DETERMINATION OF EFFECT SIZE FOR MODELLING IN BODE[3]:

A Worked Example of the Effect of Reducing Dietary Saturated Fat Intake on Cardiovascular Events

Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme (BODE[3])

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Competing Interests

The authors have no competing interests.

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1 Introduction

The Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme (BODE[3]) aims to estimate the impact and cost-effectiveness of selected interventions using Markov models or multistate lifetables (Blakely, Foster et al. 2011). The BODE[3] programme includes the New Zealand Assessing Cost-Effectiveness: Prevention (NZACE-Prevention) study, which specifically addresses preventive interventions. In this study, effect size of interventions for input into modelling is determined by a literature review. The aim is to determine the best estimate, rather than attempting to collate all evidence.

A principle of BODE[3] (and thus NZACE-Prevention) is that existing systematic reviews and meta-analyses will be used to determine effect size where an appropriate, high-quality review exists (Blakely, Foster et al. 2011). This approach is largely pragmatic. Systematic reviews are highly time- and resource-intensive, and can take several months or more to complete comprehensively. This would not be the best use of the Project's resources when organisations such as the Cochrane Collaboration, the Campbell Collaboration and other health technology assessment (HTA) bodies have the resources to produce systematic reviews to high standards.

The methods for carrying out a literature search to derive the effect size for BODE[3] modelling has been previously presented in detail (Foster 2011). The current report applies these methods to a worked example.

Reducing dietary saturated fat intake through a range of interventions, including a "saturated fat tax", to improve cardiovascular health was identified as being of interest for analysis by NZACE-Prevention (Wilson, Blakely et al. 2010). The outcome to be measured was the effect on incidence of coronary heart disease (CHD) or cardiovascular disease (CVD) events, rather than change in cardiovascular risk *per se* (e.g. 5- or 10-year absolute risk). To determine the effect size for this outcome, a literature review to identify appropriate systematic reviews was undertaken.

This report provides an overview of the issues surrounding reduction in dietary saturated fat intake as a preventive measure for CHD or CVD, and reports the results of the NZACE-Prevention literature review and subsequent calculations of effect size.

2 Methods

2.1 Research question

The research question was framed as: How does a reduction in intake of dietary saturated fats affect the relative risks for CVD or CHD events in adults in developed countries? The primary intervention of interest was dietary intervention aimed at reducing saturated fatty acid (SFA) intake, including replacement with polyunsaturated fatty acids (PUFAs) or other foods. Of secondary interest was data comparing CVD or CHD rates by high versus low saturated fat intake.

To allow direct input into NZACE-Prevention modelling, the desired outcome was change in incidence of cardiovascular events and related mortality, not change in cardiovascular risk factors such as lipid and lipoprotein levels or bodyweight.

2.2 Search strategy

The search aimed to identify all *high-quality* systematic reviews relevant to the research question, as per BODE[3] procedures (Foster 2011). The search is outlined in detail in Appendix 1: Summary of Search Strategy. Because of the large amount of data on the topic, searching was limited to systematic reviews published from 2000 onwards. Only reviews that described a systematic process for searching for and selecting relevant articles and extracting data were included. Systematic reviews describing effects on cardiovascular risk were excluded, as were those that described supplementation with healthy oils (rather than a reduction in saturated fat intake as the primary intervention) or multifactorial interventions.

The search was designed as a 3-step process:

1. Relevance screening
   - based on the title (and abstract if needed for confirmation)
   - aimed at identifying whether the paper was of possible relevance to the research question
   - excluded papers that were not reviews, did not address dietary interventions to reduce saturated fats (or high versus low saturated fat intake), or did not measure cardiovascular events as an outcome.
2. Application of inclusion and exclusion criteria:
   - based on the abstract and/or full text of papers retained after relevance screening
   - determined whether the paper met the inclusion and exclusion criteria as outlined in Appendix 1: Summary of Search Strategy

3. Application of critical appraisal
    - applied only to those papers retained after step 2
    - used Critical Appraisal Skills Programme (CASP) tool for systematic reviews.(2006)

A flow diagram of the literature search results is presented in Figure 1.

 As part of the broader BODE[3] literature search protocol (Foster 2011), a validation test was carried out to test whether doing a maximised specificity search for reviews on Medline would provide sufficient sensitivity. The first search (Search A) used the limit "reviews (best balance of sensitivity and specificity)" in Medline. This broader Medline search retrieved 300 citations of which 47 were potentially relevant (368 and 53, respectively, for all sources combined). The second search (search B) used the Medline limit "reviews (maximizes specificity)", which retrieved 19 citations, of which 10 were potentially relevant (87 and 16, respectively, for all sources combined). Importantly, after application of inclusion and exclusion criteria, the two searches identified the same 7 relevant citations, of which 5 were finally included (all sources combined; Figure 1 shaded boxes). Thus, it can be concluded that searching Medline using the limit function "reviews (maximizes specificity)" is considerably less time consuming than broader searches and equally effective at identifying the best systematic reviews.

