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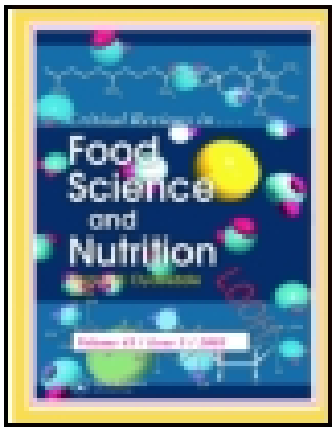


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# Saturated Fat Controversy: Importance of Systematic Reviews and Meta-analyses

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# SATURATED FAT CONTROVERSY: IMPORTANCE OF SYSTEMATIC REVIEWS AND META-ANALYSES

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This manuscript is based on a presentation by H. Szajewska at the symposium *'Palm oil'* during the 20th IUNS International Congress on Nutrition, held from September 15-20, 2013 in Granada, Spain.

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## ABSTRACT

In adults, worldwide, the number one cause of death is coronary heart disease. Current guidelines generally recommend reduced consumption of saturated fat to reduce the risk of cardiovascular disease. However, some evidence suggests that consumption of saturated fat does not increase that risk. Recently, to address the saturated fat controversy, i.e., whether or not saturated fat

intake is a risk factor for cardiovascular disease, a number of systematic reviews and meta-analyses were performed. This paper aims to provide tools for understanding both. It starts with an overview of the basic principles of systematic reviews and meta-analyses. Then, it provides examples of current evidence from systematic reviews on the relationship between saturated fat intake and the risk of cardiovascular disease. Finally, based on an example from one recent systematic review, it explains how to read a meta-analysis. Continuous updating of existing reviews, as well as the development of new systematic reviews, is needed in areas in which the role of saturated fat remains unclear.

**Keywords:** cholesterol, *trans* fats, polyunsaturated fatty acids, evidence-based medicine, forest plot.

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## INTRODUCTION

In adults, worldwide, the number one cause of death is coronary heart disease (CHD) (WHO 2010). Among its key risk factors is an inadequate diet. Saturated fats (for example, those found in meat, butter, high-fat cheese, ice cream, whole-fat milk and cream, and palm and coconut oils) and *trans* fats (for example, those found in margarines, bakery products, and many processed and fast foods) contribute to CHD, while monounsaturated and polyunsaturated fats (for example, those found in fish, olive oil, and nuts) are protective (Hu et al., 1997; Mozaffarian et al., 2010). This is because consumption of saturated fat-rich foods may adversely affect plasma cholesterol levels. Elevated plasma cholesterol concentrations, particularly LDL-cholesterol, show a strong and consistent association with the incidence of CHD (Law et al. , 1994; Tsimikas et al., 2005).

Current guidelines may vary depending on the country. However, generally, reduced consumption of *trans* fats and saturated fat is recommended for reducing the risk of cardiovascular disease (EFSA, 2010; NICE, 2010; Perk, et al. 2012; WHO, 2003). Of these, the detrimental role of *trans* fats is universally accepted. Most recently, the U.S. Food and Drug Administration announced its preliminary determination that partially hydrogenated oils, the primary dietary source of artificial *trans* fat in processed foods, are not ñgenerally recognized as safeò for use in food (US Food and Drug Administration, 2013). In contrast, the impact of saturated fat intake on the occurrence of cardiovascular disease is currently being disputed, as reflected by the title of a recent article in the British Medical Journal: *'Saturated fat is not the major issue'* (Malhotra, 2013).

To address the saturated fat controversy (i.e., whether or not saturated fat is a risk factor for cardiovascular disease), a number of systematic reviews and meta-analyses have been performed

(Hooper et al., 2012; Mente et al., 2009; Mozaffarian et al., 2010; Siri-Tarino et al., 2010). In the hierarchy of evidence, the results of a systematic review, with or without a meta-analysis, are considered to be the evidence of the highest grade (OCEBM, 2011). If available, they should be used to support clinical decision-making.

This paper aims to provide tools for understanding a systematic review and a meta-analysis. It starts with an overview of the basic principles of systematic reviews and meta-analyses of randomized and non-randomized controlled trials. Then, the article provides examples of current evidence from systematic reviews on the relationship between saturated fat intake and the risk of cardiovascular disease. Finally, based on the example of one recent systematic review, it explains how to read a meta-analysis.

