

Evidence Check

Dietary fats and cardiovascular disease

An **Evidence Check** rapid review brokered by the Sax Institute for the
National Heart Foundation. September 2017

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This report was prepared by:

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Glossary

| | |
|---------|--|
| ALA | Alpha-linolenic acid |
| CHD | Coronary heart disease |
| CHO | Carbohydrates |
| CVD | Cardiovascular disease |
| DPA | Docosapentaenoic acid |
| DHA | Docosahexaenoic acid |
| EPA | Eicosapentaenoic acid |
| HDL | High density lipoprotein |
| IHD | Ischaemic heart disease |
| LA | Linoleic acid |
| LCMUFA | Long-chain monounsaturated fatty acids |
| LDL | Low density lipoprotein |
| MI | Myocardial infarction |
| MUFA | Monounsaturated fat |
| NHFA | National Heart Foundation of Australia |
| PUFA | Polyunsaturated fat |
| N3 fats | Omega-3 fats |
| N6 fats | Omega-6 fats |
| SFA | Saturated fat |
| TC | Total cholesterol |
| TFA | Trans fatty acid |

Executive summary

Background

Over the last six years the evidence in relation to saturated and polyunsaturated fat (PUFA) and heart disease has been very strongly questioned by a small group of researchers and the media, and left the public very confused.

The National Heart Foundation of Australia (NHFA) commissioned this Evidence Check to review the most recent evidence on dietary fats and cardiovascular health. Since the Heart Foundation published their position statement Dietary Fats and Dietary Sterols for Cardiovascular Health in 2009, there have been at least six major meta-analyses regarding dietary fat and fish oil supplementation and cardiovascular health.

Review questions

This review aimed to address the following questions:

1. What is the evidence regarding the association between dietary fat consumption and the incidence of cardiovascular disease?
2. What is the evidence regarding the association between dietary fat consumption and cardiovascular disease outcomes in patients with existing cardiovascular disease?
3. What is the evidence regarding the effectiveness of manipulation of dietary fat intake as management strategy for hypercholesterolemia?
4. What is the evidence regarding:
 - a. the association between dairy product intake and CVD outcomes?
 - b. the association between coconut oil intake and CVD outcomes?

Summary of method

Given the brief of reviewing meta-analyses and systematic reviews with hard endpoints for heart attack, heart failure, cardiac death and atrial fibrillation, only peer reviewed literature (Pubmed, Embase and Cochrane library of Controlled Clinical Trials) was searched with the search terms "dietary fat OR dietary saturated fat OR dietary unsaturated fat OR dietary fish oil OR dietary omega 3 fats OR dietary omega 6 fats AND heart disease". Searches were limited to a period from 2009 to 18 November 2016. This produced 2621 unduplicated publications. The addition of systematic review to the search terms reduced the number to 528. This number was further reduced to 79 by the addition of the term meta-analysis. All meta-analyses that specifically addressed each question were included (n=42) plus 2 systematic reviews and 9 individual studies not included in the latest meta-analyses.

Evidence grading

Given that much of the evidence in relation to Question 1 came from cohort studies it can only be regarded as Level III evidence with a Grade of C (satisfactory) as it requires extrapolations from cohort studies and not interventions. For Question 2, although this included Level I evidence, it can only be regarded as Grade D (poor) due to striking inconsistencies in the evidence and the meta-analyses. For Question 3, level I evidence is available and would be given a Grade of B (good) but recommendations for long-term diet require extrapolations from short term studies. For Question 4a, the evidence is level III and Grade C (satisfactory). Question 4b has insufficient evidence to grade.

Although these ratings might be regarded as relatively low, they reflect the limited evidence base for nutrition compared with drugs, which have many large well-funded interventions on which to base policy and guidelines. As noted, much of the evidence comes from cohort studies and the associations seen in

these studies are not evidence of causation. Long term intervention studies would be required and, to date, agencies such as the NHFA or the NHMRC have not funded such studies, which are difficult and expensive.

Key findings

Q1: What is the evidence regarding the association between dietary fat consumption and the incidence of cardiovascular disease?

There is limited data on total fat and heart disease. The best most recent data is that from the combined Nurses' Health Study and Health Professionals Follow-up Study from Wang et al¹ which showed those in the highest quintile of total fat had 16% lower total mortality. Thus, higher fat compared with high GI, low fibre, carbohydrate as consumed in the USA, is associated with better outcomes. This was due to 16% lower mortality due to high polyunsaturated fat (PUFA) intake and 11% lower mortality due to high monounsaturated fat (MUFA) intake.

Saturated fat was associated with an 8% increase and trans fats; a 13% increase in total mortality compared with carbohydrate. Thus, replacing 5% of energy from saturated fats with equivalent energy from PUFA and MUFA was associated with estimated reductions in total mortality of 27% and 13%, respectively. These findings for total mortality were very similar looking at cardiovascular disease (CVD) mortality, although MUFA was not protective. Alpha-linolenic acid (ALA) was not associated with reduced mortality but marine fish oils were associated with a 4% reduction in mortality. PUFA was superior to MUFA for both total and CVD mortality in these cohorts.

Li² examined the same American cohorts and found a 20% reduction in coronary heart disease (CHD) events with a low saturated fat diet compared with carbohydrate. Low quality carbohydrate (high GI starch and sugar) was positively associated with CHD. Replacing 5% of energy intake from saturated fats with equivalent energy intake from PUFAs, MUFAs or carbohydrates from whole grains was associated with a 25%, 15%, and 9% lower risk of CHD. PUFA and MUFA were equivalent for prevention of CHD events but PUFA was superior to wholegrain carbohydrate.

Although this data comes from only two cohorts combined, the updating of dietary information every four years adds a lot of weight to the findings, which are probably more reliable than larger meta-analyses combining weaker studies. In the Predimed study (Guasch-Ferre et al. 2015) a high total fat intake (both from MUFA and PUFA) was associated with a 42–50% reduction in CVD and total mortality.³

De Souza⁴ published the most recent meta-analysis of all cohort studies and found saturated fat and carbohydrate were equivalent for CHD events and mortality in the most adjusted analysis (like the 2010 Siri-Tarino meta-analysis⁵), whereas the least adjusted analysis was borderline for CHD risk and significant for CHD mortality.

Thus, saturated fat is similar to or worse than total carbohydrate for CHD events but definitely worse than carbohydrate for total mortality.

Therefore, reducing saturated fat (and trans fat), and replacing it with PUFA and MUFA and carbohydrate of any type, will lower total mortality. Replacing it with PUFA, MUFA and whole grains will lower CHD events. Replacing saturated fat with PUFA will lower events, CVD mortality and total mortality, and is clearly superior to MUFA. PUFA can include linoleic acid (LA), alpha-linolenic acid (ALA) and fish oil.

Meta-analyses by Farvid⁶ and de Goede⁷, and data by Wu⁸ from the Cardiovascular Health Study, confirm the clear benefit of linoleic acid although there are no primary prevention trials with hard end points. ALA data is not as clear but Pan et al. found a 10% lower risk of CHD for every 1g of dietary ALA.⁹ A very recent meta-analysis by Del Gobbo et al.¹⁰ confirmed the benefit of ALA (as assessed by ALA blood measures) and fatal CHD but not total CHD. Docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) were associated with a lower risk of fatal CHD but only DPA was associated with total CHD. DPA is an elongation product of ALA and reflects its intake.

In recent meta-analyses marine fatty acids¹¹⁻¹⁷ were associated with lower total mortality and less incident heart failure; confirming earlier studies of protection from fish intake in primary prevention. Use of omega-3 fatty acids to lower post-operative atrial fibrillation is probably not indicated.

Chowdury¹⁸ in his meta-analyses essentially found no associations with dietary fat intake or blood levels of various lipids (except EPA and DHA) and CHD. Part of the reason for this is that all data was reduced to tertiles, thus narrowing the differences; and, sometimes it was converted from RR (relative risk) per SD to RR per tertile. In addition, there were seven transcription errors in the abstract which later required correction — this suggests lack of care in the data analysis and means the study carries less weight.

Q2: What is the evidence regarding the association between dietary fat consumption and cardiovascular disease outcomes in patients with existing cardiovascular disease?

There is very limited observational data for just dietary fat manipulation in secondary prevention and most of the data is focused on healthy dietary patterns, which include decreasing saturated fat and replacing it with unsaturated fat along with many other dietary changes. Better dietary patterns are related to fewer events. There are few large controlled interventions with dietary fat change; and, all are old and flawed with much difference in meta-analyses related to selection or omission of studies. There are many papers arguing over this topic.

Hooper¹⁹, in a very detailed Cochrane meta-analysis, found a 17% reduction in CVD events in interventions to lower saturated fat (regardless of what replaced it). There was a 27% reduction if PUFA replaced saturated fat and no benefit was seen with any other separate replacement macronutrient. CHD events were reduced by 24% among those achieving a total cholesterol (TC) lowering of >0.2 mmol/L. This is surprisingly large given that statin induced lowering of low density lipoprotein (LDL) cholesterol by 1 mmol/L reduces coronary events (fatal and non-fatal) by about 20%.²⁰

In relation to dietary supplementation with marine omega-3 fats, a new meta-analysis from Wen¹⁵ found death from all causes, death from cardiac causes and sudden death were reduced by 8-14%. Surprisingly this meta-analysis included the discredited Singh trial (1997)²¹ (2.2% weight) and deaths were dominated by both of the GISSI trials (one open label)^{22 23} which had 82-89% of all deaths, making the conclusions not very robust given recent trial data. Given these caveats the data can only be regarded as low quality. Casula²⁴ examined only secondary prevention studies and found greater effects for cardiac death and sudden death, and a 25% reduction in myocardial infarction (MI), but no effect on total mortality. Again, Singh²¹ was included and the Japan EPA Lipid Intervention Study (JELIS)²⁵ was not noted to be open label.

Q3: What is the evidence regarding the effectiveness of manipulation of dietary fat intake as management strategy for hypercholesterolemia?

There is no good data linking the long-term effects of a diet in which only dietary lipids are altered (particularly lower saturated fat and higher PUFA or MUFA) to lower TC or LDL. Most diets tested over the last 10 years have been portfolio diets with vegetarian protein, sterols and fibre, as well as decreased saturated fat and increased unsaturated fat. The simplest interventions have been nut interventions which can lower LDL cholesterol by 8.3% as shown in the Predimed study at 1 year.²⁶ However nuts add fibre and phytosterols which may account for part of their effect. In this study phytosterol intake rather than fat or fibre changes were weakly related to LDL changes. Phytosterols lower LDL by 0.34 mmol/L in a pooled analysis by Demonty²⁷ with a mean dose of 2.15g. A meta-analysis by Wu of eight low-fat diet studies in women showed an LDL cholesterol-lowering of 0.24 mmol/L with greater effects in premenopausal women.²⁸ Long term (>12m) effects of a low-fat diet in obese people show only a fall of 0.08 mmol/L in LDL so, short term effects are rarely maintained long term.²⁹

Mensink³⁰ performed a meta regression of short term (at least 13 days) dietary fat interventions to examine the mean changes in lipids and lipoproteins replacing 1% of energy from saturated fat with CHO, MUFA or

PUFA. For LDL cholesterol data was derived from 69 studies and showed a change of -0.033mmol/L (95%CI -0.039 to -0.027), -0.042 (-0.047 to -0.037) and -0.055 (-0.061 to -0.051) respectively (all $p < 0.001$).

Brouwer³¹ examined trans fat interventions and found that, when industrial trans was replaced by cis-MUFA (13 studies), LDL cholesterol was lowered by -0.034 (-0.042 to -0.17) while replacement of ruminant trans (4 studies) by cis-MUFA lowered LDL by -0.052 (-0.097 to -0.006) for 1% of energy exchanges.

Q4a: What is the evidence regarding the association between dairy product intake and CVD outcomes?

The Australian Dietary Guidelines³² suggested dairy was protective against CHD, and the evidence was Level I and good quality. This was based on two meta-analyses by the same author (Elwood^{33,34}); and, should be classed as Level III evidence at best and unsatisfactory. Since then, the evidence based has expanded.

Dairy is a high saturated fat food but calcium and magnesium may be protective. In relation to CHD, milk and total dairy offers no protection when compared with carbohydrate; and, replacing dairy fat with PUFA could reduce CHD by 26% in American cohorts. Low-fat dairy and cheese may be protective but the data is not uniform; although a recent meta-analysis suggested a 14% reduction in CHD with cheese.³⁵ Cheese does not appear to elevate LDL cholesterol.³⁶

Given the relative neutrality of dairy, it can be consumed for its calcium but low-fat dairy without added sugar might be preferred given some positive but inconsistent data. However, in the absence of intervention data, dairy could not be currently recommended for prevention/treatment of CHD. Given some low-fat dairy (namely many yoghurts) often has added sugar — and the positive National Health and Nutrition Examination Survey (NHANES) data on added sugar and CVD mortality — advice on swapping to low-fat dairy that contains added sugar should be reconsidered.³⁷ However, there is no data on the role of added sugar in yoghurts at influencing risk.

Q4b: What is the evidence regarding the association between coconut oil intake and CVD outcomes?

The comprehensive New Zealand Heart Foundation (NZHF) review³⁸ demonstrated that coconut fat elevated LDL cholesterol compared with unsaturated fat but not as much as butter. There is no epidemiology on coconut intake and CHD. No new data has become available since the review. Coconut fat is not recommended but, in normal use, coconut fat is not a major contributor to total fat.

Gaps in the evidence

The evidence base for interventions with hard endpoints of heart attack, heart failure, cardiac death and atrial fibrillation with low saturated fat diets and increased unsaturated fat diets is relatively small and needs expansion with both PUFA and MUFA to strengthen recommendations. These trials should be undertaken with an achievable intake of PUFA and MUFA as the older PUFA trials had very high intakes, which lead to much criticism. They also need to be much larger scale and longer than the existing ones. Intravascular ultrasound trials may be considered as a way of showing effectiveness of the diet without waiting for hard end points. Long term, large dietary fat interventions with a focus on LDL and non-HDL cholesterol need to be performed within the context of the current food supply. Specific dairy interventions with low-fat dairy and cheese are required to prove the observations are not due to confounding by unmeasured lifestyle attributes. More coconut fat interventions need to be performed.

Discussion of key findings

Replacement of saturated fat with PUFA and MUFA and any carbohydrate, is associated with lower mortality.

When replacing saturated fat, it should preferably be replaced by PUFA as it lowers risk of both CHD events and of CVD mortality. It also lowers risk of total mortality when compared with total carbohydrate. PUFA could include linoleic acid (LA), alpha-linolenic acid (ALA) and fish oil.

Replacing saturated fat with MUFA is equally effective in lowering risk of CHD events and also reduces risk of total mortality, but not as effectively as PUFA. However, it does not appear to lower risk of CVD mortality in research in American populations. Wholegrains should be the next choice as these lower risk of CHD events compared with saturated fat.

Increased total fat compared with total carbohydrate lowers total mortality risk. This is driven by increased PUFA and MUFA only as increased saturated fat intake increases total mortality risk. Increased starch and sugar increase risk of CHD events while replacement of saturated fat by wholegrains and fibre lowers risk of CHD events.

Recommendations

The combined evidence from all the studies in relation to fat suggest that people should eat less meat-derived and snack-derived saturated fat and replace this with a mix of wholegrains, unsaturated fat spreads and cooking/dipping oils and nuts.

The meta-analysis from Hooper complements the earlier one from Mozaffarian and shows that reduction of saturated fat in interventions lowers risk of CHD events. The studies from Farvid, Wang, de Goede and Li strengthen the data on linoleic acid (LA) and provide confidence that consumption of more LA leads to lower CHD events, mortality and total mortality. Although Chowdury did not agree with these findings, their data was missing cohorts and it was not updated. In addition, the epidemiology suggests benefit from replacing saturated fat with MUFA. Intervention data from Predimed suggest increasing unsaturated fat from nuts and olive oil decreases CVD events; although; polyphenols and sterols rather than the triglyceride may play a role. ALA can continue to be recommended.

Dairy is probably not protective but it is possible that dairy saturated fat may not be harmful. Dairy saturated fat appears to be neither protective nor harmful compared with total carbohydrate on CHD risk although replacing saturated fat from dairy with unsaturated fat (PUFA including omega-3 and omega-6) is likely to be associated with a reduced risk of heart disease. The evidence is relatively contradictory in that some studies find low-fat dairy, but not high-fat dairy, is protective. At the same it finds that cheese may be protective. Yoghurt is protective but it is not clear if sugar-sweetened yoghurt would provide the same protection, as these types of yoghurts have only recently replaced more traditional yoghurts.

Although coconut fat is not consumed in large amounts, it does elevate LDL cholesterol, has no proven benefits and cannot be recommended.

Whole diet changes rather than just fat changes which lower LDL cholesterol would be optimal for heart disease protection.

There is clear evidence that modulating HDL cholesterol with drugs or through genetic polymorphisms provides no benefit.

Background

Over the last six years the evidence in relation to saturated and polyunsaturated fat (PUFA) and heart disease has been very strongly questioned by a small group of researchers and the media, and left the public very confused. Much of the doubt has arisen because saturated fat did not appear to be worse than total carbohydrate for cardiac events and deaths in cohort studies while further meta-analyses of fat intervention studies suggested there was no benefit to reducing saturated fat and replacing it with PUFA without omega-3 fats. It was also suggested that linoleic acid (LA) may provoke more heart disease because it is pro-inflammatory. The recommendation for low-fat dairy has also been strongly challenged and the substitution of sugar for fat and the re-emergence of sugar as a risk factor has suggested that advice regarding low-fat dairy should be revised. These issues have all been intensely debated.

Methods

Peer review literature

Given the brief of reviewing meta analyses and systematic reviews with hard endpoints for heart attack, heart failure, cardiac death and atrial fibrillation, only the peer reviewed literature (Pubmed, Embase and Cochrane Clinical Trial Register) was searched with the search terms "dietary fat OR dietary saturated fat OR dietary unsaturated fat OR dietary fish oil OR dietary omega 3 fats OR dietary omega 6 fats AND heart disease". Searches were limited to from 2009 to 18 November 2016. This produced 2621 publications. The addition of systematic review to the search terms reduced the number to 528. This was reduced to 79 by the addition of meta-analysis. All meta-analyses that specifically addressed each question were included (n=42) plus individual studies not included in meta-analyses.

Given that much of the evidence in relation to Question 1 came from cohort studies, it can only be regarded as Level III evidence with a Grade of C as it requires extrapolations from cohort studies. For Question 2, although this included Level I evidence it can only be regarded as Grade D due to inconsistencies in the evidence and the meta-analyses mainly influenced by trial selection. For Question 3, level I evidence is available and would be given a Grade of B in that recommendations for long-term diet require extrapolations from short term studies. For Question 4a, the evidence is level III and Grade C. Question 4b has insufficient evidence to grade. Evidence in relation to fish oil and heart disease that was not included in the 2015 report by Nestel et al.³⁹ was examined. A flowchart of the literature selection process is included in Appendix 1. A summary table of the included studies is attached as Appendix 2.

