META-ANALYTIC ASSESSMENT OF BLOOD LIPID RESPONSE TO DIETARY MANIPULATION OF MACRONUTRIENT DISTRIBUTION

By

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DEDICATION

This dissertation is dedicated to my family, and those few friends who are essentially family, for their tireless support and enduring patience.

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ABSTRACT

Incorporating the best findings from current, high-quality research into routine clinical practice is the basis of evidence-based care. Chapter 1: "Systematic Review and Meta-Analysis in Evidence-Based Care" is a review of the systematic review process, including meta-analysis, aimed at clinical professionals with limited statistical training. It advocates the use of the systematic review process, outlines some general techniques, and provides selected resources where individuals can acquire additional assistance. The typical steps involved include: formulating a clear research question, defining inclusion and exclusion criteria, extracting the data and assessing the study quality, summarizing and synthesizing the evidence, and then interpreting the findings. When effort is made to minimize bias and locate as many articles on a particular topic as possible, systematic reviews and meta-analyses can produce invaluable findings for evidence-based care.

Chapter 2: "The Effect of Macronutrient Distribution on the Lipid Profile in Adults: A Systematic Review and Meta-Analysis" describes a systematic review and meta-analysis that examined the impact total macronutrients had on blood lipid levels. This chapter builds upon the concepts introduced in chapter one, and assesses the effect of manipulating macronutrient distribution on the lipid profile of adults, and compares these effects to recommendations regarding macronutrients, such as the Acceptable Macronutrient Distribution Ranges (AMDRs). Suggestions related to improving the quality of meta-analyses are also outlined, and supplemental analyses are provided at the end of the dissertation.

CHAPTER 1:

SYSTEMATIC REVIEW AND META-ANALYSIS IN EVIDENCE-BASED CARE

Introduction

Patient-centered, evidence-based care incorporates the current best findings from high-quality research into routine clinical practice that focuses on the outcomes deemed important by the patients themselves.[1-5] However, the amount of potentially relevant information is so large and expanding so quickly, that it is impossible for an individual clinician to evaluate it all, let alone keep up-to-date.[1,6] The methods used to search for information play a supporting role in evidence-based care, but with increasing workloads placed on clinicians, most choose expediency over reliability when attempting to answer pertinent questions.[2,7]

Whether it is to satisfy a personal curiosity, expand one's knowledge base on a topic, or settle an argument with a colleague, often the first stop for information is a web search engine.[8] Therefore, it is important to be somewhat familiar with how a search engine works in order to understand its inherent limitations. In general, a computer program called a crawler finds and retrieves web pages, returning them to an indexing program. This indexer sorts every word on the web page and stores the results within a large database. When someone performs a search, the query processor compares the search request to the indexed database and recommends documents that it has ranked most relevant.[9] While this system is both quick and convenient, it tends to bias internet traffic towards more popular sites.[8] A cycle occurs where web pages that are highly ranked by the search engine are more easily found by queries, and this in turn leads to these pages being linked more often by other sites, ultimately leading to an increase in their popularity. Consequently, new web pages, especially those that significantly differ from the most popular sites are less likely to be found.[8] Websites can also become more popular (and thus more highly ranked) through political, social, or financial forces (e.g. advertising and sponsored links) that have little to do with the relevancy or quality of their content.[10]

With its powerful yet simple query box, Google Scholar has become a mainstay search engine for accessing scientific materials. Despite its strengths, it still suffers from some of the same limitations as other search engines: vague definitions of what is scholarly, the lack of a standardized vocabulary, and no guarantees that the results are current, distinct, or as comprehensive as what would be found using a narrative interface like PubMed.[11,12] Unfortunately, the advanced features that characterize interfaces like PubMed are complex and require a larger investment to master, and many clinicians and researchers prefer the more simplified query format of Google Scholar.[11] Perhaps with some improvements to increase its precision, Google Scholar (or a similar search engine) may one day become a single source for accessing research, but currently it should only be used in conjunction with other search tools in order to best meet the aims of evidence-based care.[13]

Regardless of the methods used to search for information, individuals may demonstrate both cognitive and interpretive biases that can influence how clinical decisions are made.[1,7,14] Prior beliefs may exert an influence, causing someone to treat evidence differently depending on whether or not the evidence conforms to their presuppositions.[7,14] Often clinical evidence is more readily accepted when supported by biologic plausibility,[7] or through repeated exposure to the same conclusions from the literature,[14] but all of these cases may lead to a fundamental misinterpretation of research findings. Studies have shown that practitioners and patients alike are influenced by the temporal order that information is presented to them.[7] These personal biases, compounded with the biases and limitations of a chosen search strategy, can lead to suboptimal decision-making. The consequences can range from well-intended treatments doing more harm than if no treatment was given at all, to the adoption of a newer, more expensive treatment when there is no clinical difference compared to the less-expensive standard care, or even a very effective treatment being completely ignored.[3,15] The way to minimize these biases is to develop a well-defined and systematic search strategy, and then apply this strategy to credible electronic databases in order to identify and retrieve reliable evidence for evaluation.[2] Since randomized controlled trials (RCTs) are the most trusted type of primary evidence, evidence-based care would be best served by systematic reviews of many RCTs.[4]

The results from a single article are not representative of a population,[16] and should not be used to shape clinical decisions or healthcare policies, since a single trial cannot detect or exclude a modest effect between two treatments.[6] In order to answer questions that cannot be addressed by a single trial, and resolve debate when trial results are in conflict, systematic review and meta-analysis should be utilized. Systematic review and meta-analysis are two distinct, but related processes. A systematic (or qualitative) review is a form of literature review that utilizes a systematic and transparent approach to minimize biases and random errors.[6] Systematic reviews should be viewed as observational studies of the evidence; they apply explicit inclusion and exclusion criteria for potential studies, and would be similar to the description of recruitment and selection processes for a primary study.[17] Meta-analysis (or quantitative review) provides a mechanism to integrate study findings according to sample and study design characteristics, type and duration of the intervention, and the type of response variables. In comparison to a primary study, meta-analysis would be the actual experimental intervention, substituting individual studies (or their treatment groups) for subjects.[18,19] It is possible to have a systematic review without a meta-analysis, or even without any studies meeting the inclusion criteria; such "empty reviews" may still be useful in identifying areas of potential research.[20] However, a proper meta-analysis should always include studies from a systematic review to minimize bias.[6,20]