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## SYSTEMATIC REVIEW & META-ANALYSIS EXPLAINED

Every meta-analysis is based on a systematic review. The latter is defined as a review of a clearly formulated question that uses predefined criteria to identify, select and critically appraise relevant research and to collect and analyze data from studies that are included in the review (Higgins and Green, 2008). A meta-analysis is a name that is given when statistical methods are used in a systematic review for combining the results of included trials to produce a single estimate of the effect of a particular intervention (Higgins and Green, 2008).

There are a number of reasons to perform a meta-analysis, including increasing the power (i.e., the chance that a trial will detect, as statistically significant, an intervention effect of a specified size, if one actually exists) and increasing the precision in estimating effects (i.e., narrowing the confidence interval around the effects). Of note, a statistical significance means there is

statistical evidence that there is a difference; it does not mean the difference is clinically or biologically important. Moreover, a meta-analysis helps to answer questions not raised by individual studies, to resolve controversies arising from studies with conflicting results, and to generate new hypotheses for future studies (Higgins and Green, 2008).

For a systematic review, every step needs to be planned. More and more often, it is also documented in a review protocol published prior to the start of the review. For details, see the Cochrane Collaboration (www.cochrane.org), which has developed guidance on conducting a systematic review. In brief, the first step is to formulate the review question (the problem). The use of the acronym PICO is helpful, as the key components of a research question about the effectiveness of an intervention should address the types of participants (P), interventions (I), comparisons (C), and outcomes (O) of interest. The second step of a systemic review is to search for studies based on predefined inclusion and exclusion criteria. Failure to identify all relevant studies is one of the challenges of a systematic review. Consequently, the searches should be as extensive as possible. Searching one database is never enough. It is advisable to search at least Medline, EMBASE, and the Cochrane Library. If possible, no restrictions on language should be applied. Inclusion of unpublished data, although challenging, reduces the risk of publication bias. The latter occurs when studies with statistically significant results are more likely to be published than studies with non-significant results. In the next step, selecting studies, collecting data, and creating evidence-based tables takes place. At this stage, the reviewers are also assessing the methodological quality of the studies, i.e., the risk of bias in the included trials. In the case of randomized controlled trials (RCTs), adequacy of sequence generation, allocation concealment,

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and blinding of investigators, participants, outcome assessors, and data analysts; intention-to-treat analysis; and comprehensive follow-up (Ó80%) are usually assessed. In the final stage, the authors synthesize data from included studies and meta-analyses, if appropriate. To ensure transparency and reproducibility, each step must be carefully documented (Higgins and Green, 2008). The take home message is that it is always appropriate to perform a systematic review, and every meta-analysis should be preceded by a systematic review. However, not every systematic review should be finalized with a meta-analysis; in fact, it is sometimes erroneous and even misleading to perform a meta-analysis. While it is unrealistic to expect absolute similarity of all the studies, comparability is needed. In principle, data should only be pooled if they are homogeneous, i.e., the participants, interventions, comparisons, and outcomes must be similar (homogeneous) or at least comparable (Higgins and Green, 2008).

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**SATURATED FAT AND THE RISK OF CARDIOVASCULAR DISEASE**

A number of recent systematic reviews and meta-analyses have assessed the relationship between saturated fat intake and the risk of cardiovascular disease (Hooper et al., 2012; Mente et al., 2009; Mozaffarian et al., 2010; Siri-Tarino et al., 2010). A brief description of some of them is presented below. For more details, see other articles in this supplement.

In 2010, Siri-Tarino et al. (Siri-Tarino et al., 2010) published a meta-analysis (search date: September 2009) investigating the effects of saturated fat consumption on the risk of CHD, stroke, and cardiovascular disease (CHD inclusive of stroke). Data from 21 prospective cohort studies involving 347,747 subjects, aged 30 to 80 years, were included. The authors found insufficient evidence to support an association of dietary saturated fat intake with an increased

risk of CHD (relative risk, RR 1.07, 95% confidence interval, CI 0.96 to 1.19; P=0.22), stroke (RR 0.81, 95% CI 0.62 to 1.05; P=0.11), or cardiovascular disease (RR 1.0, 95% CI 0.89 to 1.11; P=0.95). No conclusive link between dietary saturated fat intake and cardiovascular disease incidence after adjustment for potential confounders, including other nutrients, was found. Two of the studies found a significant inverse association between dietary saturated fat intake and stroke. Overall, this review of prospective cohort studies questioned a significant association between saturated fat intake and cardiovascular risk.