Grey literature

The WHO literature was consulted and quoted as recommended as well as guidelines from the American Heart Association, European Society of Cardiology and the World Heart Federation.

Evidence grading

Unlike pharmaceutical agents for which there is an abundance of randomised controlled interventions with large numbers of subjects and meta-analyses of these interventions, nutrition contains a low number of small trials of variable quality. Thus, most nutritional recommendations are based on cohort studies and thus, based on the NHMRC evidence framework, as being of Level III-2. Comments from the Australian Dietary Guidelines regarding levels of evidence in public health nutrition are relevant here and included as Appendix 3.

Findings

Question 1: What is the evidence regarding the association between dietary fat consumption and the incidence of cardiovascular disease?

Cohort studies

Saturated and trans fat

Siri-Tarino⁵ provided data on the relationship between saturated fat and CHD (fatal and total) from 16 apparently healthy cohorts with the most recent cohort report from 2007. Updated data was provided from 6 cohorts. The Women's Health Initiative observational study (Howard 2006)⁴⁰ was not included. The most fully adjusted model was used, which in 6 cohorts included adjustment for other fats (thus examining a replacement of saturated fat for carbohydrate) while 6 adjusted for total or LDL cholesterol (which would nullify the relationship if cholesterol was the sole mediator of the effect of saturated fat on CHD). Nine studies had estimates of total CHD while 7 had estimates of fatal CHD only. Overall the group with the highest intake of saturated fat had a 7% increase in CHD (95% CI 0.96–1.19) $p=0.22$. There was significant heterogeneity ($I^2=41%$ $p=0.04$) but none of it could be explained by differences between cohorts.

Individually, 6 cohorts showed a positive relationship in subgroups or particular components of CHD and 10 did not, but this was not related to adjustment for PUFAs. A maximum 10% energy difference in saturated fat intake between extreme groups would translate into a difference in LDL cholesterol of 0.3mmol/L between these groups. Given the statin studies of a 20% lowering in CHD events per 1 mmol/L, this should translate into a CHD increase of 7–8% in the highest intake group which was observed but was not significant.

De Souza⁴ examined the intakes of saturated fat and trans fat, and CHD events and CHD mortality in 41 separate reports. Eleven cohorts provided data on saturated fat and mortality, and this showed a most adjusted multivariable risk ratio of 1.15 (95% confidence interval (CI) 0.97 to 1.36; $P=0.10$; $I^2=70%$; $P_{\text{het}}<0.001$). The least adjusted risk ratio was 1.20 (1.02 to 1.41; $P=0.02$; $I^2=74%$; $P_{\text{het}}<0.001$). Thus, compared to carbohydrate, a high intake of saturated fat has no effect on CHD mortality. Twelve cohorts provided data on CHD events and the most adjusted multivariable risk ratio was 1.06 (95% confidence interval 0.95 to 1.17; $P=0.29$; $I^2=47%$; $P_{\text{het}}=0.02$) and the least adjusted relative risk was 1.12 (1.00 to 1.26; $P=0.05$; $I^2=63%$; $P_{\text{het}}<0.001$). Thus, a high intake of saturated fat compared to carbohydrate does not appear to increase CHD events. However, total trans fat intake was associated with all-cause mortality (1.34, 1.16 to 1.56), CHD mortality (1.28, 1.09 to 1.50) and total CHD (1.21, 1.10 to 1.33). This meta-analysis added 3 new studies to Siri-Tarino.⁵ Mozzafarian⁴¹ noted in a meta-analysis of 4 prospective studies a 24%, 20%, 27% and 32% higher risk of MI or CHD death for every 2% energy of trans fatty acid (TFA) consumption isocalorically replacing carbohydrate, saturated fatty acid (SFA), cis-MUFAs and cis-PUFAs, respectively.

In Japan, the results are somewhat different from the West and may be because of the low overall fat intake. In the Japan Collaborative Cohort Study⁴² 58,672 men and women aged 40 to 79 years old were followed with 11,656 deaths over 19 years. In women, hazard ratio (HR) was lowest in the fourth quintile of total fat intake followed by the top quintile; HRs across quintiles were 1.00, 1.03 (0.94–1.11), 1.00 (0.92–1.09), 0.88 (0.81–0.96), and 0.94 (0.86–1.03). Total mortality was inversely associated with intakes of SFA, MUFA and PUFA; the lowest HR was in the top quintile of intake for SFA, MUFA and PUFA: 0.91 (95% CI, 0.83–1.00), 0.91 (0.83–0.99) and 0.88 (0.80–0.97), respectively (trend P across quintiles, 0.020, 0.012, and 0.029, respectively). The lowest risk for total mortality appeared at total fat intake of 28% of energy. Most deaths were from causes other than cardiovascular disease (CVD) and cancer. Because of these findings, meta-analyses including Japanese cohorts need to be treated with caution.

In the Japan Public Health Centre-based Prospective Study⁴³ of 81,931 adults and 610 events, a positive association was found between saturated fat intake and MI with a RR of 1.39 (0.93–2.08) p trend $p=0.046$.

Chowdury et al¹⁸ also found SFAs were unrelated to CHD with a RR of 1.02 (0.97–1.07) from 20 studies (283,963 participants, 10,518 events) but TFA intake was related with a RR of 1.16 (1.06–1.27) from 5 studies (155,270, 4,662 events). Monounsaturated fat intake was also unrelated 0.99 (0.89–1.09) from 9 cohorts (143,985, 6,020 events).

Zong⁴⁴ examined individual fatty acids in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) combined. Comparing the highest to the lowest groups of individual SFA intakes, HRs of CHD were 1.07 (95% CI 0.99 to 1.15; P_{trend}=0.05) for 12:0, 1.13 (1.05 to 1.22; P_{trend}<0.001) for 14:0, 1.18 (1.09 to 1.27; P_{trend}<0.001) for 16:0, 1.18 (1.09 to 1.28; P_{trend}<0.001) for 18:0 and 1.18 (1.09 to 1.28; P_{trend}<0.001) for all four SFAs combined after multivariate adjustment of lifestyle factors and total energy intake. Hazard ratios of CHD for replacing 1% energy from 16:0 were 0.88 (95% CI 0.81 to 0.96; P=0.002) for PUFA, 0.92 (0.83 to 1.02; P=0.10) for MUFA, 0.90 (0.83 to 0.97; P=0.01) for whole grain carbohydrates and 0.89 (0.82 to 0.97; P=0.01) for plant proteins.

The opposite results were found by Praagman⁴⁵ who examined the EPIC-Netherlands cohort (1,807 Ischaemic Heart Disease, or IHD, events) and found SFA intake was associated with a lower IHD risk HR per 5% of energy: 0.83; 95% CI: 0.74, 0.93. Substituting SFAs with animal protein, cis-MUFAs, PUFAs or CHO was associated with higher IHD risks (HR per 5% of energy: 1.27–1.37). Lower IHD risks were observed for higher intakes of SFAs from dairy sources, including butter (HRSD: 0.94; 95% CI: 0.90, 0.99), cheese (HRSD: 0.91; 95% CI: 0.86, 0.97), and milk and milk products (HRSD: 0.92; 95% CI: 0.86, 0.97).

In the Rotterdam Study, Praagman⁴⁶ found no association between total SFA and CHD. However, they did find a higher CHD risk for palmitic acid (16:0) intake (HRSD, 1.26; 95% CI, 1.05–1.15) but not for SFA with other chain lengths. Except for a higher CHD risk for substitution of SFA with animal protein (HR 5en%, 1.24; 95% CI, 1.01–1.51), substitution with other macronutrients was not associated with CHD.

In an Australian study of 1,469 older women the highest quartile of SFA intake (>31.28 g/d) had an ~16% cumulative atherosclerotic vascular mortality risk compared with ~5% in the lowest quartile (<17.39 g/d) (HR: 3.07; 95% CI: 1.54, 6.11; P = 0.001)⁴⁷.

In the Predimed observation report³ a comparison between extreme quintiles of higher SFA and trans-fat intakes were associated with 81% (HR: 1.81; 95% CI: 1.05, 3.13) and 67% (HR: 1.67; 95% CI: 1.09, 2.57) higher risk of CVD, respectively (336 events).

In conclusion, most studies did not find that SFA intake was significantly related to CHD mortality but for events there was a small, 15–20% increase with SFA in place of carbohydrate (particularly, 16:0 in some studies) but overall in the meta-analysis there was no effect. Trans fatty acids in all studies were associated with CHD events and mortality.

Linoleic acid

Farvid et al⁶ examined the association between linoleic acid (LA) and CHD which included all incident CHD outcomes: MI, ischemic heart disease (IHD), coronary artery bypass graft, sudden cardiac arrest, acute coronary syndrome and CHD deaths.

The authors included the following studies in the meta-analysis: six cohorts from the Pooling Project of Cohort Studies on Diet and Coronary Disease⁴⁸ (the Atherosclerosis Risk in Communities Study, or ARIC); Finnish Mobile Clinic Health Study (FMC); Israeli Ischemic Heart Disease Study (IIHD); Iowa Women's Health Study (IWHS); Västerbotten Intervention Program (VIP) and the Women's Health Study (WHS), to assess the association between LA and total CHD and CHD deaths; the Malmo Diet and Cancer Cohort investigators provided data; and, the NHS and the HPFS were updated from 20 years to 30 years (NHS), and from 6 years to 24 years (HPFS). Data in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) was

reanalysed to adjust for confounding variables similar to other included cohort studies in this meta-analysis. Other studies included the Monica study (Denmark), the Morgen study (Netherlands) and the MRFIT (US) study. The multivariate model included total energy, age, smoking, body mass index, physical activity, education level, alcohol intake, hypertension, fibre intake, and percent of energy from SFAs, trans fat, MUFAs, ALA, PUFAs other than LA and ALA, and protein intake. It does not contain the Kuopio data or the Glostrup data which are both small.

The LA intake was categorised mostly in tertiles but was in quintiles in 5 cohorts. Median LA intake varied for 1.1% in the lowest intake group to 7.7% of energy in the highest intake group.

The 13 cohort studies contained a total of 310,602 individuals and 12,479 total CHD events including 5,882 CHD deaths. Ten cohorts reported results for CHD events and 2 studies did not report CHD deaths. Comparing the highest to the lowest category, dietary LA was associated with a 15% lower risk of CHD events (pooled RR, 0.85; 95% CIs (95% CI): 0.78–0.92; $I^2=35.5\%$) and a 21% lower risk of CHD deaths (pooled RR, 0.79; 95% CI, 0.71–0.89; $I^2=0.0\%$). A 5% energy increment in LA intake replacing energy from saturated fat was associated with a 9% lower risk of CHD events (RR, 0.91; 95% CI, 0.86–0.96) and a 13% lower risk of CHD death (RR, 0.87; 95% CI, 0.82–0.94). There were very similar estimates with dietary LA replacing carbohydrate.

Contrary results were obtained from Chowdury et al ¹⁸ in relation to dietary total N6 PUFAs who found no relationship with coronary disease with a RR 0.98 (CI 0.90 to 1.06) in 8 cohort studies containing 206,376 participants with 8,155 events (cohorts were Morgen, MRFIT, Glostrup, Kuopio, Malmo, ATBC, NHS and HPFS). Six studies were missing compared with the Farvid meta-analysis (6 cohorts in the Pooling Project plus Denmark Monica). Seven arithmetical errors were made in the original paper which casts doubt on the whole analysis. All cohort studies were converted into tertiles of intakes regardless of how they were reported and this could introduce errors and have the effect of reducing the relative risk between groups. In the Farvid meta-analysis the NHS and HPFU were updated, as was the ATBC, and the Malmo investigators also provided more data. The data was adjusted for sex, age, BMI, history of diabetes and blood pressure (and lipids in the MRFIT study).

Wang et al ¹ reported on a meta-analysis for the combined NHS and HPFS focused on total mortality with 3,439,954 person-years of observation and 33,304 deaths. High dietary intake of fat with a lower intake of carbohydrate was associated with a 16% reduction in mortality RR of 0.84 (0.81-0.88) when comparing extreme quintiles of fat intake ($p<0.001$ for trend). RR were 1.08 (95% CI, 1.03-1.14) for saturated fat, 0.81 (95% CI, 0.78-0.84) for PUFA, 0.89 (95% CI, 0.84-0.94) for MUFA and 1.13 (95% CI, 1.07-1.18) for *trans*-fat with a $P < .001$ for trend, for all. Within the PUFA group the RR for ω -6 PUFA intake was 0.85 (0.81-0.89) $P < .001$ for trend, LA 0.82 (0.79-0.86), arachidonic acid 0.90 (0.85-0.94) and for total ω -3 PUFA intake 0.95 (0.91-0.99) $P = .03$ for trend. All the RRs were fully adjusted for all covariates. PUFA was significantly different from MUFA.

Thus, replacing 5% of energy from SFAs with equivalent energy from PUFA and MUFA was associated with estimated reductions in total mortality of 27% and 13%, respectively. In relation to CVD mortality, replacing 5% of energy from SFA was associated with a reduction of 28% (0.65-0.80) but MUFA was not associated with a significant reduction 0.96 (0.84-1.09).

Li et al ² examined the same 2 cohorts in the updated analysis (84,628 women (NHS 1980 to 2010), and 42,908 men (HPFS, 1986 to 2010) in relation to CHD risk. During 24 to 30 years of follow-up, 7,667 incident cases of CHD occurred. Higher intakes of PUFAs were significantly associated with a lower risk of CHD comparing the highest with lowest quintile for PUFAs 0.80, (0.73 to 0.88; p trend <0.0001). Carbohydrates from refined starches/added sugars were positively associated with a risk of CHD RR=1.10 (1.00 to 1.21) p trend = 0.04). Replacing 5% of energy intake from saturated fats with equivalent energy intake from PUFAs, MUFAs, or carbohydrates from whole grains was associated with a 25%, 15%, and 9% lower risk of CHD,

respectively: PUFAs, HR: 0.75, (0.67 to 0.84); $p < 0.0001$; MUFAs, HR: 0.85, (0.74 to 0.97); $p = 0.02$; carbohydrates from whole grains, HR: 0.91, (0.85 to 0.98; $p = 0.01$). PUFA was not significantly different from MUFA but it was different from wholegrains.

Thus, the studies from Farvid, Wang and Li strengthen the data on LA and provide confidence that consumption of LA leads to lower CHD events, mortality and total mortality. Although Chowdury did not agree with these findings, their data was missing cohorts and the data was not updated.

Omega 3 fatty acids

In relation to omega-3 fatty acids, Chowdury¹⁸ examined 16 studies containing 169,935 participants and 8,313 events, and showed a RR of 0.93 (0.84-1.02) for long chain omega-3 intake. However, blood levels of omega-3 fats were associated with protection (see below).

Wang et al showed that dietary ALA was not associated with total mortality 0.99 (0.95-1.03) p trend 0.8 while marine omega-3 fats were associated with a 4% reduction in total mortality in the highest quintile (95% CI 0.93-1.0) p trend = 0.002. Replacement of 0.3% of energy from carbohydrate with marine PUFA was associated with a 7% reduction in total mortality¹ (0.89-0.98) but there was no reduction in cardiovascular mortality when substituted for saturated fat. The ratio of omega-6 to omega-3 was not a predictor of mortality — it varied from 5.5 to 10.2.

ALA

ALA data is not as clear but Pan found a 10% lower risk of CHD for every 1g of dietary ALA.⁹ The association was significant in 13 comparisons that used dietary ALA as the exposure (pooled RR: 0.90; 95% CI: 0.81, 0.99; $I^2 = 49.0\%$), with similar but nonsignificant trends in 17 comparisons in which ALA biomarkers were used as the exposure (pooled RR: 0.80; 95% CI: 0.63, 1.03; $I^2 = 79.8\%$).

Thus, increasing dietary ALA is associated with a small reduction in CHD risk.

Fatty acid levels in blood as markers of linoleic and omega-3 fatty acid intake

Circulating fatty acids are a more objective measure of dietary intake and, for most fatty acids reflect, dietary intake in a linear fashion.

Imamura⁴⁹ prospectively investigated the associations of plasma phospholipid long-chain monounsaturated fatty acids (LCMUFAs) (20:1, 22:1, and 24:1) with incidence congestive heart failure in 2 independent cohorts: 3,694 older adults (mean age, 75.2 ± 5.2 years) in the Cardiovascular Health Study (CHS; 1992-2006) and 3,577 middle-aged adults (mean age, 54.1 ± 5.8 years) in the ARIC study Minnesota sub cohort (ARIC; 1987-2008). They also examined dietary correlates of circulating LCMUFAs in the CHS and ARIC studies, and US dietary sources of LCMUFAs in the 2003-2010 National Health and Nutrition Examination Survey (NHANES). In the CHS, 997 congestive heart failure events occurred during 39,238 person-years; in ARIC, 330 congestive heart failure events occurred during 64,438 person-years. After multivariable adjustment, higher levels of 22:1 and 24:1 were positively associated with greater incident congestive heart failure in both CHS and ARIC; HRs were 1.34 (95% CI, 1.02-1.76) and 1.57 (95% CI, 1.11-2.23) for highest versus lowest quintiles of 22:1, respectively, and 1.75 (95% CI, 1.23-2.50) and 1.92 (95% CI, 1.22-3.03) for 24:1, respectively (P for trend ≤ 0.03 each). A variety of foods were related to circulating LCMUFAs in CHS and ARIC, consistent with food sources of LCMUFAs in NHANES, including fish, poultry, meats, whole grains and mustard. Given this diversity of food it is difficult to base any dietary recommendations on this data.

De Goede 2013⁷ used two Dutch cohorts, two nested case-control studies from the USA and two cohort studies from Finland and Sweden on cholesteryl ester PUFA to examine the relationship of LA to fatal and non-fatal CHD. In the meta-analysis, a 5% higher LA level was associated with a 9% lower risk of fatal CHD (HR 0.91; 95% CI: 0.84–0.98). The other fatty acids were not associated with CHD. In the Dutch cohorts alone, no significant relationships were found.

Chowdhury¹⁸ examined 10 cohort studies (23,065 subjects, 3,866 events) and found no relationship between serum LA in a mix of plasma (3), phospholipid (9), CE (4) and NEFA (3) fatty acids and CHD with a RR of 0.99 (0.77–1.28). Arachidonic acid appeared to be associated with protection with a RR of 0.83 (0.74–0.92) in 10 cohorts. 13 cohorts provided data on EPA and DHA (23,065 participants, 4,624 events) with a RR of 0.78 (0.67–0.94) and 0.79 (0.67–0.93). DPA was also protective with a RR of 0.64 (0.47–0.89).