Figure 1: Flow diagram of search results for systematic reviews of reduction of dietary saturated fat intake and cardiovascular events
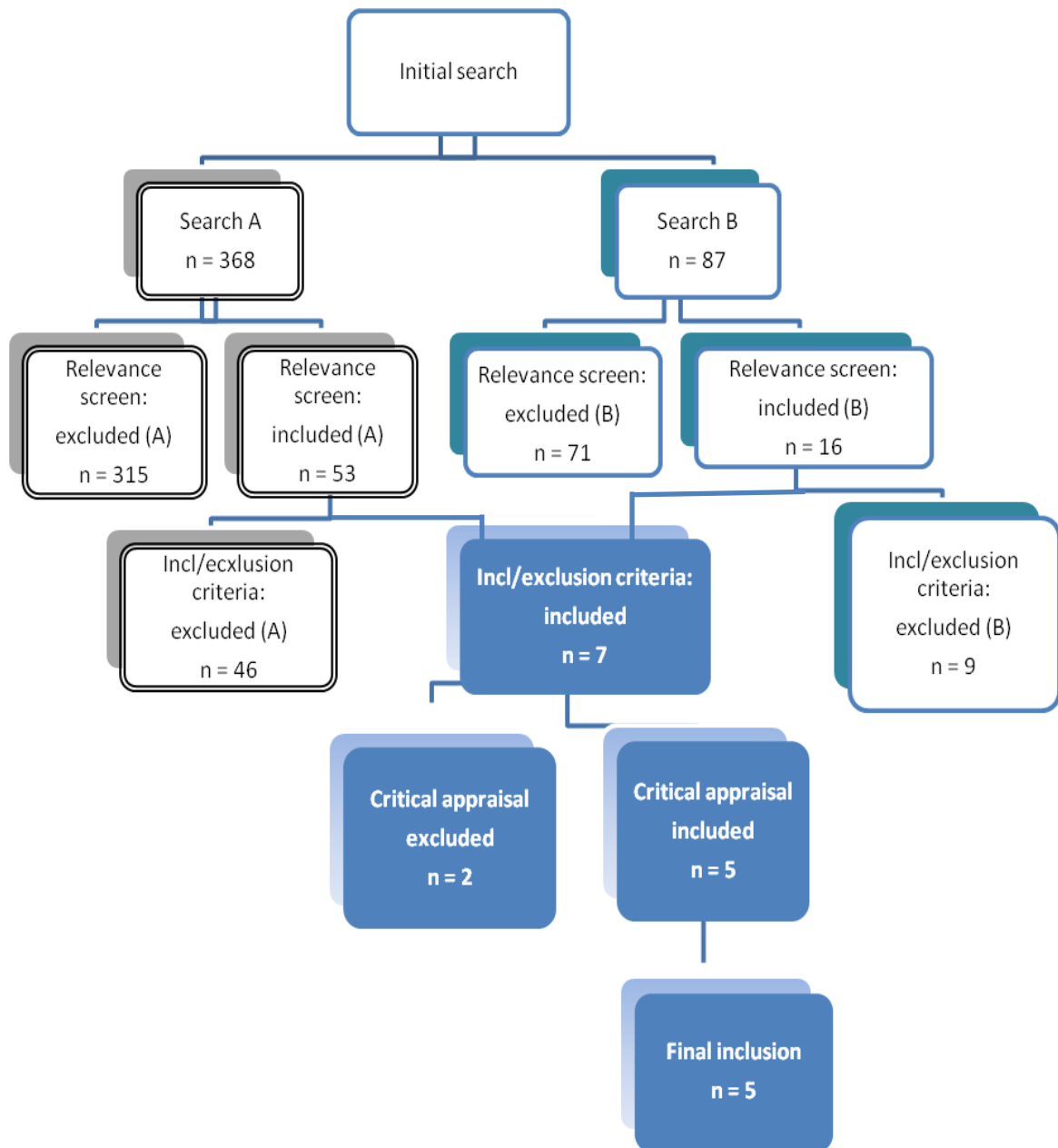
Search A used the Medline limit "reviews (best balance of sensitivity and specificity)", while search B used the Medline limit "reviews (maximizes specificity)". Searches from other sources were identical. Both searches identified the same 7 relevant papers after application of inclusion and exclusion criteria (shaded boxes).

3 Search Results

As shown in Figure 1 more than 80% of retrieved citations were discarded during relevance screening. Most of these papers were excluded because they were focussed on supplementation with specific healthy oils (e.g. omega-3 or omega-6 oils), they assessed cardiovascular risk factors and/or lipid/lipoprotein levels rather than cardiovascular events as the outcome, or the intervention was multifactorial rather than a reduction of saturated fat intake alone.

After the application of the inclusion and exclusion criteria, most papers were excluded because they were descriptive reviews rather than systematic reviews. For instance, in the broader Medline search, of the 42 potentially relevant papers discarded after application of the inclusion and exclusion criteria, 34 (81%) were excluded because they were non-systematic reviews, letters or editorials. The other most common reasons for exclusion were that the review covered a range of interventions and had inadequate details on reduction of saturated fat intake, or an updated version of the review had been published.

Two papers that met the inclusion and exclusion criteria were excluded after critical appraisal: one study had inadequate description of systematic methods (Djousse and Gaziano 2009), and the other had inadequate detail on the outcomes of interest (Hu and Willett 2002).

Quantitative estimates are required for input into BODE[3] modelling, and as such meta-analyses are preferred over qualitative reviews. Five high-quality, recent systematic reviews with meta-analyses, including a Cochrane review published in 2011 (Hooper, Summerbell et al. 2011), were identified as appropriate for determination of the effect size with regards to how reducing intake of dietary saturated fats affects the relative risks for cardiovascular disease events (Jakobsen, O'Reilly et al. 2009; Skeaff and Miller 2009; Mozaffarian, Micha et al. 2010; Siri-Tarino, Sun et al. 2010; Hooper, Summerbell et al. 2011). The meta-analyses are described in Table 1.

Additionally, the NZ Ministry of Health report "Nutrition and the Burden of Disease: New Zealand 1997-2011" was retained (Ministry of Health and University of Auckland 2003). Although this report did not meet the criteria for inclusion as a systematic review, it contained important data on burden of disease that contributed to estimation of the effect size for NZACE-Prevention.

The data extracted from these 6 papers are further discussed in the sections 5 and 6.

Table 1: Summary of methods of meta-analyses of studies of the effect on cardiovascular events of reducing saturated fat (SFA) intake in adults

	Mozaffarian et al.(2010)(Mozaffarian, Micha et al. 2010)	Jakobsen et al. (2009)(Jakobsen, O'Reilly et al. 2009)	Skeaff and Miller (2009)(Skeaff and Miller 2009)		Hooper et al. (2007)(Hooper, Summerbell et al. 2011)		Siri-Tarino et al.(2010)(Siri-Tarino, Sun et al. 2010)
Aim	To assess the impact on CHD endpoints of increased PUFA consumption, as replacement for SFA	To investigate whether energy intake from unsaturated fatty acids or carbs should replace energy intake from SFAs to prevent CHD	To summarise evidence regarding changes in dietary fat intake and risk of CHD		To assess the effect of reducing or modifying dietary fat on cardiovascular morbidity and total and cardiovascular mortality		To estimate the risk of CHD and stroke associated with increased dietary intake of SFAs
Outcome measure	"Hard" CHD events (MI, CHD death and/or sudden death). Excluded "soft" events, eg angina	Nonfatal MI and CHD death including sudden death	CHD events (inconsistently defined) and CHD death		All fatal and nonfatal CVD events (MI, angina, stroke, heart failure, peripheral vascular events, atrial fibrillation, unplanned CABG or angioplasty)		Fatal and nonfatal CVD (CHD events and stroke; not further defined)
Exposure/ intervention	Increased PUFA intake (total and/or omega-6) vs usual or control diet	5% energy intake of SFA replaced by isocaloric PUFAs or carbs	High vs low SFA intake	Decreased SFA with increased PUFA	Modified diet with increased PUFA or MUFA, with total fat intake maintained	Reduction of total fat and/or modification of dietary fats	High vs low SFA intake
Study no. and type	8 RCTs	11 cohort	9 cohort	9 RCTs	15 RCTs >6mo duration	48 RCTs >6mo duration	21 cohort
No. subjects	13,614	344,696	159,433	15,085	13,614	>70,000	347,747
Follow-up	Median 4.25 years	4-10y	5-20y	Intervention 2-5y	≤2y and ≥2y subgrouping		6-23y
Comments	Primary or secondary prevention. Excluded studies that focussed on omega-3 fats, multifactorial interventions or other major interventions.	Data for pooling available for only 11 of 14 relevant studies identified. Inclusion: criteria: ≥150 incident coronary cases; validation study of diet assessment methods; adults >35y. Exclusions: history of CVD, diabetes or cancer, extreme energy intake. PUFAs could include omega-3 and -6.	Primary or secondary prevention. Includes eight of the same RCTs of the Mozaffarian et al. meta-analysis.		Adults with any level of cardiovascular risk. Highly varied interventions. Allowed omega-3 or fish oils if part of other fat modifications, but not if given alone		Generally healthy adults

