socioeconomic status as they are generally disproportionately affected by NCDs, but pricing issues for food lower in *trans*-fatty acids would need to be carefully considered • The effect on equity and human rights might also be affected by how the recommendations are translated into policies and actions (e.g. fiscal policies, reformulation, etc.)
Acceptability	• Acceptability should generally be high as NCDs are a significant, recognized global health problem • Recommendations are in line with many national policies; however, acceptability may vary across different countries and cultural contexts • Acceptability may also be influenced by: - how the recommendations are translated into policies and actions (e.g. fiscal policies, reformulation, etc.) as some may be more acceptable than others;

[1] Highly cost-effective interventions that are also high impact and feasible for implementation even in resource-constrained settings *(83)*.

	- level of awareness of the health problem that NCDs pose (e.g. it may be less acceptable in settings where awareness is low); - potential impact on national economies; and - compatibility with existing policies
Feasibility	• Influenced by resources available, infrastructure • Feasibility has been demonstrated as large-scale reduction of *trans*-fatty acid intake has been achieved in certain settings and health benefits noted • In settings where efforts to reduce saturated fatty acid intake are planned or are already under way, feasibility should be much higher than in settings where plans are not yet in place • Widespread use and availability of certain food items high in *trans*-fatty acids may pose challenges in replacing with reduced *trans*-fatty acid alternatives • Reformulation technology and know-how for reducing or removing *trans*-fatty acids from many food items already developed and employed in many settings; however, there may be barriers to widespread availability of the technology which may impact feasibility in certain settings

Annex 8: Management of conflict of interest

(To be completed before finalization)

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