Del Gobbo¹⁰ reported on a global consortium of 19 studies with 45,637 unique individuals and 7,973 total CHD, 2,781 fatal CHD and 7,157 non-fatal MI events. ALA, DPA and DHA were associated with a lower risk of fatal CHD, with RRs per 1 SD of 0.91 (95% CI, 0.84–0.98) for ALA, 0.90 (95% CI, 0.85–0.96) for DPA, and 0.90 (95% CI, 0.84–0.96) for DHA. Although DPA was associated with a lower risk of total CHD (RR, 0.94; 95% CI, 0.90–0.99), ALA (RR, 1.00; 95% CI, 0.95–1.05), EPA (RR, 0.94; 95% CI, 0.87–1.02), and DHA (RR, 0.95; 95% CI, 0.91–1.00) were not. Although DPA is found in grass-fed beef it is also an elongation product of ALA via EPA so, ALA, DPA and EPA are markers of ALA intake, especially in low fish consumers.

Wu et al⁸ reported on the Cardiovascular Health Study (CHS) of 2,792 participants (aged ≥65 years) free of cardiovascular disease at baseline. During 34,291 person-years of follow-up (1992–2010), 1,994 deaths occurred (678 cardiovascular deaths) with 427 fatal and 418 non-fatal CHD, and 154 fatal and 399 non-fatal strokes. In multivariable models, higher LA in plasma phospholipids was associated with lower total mortality with extreme-quintile HR =0.87 (P trend=0.005). Lower death was largely attributable to cardiovascular disease causes, especially nonarrhythmic CHD mortality (HR, 0.51; 95% CI, 0.32–0.82; P trend=0.001). Circulating γ -linolenic acid, dihomo- γ -linolenic acid, and arachidonic acid were not significantly associated with total or cause-specific mortality. Evaluating both n-6 and n-3 PUFA together the lowest risk was evident with highest levels of both.

Thus, from this data linoleic acid was found to be protective for fatal CHD in 2 of 3 studies that examined it while ALA was protective in the latest and largest combined data set of blood fatty acids matching the dietary intake data.

Monounsaturated fat

Monounsaturated fat (MUFA) is difficult to study as it is frequently found in food with saturated fat, in both meat and dairy. Only in olive oil consuming countries can it be clearly separated from other foods so combining studies from different regions may cause problems with interpretation. Nevertheless, in the studies by Wang¹ and Li², MUFA was protective compared with total carbohydrate after adjustment for saturated fat and PUFA and replacing saturated fat with MUFA was associated with lower mortality.

Interventions

The Predimed study should be briefly mentioned here as it increased MUFA from virgin olive oil by 2–3% of energy and increased nut-derived polyunsaturated fat.^{26, 50} Total CVD events were reduced, although the reduction in CHD was not significant as the number of events was low. Al Khudairy⁵¹ examined 4 LA interventions of 6 months or greater duration and noted no effects on events or cardiovascular risk factors. There were no LA studies with hard endpoints.

Evidence grading

Most of the evidence was level III cohort studies and overall is Grade C for all the epidemiological associations of fat intake and CHD events, and mortality. This means there is a reasonable body of evidence that can be relied on to make public policy recommendations but differences in the meta-analyses mean it is not completely convincing.

Grey Literature

In 2016, the World Heart Federation (WHF) released a fact sheet on cardiovascular risk factors in which it⁵² states: *"it is important to note that, if your total fat intake is greater than 37% of your total calories, then, even*

if that fat is unsaturated, you increase your risk of cardiovascular disease. Saturated fat intake should not exceed 10% of total energy and, for high-risk groups, like people with diabetes, total fat intake should be 7% or less of total energy”.

There is no convincing evidence available to support this statement and it is not clear where it has come from as the federation provides no reference. Recommendations to lower total fat often lead to lower PUFA along with lower saturated fat as in the Women’s Health Initiative, with no benefit on CHD events.

No statement on total fat is made by the American Heart Association⁵³ which in general supports the conclusions of this review. This recommendation from the WHF is certainly not supported by the Predimed study³ in which the 3 upper quintiles of total fat exceeded 37% and in which the highest quintile was associated with a 42% reduction in CVD (95% CI 0.39, 0.86 P<0.01). This was true for both MUFA (50% reduction) and PUFA (32% reduction). It was also true for total mortality.

Key findings

Saturated and trans fat is associated with a higher total mortality and replacement of saturated fat with any carbohydrate, PUFA and MUFA and fish oil (marine omega-3, specifically EPA and DHA) is associated with lower mortality with PUFA being more effective than MUFA. In relation to CVD mortality, only PUFA lowers risk of CVD mortality.

In relation to events, replacing saturated fat with PUFA or MUFA is equally effective at reducing risk of CHD. Replacement with whole grains will lower risk of events but not as effectively as PUFA while replacement with sugar/starch increases risk of events.

Thus, only PUFA lowers the risk of both events and CVD mortality. PUFA could include LA, ALA and fish oil, although ALA was not related to total mortality in American studies but was related to CHD and fatal CHD.

Question 2: What is the evidence regarding the association between dietary fat consumption and cardiovascular disease outcomes in patients with existing cardiovascular disease?

Cohort studies

Most studies in this area have examined dietary patterns with less focus on just dietary fat per se.

Li⁵⁴ analysed 2,258 women from the NHS and 1,840 men from the HPFS who had survived a first MI during follow-up, and provided a pre-MI and at least 1 post-MI food frequency questionnaire. Adherence to a low carbohydrate diet high in animal sources of protein and fat was associated with higher all-cause and cardiovascular mortality — RR of 1.33 [1.06 to 1.65] for all-cause mortality and 1.51 [1.09 to 2.07] for cardiovascular mortality comparing extreme quintiles. An increase in adherence to a plant-based low carbohydrate diet (which should increase PUFA) was not associated with lower all-cause or cardiovascular mortality. Li⁵⁵ examined the alternate healthy eating index 2010 (AHEI2010) (which includes low trans <0.5% and higher PUFA (>10%) among other changes) in the same cohort (1,133 deaths) following an initial MI and found the adjusted HR was 0.76 (95% CI, 0.60-0.96) for all-cause mortality and 0.73 (95% CI, 0.51-1.04) for cardiovascular mortality when comparing the extreme quintiles of post-MI AHEI2010. A greater increase in this score comparing pre- and post- scores lead to better survival, all-cause mortality (pooled HR, 0.71; 95% CI, 0.56-0.91) and cardiovascular mortality (pooled HR, 0.60; 95% CI, 0.41- 0.86).

Interventions

Hooper et al¹⁹ performed a systematic review of 13 interventions that reduced saturated fat (planned and achieved) with or without replacement with unsaturated fat — in both men and women — where follow up occurred for at least 2 years. On this basis, the Minnesota experiment was excluded as mean intervention exposure was 12 months with no follow up beyond discharge from hospital. The Finnish Mental Hospital Study was also excluded as it had <6 cluster randomised sites. Predimed was excluded as it had no goal to reduce saturated fat in either arm. Multiple interventions were excluded (e.g. Oslo-anti smoking and fish oil). This was an update of the Cochrane study performed in 2000, 2011 and 2012, and this is the most updated intervention meta-analysis available (aside from the Ramsden study⁵⁶ which was much more selective). Six of the comparisons included only people at high risk of cardiovascular disease (i.e. they already had heart disease), four at moderate risk (diabetes) and five at low risk (three with raised cancer risk or cancer diagnosis, two with no specific health risks). Trial duration ranged from two to more than eight years, with a mean duration of 4.7 years. Interventions were of advice to alter intake in 16 of the 17 intervention arms and oil or other foods were provided in four. All food was provided in a residential facility in the Veterans Study^{57, 58}. 11 RCTs (12 comparisons) provided data on all-cause mortality (including over 55,000 participants and 3,276 deaths), 10 RCTs (12 comparisons) on CV mortality (> 53,000 participants and 1,097 cardiovascular deaths), and 11 RCTs (13 comparisons) on combined cardiovascular CVD events (> 53,000 participants and 4,377 events).

There was a 17% reduction in cardiovascular events in people who had reduced SFA compared with those on usual diet (RR=0.83, 95% CI 0.72 to 0.96, I² 65%, 11 RCTs, 53,300 participants, 4,377 people with cardiovascular events, P_{effect} 0.01. If saturated fat was replaced by PUFA, there was a 27% reduction in cardiovascular events while there were no clear effects of other replacement groups (MUFA, CHO or protein). Subgroups of participants with greater baseline SFA intake, and with greater reductions in SFA in the intervention group compared to control, showed greater effects and studies which achieved a reduction in serum total cholesterol of at least 0.2 mmol/L reduced cardiovascular events by 26%, whereas studies that did not achieve this cholesterol reduction showed no clear effect. When subgrouping by sex, effects in women (RR=1.00; 95% CI 0.88 to 1.14) were less than effects in men (RR=0.80; 95% CI 0.69 to 0.93, subgroup test P = 0.05), although this was confounded as the studies in women replaced SFA primarily by CHO which had no effect overall. There was a 17% reduction in fatal and non-fatal MI (95% CI 0.67-1.02) but no clear effect on non-fatal MI or on CHD mortality. CHD events were reduced by 24% (0.57-1.00) with

those achieving a TC lowering of >0.2 mmol/L. Overall, total cholesterol was reduced by 0.24mmol/L. This event reduction is surprisingly large given that statin induced lowering of LDL cholesterol by 1 mmol/L reduces coronary events (fatal and non-fatal) by about 20%.²⁰ It suggests many other dietary components were changed and the effect was not just related to a reduction in saturated fat and a lowering of LDL cholesterol but may relate to increases in fibre, whole grain carbohydrate and phytosterols and polyphenols from unsaturated fats. There was no difference between primary and secondary prevention.

One primary prevention study not included above was the Minnesota Coronary Experiment (MCE) because of short follow-up, which has recently been re-reported with recovered data.⁵⁶ The MCE⁵⁷ in six state mental hospitals and 1 nursing home between 1968 and 1973, randomised 9,423 men and women aged 20–97 (a small fraction of whom had Q waves on their ECG). Only 2,355 were exposed to the diet for more than 1 year because of changes in discharge policies. Saturated fat was replaced by corn oil and corn oil margarines (no omega-3 fat and probably no trans fats), and total cholesterol fell by 13.8% vs a fall of 1% in the control group. Coronary events were recorded in 131 participants in the intervention group and 121 in the control group. There were 61 CHD deaths in the intervention group and 54 in the control group with a total of 269 and 248 deaths in the whole population. Thus, the study is grossly underpowered to see any positive or negative effects of the intervention. It is instructive to compare this study to the IMPROVE-IT⁵⁹ study which required 18,144 patients with acute coronary disease to be randomised for 7 years to achieve a significant 2% absolute lowering of events with an LDL lowering of 0.4 mmol/L (a 22% lowering from 1.8 mmol/l). In this study, there were 440 deaths from CHD in the intervention group and 461 in the control group with a total of 1,215 and 1,231 deaths, respectively. No diet study will ever mimic the IMPROVE-IT study nor would compliance ever be maintained for 7 years, even to lower LDL by 0.4 mmol/L (which is a large dietary effect). Interestingly, in both control and intervention groups in the Minnesota study there was a strong correlation between reduction in cholesterol and subsequent death that remains unexplained.

Interventions were also examined by Chowdhury et al.¹⁸ There were 4 interventions with ALA (199 events/9,444 in the intervention group and 220/9,422 in the control group) with a RR of 0.97 (0.69-1.36). About one quarter of the participants had pre-existing CHD. There was a difference between fatal and non-fatal events ($p=0.045$) with a RR of 0.20 for the latter (0.05-0.81); 14 vs 44 events in a total of 423 people. This was due primarily to the Lyon Diet Heart Study⁶⁰ which made many other changes and would not usually be viewed as just an ALA intervention. This result differed from those seen with long chain omega-3 fats.

The omega-6 interventions included the Finnish Mental Hospital Study^{61,62} (primary prevention 73 events), the Minnesota Heart Survey⁶³ (mostly primary prevention 252 events), Sydney Diet Heart Study⁶⁴ (58 events), LA Veterans Study (124 events)⁶⁵, the Oslo study⁶⁶ (88 events), Medical Research Council soy study⁶⁷ (99), and DART⁶⁸ (276) plus STARS⁶⁹ (7). The RR was 0.86 (0.69–1.07) with an I^2 of 63% $p=0.012$. Excluding the Sydney study because of high levels of trans in the margarines, improved the RR to 0.81 (0.68-0.98). The total event number is low so confidence in this result is also low.

Ramsden⁵⁶ performed a meta-analysis for coronary deaths that included only the Minnesota study, the Sydney Study, the Rose Corn Oil Study, the LA vets study and the MRC soy study (LA and ALA) to produce an RR of 1.13 (0.83-1.54). Including 3 studies which they regarded as either confounded by EPA/DHA (Oslo Diet Heart Study and St Thomas Atherosclerosis Study (STARS)), or which were just diet advice (Diet and Re-infarction Trial (DART)) made the RR 1.0 (0.81-1.24). The Finnish Mental Hospital study was regarded as too flawed by drug use differences to include.

Mozaffarian performed a meta-analysis of the same data set in 2010⁷⁰ without the Sydney study but including the Finnish Mental Hospital, STARS and DART and arrived at a RR of 0.81 (0.70-0.95); a result very similar to Chowdhury. They estimated a 10% reduced CHD risk (RR=0.90, 95% CI=0.83-0.97) for each 5% increase of PUFA energy. They also computed the effects of a 5% change in energy from SFA being replaced

by PUFA from a pooled analysis of 11 cohort studies⁴⁸ and predicted a RR of 0.87 (0.77-0.97). Based on TC/HDL changes, they predicted a RR of 0.91 (0.87-0.95).

Schwingshagl and Hoffman⁷¹ performed a meta-analysis of 12 interventions containing 7,150 participants with existing disease and found no effect of dietary fat interventions. No significant associations were noted between CHD events, deaths or total mortality, and the changes from SFA, MUFA, PUFA and LA. Sensitivity analyses did not reveal a significant risk reduction for any outcome parameter when polyunsaturated fat was increased in exchange for saturated fat

Harcombe⁷² performed a meta-analysis of dietary fat interventions with 62,421 participants in 10 dietary trials: 7 secondary prevention studies, 1 primary prevention and 2 combined. The death rates for all-cause mortality were 6.45% and 6.06% in the intervention and control groups, respectively. The RR from meta-analysis was 0.991 (95% CI 0.935 to 1.051). The death rates for CHD mortality were 2.16% and 1.80% in the intervention and control groups, respectively. The RR was 0.976 (95% CI 0.878 to 1.084). Mean serum cholesterol levels decreased in all intervention groups and all but one control group. The reductions in mean serum cholesterol levels were $-11.4\% \pm 6.5\%$ for the intervention groups and $-4.7\% \pm 4.8\%$ for the control groups. Given this cholesterol difference, it is not surprising no effects on mortality were seen. Combining statin trials with 42,000 participants with total cholesterol-lowering of over 30%, no effect was seen on total or CVD mortality (Mills 2011).⁷³ It required a combined 174,000 patients from the combined Cholesterol Treatment Trialists to see a significant lowering of CVD and total mortality of 9–10%.⁷⁴

In conclusion, the limited evidence base for the LA interventions and the highly-varied nature of the trials does not allow any firm conclusions but the Hooper analysis provides weak evidence that replacing SFA with PUFA will lower CHD events.

Interventions with Omega 3 fats

Wen¹⁵ performed a meta-analysis of 14 RCTs involving 16,338 individuals in the omega-3 PUFAs group and 16,318 in the control group. Major cardiovascular events (OR, 0.93; 95% CI, 0.86 to 1.01; $P = 0.08$; $I(2) = 46\%$) were not different. Omega-3 supplementation reduced risks of death from cardiac causes, sudden cardiac death and death from all causes (OR, 0.88; 95% CI, 0.80 to 0.96; $P = 0.003$; $I(2) = 0\%$; OR, 0.86; 95% CI, 0.76 to 0.98; $P = 0.03$; $I(2) = 29\%$; and OR, 0.92; 95% CI, 0.85 to 0.99; $P = 0.02$; $I(2) = 6\%$; respectively).

Casula et al²⁴ analysed 11 randomised, double-blind, placebo controlled trials involving 15,348 patients with a history of CVD. No statistically significant association was observed for all-cause mortality (RR, 0.89; 95% CI, 0.78 to 1.02) and stroke (RR, 1.31; 95% CI, 0.90 to 1.90). Conversely, statistically significant protective effects were observed for cardiac death (RR, 0.68; 95% CI, 0.56 to 0.83), sudden death (RR, 0.67; 95% CI, 0.52 to 0.87) and MI (RR, 0.75; 95% CI, 0.63 to 0.88).

Enns et al⁷⁵ performed a meta-analysis of five trials enrolling 396 individuals with peripheral vascular disease. All included trials were of unclear or high risk of bias. There was no evidence of a protective association of omega-3 PUFA supplementation against major adverse cardiac events (pooled RR=0.73, 95% CI 0.22 to 2.41, I^2 75%, 2 trials, 288 individuals) or other serious clinical outcomes. Adverse events and compliance were poorly reported.

Of the 3 predominantly primary prevention RCTs, only one demonstrated a minor reduction in major coronary events; however, it was also an open-label study (JELIS study)²⁵. It is claimed that favourable effects of N3 fats are seen in Japan because of the high dose used (1800mg) and the high background intake of the Japanese ($>1\text{g/day}$), according to Sekikawa.⁷⁶ There have been no new ALA trials since 2010.

Post-operative atrial fibrillation

Guo et al¹⁴ performed a meta-analysis of eleven randomised controlled trials with 3,137 patients. The use of omega-3 fatty acids alone did not reduce the incidence of post-operative atrial fibrillation (AF) compared with the control (OR, 0.76; 95% CI [CI]: 0.57-1.03; $P=0.08$; $I(2) = 52\%$). However, combination therapy with

PUFA and vitamins C and E reduced the incidence of post-operative atrial fibrillation by 68% (OR, 0.32; 95%CI: 0.17-0.60; P=0.0005; I (2) =38%). Subgroup analysis indicated that the ratio of EPA/DHA 1:2 was effective in preventing post-operative atrial fibrillation (OR, 0.35; 95%CI: 0.24-0.50; P<0.00001; I (2) =0%) while other ratios were not effective.

Zhang et al.¹³ examined 8 trials with 2 687 patients. Omega-3 fats were ineffective in patients undergoing cardiac surgery compared to placebo [RR=0.86; 95% CI 0.71-1.04, p=0.110].