CABG = coronary artery bypass graft surgery; carbs = carbohydrates; CVD = cardiovascular disease; CHD = coronary heart disease; MI = myocardial infarction; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; RCT = randomised controlled trial; SFA = saturated fats

4   Overview of Saturated Fats and CVD

Before discussing the specific findings of the literature search, this section briefly outlines the relationship between saturated fats and cardiovascular disease in order to provide a context for our findings.

Higher blood levels of the smaller and denser particles of low-density lipoprotein (LDL)-cholesterol are strongly associated with atherosclerotic disease, while higher levels of high-density lipoprotein (HDL)-cholesterol levels are correlated with better cardiovascular health (Kinosian, Glick et al. 1994). Conventional wisdom has been that dietary saturated fats, the so-called "bad fats", increase cholesterol levels and thereby increase the risk for cardiovascular disease (the so-called "diet -heart hypothesis") (Weinberg 2004). It would thus seem intuitive that reducing intake of saturated fats would reduce cardiovascular risk. In line with this, public health messages have focussed on the "low-fat" message, and more recently on reducing dietary intake of saturated fat specifically. However, the relationship between reduction in dietary cholesterol intake and change in blood cholesterol levels is complex (Howell, McNamara et al. 1997). Furthermore, more recent evidence suggests that reduction of total fat or saturated fat *alone* does not significantly and consistently reduce risk of cardiovascular disease (Skeaff and Miller 2009; Siri-Tarino, Sun et al. 2010; Hooper, Summerbell et al. 2011). The benefit, if any, is dependent on what the saturated fat is replaced with in the diet (Weinberg 2004; Siri-Tarino, Sun et al. 2010).

Although data are not entirely consistent, the weight of evidence shows that replacing saturated fat with increased intake of PUFAs decreases cardiovascular risk (Jakobsen, O'Reilly et al. 2009; Skeaff and Miller 2009; Mozaffarian, Micha et al. 2010; Astrup, Dyerberg et al. 2011). Replacement of saturated fats with PUFAs lowers total cholesterol and LDL-cholesterol levels (Siri-Tarino, Sun et al. 2010). HDL-cholesterol levels are also lowered, but to a lesser extent than LDL- and total cholesterol levels. Thus, the HDL:LDL-cholesterol ratio is increased, and importantly the total:HDL-cholesterol ratio is decreased; the total:HDL-cholesterol ratio is considered to be the strongest single lipid predictor of cardiovascular death (Mensink, Zock et al. 2003; Lewington, Whitlock et al. 2007). Furthermore, replacement of saturated fats (SFAs) with PUFAs may reduce cardiovascular risk more than predicted by changes in lipid levels alone because of other non-lipid beneficial effects, e.g. on insulin resistance and systemic inflammation (Mozaffarian, Micha et al. 2010). Furthermore, benefits appear to accrue over time (Mozaffarian, Micha et al. 2010). The PUFA/SFA ratio may be more important than the SFA level alone. Data on replacement of saturated fats with monounsaturated fats is mixed.

Replacement of saturated fats with carbohydrates does not appear to reduce cardiovascular risk overall, although this may depend on the type of carbohydrate (Jakobsen, O'Reilly et al. 2009; Mozaffarian, Micha et al. 2010; Astrup, Dyerberg et al. 2011). Refined carbohydrates are known to have an adverse effect on CVD risk, while complex, low glycaemic-index (GI) carbohydrates may be neutral or possibly beneficial. Overall, replacement of saturated fats with refined carbohydrates decreases LDL levels but both total- and HDL-cholesterol are lowered to a similar extent. Thus, the total:HDL-cholesterol ratio remains the same (Mensink, Zock et al. 2003; Siri-Tarino, Sun et al. 2010). Triglyceride levels are also increased.

The only consistently demonstrated direct effect for a specific dietary fat has been for the harmful effect on cardiovascular health of synthetic trans fatty acids from partially hydrogenated vegetable oils, which are used in older-style margarines, commercial baking and deep-fried food (see Appendix 2: Trans Fatty Acids) (Mozaffarian, Katan et al. 2006).

5   Results of Literature Review

The five meta-analyses selected for determination of the effect size of modification of dietary saturated fat intake for NZACE-Prevention modelling provided data for both high versus low dietary intake of saturated fat and replacement of dietary saturated fat with PUFAs or carbohydrates. Methods of these meta-analyses are shown in Table 1.

There were considerable differences in the approaches of the meta-analyses, particularly with regards to exclusion of interventions including increased intake of omega-3 PUFAs, which may infer significant cardiovascular benefits independent of reduction in saturated fat intake (Kris-Etherton, Harris et al. 2002; Skeaff and Miller 2009). Of note, the meta-analyses of Skeaff et al. (Skeaff and Miller 2009) and Mozaffarian et al. (Mozaffarian, Micha et al. 2010) include eight of the same RCTs of SFA/PUFA replacement: Skeaff et al. (Skeaff and Miller 2009) includes one additional small RCT (n = 54).

Some fairly consistent trends in results across the meta-analyses were seen, as shown in Table 2. Comparing highest with lowest levels of saturated intake showed that having a higher saturated fat intake in itself did not increase the risk for CHD events, CVD events or CHD/CVD death (Skeaff and Miller 2009; Siri-Tarino, Sun et al. 2010). In contrast, most interventions that replaced saturated fat intake with PUFA intake significantly reduced the incidence of CHD and CVD events, while effects on mortality were more mixed (Jakobsen, O'Reilly et al. 2009; Skeaff and Miller 2009; Mozaffarian, Micha et al. 2010; Hooper, Summerbell et al. 2011). Replacing saturated fat with carbohydrates did not reduce the incidence of coronary events, and the incidence was actually significantly increased when 5% of daily energy from SFAs was replaced by carbohydrates in the analysis by Jakobsen et al. (Jakobsen, O'Reilly et al. 2009).

It was thus determined that the intervention of most interest to NZACE-Prevention for modelling was a strategy that not only reduced saturated fat intake, but also increased PUFA intake, while not having any intentional effect on carbohydrate intake.