Systematic reviews and meta-analyses have been around for centuries, although these techniques have not been applied consistently by researchers. James Lind, an 18th century Scottish naval surgeon most remembered for his work on scurvy, not only conducted perhaps the first recorded clinical trial in the Western world, but also performed the first systematic review by taking a critical and chronological appraisal of what had already been reported on the topic.[21] After Lind, researchers continued to wrestle with methods to reliably combine data from different studies, especially those with small sample sizes.[21] In 1861, work from Laplace and Gauss was originally published for astronomers in the first text book on quantitative synthesis, which contained statistical methods that inspired many of the techniques used today.[6] These techniques were later applied by Karl Pearson in 1904 to pool eleven studies on vaccine inoculations, noting that the individual studies were too small to provide a definitive conclusion on their own.[22,23] For the next half-century, statistical techniques for pooling results from different studies were not utilized on a regular basis.[21] The first quantitative synthesis that assessed the effect of a treatment was published in 1955, ironically on the placebo.[24] While performing research in educational psychology and social science, statistician Gene Glass coined the term "meta-analysis" to describe analyzing the integrated results from a collection of individual studies; his work influenced a resurgence of interest in the technique.[25] Unfortunately, methods to minimize biases in systematic reviews did not peak until the 1980s, leading to many misleading meta-analyses and strong criticism of the technique.[26-28] However, it should be noted that when systematic reviews and meta-analyses are appropriately conducted and applied, they can produce invaluable findings for both clinical and policy decisions; they have earned their place at the top of the evidence hierarchy.[29]

The goal with meta-analysis is not to immediately pool many small studies together and treat them as if they are one large trial that more closely mirrors the population being studied, but rather to determine if a reported treatment effect is consistent between studies in the analysis. If it is, then the treatment effects from these studies can be synthesized to report a common summary effect that has greater statistical and clinical significance than any of the studies individually. However, if an abundance of heterogeneity exists among the studies, the meta-analyst attempts to describe the amount of variability, as well as try to identify some its potential sources.[30]

The inferior alternatives to systematic review and meta-analysis are the narrative review and vote counting.[6,20,30] In a narrative review, the author describes the primary studies included and the selection process is rarely transparent, inherently subjective (commonly including studies that support the author's view), and the conclusions are biased. Vote counting simply counts the number of studies that describe a positive, null, or negative effect and relies on tests of significance (p-values).[6,20] Tests of statistical significance are affected by both the observed effect and the sample size; they are not equivalent to tests for clinical significance, which can be described through effect sizes.[20,30] An effect size reflects the magnitude of the treatment effect, or more generally the strength of the relationship between any two variables; when the effect size is the result of an intervention, the terms "effect size" and "treatment effect" can be used interchangeably.[30] In studies with a large number of subjects, a clinically insignificant effect will still be statistically significant, yet a clinically-significant result may be overlooked if the sample size of a study is relatively small. In contrast, systematic reviews minimize sources of bias, and meta-analyses instead deal with the magnitude of a particular effect.[30]

The goal of this article is to walk through the basic process of performing both a systematic review and meta-analysis, while providing some options and resources for those with limited statistical backgrounds. One of the more comprehensive resources available is the *Cochrane Handbook for Systematic Reviews of Interventions*[31] (Cochrane-handbook.org), although there are many other resources available on the topic.[6,15,30,32] The basic process includes the following steps: formulate a clear research question, define inclusion and exclusion criteria for potential studies, locate the studies of interest, extract the data and assess the study quality, summarize and (if appropriate) synthesize the evidence, and then interpret the findings.[6,33] The complete process involves a PRISMA statement, which comprises a 27-item checklist relating to the information that should be included in a systematic review or meta-analysis, and a diagram depicting the flow of the information through the four different phases of the systematic review (see Figure 1).[17] The PRISMA (Preferred Reporting of Meta-Analyses) statement provides uniformity to the process, and is analogous to writing a CONSORT statement for primary trials.[34]

Step 1: Formulate a Research Question

To conceptualize what question the review is trying to answer, it may be helpful to write a free-form question first, and then re-frame this question in a more structured format.[33] Each research question should specify the participants, interventions, comparisons, and outcomes involved.[31] An example of a structured question could be: "Is Treatment A more effective than Treatment B for Outcome C in Population D?"[20] The scope of a research question is important, because a question that is too broadly defined will cause the reviewer to waste additional time sorting through irrelevant articles, while a topic that is too narrow may not include all the relevant studies.[31]

Step 2: Define Inclusion and Exclusion Criteria

When recruiting for a clinical trial, determinations are made regarding which potential subjects are to be included in the study, and why any would be excluded. These choices may be based upon subject demographics, comorbidities, or medication history.[31] Not only do these criteria help define the study sample, but they also provide a context for the results and would enable others to reproduce the study design. Like with a primary study, it is imperative in a systematic review to formulate detailed inclusion and exclusion criteria, but in this case one is dealing with studies instead of individual subjects. These eligibility criteria are usually derived from the research question and can relate to such categories as: the types of studies to be included, the treatments, participants, outcomes, and lengths of follow-up. Ideally, only randomized controlled trials that report on all enrolled subjects and detail their method of allocation concealment (i.e. blinding) would be considered for inclusion.[35]

Step 3: Locate Studies of Interest

When trying to identify relevant studies for a systematic review, the search strategy should be clearly delineated, and the particular strategy implemented will depend both on the topic and database searched. In recent years, identifying randomized controlled trials for systematic reviews has become less complicated, but the contribution that a librarian or information specialist can provide is invaluable. The two most commonly searched databases for biomedical literature are MEDLINE and EMBASE. MEDLINE covers over 5600 journals,[36] over half are published in the U.S.; EMBASE covers over 7600 journals[37] from more than 70 countries. In addition, *The Cochrane Controlled Trials Register*, which is available from the Cochrane Library Online is the best single source of published trials for inclusion in systematic reviews, and features titles and abstracts from both of the aforementioned databases.[31] Access to these databases usually requires an institutional subscription, but in the case of MEDLINE, there is a freely accessible version of the database known as PubMed.