Mariani et al.¹⁶ included 12.9% (16 of 124) of trials on omega-3 fatty acids providing data on 4,677 patients. They were comprised of 8 studies (1,990 patients) that evaluated N3 PUFA effects on AF recurrence among patients with reverted AF and 8 trials (2,687 patients) on postoperative AF. Pooled RRs through random-effects models showed no significant effects on AF recurrence (RR, 0.95; 95% CI, 0.79 to 1.13; I (2), 72%) or on postoperative AF (0.86; 95% CI, 0.71 to 1.04; I (2), 53.1%). A funnel plot suggested publication bias among postoperative trials but not among persistent AF trials.

Costanza et al.¹⁷ performed a meta-analysis of 8 trials with 2,687 patients (1,337 in the intervention group) who underwent cardiac surgery. Using a random-effects model, the reduction averaged 25% (OR, 0.75; 95% CI, 0.57-1.00; P = .05). When isolated coronary artery bypass graft surgery was only considered (7 studies), a significant protection averaging 34% was observed in a fixed model (OR, 0.66; 95% CI, 0.50-0.87; P = .003; I (2) = 26%, P = .23).

Evidence Grading

The evidence for Question 2 is graded at level I evidence but it can only be regarded as Grade D due to striking inconsistencies in the evidence and the meta-analyses.

Recommendations

Replacing saturated fat with linoleic acid in patients with CHD can continue to be recommended based on the Hooper Cochrane meta-analysis despite other contrary analysis and the low quality of the evidence. There appear to be no differences between primary and secondary prevention in the effects of dietary fat change on CHD events and mortality, and the epidemiology and the interventions are consistent with each other. Based on evidence from interventions studies, marine omega-3 fats appear to reduce cardiac and sudden death in patients with CHD. However, given negative trials over the last 5 years the benefit in current patients treated with modern drugs and procedures is less clear. There is no identified benefit in atrial fibrillation.

Question 3: What is the evidence regarding the effectiveness of manipulation of dietary fat intake as management strategy for hypercholesterolemia?

It is very clear that altering fat amount and type lowers LDL cholesterol in the short-term but what is not clear is how sustained this is as compliance falls over 12 months or longer, and this is a big gap in the literature. Smart et al ⁷⁷ found no studies of low-fat diets of 6 months or longer in the literature.

Mensink ³⁰ performed a meta regression of short term (at least 13 days) dietary fat interventions to examine the mean changes in lipids and lipoproteins replacing 1% of energy from saturated fat with carbohydrate, MUFA or PUFA. For LDL cholesterol data was derived from 69 studies and showed a change in LDL cholesterol of -0.033mmol/L (95%CI -0.039to -0.027), -0.042 (-0.047 to -0.037) and -0.055 (-0.061 to -0.051), respectively (all p<0.001). Brouwer ³¹ examined trans fat interventions and found that when industrial trans was replaced by cis-MUFA (13 studies) LDL cholesterol was lowered by -0.034 (-0.042 to -0.17) while replacement of ruminant trans (4 studies) by cis-MUFA lowered LDL by -0.052 (-0.097 to -0.006) for 1% of energy exchanges. She also found that replacing trans fats with saturated fat elevated LDL cholesterol by 0.10 (0.002 to 0.18) for industrial trans and by -0.007 (-0.051 to +0.037) for ruminant trans.

There is no good data showing the long-term effects of a diet in which only lipids are altered (particularly lower saturated fat and higher PUFA or from MUFA to lower TC or LDL). Most diets tested over the last 10 years have been portfolio diets with vegetarian protein, sterols and fibre as well as decreased saturated fat and increased unsaturated fat. The simplest interventions have been nut interventions which can lower LDL cholesterol by 8.3% as in the Predimed study at 1 year. ²⁶ However, nuts add fibre and phytosterols. In this study phytosterol intake, rather than fat or fibre changes, were weakly related to LDL changes. Phytosterols lower LDL by 0.34 mmol/L in a pooled analysis by Demonty ²⁷ with a mean dose of 2.15g. A low-fat diet meta-analysis of 8 studies in women showed an LDL cholesterol-lowering of 0.24 mmol/L with greater effects in premenopausal women ²⁸. Long-term (>12m) effects of a low-fat diet in obese people show only a fall of 0.08 mmol/L in LDL. ²⁹ Plant sterols esterified with rapeseed oil lower LDL more effectively than those esterified with other unsaturated fats. ⁷⁸

Much of the new data related to meta-analyses of the cholesterol-lowering effect of high oleic oils and the cholesterol-elevating effects of palm oils and trans fats. In addition, nuts have been comprehensively evaluated in several meta-analyses. Martin ⁷⁹ did a systematic review of short term nut interventions and found little consistent responses in CVD risk factors. Del Gobbo ⁸⁰ found a dose-related lowering of LDL cholesterol in 61 trials of a variety of nuts.

Rees et al ⁸¹ conducted a systematic review of dietary advice in 52 intervention arms from 44 trials covering a wide variety of interventions and found that, with dietary advice, total dietary fat as a percentage of total energy intake fell by 4.48% (95% CI 2.47 to 6.48) and saturated fat intake fell by 2.39% (95% CI 1.4 to 3.37). Dietary advice reduced total serum cholesterol by 0.15 mmol/L (95% CI 0.06 to 0.23) and LDL cholesterol by 0.16 mmol/L (95% CI 0.08 to 0.24) after 3 to 24 months. Mean HDL cholesterol levels and triglyceride levels were unchanged.

Malhotra ⁸² performed a meta-analysis of LDL lowering dietary interventions in people with Familial Hypercholesterolemia (adults and children). The 15 trials involving 453 individuals found no overall effect of diet, although trials of plant sterols in this group showed a lowering of LDL cholesterol by 0.30 mmol/L (0.12-0.48).

Palm oil was examined by Fattore et al ⁸³ who found 51 studies ranging from substitutions of 4-43% palm oil. A meta-analysis showed that palm oil elevated LDL cholesterol by 10.8mg/dl (8 data points) compared to stearic acid, by 10.78 compared to MUFA (20 data points), by 7.3 compared to PUFA (NS 14 data points) and, to lower LDL cholesterol, was the same as lauric/myristic acid (11 data points) and trans interventions (11 data points). Thus, lauric-acid rich fat diets (such as coconut) are equivalent to palm oil and trans-rich diets in terms of LDL cholesterol elevation.

Sun⁸⁴ performed another meta-analysis of palm oil studies. Of those, 27 studies compared palm oil with vegetable oils low in saturated fat, 9 studies compared palm oil with partially hydrogenated oils and 2 studies compared palm oil with animal fat. Palm oil significantly increased LDL cholesterol by 0.24 mmol/L (95% CI: 0.13, 0.35 mmol/L; I (2) = 83.2%) compared with vegetable oils low in saturated fat. This effect was observed in randomised trials (0.31 mmol/L; 95% CI: 0.20, 0.42 mmol/L) but not in non-randomised trials (0.03 mmol/L; 95% CI: -0.15, 0.20 mmol/L; P-difference = 0.02). Among randomised trials, only modest heterogeneity in study results remained after considering the test oil dose and the comparison oil type (I (2) = 27.5%). Palm oil was not different to trans-containing fats or animal fats.

High oleic oils have been used to replace saturated fat or trans fats in 29 interventions⁸⁵. LDL cholesterol was lowered by 10.9% when saturated fat was replaced (significant in 20 of 23 comparisons), and 9.2% when trans fatty acid was replaced (6 of 6 interventions). There was no significant change in comparison with PUFA (not significant in 7 of 11 comparisons). HDL increased significantly by 5.8% in 4 of 6 comparisons with trans fats.

A further 12 trials examined the effect of cheese on LDL cholesterol and 5 were included in a meta-analysis of butter vs cheese with the same P/S ratio. Compared with butter intake, cheese intake (weighted mean difference: 145.0 g/d) reduced low-density lipoprotein cholesterol (LDL-C) by 6.5% (-0.22 mmol/l; 95%CI: -0.29 to -0.14) and high-density lipoprotein cholesterol (HDL-C) by 3.9% (-0.05 mmol/l; 95%CI: -0.09 to -0.02) but had no effect on triglycerides. Compared with intake of tofu or fat-modified cheese, cheese intake increased total cholesterol or LDL-C, as was expected on the basis of the P/S ratio of the diets.⁸⁶ A recent trial of high or low-fat cheese compared with carbohydrate on LDL cholesterol and found no effects of either cheese.³⁶

Schwingshagl⁸⁷ performed a meta-analysis on high-MUFA diets (with and without weight loss). A total of 12 studies met the inclusion criteria. Significant differences between high and low-MUFA protocols could be observed with respect to fat mass [-1.94 kg (CI -3.72, -0.17), p = 0.03], systolic blood pressure [-2.26 mm Hg (CI -4.28, -0.25), p = 0.03] and diastolic blood pressure [-1.15 mm Hg (CI -1.96, -0.34), p = 0.005] favouring the dietary protocols with >12% MUFA.

Trans fats

Mozaffarian analysed trans fatty acid interventions.⁴¹ In controlled trials, each 1% energy replacement of TFAs with SFAs, MUFAs or PUFAs, respectively, decreased the total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio by 0.31, 0.54 and 0.67; the apolipoprotein (Apo)-B/ApoA1 ratio by 0.007, 0.010 and 0.011; and lipoprotein (Lp)(a) by 3.76, 1.39 and 1.11 mg/l (P<0.05 for each).

Gayet-Boyet⁸⁸ performed a meta regression of 13 dairy trans interventions with 23 separate data points varying from 0.1 to 4.19% of energy as ruminant trans. Neither the slope nor intercept was different from zero for TC/HDL or LDL/HDL but data on LDL alone was not provided. One cheese study was included (cheese behaves differently from other dairy products) and 2 conjugated linoleic acid (CLA) studies (but not all CLA studies). Butter was the source of trans in several studies and butter saturated fat is excellent at elevating HDL cholesterol which confounds looking at the effects of LDL cholesterol when only the ratio is reported. The conclusion that ruminant trans behave differently from industrial trans is not justified by this study and further research is required.

HDL cholesterol

Given the data on the lack of association between genetic variants altering HDL cholesterol and heart disease⁸⁹⁻⁹¹, and the lack of data on the effects of dietary and drug elevation of HDL and CVD outcomes⁹²⁻⁹⁴, the evidence does not support altering HDL to change CHD risk. In addition, subjects who are heterozygous carriers of the P376L variant in the scavenger receptor B1 have significantly increased levels of plasma HDL-C. P376L carriers have a profound HDL-related phenotype and an increased risk of CHD (OR=1.79, which is statistically significant).⁹⁵

Triglyceride

A systematic review of TG lowering interventions with fish oil in 38 clinical intervention studies assessing 2,270 individuals showed a 9–26% reduction in circulating TG in studies where ≥ 4 g/day of n-3 PUFA were consumed from either marine or EPA/DHA-enriched food sources while a 4–51% reduction was found in studies where 1–5 g/day of EPA and/or DHA was consumed through supplements.⁹⁶

Evidence Grading

For Question 3 level I evidence is available and would be given a Grade of B for dietary fat changes to lower LDL cholesterol as recommendations for diet require extrapolations from short term studies.

Grey Literature

Interestingly, in their dyslipidaemia recommendations, the European Society of Cardiology⁹⁷ did not recommend an increase in unsaturated fat in place of saturated fat for lowering LDL cholesterol. It gave lowering saturated fat to lower LDL cholesterol an A grading but it was silent on with what saturated fat should be replaced. However, to lower triglyceride-rich lipoproteins, it recommended replacing saturated fat with unsaturated fat (B grade) which has a very modest effect only. Replacing carbohydrate with unsaturated fat is far more effective and this was not explicitly stated. There was also a strong focus on increasing HDL cholesterol which is not supported by the current evidence. There is data to show that increasing HDL cholesterol with drugs has no effect on CVD risk nor does genetically elevated HDL cholesterol so, there is no reason to suspect dietary fat elevation of HDL cholesterol would be beneficial.⁹¹⁻⁹⁴

Recommendations

Altering fat amount and type lowers LDL cholesterol in the short term but no good data are available showing the long-term effects of a diet that only altered lipids (particularly lower saturated fat and higher PUFA or MUFA to lower TC or LDL). Instead, available long-term evidence demonstrates dietary patterns such as the portfolio or Mediterranean diet lower LDL cholesterol.

Question 4a: What is the evidence regarding the association between dairy product intake and CVD outcomes?

The Australian Dietary Guidelines³² evidence base included two meta-analyses by Elwood^{33, 34} and relied on the 2008 one for its evidence. This paper separated out 4 case control studies of patients admitted with MI and, overall, showed significant protection for MI from milk. This is at best Level III evidence (at worse Level V) despite being a meta-analysis. It is not Level I evidence at all as there are no intervention studies. It included 11 cohort (level III) studies which were a mix of IHD events and deaths but this information was not provided consistently or correctly and they were all analysed together. The dietary variable was a mix of dairy calcium, milk, and high and low-fat dairy. They omitted the whole milk result from Hu et al⁹⁸ (RR=1.67) as it added heterogeneity and made the overall result not significant. As stated in the guide, 4 studies were positive, 10 found no association and 1 a negative association but they stated the consistency of the evidence was satisfactory, the evidence base was good and its overall grade as good (B). The evidence base in 2009 was unsatisfactory (D) based on a mix of a small number of Level III and Level IV studies.

Since then, the evidence based has expanded. Dairy is a high-saturated-fat food but calcium and magnesium may be protective.

Neutral relationship with CHD

Soedamah-Muthu et al⁹⁹ found that milk intake was not associated with risk of CHD (6 studies; RR: 1.00; 95% CI: 0.96, 1.04), nor was there an association of total dairy products (high or low-fat) and CHD.

Bendsen et al¹⁰⁰ found no association between ruminant trans fat intake and CHD risk and nor did de Souza.⁴ Also, de Souza found no association with the dairy specific fatty acid 15:0 and 17:0 plasma levels.

Alexander ¹⁰¹ in a meta-analysis of seven studies of total dairy intake and total CHD found a RR of 0.91 (95 % CI 0.80, 1.04) with significant heterogeneity (PH = 0.038, I²=52.8). Bernstein (NHS) ¹⁰² and Haring (ARIC) ¹⁰³ were included in this study but were not in the Qin ¹⁰⁴ meta-analysis below. Sub-group analysis of the three US studies showed no association between total dairy intake and risk of total CHD (0.99; 95 % CI 0.92, 1.07). Four studies evaluated total dairy intake and CHD risk among women, resulting in a RR of 0.86 (95 % CI 0.71, 1.05). Neither yoghurt nor total calcium from dairy was associated with CHD. Milk was not associated with CHD risk nor was high-fat dairy.

Qin ¹⁰⁴ found no association between dairy consumption and CHD risk (12 studies; RR=0.94, 95% CI: 0.82, 1.07). Studies included here but not in the Alexander ¹⁰¹ meta-analysis include Dalmeijer ¹⁰⁵ (Netherlands Epic), Goldbohm ¹⁰⁶ (Netherlands) Elwood ³⁴ (Wales) Ness ¹⁰⁷ (UK), Mann ¹⁰⁸ (UK). A total of 253,260 participants with 8,792 cases were included in the CHD meta-analysis. Although Bernstein ¹⁰⁹ was listed it was not included in the plot but as the RR was very close to 1 it would have made no difference. For CHD risk, a significantly decreased risk was observed with cheese consumption (RR=0.84, 95% CI: 0.71, 1.00) but not with low-fat dairy consumption (RR=1.02, 95% CI: 0.92, 1.14). High-fat dairy consumption resulted in a borderline increase in the CHD risk (RR=1.08, 95% CI: 0.99, 1.17).

The Rotterdam study ¹¹⁰, which was not in any meta-analysis, found no association between total dairy or dairy subgroups and incident or fatal CHD.

The NHS and the HPFS were updated in 2016 and included 8,974 CHD events (fatal and nonfatal). The RR for total dairy was 1.03 per 5% increase in energy from dairy fat (95% CI 0.98-1.05) compared with carbohydrate. They also calculated that replacement of 5% of energy from dairy fat with polyunsaturated fat would reduce the risk of CHD by 26% (0.68-0.81) while replacement of 0.3% energy from dairy fat with fish oil or linolenic acid would reduce CHD by 13-17% (Chen 2016)¹¹¹.

O'Sullivan ¹¹² examined CHD mortality and found no association with dairy.

Possible protective relationship

As noted by Qin ¹⁰⁴, a significantly decreased risk of CHD was observed with cheese consumption (RR=0.84, 95% CI: 0.71, 1.00).

Alexander ¹⁰¹, in a meta-analysis of seven studies, noted that four studies examined low-fat dairy intake and found a protective relationship with a RR of 0.90 (95 % CI 0.82, 0.98) while cheese appeared to be protective with a RR of 0.82 (95 % CI 0.72, 0.93) with minimal heterogeneity (PH = 0.639, I²=0.0) in 5 cohorts.

Chen ¹¹¹ examined 15 prospective studies. Most of the studies excluded prevalent CVD at baseline (14/15) and had a duration >10 years (13/15). The summary HR for high vs low cheese consumption was 0.86 (95 % CI 0.77-0.96) for CHD (8 studies, 7,631 events). This positive result clearly needs testing in intervention studies with hard endpoints.

Chowdhury ¹⁸ found no association between the dairy fatty acid 15:0 and CHD but 17:0 was inversely associated with risk (0.77, 0.67, 1.32).

The EPIC Netherlands ⁴⁵ cohort (35,597 participants) with 1,807 IHD events found total SFA intake was associated with a lower IHD risk (HR per 5% of energy: 0.83; 95% CI: 0.74, 0.93). Substituting SFAs with animal protein, cis-MUFAs, PUFAs or carbohydrates was significantly associated with *higher* IHD risks (HR per 5% of energy: 1.27-1.37), which is quite contrary to the American data. SFA from dairy sources were protective, including butter (HRSD: 0.94; 95% CI: 0.90, 0.99), cheese (HRSD: 0.91; 95% CI: 0.86, 0.97), and milk and milk products (HRSD: 0.92; 95% CI: 0.86, 0.97). ⁴⁵

Conclusions

Drouin-Chartier ¹¹³ performed a systematic review of these meta-analyses and concluded that there was good evidence that dairy was neutral in relation to coronary artery disease.

Thus, overall, dairy fat is neither protective nor harmful compared with total carbohydrate on CHD risk. It is, therefore, probably not substantially different from other saturated fat sources. Thus, benefit is seen (in American studies but not Dutch studies) with replacement of dairy saturated fat with polyunsaturated fat—linoleic acid, ALA or fish oil. Cheese may be protective but this has not been seen in American studies and needs to be further examined in these cohorts. Given low-fat dairy (particularly yoghurt) often has added sugar and the positive NHANES data on added sugar and CVD mortality,³⁷ advice on swapping to low-fat dairy which contains added sugar should be reconsidered. However, there is no data on the role of added sugar in yoghurts at influencing risk.