Table 2: Summary of results of meta-analyses on the effect of reduction in saturated fat (SFA) intake on cardiovascular events
Results are for random effects models unless otherwise stated and are for the most fully adjusted multivariate models

Study	Measure	Events	Death	Heterogeneity[a]	Comments
Highest vs lowest SFA intake					
Skeaff and Miller(Skeaff and Miller 2009)	RR highest vs lowest SFA intake	CHD events 0.93 (0.83, 1.05)	CHD death 1.14 (0.82, 1.60)	Important heterogeneity for CHD death. Heterogeneity negligible to moderate for CHD events	Increased saturated fat intake had no significant effect on CHD events or death.
	RR per 5% energy increase in SFA intake	CHD events 1.03 (0.87, 1.22)	CHD death 1.11 (0.75, 1.65)		Other fats were adjusted for such that the increased SFA intake was equivalent to replacement for carbohydrate intake in most studies.
Siri-Tarino et al(Siri-Tarino, Sun et al. 2010)	RR highest vs lowest SFA intake	CHD events 1.07 (0.96, 1.19) CVD events 1.00 (0.89, 1.19)		Moderate to important heterogeneity	Higher saturated fat intake had no significant effects on CHD events, stroke or CVD events. No significant effect modification by sex or age.
Modified diet to increase PUFA intake					
Skeaff and Miller(Skeaff and Miller 2009)	RR per 5% energy increase in PUFA	CHD events 0.84 (0.70, 1.00)*	CHD death 0.94 (0.71, 1.25)	Negligible heterogeneity	CHD events significantly decreased by 5% of daily energy increase in PUFA intake. Other fats were adjusted for such that the increased PUFA intake was equivalent to replacement for carbohydrate intake in most studies.
SFA replaced by PUFA					
Hooper et al(Hooper, Summerbell et al. 2011)	RR for SFA/PUFA modified diet vs controls Modified fats[b]	CVD events 0.82 (0.66, 1.02)	CVD death: 0.92 (0.73, 1.15)	No heterogeneity for CVD mortality for reduced and/or modified fat. Heterogeneity moderate-to-important for all other analyses.	Reduction in CVD events, but no effect on CVD death or total mortality. For the overall analysis (reduced total fat and/or modified fats), the reduction in cardiovascular events was driven primarily by fat modification and was significant only for duration >2y and in men. Notably, the significance for reduction in CVD events was lost when studies that made dietary changes other than fat, or had other systematic differences in care, were excluded. Effects did not differ by cardiovascular risk level.
	RR for SFA/PUFA modified diet vs controls Reduced total fat and/or modified fats	CVD events 0.86 (0.77, 0.96)*	CVD mortality 0.94 (0.85, 1.04)		
Skeaff and Miller(Skeaff and Miller	RR for SFA/PUFA modified diet vs controls	CHD events 0.83 (0.69, 1.00)*	CHD death 0.84 (0.62, 1.12)	Heterogeneity was low for CHD death and moderate for	Significant reduction in CHD events in the overall group and for both CHD death and events when data was limited to the 6 trials (n = 3002 participants) in which the SFA/PUFA

Study	Measure	Events	Death	Heterogeneity[a]	Comments
2009)	RR for SFA/PUFA modified diet vs controls Effective diet only[b]	CHD events 0.68 (0.49, 0.94)*	CHD death 0.52 (0.30, 0.87)*	CHD events	modified diet reduced serum cholesterol levels significantly ("effective diet").
Jakobsen et al(Jakobsen, O'Reilly et al. 2009)	RR for 5% energy SFA replaced by PUFA	CHD events 0.87 (0.77, 0.97)*	CHD death 0.74 (0.61, 0.89)*	No significant heterogeneity	CHD events and deaths significantly reduced when 5% of daily energy from SFA is replaced by PUFA No effect modification by sex or age
Mozaffarian et al(Mozaffarian, Micha et al. 2010)	RR for SFA/PUFA modified diet vs controls	CHD events 0.81 (0.70, 0.95)*	CHD death 0.80 (0.65, 0.98)*	Heterogeneity moderate, where stated	Only significant with longer duration RR for CHD events 0.73 (0.61-0.87) for longer duration[c] vs 0.91 (0.76, 1.10) for shorter duration trials
	RR for 5% energy SFA replaced by PUFA	CHD events 0.90 (0.83-0.97)*			
SFA replaced by carbohydrates					
Jakobsen et al(Jakobsen, O'Reilly et al. 2009)	HR for 5% energy SFA replaced by carbs	Coronary events* 1.07 (1.01, 1.14)	CHD death 0.96 (0.82, 1.13)	Significant heterogeneity (p < 0.05) for coronary death, but not coronary events	Risk of CHD events or death were not reduced when SFAs were replaced with carbs No effect modification by sex or age

[a] Heterogeneity classified as: I^2 <5% negligible; <25% low; 25-50% = moderate; >50% = important, and; >75% = substantial

[b] Most modified fat diets reduced SFA and increased PUFA or, less commonly, MUFA intake. However, the magnitude of decrease in SFA intake was not always clearly defined

[c] Longer duration than the median of 4.25 years

CHD = coronary heart disease; CVD = cardiovascular heart disease; HR = hazard ratio; MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; RR = relative risk; SFA = saturated fatty acids

* significant effect (p ≤ 0.05 or 95% CI indicative of significance)

6 Estimation of Effect Size: SFA replaced by PUFA

While overall there is a lot of variability in the outcomes of individual trials for dietary modification, there is a reasonable degree of consistency in findings from meta-analyses showing that the incidence of CHD or CVD events is reduced when SFAs are replaced with PUFAs, although results with regards to reduction in cardiovascular death are mixed (see Table 2).

6.1 Primary Outcome

When considering robustness of evidence, a systematic review of RCTs is considered to be the highest level of evidence (Foster 2011). Thus, for NZACE-Prevention modelling the 2010 meta-analysis by Mozaffarian et al. (Mozaffarian, Micha et al. 2010) was considered to be the best source for estimating the intervention effect size of replacing SFAs with PUFAs. The meta-analysis was of 8 RCTs of >1 year's duration (13,614 participants). Studies of both primary and secondary prevention of CHD were included. Only "hard" CHD endpoints (myocardial infarction [MI], CHD death and/or sudden death) were included in the meta-analysis (Mozaffarian, Micha et al. 2010). Because this analysis considered only these hard endpoints and was focussed solely on SFA/PUFA replacement, the Mozaffarian et al. meta-analysis was preferred over the Skeaff et al. meta-analysis of the same RCTs (plus one additional small RCT). The Skeaff et al. meta-analysis was inconsistent in which CHD events were included as endpoints, and analysed a wide range of exposures/interventions and thus provided less detail on SFA/PUFA replacement (Skeaff and Miller 2009).