PubMed grants free access to the entirety of MEDLINE, and searching this database may also include additional manuscripts and articles not yet indexed with Medical Subject Headings (MeSH). MeSH are standardized words or phrases maintained by the National Library of Medicine. Trained indexers recognize the same topic being expressed in different terms and create a thesaurus, so if an individual searches for a particular term, it will automatically include synonymous terms related to the same topic. As mentioned earlier, one of the limitations of search engines like Google Scholar is the lack of a controlled vocabulary.[11] (Incidentally, EMBASE utilizes a similar, but distinct group of subject terms known as EMTREE.)

For example, if one was interested in finding articles that studied the effects of carbohydrate restriction between the years 2002 to 2010, s/he might just search for the terms "carbohydrate-restricted diets". However, such a search may miss any articles that instead refer to the dietary intervention as a "low carbohydrate diet", or studied a specific diet like the Atkins Diet. Medical Subject Headings recognize that all these terms are related to the same topic and group them appropriately. In this case, the MeSH is "Diet, Carbohydrate-Restricted", and is defined as a diet containing limited amounts of carbohydrate.[38] The synonymous terms listed include plurals and variations:

- Carbohydrate-Restricted Diet(s)
- Diet(s), Carbohydrate Restricted
- Diet(s), Low Carbohydrate
- Carbohydrate Diet(s), Low
- South Beach Diet
- Beach Diet, South
- Diet, South Beach
- Atkins Diet
- Diet, Atkins

Using any one of these terms will automatically include the others in the search, making MeSH a way to discover variants of a topic and potentially reduce the number of terms in a search.

It is important to know that MeSH do not exist for all topics and articles, especially those recently published in PubMed have not yet been indexed and would be missed by a search solely using MeSH. In addition, a search using a new medical subject heading is not retroactive, meaning that one could miss any article that was published before that term was indexed. In the example above, "carbohydrate-restricted diet" was introduced in 2006, and so a search from 2002 to 2010 would not capture articles prior to when that term was introduced. Referring back to the MeSH Database,[38] one would see that before 2006, diets that restricted carbohydrate were indexed under the MeSH of "Dietary Carbohydrates" (1973-2005) or more generally "Diet Therapy" (1974-2005). One limitation of medical subject headings is that they can decrease the sensitivity of a search, and it is therefore recommended that searches of MEDLINE or PubMed include a complementary strategy with text words in addition to MeSH.[39]

When developing a search strategy based on text words, it is important to brainstorm a comprehensive list of possible variants for terms related to the topic of interest. Consider related terms, synonyms, hyphenation, and even British spelling (e.g. colour). Most databases allow the use of some form of truncation and wildcards to help find variants of terms. For example, by truncating the word "damage" to *damage**, the search is now valid for the terms: damage, damaged, and damaging. Using a wildcard term like “m?n” could be used for either the terms *man* or *men*. Such practices vary between the services providing access to a particular database, so be sure to tailor each search strategy appropriately.[31]

As more and more terms are added to a search strategy, some consideration needs to be made as to how they are combined, and the use of Boolean operators (AND, OR, and NOT) is commonly employed. Generally, one should choose a single topic, and create a set of terms from all its synonyms and variants, utilizing the “OR” operator between each one. If there is a second topic, the process is repeated within that set of terms, again using the “OR” operator. When one is satisfied with the individual sets of terms, they can be combined using the “AND” operator. The Cochrane Handbook discourages the use of the “NOT” operator whenever possible because it may eliminate pertinent articles from a search. If one was interested only with studies conducted on adults, it may be tempting to add a filter like “NOT juveniles”. The concern here is that it may eliminate any studies that reported data on both juveniles and adults, denying that information from the systematic review.[31]

Depending on the topic, it may be appropriate to search additional databases related to psychology, pharmaceuticals, nursing, or other fields. Again, each database may require a modified search strategy, so keep a record of each one for the sake of transparency and reproducibility. An effort should also be made to find some unpublished or “grey literature”, including dissertations and theses; Rothstein and Hopewell have written extensively on this topic.[15]

A schematic similar to Figure 1 below should be included in a systematic review, illustrating the flow of information through the phases of the review, similar to study design schematics for primary trials. Multiple databases should be searched, any duplicates removed, and then the remaining articles should be screened against eligibility criteria. Some may be identified for exclusion upon reading their title and abstract, while others will require a more in-depth appraisal; in either case, the reasoning for why each article was excluded should be documented and made available.

Step 4: Data Extraction and Study Quality Assessment

After the studies are retrieved and screened, the data from the articles need to be extracted onto coding forms before being entered into a database; during the extraction process, the quality of each study should be assessed and recorded. There is usually no need to create a coding form from scratch, and searching for systematic reviews and meta-analyses on similar topics will usually yield a form that can be modified to suit one's needs.[20] Ideally, two people should be coding the articles independently, with a third person available to resolve discrepancies.[6]

Study quality assessment is an important, although often overlooked, portion of a systematic review. A randomized, double-blind, placebo-controlled trial will tend to have less biases than a quasi-random, non-blinded trial. If the studies included in the systematic review are of lower methodological quality and demonstrate various sources of bias, then the results of the meta-analysis will also be biased. The Cochrane Collaboration's tool for assessing risk of bias is commonly used for RCTs, and a detailed