Recommendations

Dairy saturated fat appears to be neither protective nor harmful compared with total carbohydrate on CHD risk although replacing saturated fat from dairy with unsaturated fat (PUFA including omega-3 and omega-6) is likely to be associated with a reduced risk of heart disease. In relation to dairy food categories, the research suggests yoghurts may have a protective role in terms of heart disease risk while cheese does not appear to raise LDL cholesterol.

Further research is required to develop more consistent data on the role of particular dairy food categories. Given the relative neutrality of dairy, it can be consumed for its calcium but low-fat dairy (without added sugar) might be preferred. However, more data is required as the evidence is all association from epidemiology and no studies with hard end points have been performed. Interventions with CHD risk markers are limited and do not provide supportive evidence.

Question 4b: What is the evidence regarding the association between coconut oil intake and CVD outcomes?

The comprehensive NZHF review³⁸ demonstrated that coconut fat elevated LDL cholesterol; not as much as butter, but certainly significantly compared with unsaturated fat. There is no epidemiology on coconut intake and CHD. No new data has become available since this report.

Evidence Grading

For Question 4a, the evidence is level III and Grade C. Question 4b has insufficient evidence to grade although the NZHF review is excellent.

Recommendations

Due to its effect on LDL cholesterol, caution with extensive use of coconut oil should be recommended.

Gaps in the evidence

The evidence base for interventions with hard endpoints with low saturated fat diet and increased unsaturated fat diet is relatively small and needs expansion with both PUFA and MUFA to strengthen recommendations. These trials should be performed with an achievable intake of PUFA and MUFA as the older PUFA trials had very high intakes which led to much criticism. They also need to be much larger scale and longer than the existing ones. Intravascular ultrasound trials may be considered as a way of showing effectiveness of the diet without waiting for hard end points.

The evidence base needs up to date dietary interventions that are modest in scale (and thus sustainable long term) in patients with coronary disease as well as in primary prevention, which applies the most robust evidence on dietary risk factors (i.e. an increase in unsaturated fat and reduction in saturated fat). The Predimed study showed it is possible to do a relatively simple intervention in a large, high-risk population, maintain this for 4–5 years and achieve differences in hard endpoints, as well as risk factors. Dairy foods also need to be tested in long-term, endpoint driven studies. Ruminant trans need to be further examined.

Long-term, large dietary fat interventions with a focus on LDL and non-HDL cholesterol need to be performed within the context of the current food supply. Specific dairy interventions with low-fat dairy and cheese are required to rule out the possibility that the observations are due to confounding by unmeasured lifestyle attributes. More coconut fat interventions need to be performed.

Discussion of findings

The combined evidence from all the studies in relation to fat suggest that people should eat less meat-derived and snack-derived saturated fat and replace this with a mix of wholegrains, unsaturated fat spreads and cooking/dipping oils and nuts. Dairy is relatively neutral compared to total carbohydrate for CHD so, they can be used as a good source of calcium. The current data on cheese is not convincing enough to recommend it to prevent CHD. Low-fat dairy with added sugar is an area that needs further examination as high sugar intake has recently emerged again as a risk factor for CHD.

One key outcome is that low quality carbohydrate is a risk for mortality compared with unsaturated fat; although saturated fat is associated with greater total mortality compared with total carbohydrate but equivalent in terms of CHD events. This is not unexpected given the expected reduction in events with the change in LDL cholesterol, if saturated fat acts only through LDL cholesterol. However, the large benefit seen with the substitution of saturated fat by PUFA and MUFA suggests that benefit is not just due to LDL cholesterol changes. While PUFA and MUFA have positive effects on other biochemical systems, saturated fat has negative effects which may be matched by starch/sugar.

Recommendations

Saturated and trans fat is associated with a higher total mortality and replacement of saturated fat with any carbohydrate, PUFA and MUFA and fish oil (marine omega-3, specifically EPA and DHA) is associated with lower mortality with PUFA being more effective than MUFA. In relation to CVD mortality, only PUFA lowers the risk of CVD mortality. In relation to events, replacing saturated fat with PUFA or MUFA is equally effective at reducing the risk of CHD events. Replacement with whole grains will lower the risk of events but not as effectively as PUFA while replacement with sugar/starch increases the risk of events. Thus, only PUFA lowers both events and CVD mortality. PUFA could include linoleic acid, ALA and fish oil, although ALA was not related to total mortality in American studies but was related to CHD and fatal CHD events.

The evidence supports recommending replacing saturated fat with linoleic acid in patients with CHD based on the Hooper Cochrane meta-analysis which, along with other recent studies, provides confidence that increasing linoleic acid consumption leads to lower risk of CHD events, mortality and total mortality. There appear to be no differences between primary and secondary prevention in terms of reduction in the risk of CHD events and mortality when replacing saturated fats with PUFA. Based on evidence from intervention studies, marine omega-3 fats appear to reduce cardiac and sudden death in patients with CHD. However, given negative trials over the last five years, the benefit in current patients treated with modern drugs and procedures is less clear. There is no benefit in atrial fibrillation.

Altering fat amount and type lowers LDL cholesterol in the short-term but no good data showing the long-term effects of a diet in which lipids are altered in isolation (particularly lower saturated fat and higher PUFA or MUFA to lower TC or LDL) are available. Instead, available long-term evidence demonstrates dietary patterns such as those followed in the portfolio or Mediterranean diet lower LDL cholesterol.

Dairy saturated fat appears to be neither protective nor harmful compared with total carbohydrate on CHD risk, although replacing saturated fat from dairy with unsaturated fat (PUFA including omega-3 and omega-6) is likely to be associated with a reduced risk of heart disease. In relation to dairy food categories, the research suggests yoghurts may have a protective role in terms of heart disease risk while cheese does not appear to raise LDL cholesterol. Further research is required to develop more consistent data on the role of particular dairy food categories. Given the relative neutrality of dairy it can be consumed for its calcium but low-fat dairy (without added sugar) might be preferred. Caution should be recommended with extensive use of coconut oil.

Dietary quality is associated with better outcomes following heart attack. The evidence supports recommending a global higher quality diet which includes fat changes, different protein sources and more whole grains and fibre. The combined evidence from all the studies in relation to fat suggest that people should eat less meat-derived and snack-derived saturated fat and replace this with a mix of wholegrains, unsaturated fat spreads and cooking/dipping oils and nuts.

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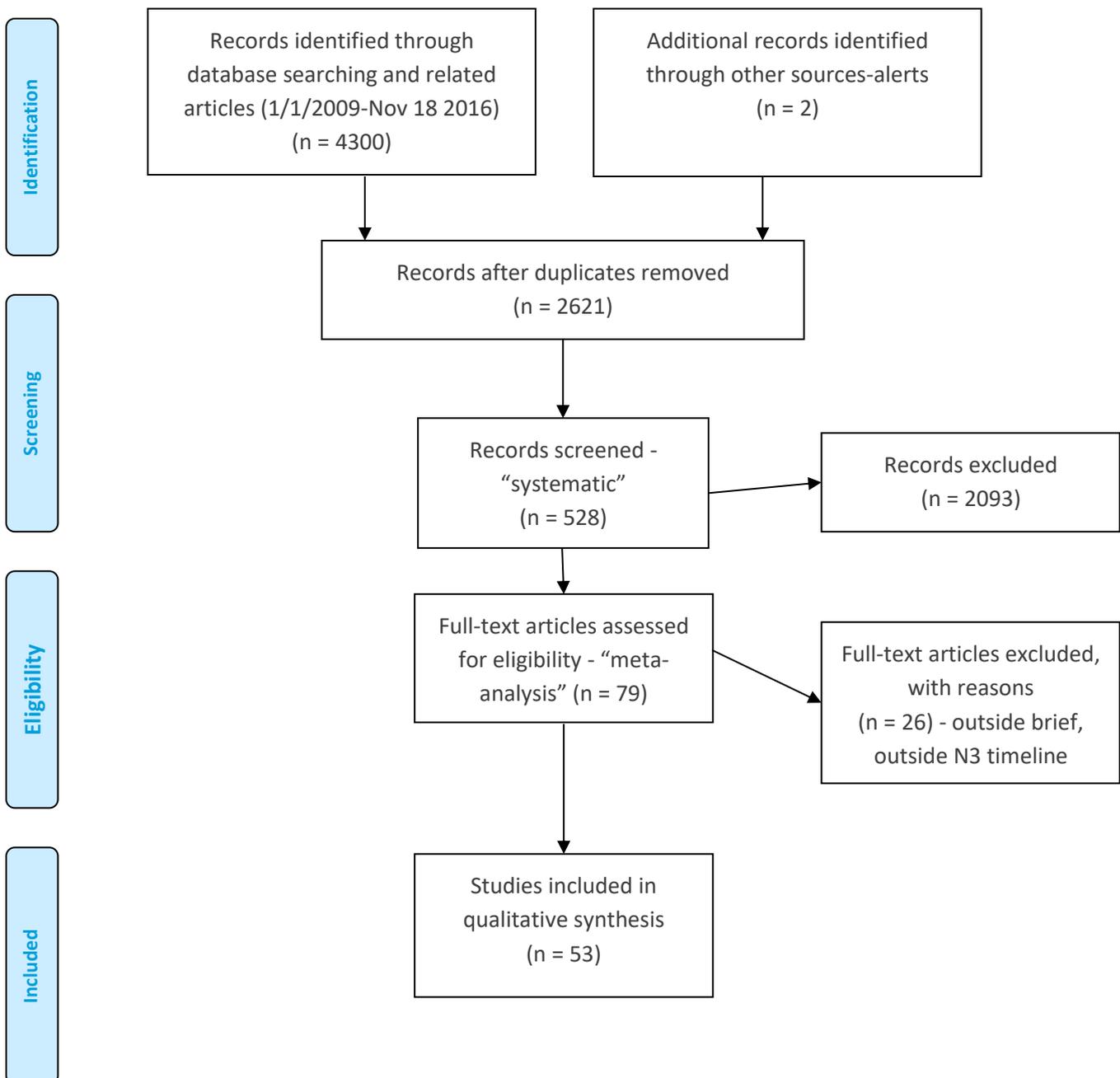
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Appendices

Appendix 1 - PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Appendix 2 - Evidence table

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
|-----------------------------------|---|---------------------------------|------------------------|---|--|---|---|---|
| Question 1 Types of fat | | | | | | | | |
| Praagman et al 2016 ⁴⁶ | Cohort Study The Rotterdam Study | III-2 | Population without CVD | 4722 men and women (>/=55 years) were included follow-up of 16.3 years 659 CHD events | Association between SFA and CHD, food source, carbon chain length of SFA, and the substituting macronutrient | Total SFA intake was not associated with CHD risk HR per 5 en%, 1.13; 95% CI, 0.94-1.22), and neither was SFA from specific food sources. A higher CHD risk was observed for palmitic acid (16:0) intake (HRSD, 1.26; 95% CI, 1.05-1.15) but not for SFA with other chain lengths. Except for a higher CHD risk for substitution of SFA with animal protein (HR 5en%, 1.24; 95% CI, 1.01-1.51), substitution with other macronutrients was not associated with CHD. | Authors conclude Higher intake of palmitic acid, which accounts for approximately 50% of the total SFA intake, was associated with a higher CHD risk, as was substitution of total SFA with animal protein. Nevertheless, we found no association between total SFA intake and CHD risk, which did not differ by food source. | 18:0 is another major saturated fat which is neutral in terms of lipids so may not be related to CHD. |
| de Souza et al 2015 ⁴ | Systematic review and meta-analysis of prospective cohort studies | III-2 | Population without CVD | For saturated fat, 3 to 12 studies for each association were pooled (5 to 17 comparisons with 90,501- | Saturated fat and/or total trans fat | Saturated fat and all-cause mortality RR=0.99, 95% C 0.91 - 1.09 CVD mortality 0.97, 0.84 to 1.12, Total CHD 1.06, 0.95 to 1.17 Ischemic stroke 1.02, 0.90 to 1.15 Type 2 diabetes 0.95, 0.88 to 1.03 Total trans-fat intake and all-cause mortality 1.34, 1.16 to 1.56, CHD mortality 1.28, 1.09 to 1.50, | Overall saturated fat intake was not associated with mortality Total trans-fat intake was associated with all-cause mortality, CHD and total CHD but not ischemic stroke or type 2 diabetes. | Similar outcome to Siri-Tarino. |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
|-----------------------------------|---|---------------------------------|------------------------|--|--------------------------|---|--|---|
| | | | | 339,090 participants). For trans fats, 1 to 6 prospective cohort studies for each association were pooled (2 to 7 comparisons with 12,942-230,135 participants). | | Total CHD 1.21, 1.10 to 1.33 Ischemic stroke 1.07, 0.88 to 1.28 Type 2 diabetes 1.10, 0.95 to 1.27. Industrial (not ruminant) trans fats were associated with CHD mortality (1.18 (1.04 to 1.33) v 1.01 (0.71 to 1.43)) and CHD (1.42 (1.05 to 1.92) v 0.93 (0.73 to 1.18)). Ruminant trans-palmitoleic acid was inversely associated with type 2 diabetes (0.58, 0.46 to 0.74). | Industrial, but not ruminant, trans fats were associated with CHD mortality | |
| Bendsen et al 2011 ¹⁰⁰ | Systematic review and meta-analysis of cohort studies | III-2 | Population without CVD | 6 published and 2 unpublished prospective cohort studies | TFA and the risk of CHD | RR estimates for comparison of extreme quintiles of total-TFA intake (corresponding to intake increments ranging from 2.8 to approximately 10 g/day) were 1.22 (95% CI: 1.08-1.38; P=0.002) for CHD events and 1.24 (1.07-1.43; P=0.003) for fatal CHD. Ruminant-TFA intake (increments ranging from 0.5 to 1.9 g/day) was not significantly associated with risk of CHD (RR=0.92 (0.76-1.11); P=0.36), and neither was industrial-TFA intake, although | Authors conclude Analysis suggests that industrial-TFA may be positively related to CHD, whereas ruminant-TFA is not, but the limited number of available studies prohibits any firm conclusions concerning whether the source of TFA is important. The null association of ruminant-TFA with CHD risk | No statistical difference between ruminant and industrial trans |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
|-------------------------------------|---|---------------------------------|---|--|---|---|--|----------------|
| | | | | | | there was a trend towards a positive association (RR=1.21 (0.97-1.50); P=0.09). | may be due to lower intake levels. | |
| Siri-Tarino et al 2010 ⁵ | Meta-analysis of prospective cohort studies | III-2 | Population without CVD | 21 studies 5-23 y of follow-up 347,747 subjects | Saturated fat | 11,006 people developed CHD or stroke. The pooled relative risk estimates that compared extreme quantiles of saturated fat intake were 1.07 (95% CI: 0.96, 1.19; P = 0.22) for CHD, 0.81 (95% CI: 0.62, 1.05; P = 0.11) for stroke, and 1.00 (95% CI: 0.89, 1.11; P = 0.95) for CVD. | No association between saturated and an increased risk of CHD, stroke, or CVD. | |
| Li et al 2015 ² | Combination of 2 Cohort studies | III-2 | Population without CVD NHS, 1980 to 2010, and HPFS, 1986 to 2010 | 84,628 women 42,908 men 24 to 30 years of follow-up 7,667 incident cases of CHD | SFA compared with unsaturated fats and different sources of carbohydrates | Higher intakes of PUFAs and CHO from whole grains were associated with a lower risk of CHD (highest vs lowest quintile) HR: 0.80, 95% CI:0.73 to 0.88; p trend <0.0001 for PUFAs and HR: 0.90, 95% CI: 0.83 to 0.98; p trend = 0.003 for carbohydrates from whole grains. CHO from refined starches/added sugars were positively associated with a risk of CHD (HR: 1.10, 95% CI: 1.00 to 1.21; p trend = 0.04). Replacing 5% of energy from SFA with PUFAs, MUFAs, or CHO from whole grains was associated with a 25%, 15%, and 9% lower risk of CHD, respectively (PUFAs, HR: | PUFAs and CHO from whole grains associated with lower risk of CHD Replacing saturated fat with MUFA, PUFA or whole grains is beneficial | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | 0.75, 95% CI: 0.67 to 0.84; p < 0.0001; MUFA, HR: 0.85, 95% CI: 0.74 to 0.97; p = 0.02; CHO from whole grains, HR: 0.91, 95% CI: 0.85 to 0.98; p= 0.01). | | |
| Zong et al 2016 ⁴⁴ | 2 prospective longitudinal cohort studies combined | | Population without CVD | 73,147 women NHS ¹ (1984-2012) and 42 635 men HPFS ² (1986-2010), Self-reported incidence of coronary heart disease (n=7035) | Saturated fatty acids and the risk of CHD | Comparing the highest to the lowest groups of individual SFA intakes, HRs of CHD were 1.07 (95% CI 0.99 to 1.15; Ptrend=0.05) for 12:0, 1.13 (1.05 to 1.22; Ptrend<0.001) for 14:0, 1.18 (1.09 to 1.27; Ptrend<0.001) for 16:0, 1.18 (1.09 to 1.28; Ptrend<0.001) for 18:0, and 1.18 (1.09 to 1.28; Ptrend<0.001) for all four SFAs combined (12:0-18:0), after multivariate adjustment of lifestyle factors and total energy intake. HRs of CHD for isocaloric replacement of 1% energy from 12:0-18:0 were 0.92 (95% CI 0.89 to 0.96; P<0.001) for PUFA, 0.95 (0.90 to 1.01; P=0.08) for MUFA, 0.94 (0.91 to 0.97; P<0.001) for whole grain carbohydrates, and | Author's conclusion Higher dietary intakes of major SFAs are associated with an increased risk of CHD including 18:0 which however is a good marker of meat fat | Note in these 2 studies the association of total SFA is twice as strong as in the Siri-Tarino and de Souza meta-analyses. |