In another meta-analysis (search date: June 2007), Mente et al. (Mente et al., 2009) included prospective cohort studies or randomized trials that investigated dietary exposures in relation to CHD. Pooled estimates from cohort studies showed that higher intakes of eggs, meat, milk products, polyunsaturated fatty acids, saturated fatty acids, and total fat were not significantly associated with an increased risk of CHD. A significant benefit (a significantly lower risk of CHD) was associated with a ñMediterraneanò dietary pattern. This dietary pattern emphasizes a higher intake of vegetables, legumes, fruits, nuts, whole grain products, cheese or yogurt, fish, and mono- and polyunsaturated fats, especially olive oil; moderate consumption of alcohol, mainly wine; and a low consumption of red meat. An increased risk of CHD was found with intake of *trans*-fatty acids and foods with a high glycemic index or load. Only a relatively small number of cohort studies have shown that either a higher intake of polyunsaturated fatty acids or a lower intake of saturated fatty acids is related to a reduced risk of CHD. More research is needed to clarify the benefit with respect to polyunsaturated fatty acids. Data from RCTs are limited.

Mozaffarian et al. (Mozaffarian et al., 2010) systematically reviewed the effects of increased

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polyunsaturated fatty acid (PUFA) consumption as a replacement for saturated fat on CHD endpoints. This systematic review (search date: June 2009) of eight RCTs, involving 13,614 participants, found that consuming a diet containing PUFA (on average, 14.9% of total energy intake) instead of saturated fat reduced CHD events by 19% (RR 0.81, 95% CI 0.7 to 0.95). In other words, for each 5% increase in the proportion of energy obtained from PUFA, there was 10% reduction in the risk of CHD events. The benefits of PUFA consumption increased with longer duration of trials. Overall, this meta-analysis of RCTs found that the increased consumption of PUFA instead of saturated fat reduced the risk of CHD events. However, it remains unclear whether the effect was due to reducing saturated fat intake or increased PUFA consumption.

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**UNDERSTANDING META-ANALYSES**

To help the reader understand systematic reviews and meta-analyses, in this section one recent Cochrane review (Hooper at al., 2012) on saturated fat is discussed. This is an updated review of the 2001 review (Hooper et al., 2001)

*Overview*

The authors' objective was to evaluate the effects of reduction and /or modification of dietary fats on mortality, cardiovascular mortality, cardiovascular morbidity, and some individual outcomes in adults. A meta-analysis was based on a systematic review of existing studies. The authors searched the Cochrane CENTRAL Register, MEDLINE, and EMBASE through June 2010. Reference lists of relevant studies and reviews were checked for additional studies. There were no language restrictions. The authors independently searched for RCTs stating the intention to

reduce or modify fat or cholesterol intake in an adult population over at least 6 months. Two reviewers independently assessed the quality of the studies using the Cochrane Collaborationôs tool for assessment of risk of bias. Two reviewers independently extracted data to calculate the RR (with 95% CI) using a random effects model. The latter makes the assumption that individual studies are estimating different treatment effects. Any disagreements were resolved by discussion. When necessary, authors were contacted for additional data. Publication bias was assessed by means of a funnel plot. Statistical heterogeneity was evaluated for each outcome by the $I^2$ statistic.

Compared to the 2001 review that included 27 trials (Hooper at al., 2001), a total of 48 RCTs, almost exclusively from industrialized countries and of at least 6 monthsô duration, were included in the 2012 review. The authors compared a reduced fat diet and a usual or control diet (25 comparisons, more than 65,000 participants); a modified fat diet and a usual or control diet (15 comparisons, n=13,004); a reduced and modified fat diet and a usual or control diet (10 comparisons, n=4,931); and a low fat and modified fat diet (9 comparisons, n=1290). Many of the included studies had some methodological limitations, with blinding being the major problem. For the primary outcomes, pooled results showed that lowering saturated fat intake by limiting and/or modifying dietary fat consumption reduced the risk of combined cardiovascular events, which included any of the following data available from a trial: cardiovascular deaths, cardiovascular morbidity (non-fatal myocardial infarction, angina, stroke, heart failure, peripheral vascular events, atrial fibrillation), and unplanned cardiovascular interventions (coronary artery bypass surgery or angioplasty) (RR 0.86, 95%CI 0.77 to 0.96). However, subgrouping suggests that this reduction in combined cardiovascular events was only seen in

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trials of at least 2 yearsô duration and in studies of men (not of women).