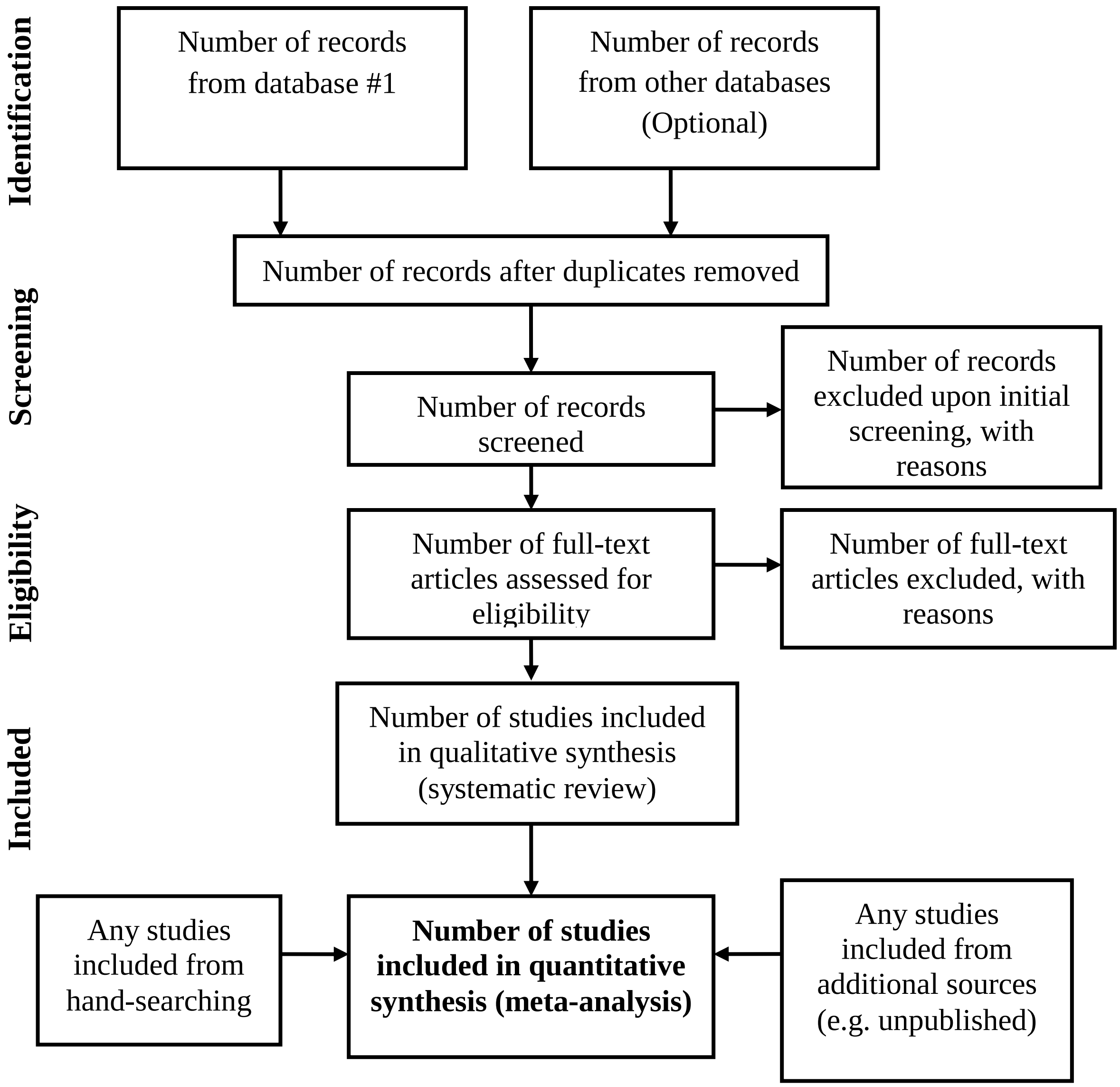


Figure 1. Sample PRISMA four-phase flow diagram.[17]

description can be found in chapter 8 of the Cochrane Handbook Online.[31] The organization strongly discourages the use of quality scales for the assessment of risk, stating these tools are ineffective.[31] Regardless of the tool used, reviewers are encouraged to collect and report information directly from the articles, and then compile these findings into a visual record that displays the risk of different forms of bias.

Step 5: Summary and Synthesis (Meta-Analysis)

When testing a new treatment, a clinician is usually not interested in whether the treatment had any effect at all (as would be the case in significance testing), but rather what was the estimated size of the effect.[40] Meta-analysis moves away from questions regarding the viability of the null hypothesis, and towards questions regarding the magnitude of the treatment effect.[30] In general, an effect size is the relationship between any two variables, and is the primary currency in a meta-analysis. Some studies will directly report effect sizes, but in other cases is it up to the meta-analyst to calculate them. The calculated effect size will depend on what types of data are reported by the study, and are based on either means, binary, or correlational data.[15]

A basic example involving means would be a set of studies that reported means, standard deviations, and sample sizes for both a pre-treatment and post-treatment outcome variable, like LDL cholesterol reported in milligrams-per-deciliter (mg/dL). Since all the studies in this example reported their outcomes using the same scale and methodology, unstandardized (raw) mean differences would be an appropriate treatment effect for the synthesis.[30] This has an advantage of retaining the same metric as the original outcome (e.g. mg/dL), and the treatment effect carries clinical significance (e.g.

change in mean LDL concentration)[41]. The raw mean difference is simply the difference between the two measured time points (Post-Pre); the order of the time points is not significant as long as it is consistently followed.[30] A post-treatment minus pre-treatment calculation has the advantage because the sign of the treatment effect provides information about the direction of change.

If the example contained some studies that used a new or different method to analyze LDL cholesterol, then raw mean difference should not be used as the effect size. Instead, one would use a standardized mean difference, such as Cohen's d, which is calculated as the difference in the two means divided by the within-groups standard deviation pooled across the groups ($d = mean_1 - mean_2/S_{within}$).[6] S_{within} can be calculated through:[30]

$$\sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}$$

where n represents the sample size of each group, and S is their respective standard deviations.

Hedge's g is another standardized mean index featuring an adjustment for small samples (less than ten) through a correction factor (J):[30]

$$J = 1 - \frac{3}{4df - 1}$$

The term (df) represents the degrees of freedom used to calculate the within-groups standard deviation, which is ($n_1 + n_2 - 2$). Hedge's g is computed by multiplying the

Cohen's d index by the correction factor J, and this is generally viewed as the preferred standardized mean index, regardless of sample size.

These analyses could be calculated by hand, but the use of software is more convenient and reliable when dealing with many studies in a database. It would be unrealistic to assume a comprehensive understanding of meta-analysis can be achieved here in a few pages, so this paper aims to provide some resources, and then discuss some critical decision points related to the analysis. Since this process deals with statistical analyses, the choice of software is important. While many statistical software packages can perform aspects of meta-analysis, including formulas found in Microsoft Excel, programs designed specifically for meta-analysis tend to appropriately modify their statistical models for meta-analysis and be much more user-friendly.