¹ NHS: Nurses' Health Study² HPFS: Health Professionals Follow-up Study

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | 0.93 (0.89 to 0.97; P=0.001) for plant proteins. For individual SFAs, the lowest risk of CHD was observed when the most abundant SFA, 16:0, was replaced. Hazard ratios of coronary heart disease for replacing 1% energy from 16:0 were 0.88 (95% CI 0.81 to 0.96; P=0.002) for PUFA, 0.92 (0.83 to 1.02; P=0.10) for MUFA, 0.90 (0.83 to 0.97; P=0.01) for whole grain carbohydrates, and 0.89 (0.82 to 0.97; P=0.01) for plant proteins. | | |
| Wakai et al 2014 ⁴² | Prospective cohort study | III-2 | Population without CVD | 58,672 men and women aged 40 - 79 years median follow-up 19.3 years 11,656 deaths | Total fat Fat intakes estimated using a FFQ | HRs across quintiles of total fat intake for total mortality were 1.00, 1.03 (95% CI, 0.95-1.12), 1.02 (0.94-1.10), 0.98 (0.90-1.07), and 1.07 (0.98-1.17). In women, total mortality was inversely associated with intakes of total fat. HR was lowest in the second highest quintile of intake (0.88; 95% CI, 0.81–0.96) | Overall no association between total fat and total mortality. Inverse association in women | Outlier -an effect of very high CHO intake and low total fat intake |
| Wang et al 2016 ¹ | 2 large ongoing cohort studies | III-2 | Population without CVD | 83,349 women NHS (Jul 1, 1980 - Jun 30, 2012) and 42,884 men HPFS | Total fat | HRs comparing extreme quintiles of total fat compared with total CHO for total mortality, 0.84; 95% CI, 0.81-0.88; P < .001 for trend | Weak positive association between SFA and trans fat and mortality Total fat compared with total CHO was inversely | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | During 3,439,954 person-years of follow-up (32 years) 33,304 deaths documented. | | HRs of total mortality comparing extreme quintiles of specific dietary fats 1.08 (95% CI, 1.03-1.14) for SFA 0.81 (95% CI, 0.78-0.84) for PUFA, 0.89 (95% CI, 0.84-0.94) for MUFA 1.13 (95% CI, 1.07-1.18) for trans-fat (P < .001 for all). Replacing 5% of energy from SFA with 5% PUFA and MUFA for total mortality (HR, 0.73; 95% CI, 0.70-0.77) and 13% (HR, 0.87; 95% CI, 0.82-0.93), respectively. HR for total mortality comparing extreme quintiles of omega-6 PUFA intake was 0.85 (95% CI, 0.81-0.89; P < .001 for trend). Marine omega-3 PUFA was associated with 4% lower total mortality (HR comparing extreme quintiles, 0.96; 95% CI, 0.93-1.00; P = .002 for trend). | associated with total mortality. Inverse association between MUFA and PUFA (including omega-3 PUFA) and mortality. | |
| Pan et al 2012 ⁹ | Meta-analysis of prospective and retrospective studies. | III-2 | Population without CVD | 27 original studies 251,049 individuals 15,327 CVD events | ALA | Overall pooled RR was 0.86 (95% CI: 0.77, 0.97; I (2) = 71.3%). [significant in 13 comparisons that used dietary ALA as the exposure (pooled RR: 0.90; 95% CI: 0.81, 0.99; I (2) = 49.0%), 17 | Results favour an inverse relationship between ALA intake and CVD risk reduction | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | comparisons in which ALA biomarkers were used as the exposure were not significant (pooled RR: 0.80; 95% CI: 0.63, 1.03; I (2) = 79.8%).] | | |
| Del Gobbo et al 2016 ¹⁰ | Prospective (cohort, nested case-control) or retrospective studies with circulating or tissue omega-3 biomarkers and ascertained CHD | III-2 | Population without CVD | 19 studies 45,637 unique individuals 7,973 total CHD, 2,781 fatal CHD, 7,157 non-fatal MI events | Omega-3 PUFA | Omega-3 biomarkers ALA, DPA, and DHA were associated with a lower risk of fatal CHD, Relative risks (RRs) of 0.91 (95% CI, 0.84-0.98) for ALA, 0.90 (95% CI, 0.85-0.96) for DPA, and 0.90 (95% CI, 0.84-0.96) for DHA. DPA was associated with a lower risk of total CHD (RR, 0.94; 95% CI, 0.90-0.99), but ALA (RR, 1.00; 95% CI, 0.95-1.05), EPA (RR, 0.94; 95% CI, 0.87-1.02), and DHA (RR, 0.95; 95% CI, 0.91-1.00) were not. | Results favour an inverse relationship between ALA, DPA, and DHA and fatal CHD and DPA and a lower risk of total CHD | |
| de Goede et al 2013 ⁷ | Nested case-control study and dose-response meta-analysis of prospective studies on cholesteryl ester PUFA | III-2 | Population without CVD | Data from 2 population-based cohort studies in Dutch adults followed for 8-19 years. Meta-analysis of plasma fatty acid from pooled Dutch data | PUFA | After adjustment for confounders, the OR (95%CI) for fatal CHD per SD increase in plasma linoleic acid was 0.89 (0.74-1.06). Additional adjustment for plasma total cholesterol and systolic blood pressure attenuated this association (OR, 0.95; 95%CI: 0.78-1.15). Arachidonic acid was not associated with fatal CHD (OR per SD:1.11; 95%CI: 0.92-1.35). The ORs (95%CI) for fatal CHD for an | | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | with results of two nested case-control studies from the USA and 2 cohort studies from Finland and Sweden. 279 incident cases of fatal CHD and randomly selected 279 controls | | SD increase in n-3 PUFA were 0.92 (0.74-1.15) for alpha-linolenic acid and 1.06 (0.88-1.27) for EPA-DHA. In the meta-analysis, a 5% higher linoleic acid level was associated with a 9% lower risk (relative risk: 0.91; 95% CI: 0.84-0.98) of CHD. The other fatty acids were not associated with CHD. | | |
| Wu et al 2014 ⁸ | Cohort study | III-2 | Population without CVD | 2,792 participants (aged ≥65 years) free of CVD at baseline 34,291 person-years of follow-up (1992-2010), 1994 deaths occurred (678 CV deaths), with 427 fatal | PUFA plasma phospholipid n-6 PUFA and N3 PUFA were measured at baseline | Higher LA was associated with lower total mortality, with extreme-quintile HR =0.87 (P trend=0.005). Lower death was largely attributable to CVD causes, especially nonarrhythmic CHD mortality (HR, 0.51; 95% CI, 0.32-0.82; P trend=0.001). Circulating gamma-linolenic acid, dihomo-gamma-linolenic acid, and arachidonic acid were not significantly associated with total or cause-specific mortality (e.g., for arachidonic acid and CHD | | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | and 418 non-fatal CHD, and 154 fatal and 399 non-fatal strokes. | | death, the extreme-quintile HR was 0.97; 95% CI, 0.70-1.34; P trend=0.87). Evaluated semiparametrically, LA showed graded inverse associations with total mortality (P=0.005). Evaluating both n-6 and n-3 PUFA, lowest risk was evident with highest levels of both. | | |
| Chowdhury at al 2014 ¹⁸ | Prospective, observational studies and RCTs | III-2 and I | Population without CVD | 32 observational studies of dietary intake, 530,525 participants; 17 observational studies of fatty acid biomarkers 25,721 participants 27 RCTs of fatty acid supplements with 103,052 participants. | ALA, MUFA and PUFA | In prospective cohort studies with 157,258 participants and 7,431 events, relative risks for coronary disease were for SFA RR=1.03 (95% CI, 0.98 to 1.07) based on 20 studies, 276,763 participants and 10,155 events. For total MUFA RR=1.00 (CI, 0.91 to 1.10) based on 9 studies, 144 219 participants and 6031 events. For ALA RR=0.99 (CI, 0.86 to 1.14) in prospective cohort studies with 157 258 participants and 7,431 events. RR for total long-chain omega-3 fatty acids was 0.87 (CI, 0.78 to 0.97) based on 16 studies, 422 786 participants and 9,089 events. RR for total omega-6 fatty acids was 0.98 (CI, 0.90 to 1.06) based | No evidence to support reducing saturated fat or increasing ALA, MUFA or N6 PUFA in observational studies and increasing N6 PUFA in RCTs. Trans fat and long chain omega 3 studies were positive. | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | on 8 studies, 206,376 participants and 8,155 events. RR for the effect of omega-6 fatty acids RCTs was 0.86 (CI, 0.69 to 1.07) based on 8 studies, 459 events/7,245 participants in intervention group and 515 events/ 7,231 participants control group. | | |
| Wen et al 2014 ¹⁵ | Meta-analysis of randomised controlled trials. | I | Population without CVD | 14 studies with 16,338 individuals in the Omega-3 PUFAs group and 16,318 in the control group | Omega-3 PUFA | No effect of omega-3 PUFAs on major CV events OR, 0.93; 95% CI, 0.86 to 1.01; P=0.08; I (2) =46%. Reduced risks of death from cardiac causes, sudden cardiac death and death from all causes OR, 0.88; 95% CI, 0.80 to 0.96; P=0.003; I (2) =0%; OR, 0.86; 95% CI, 0.76 to 0.98; P=0.03; I (2) =29%; and OR, 0.92; 95% CI, 0.85 to 0.99; P=0.02; I (2)=6%; respectively | Evidence of benefit of omega 3 PUFA in interventions- reduced risks of death from cardiac causes, sudden cardiac death and death from all causes | |
| de Oliveira et al 2013 ¹¹⁴ | Cohort study | III-2 | Population without CVD | 2,837 US adults (Cardiovascular Health Study) | Dietary PUFAs estimated using a FFQ | Circulating n-3 EPA and DHA were inversely associated with incident CVD, with extreme-quartile HRs (95% CIs) of 0.49 for EPA (0.30 to 0.79; P trend=0.01) and 0.39 for DHA (0.22 to 0.67; P trend<0.001). | Associations with CVD of self-reported dietary PUFA were consistent with those of the PUFA biomarkers. All associations were similar across racial-ethnic groups, | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | Incident CVD events (incl. CHD and stroke; n=189) were prospectively identified through 2010 during 19,778 person-years of follow-up. | | n-3 DPA was inversely associated with CVD in whites and Chinese, but not in other race/ethnicities (P-interaction=0.01). No significant associations with CVD were observed for circulating n-3 ALA or n-6 PUFA (LA, arachidonic acid). | except those of docosapentaenoic acid. | |
| Guasch-Ferré et al 2016 ³ | Observational cohort derived from RCT population. | III-2 | Participants at high CVD risk | 7038 participants at high CVD risk from the PREDIMED study 6 years of follow-up, 336 CVD cases and 414 total deaths. | Total fat intake and fat subtypes and risk of CVD (MI, stroke, or death from CV causes) and CV and all-cause death. | HRs (95% CIs) for CVD for those in the highest quintile of total fat, monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA) intake compared with those in the lowest quintile were 0.58 (0.39, 0.86), 0.50 (0.31, 0.81), and 0.68 (0.48, 0.96), respectively. In the comparison between extreme quintiles, higher saturated fatty acid (SFA) and trans-fat intakes were associated with 81% (HR: 1.81; 95% CI: 1.05, 3.13) and 67% (HR: 1.67; 95% CI: 1.09, 2.57) higher risk of CVD. Inverse associations with all-cause death were also observed for PUFA and MUFA intakes. Isocaloric replacements of SFAs | Authors conclude: Intakes of MUFAs and PUFAs were associated with a lower risk of CVD and death, whereas SFA and trans-fat intakes were associated with a higher risk of CVD. The replacement of SFAs with MUFAs and PUFAs or of trans fat with MUFAs was inversely associated with CVD. | |

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| | | | | | | with MUFAs and PUFAs or trans-fat with MUFAs were associated with a lower risk of CVD. SFAs from pastries and processed foods were associated with a higher risk of CVD. | | |
| Al-Khudairy et al 2015 ⁵¹ | Cochrane review of RCTs lasting min. 6 months | I | Healthy adults or adults at high risk of CVD | 4 RCTs (5 papers) that randomised 660 participants | Increasing omega 6 in place of SFA or MUFA or CHO Decreasing omega 6 intake in place of CHO or protein (or both) Compared with no advice, no supplements placebo, control or usual diet | No RCTs of omega 6 intake reporting CVD clinical events. 3 trials investigated the effect of increased omega 6 intake on lipid levels (TCI, LDL-cholesterol, and HDL-cholesterol, 2 trials reported TG, and 2 trials reported BP (diastolic and systolic blood pressure). 2 trials, one with 2 relevant intervention arms, investigated the effect of decreased omega 6 intake on BP and lipid levels (TC, LDL-cholesterol, and HDL-cholesterol) and one trial reported TG. No statistically significant effects of either increased or decreased omega 6 intake on CVD risk factors were found. | Authors conclude We found no studies examining the effects of either increased or decreased omega 6 on our primary outcome CVD clinical endpoints and insufficient evidence to show an effect of increased or decreased omega 6 intake on CVD risk factors such as blood lipids and blood pressure. Very few trials were identified with a relatively small number of participants randomised. | |
| Farvid et al 2014 ⁶ | Systematic review and meta-analysis | III-2 | Population without CVD | 13 published and unpublished | Linoleic acid | Highest compared with lowest category, dietary LA was associated with a 15% lower risk | Authors conclude In prospective observational studies, dietary LA intake is | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | of prospective cohort studies | | | cohort studies with a total of 310,602 individuals and 12,479 total CHD events, including 5882 CHD deaths. | | of CHD events (pooled RR, 0.85; 95% CI, 0.78-0.92; I (2) =35.5%) and a 21% lower risk of CHD deaths (pooled RR, 0.79; 95% CI, 0.71-0.89; I (2) =0.0%). A 5% of energy increment in LA intake replacing energy from saturated fat intake was associated with a 9% lower risk of CHD events (RR, 0.91; 95% CI, 0.87-0.96) and a 13% lower risk of CHD deaths (RR, 0.87; 95% CI, 0.82-0.94). | inversely associated with CHD risk in a dose-response manner. These data provide support for current recommendations to replace saturated fat with polyunsaturated fat for primary prevention of CHD. | |

Question 2: Types of fat in people with existing CVD

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| Hurcomb et al 2016 ⁷² | Systematic review and meta-analysis of RCTs | I | 7 secondary prevention studies 1 primary prevention 2 combined | 62,421 participants in 10 dietary trials (note compared with 15 from Hooper meta-analysis) | Relationship between dietary fat, serum cholesterol and development of CHD | Death rates for all-cause mortality were 6.45% in intervention and 6.06% in control. RR=0.991 (95% CI 0.935 to 1.051). Death rates for CHD mortality were 2.16% in intervention and 1.80% in control. RR=0.976 (95% CI 0.878 to 1.084). Serum cholesterol levels decreased in all intervention groups and all but one control group with significant reductions in the intervention groups. No significant differences in CHD or all-cause mortality. | Authors conclude The current available evidence found no significant difference in all-cause mortality or CHD mortality, resulting from the dietary fat interventions. | Mortality is probably not the most important end point but would rank equally with reduction in events |
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| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| Ramsden et al 2016 ⁵⁶ | Minnesota Coronary Experiment (1968-73) a double blind RCT Systematic review and meta-analyses of RCTs | II | 1 nursing home and 6 state mental hospitals | Unpublished data for the randomised cohort of 9,423 women and men aged 20-97; 2,355 participants exposed to the study diets for a year or more; 149 completed autopsy files. 5 RCTS (n=10,808) | Replaced saturated fat with linoleic acid (from corn oil and PUFA margarine believed to be trans free but not proven). Control diet was high in saturated fat from animal fats, common margarines, and shortenings (trans containing). | Reduction in serum cholesterol in intervention compared with controls (P<0.001). 22% higher risk of death for each 30 mg/dL (0.78 mmol/L) reduction in serum cholesterol in covariate adjusted Cox regression models (HR 1.22, 95% CI 1.14 to 1.32; P<0.001). There was no evidence of benefit in the intervention group for coronary atherosclerosis or MIs. In meta-analyses, these cholesterol lowering interventions showed no evidence of benefit on mortality from CHD (1.13, 0.83 to 1.54) or all-cause mortality (1.07, 0.90 to 1.27). | No mortality benefit of replacing saturated fat with linoleic acid. Increased risk of death from reduction in serum cholesterol. | Unexplained association between lowering of cholesterol and subsequent death (similar to statin effect in reverse) |
| Hooper et al 2015 ¹⁹ | Systematic review of RCTS with intervention of at least 24 months; with mortality or | 1 | Adult humans with or without CVD | 15 randomised controlled trials (RCTs) (17 comparisons, 59,000 participants), | Reducing saturated fat intake and replacing it with CHO, PUFA or MUFA and/or protein on | Reducing dietary saturated fat reduced the risk of CV events by 17% (RR=0.83; 95% CI 0.72 to 0.96, 13 comparisons, 53,300 participants of whom 8% had a cardiovascular event, I(2) 65%, GRADE moderate quality of evidence), but effects on all-cause | Overall the data supports a reduction in risk of combined CV events from saturated fat reduction and replacement with PUFA. | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | CV morbidity data available | | | | mortality and CV morbidity, using all available randomised clinical trials. | mortality (RR=0.97; 95% CI 0.90 to 1.05; 12 trials, 55,858 participants) and CV mortality (RR=0.95; 95% CI 0.80 to 1.12, 12 trials, 53,421 participants) were less clear (both GRADE moderate quality of evidence). There was some evidence that reducing saturated fats reduced the risk of MI (fatal and non-fatal, RR=0.90; 95% CI 0.80 to 1.01; 11 trials, 53,167 participants), but evidence for non-fatal MI (RR=0.95; 95% CI 0.80 to 1.13; 9 trials, 52,834 participants) was unclear and there were no clear effects on stroke (any stroke, RR=1.00; 95% CI 0.89 to 1.12; 8 trials, 50,952 participants). | | |
| Casula et al 2013 ²⁴ | Meta-analysis of randomised, placebo controlled trials | 1 | Patients with a history of CVD | 11 randomised, double-blind, placebo controlled trials 15,348. | Omega-3 PUFA at least 1 g /day | No benefit for all-cause mortality RR, 0.89; 95% CI, 0.78 to 1.02) and stroke (RR, 1.31; 95% CI, 0.90 to 1.90). Protective effects for cardiac death RR, 0.68; 95% CI, 0.56 to 0.83 sudden death (RR, 0.67; 95% CI, 0.52 to 0.87), and MI RR, 0.75; 95% CI, 0.63 to 0.88). | Evidence of benefit for cardiac death, sudden death and MI | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| Writing Group for the AREDS2 Research Group 2014 ¹¹⁵ | Randomised blinded clinical trial Ancillary study of the Age-Related Eye Disease Study 2 (AREDS2) | II | Participants with stable, existing CVD (>12 months since initial event) | 4,203 participants were eligible 459 CVD events | Omega-3 PUFA 350-mg DHA + 650-mg EPA, &/or macular xanthophylls (10-mg lutein + 2-mg zeaxanthin) | No reduction in the risk of CVD or secondary CVD outcomes was seen for the DHA + EPA (primary outcome: HR [HR], 0.95; 95% CI, 0.78-1.17) or lutein + zeaxanthin (primary outcome: HR, 0.94; 95% CI, 0.77-1.15) groups. | No evidence of benefit of PUFA or PUFA + lutein and zeaxanthin | |
| Schwingsha -ckl et al 2014 ⁷¹ | Systematic review, meta-analysis and meta-regression | I | Participants with established CHD | 12 studies with 7150 participants | Reduced or modified fat diets versus control diets | No significant risk reduction could be observed considering all-cause mortality (relative risk (RR) 0.92, p=0.60; I(2)=59%) and CV mortality (RR=0.96, p=0.84; I(2)=69%), combined CV events (RR=0.85, p=0.30; I(2)=75%) and MI (RR=0.76, p=0.13; I(2)=55%) comparing modified fat diets versus control diets. Results confirmed for the reduced fat versus control diets (RR=0.79, p=0.47; I(2)=0%), (RR=0.93, p=0.66; I(2)=0%), (RR=0.93, p=0.71; I(2)=57%) and (RR=1.18, p=0.26; I(2)=18%). | Authors conclude The present systematic review provides no evidence (moderate quality evidence) for the beneficial effects of reduced/modified fat diets in the secondary prevention of coronary heart disease. Recommending higher intakes of PUFA in replacement of SFA was not associated with risk reduction. | |
| Enns et al 2014 ⁷⁵ | Systematic review and | 1 | Peripheral arterial disease | 5 trials, 396 individuals | Omega-3 PUFA supplements | Omega-3 PUFA supplementation and major adverse cardiac events (pooled RR=0.73, 95% CI 0.22 to | No benefit of omega -3 supplements in PAD | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | meta-analysis of RCTs | | | | | 2.41, I2 75%, 2 trials, 288 individuals, NS) | | |
| Guo et al 2014 ¹⁴ | Meta-analysis of RCTs | 1 | Postoperative atrial fibrillation | 11 studies with 3,137 patients | Omega-3 PUFA supplements | PUFA compared with control OR, 0.76; 95% CI: 0.57-1.03; P=0.08; I(2)=52%). PUFA and vitamins C and E was effective OR, 0.32; 95%CI: 0.17-0.60; P=0.0005; I(2)=38%). Subgroup analysis indicated that the ratio of EPA/DHA 1:2 was effective OR, 0.35; 95%CI: 0.24-0.50; P<0.00001; I(2)=0%) | No evidence for PUFA alone. Evidence that PUFA and Vitamins C and E are effective in the prevention of POAF. EPA/DHA ratio was significant. | |
| Zhang et al 2014 ¹³ | Meta-analysis of RCTs | 1 | Postoperative atrial fibrillation | 8 studies 2687 patients | Omega-3 PUFA supplements | PUFA compared to placebo [RR=0.86; 95% CI 0.71-1.04, p=0.110]. EPA/DHA ≤1 (2studies) RR=0.476 (CI 0.305–0.743) p= 0.001 | No evidence for an effect of PUFA compared to placebo EPA/DHA ratio was significant | |
| Imamura et al ⁴⁹ | Prospective cohort study | III-2 | Congestive heart failure 3,694 older adults in Cardiovascular Health Study (CHS; 1992-2006) and 3,577 middle-aged adults (mean age, | In CHS, 997 congestive heart failure events occurred during 39 238 person-years; in ARIC, 330 events congestive heart failure events | Long-chain MUFA (20:1, 22:1, 24:1) | After multivariable adjustment, higher levels of 22:1 and 24:1 were positively associated with greater incident congestive heart failure in both CHS and ARIC; HR 1.34 (95% CI, 1.02-1.76) and 1.57 (95% CI, 1.11-2.23) for highest versus lowest quintiles of 22:1, respectively, and 1.75 (95% CI, 1.23-2.50) and 1.92 (95% CI, 1.22-3.03) for 24:1, respectively (P for trend </=0.03 each). | Authors conclude: Higher circulating levels of 22:1 and 24:1, with apparently diverse dietary sources, were associated with incident congestive heart failure in 2 independent cohorts, suggesting possible cardiotoxicity of LCMUFAs in humans. | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | 54.1+/-5.8 years) in the Atherosclerosis Risk in Communities Study, Minnesota sub-cohort | occurred during 64,438 person-years. | | We further examined dietary correlates of circulating LCMUFAs in CHS and ARIC and US dietary sources of LCMUFAs in the 2003-2010 National Health and Nutrition Examination Survey (NHANES). A variety of foods were related to circulating LCMUFAs in CHS and ARIC, consistent with food sources of LCMUFAs in NHANES, including fish, poultry, meats, whole grains, and mustard. | | |