For the other primary outcomes, no effect of dietary fat changes was seen on total mortality (RR 0.98, 95% CI 0.93 to 1.04) or cardiovascular mortality (RR 0.94, 95% CI 0.85 to 1.04). As only a few studies compared reduced fat diets with modified fat diets, a direct comparison was not performed. The authors concluded that this systematic review showed that the reduction or modification of dietary fat intake (replacing some saturated fats with plant oils and unsaturated spreads), but not a reduction in total fat intake, results in reductions in cardiovascular events, but only in trials of at least 2 years duration. Saturated fat intake was provided in only some trials, but did not have an effect. Among other factors that were evaluated, gender was important (reduced risk of cardiovascular events in men, but not in women), as was the setting (reduced risk of cardiovascular events only in community, but not in residential, settings). Finally, the publication date was important; only studies published in the 1960s through 1990s showed the reduced risk.

*Interpretation of a forest plot*

A quick way to visualize the results of a meta-analysis is a forest plot. This is a graphic display of the results from individual studies together with the combined result. The authors of the Cochrane review performed a number of separate analyses. Among them, there are three forest plots for the primary outcomes (i.e., total mortality, cardiovascular mortality, and combined cardiovascular events). The **Figure** shows an interpretation of one of the forest plots, showing a meta-analysis of combined cardiovascular events in RCTs comparing the effects of fat modification or reduction versus consumption of a usual diet.

The results of 23 comparisons are presented. The study identifications are listed in a column on

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the left side of the figure. The vertical line is called the line of no effect (RR equals 1.0). The black square in the middle of each horizontal line represents the point estimate of the difference between groups (the best single estimate of the benefit or effect) and is presented as the relative risk (RR). The horizontal lines represent the 95% CI for this estimate. The horizontal line may or may not cross the line of no effect. If the horizontal line that represents the results of an individual trial does not visually cross the line of no effect (i.e., if the CI for RR does not include 1), there is a 95% chance that there is a real difference between the groups. On the other hand, if the horizontal line does cross the line of no effect (i.e., if the CI for RR includes 1), there is no significant difference between treatments and/or the sample size is too small to allow confidence about where the true result lies.

The area of the black squares reflects the weight each study contributes to the meta-analysis. A precise study (with a high number of subjects and a low variance) has a higher weight compared with an imprecise study (with a small number of subjects and a high variance).

The center of the diamond below all of the horizontal lines represents the pooled treatment effect (RR 0.86). The horizontal tips of the diamond represent the 95% CI (in our example, 0.77 to 0.96). The diamond does not cross the line of no effect. Thus, this meta-analysis showed that the use of reduced or modified fat diets compared with consumption of a usual diet reduced the risk of combined cardiovascular events (reduction of 14%). The diamond crossing the midline (the line of no effect) would represent inconclusive results.

The forest plot allows one, at a glance, to assess heterogeneity (the amount of variation in the studies). If the CIs (represented by horizontal lines) all overlap to some extent, the trials are

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homogeneous. On the other hand, if some CIs (horizontal lines) do not overlap at all, there is a high degree of heterogeneity. In our example, all of the CIs overlapped, and thus, the trials were considered to be homogeneous.

*Strengths and limitations of the review*

This large Cochrane review addressed a well□defined question in terms of the study design, participants, interventions, comparisons, and outcomes. It included only RCTs (as do almost all Cochrane reviews) and excluded observational studies, case series studies, and case-control studies. The authors searched several relevant databases and made efforts to find further information by reviewing reference lists. No restrictions on language were applied. The authors attempted to minimize distortion of results or bias during the review by carrying out the study selection, quality assessment, and data extraction processes using two independent reviewers. Full details of all included (and excluded) studies were presented. A number of data came from older studies (published in the 1960s and in the 1990s). Over time, dietary habits may have changed, which needs to be taken into account. Statistical heterogeneity was assessed appropriately. The studies included in the review represent a subset of all relevant studies assessing the effect of modified fat diets on classic cardiovascular risk factors, so the authorsô conclusions should be treated with caution.