In the Mozaffarian et al. meta-analysis, both CHD events and CHD death were reduced by about 20%, and this was statistically significant (see Table 2). The RR for reduction in CHD events per 5% of daily energy SFA/PUFA replacement was 0.90 (95% CI: 0.83, 0.97) (Mozaffarian, Micha et al. 2010).

The 8 RCTs included in the Mozaffarian et al. meta-analysis are shown in Table 3 (Leren 1966; Dayton, Pearce et al. 1968; Medical Research Council 1968; Leren 1970; Turpeinen, Karvonen et al. 1979; Miettinen, Turpeinen et al. 1983; Burr, Fehily et al. 1989; Frantz, Dawson et al. 1989; Watts, Lewis et al. 1992; Ness, Hughes et al. 2002). Only 2 of the individual studies showed a significant effect of SFA/PUFA modification on CHD events, with RRs of 0.75 (0.57, 0.99) (Leren 1970) and 0.55 (0.34, 0.88) (Turpeinen, Karvonen et al. 1979), respectively. None had a significant effect on CHD death.

With intervention, levels of PUFA intake increased to 8-20% of daily energy, compared with 4-6% in controls (Mozaffarian, Micha et al. 2010). The absolute difference in PUFA dietary intake between controls and intervention as the percentage of total daily energy consumption was 9-16% across the studies other than the DART and STARS studies where the increase was only 2.5−2.8%. The

reduction in serum cholesterol level versus controls was 0.75−1.1 mmol/L across the studies, except for a notably lower reduction of 0.26 mmol/L in the DART study (Burr, Fehily et al. 1989).

A possibly important limitation in terms of applicability of the results of the eight individual RCTs is that all but 2 studies were initiated prior to 1970 (Leren 1966; Dayton, Pearce et al. 1968; Medical Research Council 1968; Leren 1970; Turpeinen, Karvonen et al. 1979; Miettinen, Turpeinen et al. 1983; Burr, Fehily et al. 1989; Frantz, Dawson et al. 1989; Watts, Lewis et al. 1992; Ness, Hughes et al. 2002). Only two of the studies were double-blind, but all had blinded assessment of outcome. Six of the 8 studies were in men, however the largest study (n = 9057) included women (Frantz, Dawson et al. 1989). The smaller number of events in women makes it hard to determine if there are sex-dependent differences in the individual trials. Most studies only enrolled participants aged <65y, and the mean or median age was most frequently in the early- to mid-50s. Where reported, smoking, blood pressure and body weight were considered unlikely to be significant confounders or were adjusted for (Leren 1966; Medical Research Council 1968; Turpeinen, Karvonen et al. 1979; Miettinen, Turpeinen et al. 1983; Frantz, Dawson et al. 1989; Watts, Lewis et al. 1992). Whether issues around adherence have distorted the results of the studies is discussed in section 6.3.

Given these potential limitations of the studies included in the meta-analysis by Mozaffarian et al., it was important to establish that the estimate of this meta-analysis was in line with other evidence.

Table 3: Description and results of individual randomised, controlled trials included in the Mozaffarian et al meta-analysis (Mozaffarian, Micha et al. 2010) of the effect on coronary heart disease (CHD) of replacing saturated fat (SFA) with polyunsaturated fats (PUFAs).
Events are defined as per the Mozaffarian et al. meta-analysis: "hard" CHD events (MI, CHD death and/or sudden death) only.

Study (year study started)	Veterans (1959)(Dayton, Pearce et al. 1968)	MRC soya-bean oil (1960)(Medical Research Council 1968)	Oslo Diet-Heart Study (1956)(Leren 1966; Leren 1970)	Finnish Mental Hospital Study (1959)		Minnesota Coronary Survey (1968)(Frantz, Dawson et al. 1989)	DART (1983)(Burr, Fehily et al. 1989; Ness, Hughes et al. 2002)	STARS (1992)(Watts, Lewis et al. 1992)
				Men(Turpeinen, Karvonen et al. 1979)	Women(Miettinen, Turpeinen et al. 1983)			
Design	Double-blind N = 846	Assessor blind N = 393	Assessor blind N = 412	Assessor blind, crossover study of 2 x 6y periods in 2 hospitals		Double-blind N = 9057	Assessor blind N = 2033	Assessor blind N = 55
				N = 444/478 for diet/control period	N = 372/341 for diet/control period			
Population	Men 54-88y (mean 65y) +/- CHD	Men ≤60y Post MI	Men 30-64y (mean 56y) Post MI	Men 34-64y	Women 44-64y	Men + women Median 45-49y +/- CHD	Men <70y (mean 56y) Post MI	Men <66y (mean 50y) CHD
				No evidence of CHD				
Setting	Domiciliary care unit (intermittent)	Free-living	Free-living	Institutional		Institutional	Free-living	Free-living
Intervention	Meals provided: ↓cholesterol, ↑PUFA, phytosterols	Dietary instruction: ↓SFA (↓fat from meat, dairy, egg yolks etc) ↑ PUFA (85g soya-bean oil daily)	Dietary instruction: ↓SFA/cholesterol, (↓fat from meat, dairy, egg yolks etc), ↑ fruit and vege, fish, nuts, and PUFAs (soya-bean oil ≈50-100g/day)[d]	Meals provided: dairy fat replaced by vegetable oils (mainly soya-bean oil)		Meals provided: ↑PUFA; ↓SFA/cholesterol	Dietary advice: ↓ total fat, ↑PUFA/SFA ratio to 1 (± fish and fibre advice)	Dietary advice (some food provided): ↓ total fat/cholesterol,↑ omega-3/6, ↑ soluble fibre
Duration of intervention	Max 8y	2-7y	5y	6y (mean observation time 3-4y)		Mean 1y (max 4.5)	2y	3y
Adherence with intervention	49%	85%	Excellent: 62% Good: 22%	Good (institutionalised participants)		NA	NA	NA