Comprehensive Meta-Analysis or CMA (BioStat, Inc., meta-analysis.com) is a relatively easy-to-use software package for meta-analysis. Data can be imported directly from spreadsheets, various effect sizes can be calculated automatically, and an assortment of syntheses can be performed with a few mouse-clicks. The software is user-friendly, the customer support is prompt, and there are discounted and trial versions of the software available. STATA (StataCorp LP, stata.com) is a command-line statistical program that can perform meta-analysis and meta-regression, as well as an assortment of other general statistical operations. While the program is solid, and supported by their own journal, the command-line interface may not be very welcoming to novices. Mix 2.0 (BiostatXL, meta-analysis-made-easy.com) is a meta-analysis add-in for Microsoft Excel 2007 or later. While there is a free version available, it does not allow for the conversion of different effect sizes, but still may be a great option for those on a budget who are comfortable with Excel.

Once effect sizes have been computed for each study, the goal of a meta-analysis is usually to combine them to achieve a weighted summary effect from the included studies, which is designed to estimate the “true effect” within the population of interest.[32] Regardless of what specific index is used as the effect size (for example raw mean difference, standardized mean difference, odds ratio, risk ratio, and so on), the formulas for calculating the summary effect, assessing heterogeneity among the studies, and other related analyses are still the same.[30] Simply calculating the arithmetic mean of the various effect sizes would be inappropriate, because smaller studies are more prone to error and bias, and should therefore receive less weight than studies with greater precision.[6] Therefore, the weight or contribution a particular study has on the summary effect is directly related to the precision of the study; sample size is the primary factor in precision, but both the variation between different studies and within individual studies may impact how weights are assigned, depending on the chosen model.[30,42] When considering statistical models for pooling studies and evaluating the variation in their effect sizes, most meta-analyses are based on either the fixed-effect model or the random-effects model.[6,15,30] The two models utilize different procedures when assigning a weight to each study during the process of computing the summary effect, and the choice between the models depends on inferences made regarding the collection of studies.[15,20,30]

The fixed-effect model assumes that all studies included in the meta-analysis are sampled from the same population, and therefore share a common (true) effect size.[18,20,30,32] Consistent with this model, the only reason the effect size would vary between studies is due to random sampling error; if each of the studies had an infinite sample size, the observed effects would all be identical and match the true effect seen in the population.[3,6,18,20,30,32] The fixed-effect model assigns a weight to each study that is equal to the inverse of the study's variance.[15] Consequently, information from smaller studies is largely ignored, because better estimation of the identical effect size can be obtained from the studies with larger sample sizes and greater precision.[30]

An example of a fixed-effect model might be a pharmaceutical company that wants to test a new liquid enteral supplement. Perhaps the researchers initially recruited one thousand subjects who met the same inclusion criteria for all pertinent variables, and from this cohort they randomly assigned ten equal samples of one hundred subjects each to receive the new supplement. Assuming that the researchers, methodology, compliance, and other aspects of the trial were consistent, a fixed-effect model would be appropriate since the observed effect should be the same for each sample group, and also identical to the true effect seen in the population (or cohort in this case). Since the conditions described in this example do not apply to many clinical trials, the fixed-effect model is not usually applicable.

If the subjects, treatments, or other factors vary between the studies in a meta-analysis, then one might witness similar effects for the different trials, but the observed effects probably won't be identical.[20] Instead of estimating a single true effect, the random-effects model assumes that the average effect size in the population is randomly distributed, and the central point of this distribution represents the summary effect.[6,30,32]

Unlike the fixed-effect model, each study in a random-effects model contributes to the summary effect differently, and therefore needs to be represented.[30] The weight assigned to the effect sizes from individual studies is still computed as the inverse of its total variance, however in this model there is an additional source of variation. This model includes the within-study variation due to sampling error, in addition to the between-study variation, also known as tau-squared (T^2).[20,30,43] Between-study variation is reliably estimated (often by software) through the "method of moments", also known as the DerSimonian and Laird method, although analyses with less than five studies may benefit from alternative models.[44] Another way to estimate tau-squared is known as "restricted maximum likelihood" (REML), and this method tends to estimate tau-squared more accurately,[6] although the differences between the methods are likely to be small. When utilizing the random-effects model, extreme studies with large sample sizes lose influence, whereas those with small sample sizes will gain influence; the additional source of variation also tends to produce wider confidence intervals.[20,30] It is important to remember that the choice between the models discussed needs to be made based on the available data, as opposed to whichever provides the most favorable summary effect.

After the data have been entered, and the appropriate model chosen, the meta-analysis can be performed utilizing a preferred software package. The results of a meta-analysis are usually presented in the form of a forest plot, which has been around since the early 1980s. Figure 2 below shows a sample forest plot of four hypothetical studies:

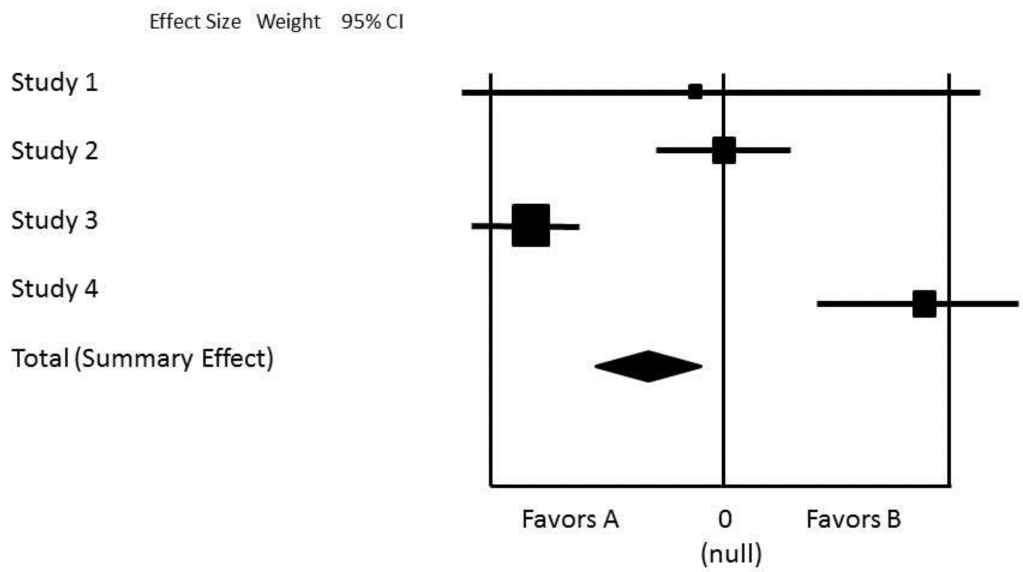


Figure 2: Sample Forest Plot

In a forest plot, a table of summary data is listed for each study containing: the effect size, the assigned weight, confidence intervals, model used, and information about the heterogeneity of the studies (not shown here). To the right of the summary table, each of the studies is represented by a line; the width of the line characterizes the confidence intervals for the effect sizes.[45,46] The confidence interval of the treatment effect denotes the boundaries within which 95% of the samples would fall; it also focuses attention on the estimate and precision of the treatment effect.[45,47] The midpoint of the square that appears on each line corresponds to the effect size of that study, and the area of the square relates to the weight assigned to the study, which is dependent upon the particular model chosen.[30] The diamond that appears at the bottom of the forest plot is the summary effect of the synthesis, which is the best estimate of the true effect in the population. The width of the diamond represents the confidence interval of the summary effect, and is the chance (e.g. 95%) that the true effect in the population will be within the specified range.[30] Along the horizontal axis of the forest plot is information about the treatments or conditions compared in the meta-analysis. Usually there is a vertical line denoting no difference between the compared treatments (the null hypothesis), and labels denoting whether the effect size for an individual study favored one treatment or the other. (If the effect size was the aforementioned raw mean difference between a pre- and post-treatment, the axis might describe a decrease or increase in the effect size instead.)

Considering the studies presented in Figure 2, the first study has a small square and a very wide confidence interval, denoting that the weight of this study is relatively small and there is insufficient evidence to draw a conclusion. Study 2 has a relatively narrow confidence interval and the midpoint of the square lies on the null, indicating that the two treatments were deemed to be equal. Study 3 also has a narrow confidence interval, significantly favors treatment A, and the large size of the square indicates that this study received significantly more weight than the others. Finally, study 4 significantly favors treatment B, but has a wider confidence interval and contributed about as much weight to the summary effect as Study 2, but not nearly as much as Study 3. The summary effect represented by the diamond shows that a synthesis of these four studies favors treatment A, a lot of this likely being attributed to the weight of Study 3. After the forest plot has been created and evaluated, the amount of heterogeneity needs to be quantified, and if it is significant, the meta-analyst should make attempts to identify potential sources through analysis of subgroups and/or meta-regression.

While the minimum number of studies required for a meta-analysis is two, it is important to consider both the number of studies, as well as the total number of subjects contained in the analysis before evaluating the strength of the results. A helpful guideline is to calculate the "optimal information size (OIS)", which is the number of subjects that would be recruited into a single, well-powered hypothetical trial that would qualify for the meta-analysis.[48] (There are a number of on-line sample size calculators if one's chosen statistical software package does not include the capability.) This number is then compared to the total number of subjects in the proposed systematic review and meta-analysis, and the quality of the evidence may be rated down if: the OIS is larger than the number of subjects in the meta-analysis, the 95% confidence interval of the summary effect includes the null, and the confidence interval that crosses the null fails to exclude an important effect.[48]

As previously described, studies will often differ based on a variety of factors, and such differences are described as either methodological or clinical heterogeneity.[49] When the between-study variation is found to be greater than what would be expected by chance alone, this is known as statistical heterogeneity, and it is important to quantify this in a meta-analysis in order to apply the findings in a useful way.[49,50] To do this, the total amount of observed between-study variation is computed and then compared to how much the effect sizes would be expected to vary if the true effect was identical for all the studies. Any excess variation is then deemed to reflect actual heterogeneity.[30]

The Q-statistic is commonly employed to test the null hypothesis that all the studies in the meta-analysis share a common effect size, and thus there is no heterogeneity; if its p-value is less than 0.05, then the studies do not share a common effect size.[30,50] Since it is a test of significance, the Q-statistic does not provide an estimate of the magnitude of the true dispersion, and other statistics are required instead.[30] One of these more insightful statistics is Tau-squared, which was already described as the estimated variation between studies. It can be useful, along with its square root (Tau), because they are in the same metric scale as the effect sizes themselves, and are not sensitivity to the number of studies included in the meta-analysis.[15,30] When calculating Tau-squared, the Q-statistic appears in the equation, and so both are commonly reported by software.

A more intuitive statistic of heterogeneity is I-squared (I^2), which reflects what proportion of the total variance represents real differences between the observed effect sizes, and acts as a measure of the inconsistency across the studies in the meta-analysis.[30,50,51] I-squared is reported on a scale of 0-100%, a value of zero indicating a homogenous group of studies, and a high value suggests the need to explore some of the sources of variance.[15,30,50] The parameter is neither sensitive to the metric of the effect size, not the number of studies included in the meta-analysis.[30]

Explaining heterogeneity among the trials in a meta-analysis can be challenging, but also might uncover interesting avenues for discussion.[52] An analyst may wish to perform separate meta-analyses to compare subgroups on the basis of gender, treatment dosage, study duration, and so forth. If one wished to analyze the association between the treatment effect and a study characteristic, a meta-regression can be performed.[22,53] This technique can not only explore sources of bias, or determine the impact of a particular covariate, but can also create regression equations that help explain how a one unit increase in a covariate would influence the summary effect.[6,30,54] Before a subgroup analysis or meta-regression is conducted, consideration needs to be made regarding missing data. A commonly implemented method to handle missing data is the complete-case analysis, where only those studies that report on all variables of interest are included in the analysis. Other methods worth consideration include substituting a missing variable for the mean of that variable from those remaining studies that do report it.[15]