Question 3: Dietary fat intake and hypercholesterolemia

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| Rees et al 2013 ⁸¹ | Cochrane systematic review Randomised studies with no more than 20% loss to follow-up, lasting at least 3 months and involving healthy adults comparing | I | Population without CVD | 44 trials with 52 intervention arms comparing dietary advice with no advice were included in the review 18,175 participants or clusters | To assess the effects of providing dietary advice to achieve sustained dietary changes or improved cardiovascular risk profile among healthy adults | TC decreased by 0.15 mmol/L (95% CI 0.06 to 0.23) LDL cholesterol decreased by 0.16 mmol/L (95% CI 0.08 to 0.24) after 3 to 24 months. BP decreased by 2.61 mm Hg systolic (95% CI 1.31 to 3.91) and 1.45 mm Hg diastolic (95% CI 0.68 to 2.22) 24-hour urinary sodium excretion decreased by 40.9 mmol (95% CI 25.3 to 56.5) after 3 to 36 months. | Authors' conclusions: Dietary advice appears to be effective in bringing about modest beneficial changes in diet and cardiovascular risk factors over approximately 12 months, but longer-term effects are not known. | |
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| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | dietary advice with no advice or minimal advice. | | | were randomised. 2 trials analysed incident CVD events (TOHP I/II). Follow-up was 77% complete at 10 to 15 years after the end of the intervention | | Dietary advice increased fruit and vegetable intake by 1.18 servings/day (95% CI 0.65 to 1.71). Dietary fibre intake increased by 6.5 g/day (95% CI 2.2 to 10.82) Total dietary fat as a % of total energy intake fell by 4.48% (95% CI 2.47 to 6.48) and saturated fat intake fell by 2.39% (95% CI 1.4 to 3.37). Estimates of event rates lacked precision but suggested that sodium restriction advice probably led to a reduction in CV events (combined fatal & non-fatal events) plus revascularisation (TOHP I hazard ratio (HR) 0.59, 95% CI 0.33 to 1.08; TOHP II HR 0.81, 95% CI 0.59 to 1.12). | | |
| Kelley et al 2012 ¹¹⁶ | Meta-analysis of RCTs | I | Population without CVD | 6 studies 788 men and women | Effects of diet (D), aerobic exercise (E) or both (DE) on blood lipid and lipoprotein concentrations in adults | Non-overlapping 95% CIs were observed for diet and diet+exercise with respect to lowering TC, LDL-C and TG while reductions were limited to TG for exercise alone. No significant changes in HDL-C were observed. When compared to E, reductions in TC and LDL-C were greater for diet and diet+exercise (p < 0.05 for all). | Authors conclude that diet, especially diet+exercise, are superior to exercise alone for improving selected lipids and lipoproteins in adults. | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| Schwingshackl et al 2012 ¹¹⁷ | Systematic reviews and meta-analyses of RCTs and cohort studies | I | Population without CVD | 16 studies | MUFA | <p>Several studies indicated an increase of HDL-cholesterol and a corresponding decrease in TG following a MUFA-rich diet. Effects on TC and LDL-cholesterol not consistent, but not detrimental.</p> <p>Values for systolic and diastolic blood pressure were found to be reduced both during short- and long-term protocols using high amounts of MUFA as compared to low-MUFA diets.</p> <p>Data from meta-analyses exploring evidence from long-term prospective cohort studies provide ambiguous results with respect to the effects of MUFA on risk of coronary heart disease (CHD).</p> <p>One meta-analysis reported an increase in CHD events, however, most meta-analyses observed a lesser number of cases in participants on a high-MUFA protocol.</p> | <p>Authors conclude: Although no detrimental side effects of MUFA-rich diets were reported in the literature, there still is no unanimous rationale for MUFA recommendations in a therapeutic regimen. Lowering of TG may be valuable.</p> | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| Schwingsha-ckl et al 2011 ⁸⁷ | Systematic review and meta-analysis of RCTs | I | Population without CVD | 12 studies met the inclusion criteria | Diets with MUFA (>12%) were compared to those with <=12% | Significant differences between high- and low-MUFA protocols could be observed with respect to fat mass [-1.94 kg (CI -3.72, -0.17), p = 0.03], systolic blood pressure [-2.26 mm Hg (CI -4.28, -0.25), p = 0.03] and diastolic blood pressure [-1.15 mm Hg (CI -1.96, -0.34), p = 0.005] favouring the dietary protocols with >12% MUFA. | | |
| Schwingsha-ckl et al 2013 ²⁹ | Systematic review and meta-analysis of RCTs | I | Overweight or obese patients | 32 studies | Effects of low-fat vs high-fat diets on blood lipid levels | Decreases in TC (WMD -4.55 mg/dL [-0.12 mmol/L], 95% CI -8.03 to -1.07; P=0.01) and LDL cholesterol (WMD -3.11 mg/dL [-0.08 mmol/L], 95% CI -4.51 to -1.71; P<0.0001) seen after low-fat diets, Rise in HDL cholesterol (WMD 2.35 mg/dL [0.06 mmol/L], 95% CI 1.29 to 3.42; P<0.0001) and reduction in TG levels (WMD -8.38 mg/dL [-0.095 mmol/L], 95% CI -13.50 to -3.25; P=0.001) on high-fat diet. Effects of low-fat vs high-fat diets on TC and LDL cholesterol levels abolished in energy restricted diets. Lower TC associated with lower intakes of SFA and higher intakes of PUFA, increases in HDL | Overall low-fat diet improves TC and LDL-cholesterol Higher fat diets increase HDL and decrease in TG. Lower TC associated with lower SFA and higher PUFA Higher HDL cholesterol related to higher MUFA. | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | cholesterol related to higher total fat from MUFA fat in high-fat diets (~17% of total energy from MUFA, ~8% from PUFA), higher TG associated with higher intakes of CHO. | | |
| Gayet-Boyer et al 2014 ⁸⁸ | Systematic review and meta-analysis of RCTs | I | Population without CVD | 13 studies 23 independent experimental groups of subjects | Ruminant TFA intake, impact on changes in the total cholesterol: HDL-cholesterol (TC:HDL-C) ratio. | No relationship between R-TFA intake up to 4.19% of daily (EI) and changes in CV risk factors such as TC:HDL-C and LDL-cholesterol (LDL-C):HDL-C ratios. | | |
| Mozaffarian et al 2009 ⁴¹ | Meta-analysis of blood lipid and lipoprotein effects of TFA consumption from RCTs and prospective cohort studies | I | Population without CVD | 13 randomised trials included in the meta-analysis of blood lipid and lipoprotein effects of TFA consumption prospective observational studies | | The effects on CHD risk for replacing 7.5% of energy from three different partially hydrogenated vegetable oils (PHVO) (containing 20, 35 or 45% TFAs) with butter, lard, palm or vegetable oils were calculated. In RCTs each 1% energy replacement of TFAs with SFAs, MUFAs or PUFAs, respectively, decreased the TC/HDL-C ratio by 0.31, 0.54 and 0.67; the apolipoprotein (Apo)-B/ApoAI | Authors conclude: Effects on CHD risk of removing PHVO from a person's diet vary depending on the TFA content of the PHVO and the fatty acid composition of the replacement fat or oil, with direct implications for reformulation of individual food products. Accounting for the summed effects of TFAs on multiple | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | 4 prospective cohort studies reporting on the association of habitual dietary consumption of TFAs with incidence of CHD events were included | | ratio by 0.007, 0.010 and 0.011; and lipoprotein (Lp)(a) by 3.76, 1.39 and 1.11 mg/l (P<0.05 for each). CHD risk would be variably decreased by different fats and oils replacing 7.5% of energy from 20% TFA PHVO (CHD risk reduction: -2.7% (butter) to -9.9% (canola)); 35% TFA PHVO (-11.9% (butter) to -16.0% (canola)); or 45% TFA PHVO (-17.6% (butter) to -19.8% (canola)). In prospective cohort studies, each 2% energy replacement of TFAs with SFAs, MUFAs or PUFAs would lower CHD risk by 17% (95% CI=7-25%), 21% (95% CI=12-30%) or 24% (95% CI=15-33%), respectively. On the basis of these associations in observational studies, CHD risk would be variably decreased by different fats and oils replacing 7.5% of energy from 20% TFA PHVO (CHD risk reduction: +0.5% (butter) to -21.8% (soybean)); 35% TFA PHVO (-14.4% (butter) to -33.4% (soybean)); or 45% TFA PHVO (-22.4% (butter) to -39.6% (soybean)). The demonstrated effects on TC/HDL-C, ApoB/ApoA1, | CHD risk factors provides more accurate estimates of potential risk reduction than considering each risk factor in isolation, and approaches the estimated risk reduction derived from prospective cohort studies. | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | Lp(a), and CRP in randomized feeding trials together accounted for approximately 65-80% and approximately 50% of the estimated risk reduction for replacing PHVO with animal fats and vegetable oils, respectively, that would be calculated from prospective cohort studies. | | |
| Wu et al 2014 ²⁸ | Meta-analysis of RCTs | I | Population without CVD Pre- and post-menopausal women. | 8 RCTs were included representing 22 groups (11 intervention and 11 control groups). 1,536 women (900 in the intervention group and 636 in the control group) | Low-fat diet, in comparison with participants' usual diet, on serum lipids in | Low-fat diet was found to induce significant reductions in TC (random-effects model: mean difference [MD], -0.49 mmol/L; 95% CI, -0.69 to -0.29; I = 42%; Peffect < 0.00001), HDL-C (MD, -0.12 mmol/L; 95% CI, -0.20 to -0.05; I = 49%; Peffect = 0.00006), and LDL-C (MD, -0.24 mmol/L; 95% CI, -0.38 to -0.09; I = 42%; Peffect = 0.001) for two groups. Low-fat diet was efficacious in reducing TC, HDL-C, and LDL-C in premenopausal women but did not significantly reduce the same outcomes in postmenopausal women. There were no statistically significant differences in TG and | Authors conclude Overall results suggest that a low-fat diet is efficacious in reducing the concentrations of TC, HDL-C, and LDL-C but not in reducing TG and TC-to-HDL-C ratio in women. A low-fat diet is efficacious in reducing TC, HDL-C, and LDL-C in premenopausal women. | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | TC-to-HDL-C ratio between a low-fat diet and the participants' usual diet (TG: MD, 0.04 mmol/L; 95% CI, -0.02 to 0.11; I = 0%; Peffect = 0.16; TC-to-HDL-C ratio: MD, 0.08 mmol/L; 95% CI -0.21 to 0.36; I = 0%; P effect = 0.59) in two groups. | | |

Palm oil

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| Fattore et al ⁸³ | Systematic review and meta-analysis of dietary intervention trials. | I | Population without CVD | 51 studies were included | Palm oil (PO) Intervention times ranged from 2 to 16 wk, and different fat substitutions ranged from 4% to 43%. | Comparison of PO diets with diets rich in stearic acid, monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) showed significantly higher TC, LDL cholesterol, apolipoprotein B, HDL cholesterol, and apolipoprotein A-I, whereas most of the same biomarkers were significantly lower when compared with diets rich in myristic/lauric acid. Comparison of PO-rich diets with diets rich in trans fatty acids showed significantly higher concentrations of HDL cholesterol and apolipoprotein A-I and significantly lower apolipoprotein B, triacylglycerols, and TC/HDL cholesterol. Stratified and meta-regression analyses showed that | Authors conclude: Both favourable and unfavourable changes in CHD/CVD risk markers occurred when PO was substituted for the primary dietary fats, whereas only favourable changes occurred when PO was substituted for trans fatty acids. Additional studies are needed to provide guidance for policymaking. | |
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| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | the higher concentrations of TC and LDL cholesterol, when PO was substituted for MUFAs and PUFAs, were not significant in young people and in subjects with diets with a lower percentage of energy from fat. | | |

Soybean oil

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| Hunter et al 2010 ¹¹⁸ | Systematic review of epidemiologic and clinical studies that evaluated the relation between stearic acid (STA) and (CVD) risk factors | III-2 | Population without CVD | 21 epidemiologic studies 22 human trials with changes in serum LDL cholesterol, HDL cholesterol, triglycerides, and lipoprotein(a) [Lp(a)] after feeding diets high in STA (45–66) (Table 1). | High stearic acid (STA) soybean oil is a trans-free, oxidatively stable, non-LDL-cholesterol-raising oil | Comparison to other saturated fatty acids, STA lowered LDL cholesterol, was neutral with respect to HDL cholesterol, and lowered the ratio of total to HDL cholesterol. Compared with unsaturated fatty acids STA tended to raise LDL cholesterol, lower HDL cholesterol, and increase the ratio of total to HDL cholesterol. In 2 of 4 studies, high-STA diets increased lipoprotein(a) compared to diets high in saturated fatty acids. 3 studies showed increased plasma fibrinogen when dietary STA exceeded 9% of energy (the | T FA intake should be reduced as much as possible because of its adverse effects on lipids and lipoproteins. The replacement of TFA with STA compared with other saturated fatty acids in foods that require solid fats beneficially affects LDL cholesterol, the primary target for CVD risk reduction; unsaturated fats are preferred for liquid fat applications. Research is needed to evaluate the effects of STA on emerging CVD risk markers such as fibrinogen and to | |
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| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | current 90th percentile of intake is 3.5%). Replacing industrial TFAs with STA might increase STA intake from 3.0% (current) to approximately 4% of energy and from 4% to 5% of energy at the 90th percentile. One-to-one substitution of STA for TFAs showed a decrease or no effect on LDL cholesterol, an increase or no effect on HDL cholesterol, and a decrease in the ratio of total to HDL cholesterol. | understand the responses in different populations. | |
| Huth et al 2015 ⁸⁵ | Systematic review of controlled clinical trials | I | Population without CVD | | High-oleic acid soybean oil (H-OSBO) | Studies that replaced saturated fats or oils with HO oils showed significant reductions in total cholesterol (TC), LDL cholesterol, and apolipoprotein B (apoB) (P < 0.05; mean percentage of change: -8.0%, -10.9%, -7.9%, respectively), whereas most showed no changes in HDL cholesterol, triglycerides (TGs), the ratio of TC to HDL cholesterol (TC:HDL cholesterol), and apolipoprotein A-1 (apoA-1). Replacing TFA-containing oil sources with HO oils showed significant reductions in TC, LDL cholesterol, apoB, TGs, TC:HDL cholesterol and increased HDL | These findings suggest that replacing fats and oils high in SFAs or TFAs with either H-OSBO or oils high in n-6 PUFAs would have favourable and comparable effects on plasma lipid risk factors and overall CHD risk | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | cholesterol and apoA-1 (mean percentage of change: -5.7%, -9.2%, -7.3%, -11.7%, -12.1%, 5.6%, 3.7%, respectively; P < 0.05). In most studies that replaced oils high in n-6 PUFAs with equivalent amounts of HO oils, TC, LDL cholesterol, TGs, HDL cholesterol, apoA-1, and TC:HDL cholesterol did not change. | | |