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| Study (year study started) | Veterans (1959)(Dayton, Pearce et al. 1968) | MRC soya-bean oil (1960)(Medical Research Council 1968) | Oslo Diet-Heart Study (1956)(Leren 1966; Leren 1970) | Finnish Mental Hospital Study (1959) | | Minnesota Coronary Survey (1968)(Frantz, Dawson et al. 1989) | DART (1983)(Burr, Fehily et al. 1989; Ness, Hughes et al. 2002) | STARS (1992)(Watts, Lewis et al. 1992) |
				Men(Turpeinen, Karvonen et al. 1979)	Women(Miettinen, Turpeinen et al. 1983)			
No. of CHD events: intervn/control	53/71	45/51	61/81 (5y)	25/47	27/46	131/121	132/144	2/5
• RR (95% CI)[a]	0.74 (0.53, 1.03)	0.86 (0.61, 1.22)	0.75 (0.57, 0.99)*	0.55 (0.34, 0.88)*	0.64 (0.41, 1.00) [ns after age adjustment]	1.08 (0.84, 1.37)	0.91 (0.72, 1.16) adj	0.41 (0.09, 1.96)
No. of CHD/CVD deaths: intervn/control	18/27 CHD	27/25 CVD	37/50 CHD 38/52 CVD	6/12 CHD	3/3 CHD	269/248 All	97/97 CHD	
• RR (95% CI)	0.66 (ns)	1.05 (ns)	0.74 CHD (ns) 0.73 CVD (ns)	≈0.5 (ns; not further reported)	≈1 (ns; not further reported)	1.08 (ns)	1.00 (0.77, 1.30) adj	
Other outcomes	RR CVD events: 0.72* (P = 0.04)		RR deaths at 11y follow-up: 0.84 CHD (ns) 0.86 CVD (ns)				Adj RR CHD deaths at 10y follow-up: 0.89 (0.77, 1.02)	
Time-lag/attenuation	Effect of intervn greater after y6		Significant reduction in CHD events seen only from year 3 on.	Protective effect of diet against CHD was lost once diet stopped (i.e. in the control crossover period)				
Comments	CVD events significantly reduced only in those aged <65y		CHD events reduced significantly only in those aged <60y.	Note loss to follow-up of approx 11-12% per year (completion rate 45%)				

[a] Where data were not available from the original report, data calculated for the meta-analysis by Mozaffarian et al.(Mozaffarian, Micha et al. 2010) were used.

* Statistically significant result.

Adj = adjusted for confounders; CHD = coronary heart disease; CI = confidence interval; DART = Diet and Reinfarction Trial; MI = myocardial infarction; MRC = (UK) Medical Research Council; NA = not applicable or data not available; ns = not significant; RR = relative risk; STARS = St Thomas Atherosclerosis Regression Study.

6.2 Supporting Evidence

As noted above, the meta-analysis of RCTs by Mozaffarian et al. that included only "hard" CHD events calculated a 19% reduction in CHD events overall [RR 0.81 (0.70, 0.95)], and a 10% reduction in CHD events per 5% daily energy from SFA replaced with PUFA [RR 0.90 (0.83-0.97)] (Mozaffarian, Micha et al. 2010). Results from the other meta-analyses suggest that this estimate is reasonable CHD events.

The 2009 pooled analysis by Jakobsen et al. (Jakobsen, O'Reilly et al. 2009), involving 11 cohort studies and almost 350,000 participants, has been described as robust and of higher quality than earlier meta-analyses (Skeaff and Miller 2009; Mozaffarian, Micha et al. 2010). This analysis also included only "hard" CHD events. Replacing 5% of daily energy from SFAs with PUFAs reduced coronary events by 13% (HR 0.87; 95% CI 0.77, 0.97). Furthermore, an expert panel concluded that in Western countries a 1% replacement of energy from SFAs with PUFAs reduces the incidence of CHD by 2-3%. Assuming a linear relationship, a 5% replacement would thus be predicted to reduce the CHD incidence by 10-15% (Astrup, Dyerberg et al. 2011).

Despite differences in the endpoints included in CHD events, Skeaff et al. reported a similar overall 17% reduction in any CHD event (RR 0.83; 95% CI: 0.69, 1.00; p = 0.05) (Skeaff and Miller 2009). A Cochrane review (Hooper, Summerbell et al. 2011) also reported a reduction in CVD events of 18% (RR 0.82; 95% CI: 0.66, 1.02), but the fat modification interventions in this analysis were only loosely defined and may not be comparable with the other meta-analyses; replacement with MUFAs as well as PUFAs was included.

The effect of fat modification on risk of CHD death was highly variable between the different meta-analyses, being not significant in most analyses, but as high as a 26% reduction per 5% of daily energy SFA/PUFA replacement in Jakobsen et al. (Jakobsen, O'Reilly et al. 2009). The latter estimate requires further validation given that the reduction in CHD events in this analysis was only 13%.

6.2.1 Correlation to Plasma Cholesterol Levels

The effect size calculated in the Mozaffarian et al. meta-analysis (Mozaffarian, Micha et al. 2010) is further supported by considering the correlation of the reduction in CHD events with the change in plasma total cholesterol levels. In response to a 9.9% of daily energy SFA/PUFA replacement in this analysis, total cholesterol levels were reduced by a mean 0.76 mmol/L. This was associated with a 19% reduction in CHD events (RR = 0.81). Thus, there was a 24% reduction in risk per 1 mmol/L reduction in total cholesterol levels (RR = 0.76; 95% CI 0.62, 0.93) in this meta-analysis (Mozaffarian, Micha et al. 2010).

This is very close to estimations from a meta-analysis by the Prospective Studies Collaboration (PSC) of blood cholesterol and vascular mortality that involved 61 studies and almost 900,000 participants. The RR for CHD mortality for each 1 mmol/L lower usual total cholesterol was 0.44 to 0.85, depending on age; averaged over all ages, the RR is approximately 0.7 (Lewington, Whitlock et al. 2007). Using the RR figure of 0.7, the reduction in cholesterol achieved in the Mozaffarian et al. meta-analysis would be predicted to reduce CHD death by about 23%; the reduction in CHD death observed in the meta-analysis was 20% (Mozaffarian, Micha et al. 2010). Mozaffarian et al. also calculated from other data that a 5% of daily energy increase in PUFA replacing SFA would be predicted to reduce CHD events by 9% based on changes in the TC:HDL-C ratio (RR 0.91; 95% CI: 0.87, 0.95); the observed RR was 0.90 (Mozaffarian, Micha et al. 2010).

Our preferred estimate for use in NZACE-Prevention modelling is further supported by data used by the Ministry of Health in modelling the burden of disease associated with high blood cholesterol levels in the New Zealand population in 2003 (Ministry of Health and University of Auckland 2003). In their estimates, a 1% of daily energy decrease in SFAs replaced with PUFAs would decrease total cholesterol levels by 0.078 mmol/L. If linear, this equates to a reduction of total cholesterol levels by 0.39 mmol/L when there is a 5% of daily energy SFA/PUFA substitution, which is almost identical to that observed from the Mozaffarian et al. meta-analysis (0.38 mmol/L per 5% daily energy SFA/PUFA replacement). The Ministry of Health modelled that a 1 mmol/L decrease in total cholesterol would reduce CHD by 30-73% depending on age. The estimate for 55-64 year olds was 44% (Ministry of Health and University of Auckland 2003). These data predict that if a 55-64 year-old replaces 5% of daily energy from SFAs with PUFAs CHD would be reduced by 17%.