*What does this review add?*

The authors stated that their ófindings are suggestive of a small but potentially important reduction in cardiovascular risk with the modification of dietary fat, but not total fat reduction, in longer trials. Lifestyle advice to all those at risk of cardiovascular disease and to lower risk population groups, should continue to include permanent reduction of dietary saturated fat and

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partial replacement by unsaturates. The ideal type of unsaturated fat is unclearô (Hooper et al. 2012).

## SUMMARY

The relationship between saturated fat intake and cardiovascular disease remains a subject of debate. Some recent evidence suggests that intake of saturated fat does not increase the risk of cardiovascular disease. Current guidelines generally recommend reduced consumption of saturated fat to reduce the risk of CHD. However another aspect of the ongoing debate is whether saturated fat should be replaced with carbohydrate, protein, or unsaturated fats. For answering all of these questions, performing a systematic review and meta-analysis, primarily of RCTs, is considered to be the best study design. The strengths as well as the limitations of this approach have to be well understood. Continuous updating of existing reviews, as well as development of new systematic reviews, is needed in areas in which the role of saturated fat remains unclear.

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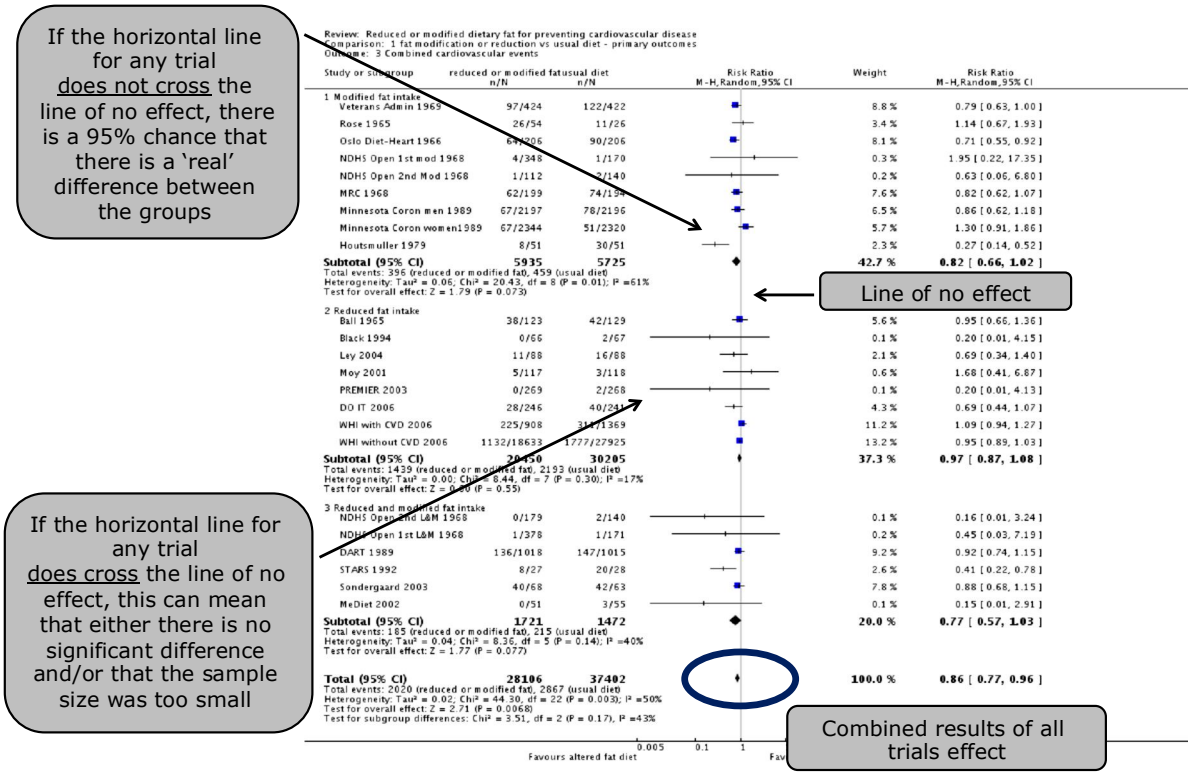


**Figure 1.** Interpretation of a forest plot showing a meta-analysis of combined cardiovascular events in RCTs comparing the effects of fat modification or reduction versus consumption of a usual diet (Hooper et al. 2012).

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