Nuts

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| Del Gobbo et al 2015 ⁸⁰ | Systematic review, meta-analysis, and dose-response of 61 controlled intervention trials | I | Adults aged ≥ 18 y without prevalent CVD | 61 studies n = 2582 | Tree nuts walnuts, pistachios, macadamia nuts, pecans, cashews, almonds, hazelnuts, and Brazil nuts Interventions ranged from 3 to 26 weeks | Nut intake (per serving/d) lowered total cholesterol (-4.7 mg/dL; 95% CI: -5.3, -4.0 mg/dL), LDL cholesterol (-4.8 mg/dL; 95% CI: -5.5, -4.2 mg/dL), ApoB (-3.7 mg/dL; 95% CI: -5.2, -2.3 mg/dL), and triglycerides (-2.2 mg/dL; 95% CI: -3.8, -0.5 mg/dL) with no statistically significant effects on other outcomes. The dose-response between nut intake and total cholesterol and LDL cholesterol was nonlinear (P-nonlinearity < 0.001 each); stronger effects were observed for ≥ 60 g nuts/d. Significant | Authors' conclusions: Tree nut intake lowers total cholesterol, LDL cholesterol, ApoB, and triglycerides. The major determinant of cholesterol lowering appears to be nut dose rather than nut type. Our findings also highlight the need for investigation of possible stronger effects at high nut doses and among diabetic populations. | |
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| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | heterogeneity was not observed by nut type or other factors. For ApoB, stronger effects were observed in populations with type 2 diabetes (-11.5 mg/dL; 95% CI: -16.2, -6.8 mg/dL) than in healthy populations (-2.5 mg/dL; 95% CI: -4.7, -0.3 mg/dL) (P-heterogeneity = 0.015). Little evidence of publication bias was found. | | |
| Ferguson et al 2016 ⁷⁸ | Systematic review and meta-analysis of RCTs | I | Population without CVD | Published RCTs from 1990 investigating the effects of dietary PS intervention (>=1.5g per day) on total cholesterol and LDL-C were included. 32 RCTs (RC, n=15; SS, n=9; D, n=8) were included. | Phytosterol (PS) fortified foods e.g. fat spreads and dairy products. The predominant fats used are soybean/sunflower (SS) or rapeseed/canola (RC) oils and animal fat (D) in dairy products. | This review aimed to investigate whether the carrier fat is a determinant of the hypocholesterolaemic effects of PS fortified foods. All fat groups significantly reduced TC and LDL-C (p<0.01). When compared across different carrier fats, RC as the main carrier fat, reduced LDL-C significantly more than the SS spreads (p=0.01). | Authors' conclusions: A combination of monounsaturated fatty acid rich spread with adequate amounts of omega-3 fatty acids (as evident in RC spreads) may be the superior carrier fat for the delivery of PS for optimal blood cholesterol-lowering. | |
| Martin et al 2016 ⁷⁹ | Systematic review of | I | Healthy adults or | 5 trials (435 participants) | All trials examined the | Trials were small and short term. All 5 trials reported on CVD risk | Authors' conclusions: | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | RCTs lasting at least 3 months | | adults at moderate and high risk of CVD | randomised) and one ongoing trial. | provision of nuts to increase consumption rather than dietary advice. | factors. 5 of these trials provided data in a useable format for meta-analyses, but heterogeneity precluded meta-analysis for most of the analyses. Variable and inconsistent effects of nut consumption on CVD risk factors (lipid levels and blood pressure). Three trials monitored adverse events. 3 trials reported no significant weight gain with increased nut consumption. None of the included trials reported on other secondary outcomes, occurrence of type 2 diabetes as a major risk factor for CVD, health-related quality of life and costs. | Currently there is a lack of evidence for the effects of nut consumption on CVD clinical events in primary prevention and very limited evidence for the effects on CVD risk factors. | |

Question 4a What is the evidence on the association between dairy product intake and CVD outcomes?

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| O'Sullivan et al 2013 ¹¹² | Meta-analysis | III-2 | Population without CVD | 26 publications with individual dietary data and all-cause, total cancer, or | Different sources of saturated fat and risk of mortality (dairy and meat) | Pooled relative risk estimates demonstrated that high intakes of milk, cheese, yoghurt, and butter were not associated with a significantly increased risk of mortality compared with low intakes. High intakes of meat and processed meat were significantly | Authors' conclusions: The overall quality of studies was variable. Associations varied by food group and population but dairy foods not associated with increased risk of CVD mortality while meat was. This may be because of | |
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| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | cardiovascular mortality | | associated with an increased risk of mortality but were associated with a decreased risk in a sub-analysis of Asian studies. | factors outside saturated fat content of individual foods | |
| Alexander et al 2016 ¹⁰¹ | Meta-analysis of prospective cohort studies of dairy intake and CVD | III-2 | Population without CVD | | Total dairy intake, individual dairy products, low/full-fat dairy intake, Ca from dairy sources | Statistically significant summary relative risk estimates (SRRE) below 1.0 were observed, for total dairy intake and stroke (SRRE=0.91; 95% CI 0.83, 0.99), cheese intake and CHD (SRRE=0.82; 95% CI 0.72, 0.93) and stroke (SRRE=0.87; 95% CI 0.77, 0.99), and Ca from dairy sources and stroke (SRRE=0.69; 95% CI 0.60, 0.81). Little evidence for inverse dose-response relationships between the dairy variables and CHD and stroke after adjusting for within-study covariance. | Results show that dairy consumption may be associated with reduced risks of CVD, although additional data are needed to more comprehensively examine potential dose-response patterns. | |
| Qin et al 2015 ¹⁰⁴ | Updated meta-analysis of prospective cohort studies | III-2 | Population without CVD | 22 studies | Dairy consumption and risk of CVD | Inverse association between dairy intake and overall CVD risk [9 studies RR=0.88, 95% CI: 0.81, 0.96] and stroke (12 studies; RR=0.87, 95% CI: 0.77, 0.99). No association between dairy intake and CHD risk (12 studies; RR=0.94, 95% CI: 0.82, 1.07). Stroke risk was reduced by intake of low-fat dairy (6 studies; | Modest benefit of dairy intake and CVD and stroke but not CHD. Small benefit on stroke risk of low-fat dairy and cheese. Moderate benefit of cheese on CHD risk. | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | | | RR=0.93, 95% CI: 0.88, 0.99) and cheese (4 studies; RR=0.91, 95% CI: 0.84, 0.98), CHD risk was lowered by cheese consumption (7 studies; RR=0.84, 95% CI: 0.71, 1.00). | | |
| Soedamah-Muthu et al 2011 ⁹⁹ | Meta-analysis of prospective cohort studies | III-2 | Population without CVD | 17 studies There were 2283 CVD, 4391 CHD, 15,554 stroke, and 23,949 mortality cases. | Milk and dairy consumption | Inverse association between milk intake and risk of overall CVD [4 studies; relative risk (RR): 0.94 per 200 mL/d; 95% CI: 0.89, 0.99]. Milk intake was not associated with risk of CHD (6 studies; RR: 1.00; 95% CI: 0.96, 1.04), stroke (6 studies; RR: 0.87; 95% CI: 0.72, 1.05), or total mortality (8 studies; RR per 200 mL/d: 0.99; 95% CI: 0.95, 1.03). No significant association between milk intake per 200 mL/d and all-cause mortality (RR: 0.99; 95% CI: 0.95, 1.03). No association between total dairy (n = 4) (RR: 1.02; 95% CI: 0.93) total high-fat (n = 4 studies) (RR: 1.04; 95% CI: 0.89, 1.21) and total low-fat (n = 3 studies) (RR: 0.93; 95% CI: 0.74, 1.17 dairy intake and CHD risk. | Modest benefit of milk on total CVD risk but not CHD. | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| Chen et al 2016 ¹¹¹ | Prospective cohort studies | III-2 | Population without CVD HPFS NHS (1980-2012) NHS II (1991-2011) | 43,652 men 87,907 women 90,675 women with 5,158,337 person-years of follow-up During 5,158,337 person-years of follow-up 14,815 incident CVD cases including 8,974 CHD occurred cases (non-fatal MI or fatal CHD) 5,841 stroke cases | Dairy fat and other fat intakes assessed every 4 years using validated FFQ | Compared with an equivalent amount of energy from CHO (excluding fruit and vegetables), dairy fat intake was not significantly related to risk of total CVD (for a 5% increase in energy from dairy fat, RR=1.02; 95% CI: 0.98, 1.05) The effects of exchanging different fat sources, the replacement of 5% of energy intake from dairy fat with equivalent energy intake from PUFA or vegetable fat was associated with 24% (RR: 0.76; 95% CI: 0.71, 0.81) and 10% (RR: 0.90; 95% CI: 0.87, 0.93) lower risk of CVD, respectively, whereas the 5% energy intake substitution of other animal fat with dairy fat was associated with 6% increased CVD risk (RR: 1.06; 95% CI: 1.02, 1.09). | Replacing dairy fat with equivalent energy intake from PUFA and vegetable fat was protective against CVD. | |
| Drouin-Chartier et al 2016 ¹¹³ | Systematic review of meta-analyses of prospective population studies | 1 | Population without CVD | | To determine if dairy product consumption is detrimental or beneficial to | High-quality evidence supports favourable associations between total dairy intake and hypertension risk Moderate-quality evidence suggests favourable associations between intakes of total dairy, low-fat | Authors' conclusions: Data from this systematic review indicate that the consumption of various forms of dairy products shows either favourable or neutral associations with | |

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| | | | | | cardiovascular health | dairy, cheese, and fermented dairy and the risk of stroke; intakes of low-fat dairy and milk and the risk of hypertension. High-to-moderate quality evidence supports neutral associations between the consumption of total dairy, cheese, and yoghurt and CVD risk; the consumption of any form of dairy, except for fermented, and CAD risk; the consumption of regular- and high-fat dairy, milk, and yoghurt and stroke risk; the consumption of regular- and high-fat dairy, cheese, yoghurt, and fermented dairy and hypertension risk. | cardiovascular-related clinical outcomes. | |
| Drouin-Chartier et al 2016 ¹¹⁹ | Narrative review | | Population without CVD | | | This comprehensive assessment of evidence from RCTs suggests that there is no apparent risk of potential harmful effects of dairy consumption, irrespective of the content of dairy fat, on a large array of cardiometabolic variables, including lipid-related risk factors, blood pressure, inflammation, insulin resistance, and vascular | Authors' conclusions: Thus, the focus on low-fat dairy products in current guidelines apparently is not entirely supported by the existing literature and may need to be revisited on the basis of this evidence. | |

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| | | | | | | function. This suggests that the purported detrimental effects of SFAs on cardiometabolic health may in fact be nullified when they are consumed as part of complex food matrices such as those in cheese and other dairy foods. | | |
| Chen et al 2016 ³⁵ | Meta-analysis of prospective observational studies | III-2 | Population without CVD | 15 prospective studies | High vs. low cheese consumption | RR for high vs. low cheese consumption was 0.90 (95 % CI 0.82-0.99) for total CVD (7 studies, 8076 events), 0.86 (95 % CI 0.77-0.96) for CHD (8 studies, 7631 events), 0.90 (95 % CI 0.84-0.97) for stroke (7 studies, 10,449 events). The restricted cubic model indicated evidence of nonlinear relationships between cheese consumption and risks of total CVD (P nonlinearity < 0.001) and stroke (P nonlinearity = 0.015), with the largest risk reductions observed at the consumption of approximately 40 g/d. | Authors' conclusions: Evidence suggests a nonlinear inverse association between cheese consumption and risk of CVD. | |
| Praagman et al 2015 ¹¹⁰ | Cohort study | III-2 | Population without CVD | 4,235 participants of the Rotterdam Study aged 55 and over | Total dairy and dairy subgroups in relation to incident CVD events | Median intake of total dairy was 397 g/day, mainly low-fat dairy products (median intake of 247 g/day). Total dairy, milk, low-fat dairy, and fermented dairy were not | Authors' conclusions: In this long-term follow-up study of older Dutch subjects, total dairy consumption or the intake of specific dairy products | |

| Author, year | Study type | Level of evidence (NHMRC grade) | Population / setting | n (number of studies, number of participants) | Intervention/ comparator | Outcomes | Direction/ magnitude of effect | Comment/ notes |
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| | | | | who were free (CVD) and diabetes at baseline (1990-1993). Median follow-up of 17.3 years, 564 strokes (182 fatal) and 567 CHD events (350 fatal) occurred. | | significantly related to incident stroke or fatal stroke ($p > 0.2$ for upper vs. lower intake categories). High-fat dairy was significantly inversely related to fatal stroke (HR of 0.88 per 100 g/day; 95% CI 0.79, 0.99), but not to incident stroke (HR of 0.96 per 100 g/day; 95% CI 0.90, 1.02). Total dairy or dairy subgroups were not significantly related to incident CHD or fatal CHD (HRs between 0.98 and 1.05 per 100 g/day, all $p > 0.35$). | was not related to the occurrence of CVD events. The observed inverse association between high-fat dairy and fatal stroke warrants confirmation in other studies. | |
| Praagman et al 2016 ⁴⁵ | European Prospective Investigation into Cancer and Nutrition (EPIC)- Netherlands cohort | III-2 | Population without CVD 12 y of follow-up of participants from EPIC | 35,597,1807 IHD events occurred | Baseline (1993-1997) SFA intake measured with a FFQ | Total SFA intake was associated with a lower IHD risk HR per 5% of energy: 0.83; 95% CI: 0.74, 0.93 Substituting SFAs with animal protein, cis MUFAs, PUFAs or CHO was associated with higher IHD risks (HR per 5% of energy: 1.27-1.37). Lower IHD risks were observed for higher intakes of SFAs from dairy sources, including butter (HRSD: 0.94; 95% CI: 0.90, 0.99), cheese (HRSD: 0.91; 95% CI: 0.86, 0.97), | Overall the data supports an association between higher total SFA intake and lower IHD risk-the opposite to most of the literature. | |

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| | | | | | | and milk and milk products (HRSD: 0.92; 95% CI: 0.86, 0.97). | | |
| Eyres et al 2016 ³⁸ | Narrative review | | Population without CVD | 8 clinical trials 13 observational studies The majority examined the effect of coconut oil or coconut products on serum lipid profiles | Coconut oil, coconut milk, or coconut cream in humans | Coconut oil generally raised TC and LDL cholesterol to a greater extent than cis unsaturated plant oils, but to a lesser extent than butter. The effect of coconut consumption on the ratio of total cholesterol to high-density lipoprotein cholesterol was often not examined. Observational evidence suggests that consumption of coconut flesh or squeezed coconut in the context of traditional dietary patterns does not lead to adverse cardiovascular outcomes. However, due to large differences in dietary and lifestyle patterns, these findings cannot be applied to a typical Western diet. | Authors' conclusions: Overall, the weight of the evidence from intervention studies to date suggests that replacing coconut oil with cis unsaturated fats would alter blood lipid profiles in a manner consistent with a reduction in risk factors for CVD. | |

Appendix 3 Comments from the Australian Dietary Guidelines in relation to evidence quality

"The NHMRC followed critical appraisal processes to ensure rigorous application of the review methodology. Data were extracted from included studies and assessed for strength of evidence, size of effect and relevance of evidence according to standardised NHMRC processes. The components of the body of evidence – evidence base (quantity, level and quality of evidence); consistency of the study results; clinical impact; generalisability; and applicability to the Australian context – were rated as excellent, good, satisfactory or poor according to standard NHMRC protocols.

The reviewers then summarised the evidence into draft body of evidence statements. The Working Committee advised that a minimum of five high quality studies was required before a graded evidence statement could be made. The individual studies in meta-analyses were considered as separate studies. The evidence statements were graded A to D according to standard NHMRC protocols:

- *Grade A (convincing association) indicates that the body of evidence can be trusted to guide practice*
- *Grade B (probable association) indicates that the body of evidence can be trusted to guide practice in most situations*
- *Grade C (suggestive association) indicates that the body of evidence provides some support for the recommendations but care should be taken in its application*
- *Grade D indicates that the body of evidence is weak and any recommendation must be applied with caution.*

Once the evidence statements had been drafted and graded, NHMRC commissioned an external methodologist to ensure that review activities had been undertaken in a transparent, accurate, consistent and unbiased manner. This was to ensure that the work could be double-checked easily by other experts in nutrition research.

In this way, the Evidence Report was used to develop the graded evidence statements included in these Guidelines. It is important to note that these grades relate to individual diet-disease relationships only – the Guidelines summarise evidence from a number of sources and across a number of health/disease outcomes.

Levels of evidence in public health nutrition

Randomised controlled trials provide the highest level of evidence regarding the effects of dietary intake on health. However, as with many public health interventions, changing the diets of individuals raises ethical, logistical and economic challenges. This is particularly the case in conducting randomised controlled trials to test the effects of exposure to various types of foods and dietary patterns on the development of lifestyle-related disease.

Lifestyle-related diseases generally do not develop in response to short-term dietary changes; however short-term studies enable biomarkers of disease to be used to evaluate the effects of particular dietary patterns. The question of how long dietary exposure should occur to demonstrate effects on disease prevention is subject to much debate. While it may be possible to conduct a dietary intervention study for 12 months or more to examine intermediate effects, there would be many ethical and practical barriers to conducting much longer, or indeed, lifelong, randomised controlled trials with dietary manipulation to examine disease prevention.

As a result, evidence in the nutrition literature tends to be based on longer term observational studies, leading to a majority of Grade C evidence statements, with some reaching Grade B, where several quality studies with minimal risk of bias have been conducted. For shorter term and intermediary effects, particularly when studying exposure to nutrients and food components rather than dietary patterns, Grade A is possible.

The relatively high proportion of evidence statements assessed as Grade C should not be interpreted as suggesting lack of evidence to help guide practice. However, care should still be applied in applying this evidence for specific diet-disease relationships, particularly at the individual level.

Health professionals and the public can be assured that the process of assessing the scientific evidence provides for the best possible advice. Only evidence statements graded A, B, or C influenced the development of these Guidelines."