6.3 Adherence

It would be expected that poor adherence with dietary interventions would bias towards the null. If studies included in the Mozaffarian et al. meta-analysis had better levels of adherence than could be expected in the real world, the observed benefit of fat modification would be overestimated. Three of the RCTs included in the meta-analysis were carried out in institutional settings where meals (randomised to be normal diet or SFA/PUFA modified) were provided, and participants had limited access to other food. A fourth study provided meals approximately half of the time. These studies would achieve a level of compliance that would be unlikely in the real world. However, outcomes were not significantly better in the 4 institutional studies than in the 4 free-living studies: RR for CHD events 0.76 (95% CI: 0.55, 1.04) vs 0.84 (95% CI: 0.72, 0.98) (Mozaffarian, Micha et al. 2010).

Nevertheless, there is evidence that the level of compliance with the SFA/PUFA modified diet does affect the decrease in serum cholesterol that is achieved (Leren 1966; Frantz, Dawson et al. 1989). For instance, in the Skeaff et al. (Skeaff and Miller 2009) meta-analysis, the reduction in risk of CHD was

much greater when only studies in which the SFA/PUFA intervention reduced serum cholesterol levels significantly were included: the RR for CHD events was 0.68 (0.49, 0.94) compared with 0.83 (0.69, 1.00) when all studies were included.

The data from the Mozaffarian et al. (Mozaffarian, Micha et al. 2010) and the Skeaff et al. (Skeaff and Miller 2009) meta-analyses suggest that a significant reduction in risk of CHD is maintained even when adherence is less than ideal, although the magnitude of the reduction may be somewhat less.

Of note is that adherence is likely to vary with the type of intervention. For example, adherence might tend to be higher with an environmental intervention such as higher prices for foods high in saturated fat (e.g., the result of a Danish-style saturated fat tax). However, adherence might be lower with an intervention such as a mass media campaign promoting a healthier diet. Even so, it is encouraging that the New Zealand population has over recent decades been making some favourable dietary shifts to reduce saturated fat intake (i.e., consuming more margarine relative to butter and consuming more low-fat milk relative to whole milk).

6.4   Time lag and attenuation

Most studies reported outcomes for only the duration of the intervention, which often varied depending on how long the participant was willing to continue the prescribed diet. Thus, the reductions in risk stated in Table 2 are over variable lengths of time. The reduction in risk of CHD described by Mozaffarian et al. occurs over a median duration of 4.25 years (Mozaffarian, Micha et al. 2010).

In the RCTs of SFA/PUFA modification, serum cholesterol levels decreased rapidly in the first 3-6 months of the trial, and thereafter differences between intervention and control groups were maintained over the duration of the trial (Leren 1966; Medical Research Council 1968; Burr, Fehily et al. 1989; Frantz, Dawson et al. 1989). However, there appears to be a lag between reduction in serum cholesterol levels and benefit in terms of reduction in CHD. In the meta-analysis by Mozaffarian et al. there was only a significant effect on CHD events in trials greater than the median of ≥4.25 years' duration (Mozaffarian, Micha et al. 2010). The RR for CHD events for the 4 trials with a shorter duration was 0.91 (0.76, 1.10) versus 0.73 (0.61, 0.87) for those of longer duration. The study duration was found to be an independent determinant of the magnitude of risk reduction, with it being estimated that every additional year of the SFA/MUFA modified diet reduced the relative risk by an additional 9.2% compared with the control group (Mozaffarian, Micha et al. 2010). Similarly, fat modification significantly reduced CVD events only when the duration of the intervention was >2y in Hooper et al (Hooper, Summerbell et al. 2011).

The Finnish RCTs of SFA/PUFA replacement provide important information on attenuation because of their crossover design (Turpeinen, Karvonen et al. 1979; Miettinen, Turpeinen et al. 1983). Two hospitals were involved with one hospital providing a low-SFA/high-PUFA diet for 6 years and the other providing a normal diet for 6 years, with each then crossing over to provide the other diet for 6 further years. After completing the SFA/PUFA diet stage and returning to the normal diet in the second phase within the same hospital, not only did reductions in serum cholesterol levels rapidly reverse but the protective effect against CHD also reversed. This suggests that any cardiovascular benefit of fat modification is not maintained after the diet is stopped.

6.5   Effect modification by age and sex

While some individual RCTs have reported that the effect of fat modification on CHD events is only significant in those aged less than 60-65y (Leren 1966; Dayton, Pearce et al. 1968), the meta-analyses of cohort studies by both Siri-Tarino et al. (Siri-Tarino, Sun et al. 2010) and Jakobsen et al. (Jakobsen, O'Reilly et al. 2009) reported that there was no effect modification by sex or age.

However, some caution is required because most studies did not include the more elderly (>70y).

6.6   Primary vs Secondary Prevention

The studies of SFA/PUFA modification included in the Mozaffarian et al meta-analysis were of primary and/or secondary prevention of CHD (see Table 3). For the 4 studies that analysed predominantly primary prevention populations the RR for CHD events was 0.76 (95% CI: 0.55, 1.04), while it was 0.84 (0.72, 0.98) for the 4 studies that analysed secondary prevention. Primary versus secondary prevention was not found to be a significant determinant of the risk reduction. Thus, the overall result from Mozaffarian et al. (RR for CHD events = 0.81) can be applied across a general population.

7   Conclusions

A literature search identified 5 meta-analyses of potential relevance for determining the effect size for interventions aimed at reducing dietary intake of saturated fat for NZACE-Prevention modelling.

From these meta-analyses and other background information, it was determined that reducing saturated fat intake alone did not reduce cardiovascular risk, and neither did replacing saturated fats with carbohydrates. Cardiovascular risk is reduced only by replacing saturated fats with polyunsaturated fats.

The best evidence for the effect of SFA/PUFA modification comes from the meta-analysis of RCTs conducted by Mozaffarian et al. which found that "hard" CHD events were reduced by 10% per 5% of daily energy from SFAs that is replaced with PUFAs (RR 0.90; 95 CI: 0.83, 0.97), and that SFA/PUFA replacement of 10% of energy reduces CHD events correspondingly by about 20% (Mozaffarian, Micha et al. 2010). Whether a linear relationship is maintained for greater SFA/PUFA substitution is not known. However, there is a ceiling for the magnitude of SFA/PUFA substitution that can occur in New Zealand, which is probably around 10% of daily energy or less: New Zealanders currently consume on average 13% of daily energy as saturated fat (University of Otago and Ministry of Health 2011).

Data from the other meta-analyses and studies of the correlation between changes in plasma cholesterol levels and reduction in CHD risk support the estimate from Mozaffarian et al. of a 10% reduction in CHD events per 5% of daily energy SFA/PUFA substitution. As a whole, this consistency suggests that while the data included in the Mozaffarian et al. meta-analysis have some limitations, any systematic bias is very probably not sufficient to invalidate the estimate. Important potential confounders were adjusted for or had minimal impact. Thus, this estimate is appropriate for use in NZACE-Prevention modelling. Consideration of random error can be incorporated into our models by conducting sensitivity analyses around the 95% confidence interval (lower 0.83, upper 0.97) of the Mozaffarian estimate (Mozaffarian, Micha et al. 2010), which is likely to have a log-normal distribution. Note that while not important for this example, understanding heterogeneity of effect and cost across demographic and socioeconomic strata is a key focus for BODE[3], and thus some analyses will need to consider effectiveness by sex, age, ethnicity and socioeconomic deprivation level.

The modelling should account for time lag and attenuation. It should be assumed that the protective effect of a fat-modified diet is lost once the diet is discontinued. While reductions in serum cholesterol levels occur rapidly, there appears to be a time lag until this clinically reduces risk of CHD. In future health economic modelling we may consider the most biologically plausible time frame for risk

reduction, which is likely a linear reduction in risk up to the full risk reduction effect. This is compatible with findings from the Lyon Diet Heart Study where the intervention group showed immediate (first month) survival differences from the control group (see the graph in Logeril et al.) (de Lorgeril, Salen et al. 1999). Furthermore, a scenario analysis to account for worse than anticipated adherence by halving the effect size may be appropriate.

Data on reducing the risks of cardiovascular death are more mixed, and methods to ensure that this uncertainty is adequately incorporated into NZACE-Prevention modelling will be needed.

To put the potential effect of SFA/PUFA modification into context, use of statins has been found to reduce the risk of CHD death by 22% and major coronary events by 25% over 5 years (Baigent, Keech et al. 2005).

Data on replacement of SFA with monounsaturated fats are inadequate to draw conclusions. However, for NZACE-Prevention modelling purposes it is worth noting that olive oil while high in monounsaturated fat also has a range of other anti-atherogenic effects (Covas 2007) that would need to be considered in any modelling around cardiovascular disease.

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Appendix 1: Summary of Search Strategy

Summary of Literature Search on Saturated Fats	
DATE: 20/6/11	
1. Research question	
How does a reduction in intake of dietary saturated fats affect the relative risks for cardiovascular disease (CVD) or coronary heart disease (CHD) events in adults in developed countries?	
P (population) = Adults in developed countries	
I (intervention/exposure) = (i) Dietary intervention aimed at reducing saturated fat intake, including replacement with polyunsaturated fats (PUFAs) or other foods; (ii) Comparison of CVD/CHD rates by high versus low saturated fat levels or intake	
C (Comparisons) = (i) No dietary intervention; (ii) Low dietary saturated fat intake	
O (outcome) = CVD/CHD events	
2. Inclusion and Exclusion Criteria	
Inclusion	Exclusion
All systematic reviews relevant to the research question published from 2000 onwards	Opinion pieces, non-systematic reviews and non-clinical research papers Descriptive and/or mechanistic studies
Outcome = CVD/CHD events	Outcome cardiovascular risk factors rather than cardiovascular events
Exposure: (i) = Intervention to reduce dietary saturated fat intake	High-risk populations rather than general population
Exposure: (ii) = Comparison of high versus low levels of fat intake	Multifactorial interventions
Studies conducted in developed countries (OECD criteria)	Focus on *supplementation* with specific healthy oils (e.g. omega-6 or omega-3) rather than primary reduction in saturated fat
	Use of cholesterol-lowering or other anti-hyperlipidaemic drugs
	Due to the large amount of data, systematic reviews that covered a range of dietary components, rather than focussing on fats, were also excluded
3. Search strategy	
Keywords	Limits
Dietary cholesterol	English language
Saturated fats	Human
Dietary fats	Publication year 2000-present
Cardiovascular disease	
4. Sources	
• Medline	

• NZ Ministry of Health publications
• Cochrane library
• DARE and HTA databases
• Snowballing

Search string

Example search string: Medline

1   exp Cardiovascular Diseases/co, di, dh, dt, ec, ep, eh, et, mo, nu, pa, pp, pc, rh, th [Complications, Diagnosis, Diet Therapy, Drug Therapy, Economics, Epidemiology, Ethnology, Etiology, Mortality, Nursing, Pathology, Physiopathology, Prevention & Control, Rehabilitation, Therapy] (682790)

2   dietary fats/ or butter/ or exp cholesterol, dietary/ (19613)

3   1 and 2 (2956)

4   limit 3 to (english language and humans and yr="2000 -Current") (1270)

SEARCH A (as per **Error! Reference source not found.**)

5   limit 4 to "reviews (best balance of sensitivity and specificity)" (309)

6   remove duplicates from 5 (302)

SEARCH B (as per **Error! Reference source not found.**)

7   limit 4 to "reviews (maximizes specificity)" (22)

8   remove duplicates from 7 (20)

Appendix 2: Trans Fatty Acids

Given the harmful effects of synthetic trans fatty acids used in commercial cooking and deep frying, at first glance this would appear to be a potential candidate for NZACE-Prevention modelling.

The risk of coronary heart disease (CHD), even at relatively low levels of consumption of trans fatty acids (e.g. 2-3% of total daily energy intake), is significantly increased. In a meta-analysis of 4 prospective cohort studies involving nearly 140,000 subjects, the RR for CHD for a 2% increase in daily energy in trans fatty acids (replacing carbohydrate) was 1.23 (1.11 to 1.37; P<0.001) (Mozaffarian, Katan et al. 2006). The risk for cardiovascular events associated with synthetic trans fatty acids is greater than that of saturated fats (Astrup, Dyerberg et al. 2011).

Because of this risk, a number of countries have introduced legislation to limit use of trans fatty acids in commercial food. However, Food Standards Australia New Zealand has calculated that the intake of trans fatty acids in New Zealand is low at only 0.6% of daily energy intake (Food Standards Australia New Zealand December 2010). This is lower than WHO recommendations of 1%. Furthermore, more than half of trans fatty acid intake in New Zealand is estimated to be from natural sources. Natural trans fatty acids that occur in low levels in meat and dairy products appear to not have an adverse impact on cardiovascular health, although current evidence is limited (Mozaffarian, Katan et al. 2006; Gebauer, Chardigny et al. 2011).

Given the relatively low potential health impact of trans fatty acids in New Zealand, it would not be of value for NZACE-Prevention to model it. Furthermore, recent educational initiatives to further reduce use of trans fatty acids have been successful in New Zealand and Australia, and the government considers the current non-regulatory strategies to be adequate (Food Standards Australia New Zealand December 2010).