Step 6: Interpret the Findings

When conducting a systematic review, one is searching for a sample of studies among the population of all potential studies available on a topic. It is not possible to obtain all the information on a particular subject, as some data are never published or even reported, especially if they fail to achieve statistical significance. Therefore, every systematic review will contain some sort of inherent bias, and it is up to the reviewer to identify, report, and minimize its sources.[23] It is important to clarify the difference between bias and imprecision. If articles are missing from a search due to a random occurrence, this is known as imprecision, and the impact on the systematic review will be minimal. The source of imprecision is generally sampling variation from a smaller number of included studies. Bias, on the other hand, is when the studies missing from a search are systematically different from those that were able to be located.[31]

Studies that report positive results, high treatment effects, or statistically significant results tend to be published more often or even multiple times; published studies are more likely to be included in systematic reviews and meta-analyses, and this constitutes publication bias.[30,55,56] Time-lag (or pipeline) is a form of publication bias where the time it takes for research findings to be published varies depending upon the nature and direction of the results.[55] In some fields, the time to publication may be twice as long for null results compared to those that are statistically significant,[57] but this difference may be attributable to variations between the time from study completion to publication.[55] Publication bias may overestimate the true effect of a treatment, or conceal a potentially adverse effect.[30] Luckily, there is a graphical test that can be utilized to help detect the potential for publication bias.[24,30,58]

A traditional funnel plot features a plot of an effect size, (such as the mean difference in LDL cholesterol) along the X axis, and either the sample size or variance along the Y axis. If there is no bias present, the plot will be symmetrical and should resemble an inverted funnel. One can modify the plot by choosing the standard error along the Y axis instead, and this has the effect of spreading out the smaller studies towards the bottom of the graph, making it easier to identify individual studies. Below is a funnel plot of studies determining the effect of carbohydrate-restriction on serum LDL cholesterol, depicted here merely for the purposes of explanation. In this example, the change in mean LDL cholesterol was plotted along the X-axis against the standard error of the study across the Y-axis. The plot, created by CMA (BioStat, version 2.0), is shown below as Figure 3:

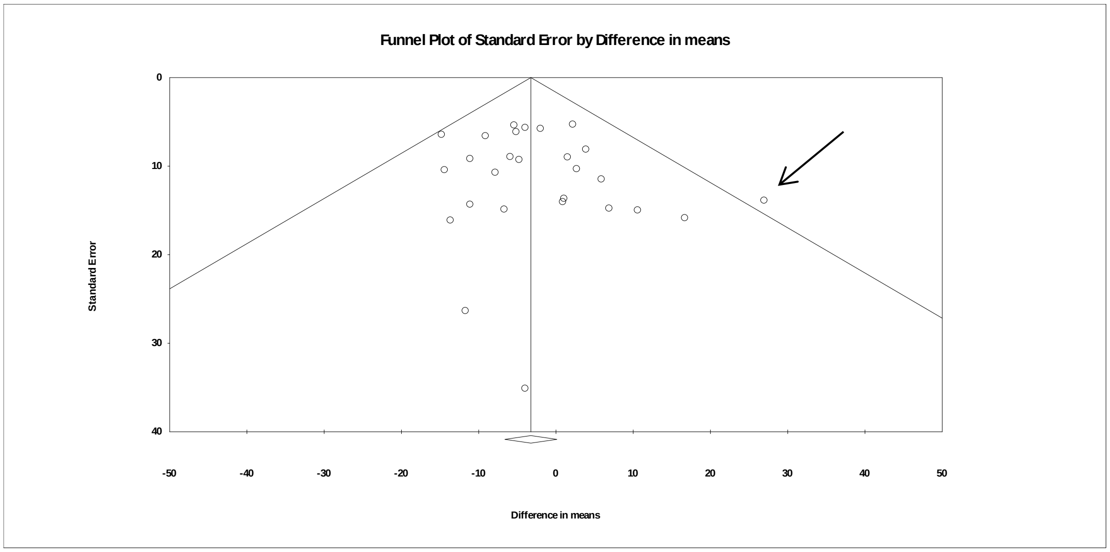


Figure 3: Sample funnel plot.

Upon examination, there seems to be a point of asymmetry on the right side of this funnel plot, indicated by the arrow. Duval and Tweedie[59] developed a method that allows one to impute studies missing from the analysis. The method is known as "Trim-and-Fill", as the method initially trims the asymmetric studies from the right-hand side to locate the unbiased effect, and then fills the plot by re-inserting the trimmed studies back on the right, as well as their imputed counterparts to the left of the mean effect.[15] The model of the funnel plot (fixed versus random) should mirror the choice of model for the meta-analysis. The program provides the summary effect from the observed studies, but also can estimate how the summary effect would change if all the missing studies were imputed (in this hypothetical case, the Trim-and-Fill procedure predicted a greater decrease in LDL cholesterol by 0.5mg/dL). Visually, one can see an additional black point that has been imputed on the left side of graph below (Figure 4), indicating a single point of asymmetry for this funnel plot, again indicated by an arrow:

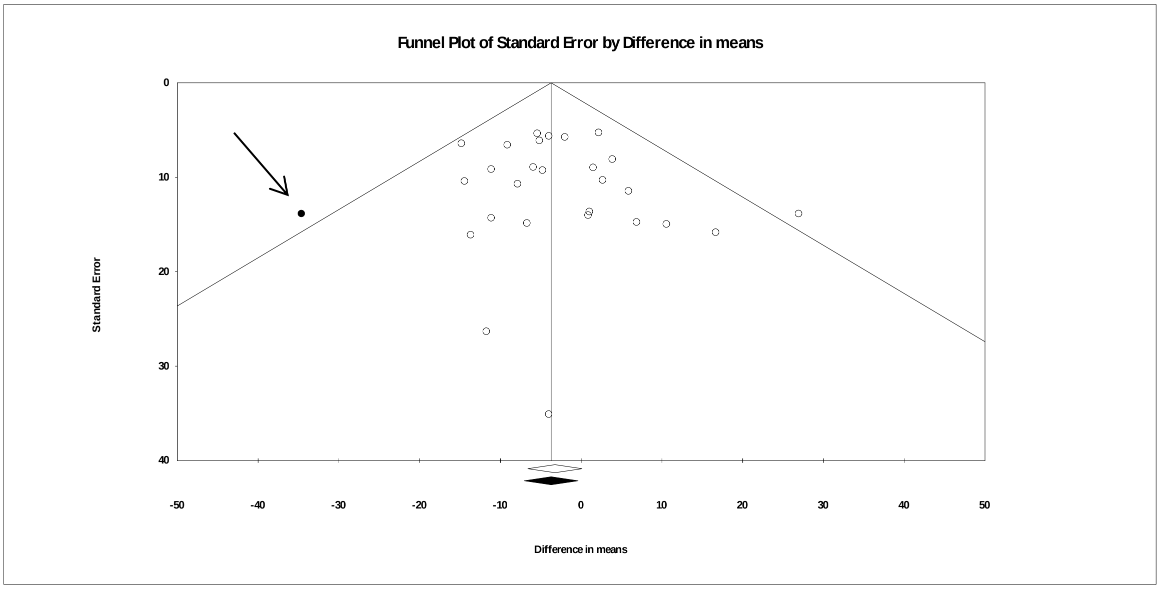
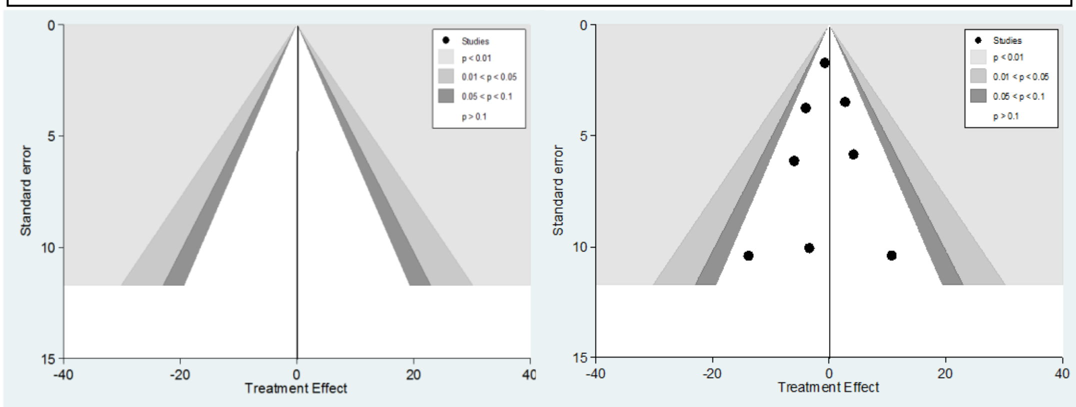


Figure 4: Sample of a trim-and-fill funnel plot.

When there is clear evidence of asymmetry, it cannot be assumed that this reflects publication bias.[24,30] Small studies may produce larger effect sizes when their design and analytic methods are less rigorous, or when a treatment is implemented with greater care than larger studies. Thus, the funnel plot is a generic tool to examine the tendency for smaller studies to show larger treatment effects.[6,58] Other possibilities for asymmetry include: poor methodological quality of the study, true heterogeneity, or random chance.[60] Visual inspection of funnel plots is subjective and should be balanced with

Figure 5: Example of a contour enhanced funnel plot.
(Example of bias-free symmetry shown on the right.)



additional analyses. One should instead report that “if the asymmetry is due to bias, the analyses suggest that the adjusted effect would fall in the range of…”[30] To assist with interpreting funnel plots, it is recommended to create funnel plots enhanced with contours of statistical significance (see Figure 5). If studies appear to be missing in the areas of non-significance (i.e. the inner-white area of the plot in Figure 5), publication bias is plausible; if the missing studies are in areas that are statistically-significant (which was harder to determine in Figures 3 and 4), publication bias is less likely.[61] The contour funnel plots above were created using the “confunnel” command in STATA (STATA v.12, StataCorp LP).

Language can be another source of bias in systematic reviews, as English journals and electronic databases tend to be searched more frequently, and statistically significant results are more likely to be published in English.[24,62] Juni et al. states that excluding non-English trials will have little impact on the summary effect in a meta-analysis, but recommends that a comprehensive literature search should be followed up with a careful assessment of trial quality.[62] For the purposes of transparency, a systematic review should report every article that was excluded from the systematic review due to language, and consider what percentage of the total number of studies assessed for eligibility this comprises. (In MEDLINE, the language filter only excludes records that do not have an available translation in the language of interest.) There are other sources of bias related to the design of the study itself, and these should be documented and summarized within a systematic review, using a tool like The Cochrane Collaboration's tool for assessing risk of bias.

Selection bias involves some difference in the composition of the study groups, and can be eliminated through proper randomization.[20,31,55] If a search strategy only included randomized controlled trials, it would essentially eliminate selection bias, assuming that the studies were properly randomized. Many studies do not report the method used to conceal their allocation sequence, and this should be noted when assessing bias. Performance bias refers to some difference in the treatment provided to subjects, and this can be minimized through adequate blinding of subjects and researchers to the intervention received.[20,31,55] It can be difficult for participants to be blinded to their treatment in dietary trials,[63] but the use of metabolic kitchens, specially prepared meals, or food substitutes can help reduce this form of bias. Detection bias describes a systematic difference in how outcomes are reported between groups.[20,55] Again, adequate blinding of those assessing the outcomes will minimize this form of bias.[31] Research has shown that randomized controlled trials that do not use a double-blind method of concealment tend to produce estimated treatment effects that appear more beneficial.[35] Attrition bias involves differences in dropouts and withdrawals that alter the outcome data, and the numbers and reasons for attrition should be described for each study, and evaluated by the reviewer.[20,31] Reporting bias describes the tendency of a publication to selectively report outcomes. If a research article describes five outcome variables that they plan to test, but only report on the two statistically-significant outcomes, this should be noted in the systematic review. Finally, carryover is a form of bias specific to crossover trials, occurring when the treatment of one crossover trial period can influence the outcome in subsequent treatment periods.[64] By ensuring adequate run-ins and wash-out periods, and reporting the outcomes between treatment periods, this form of bias can be minimized.

Decisions made during any step of the process of performing a systematic review and/or meta-analysis can affect the final results, so it is often wise to perform a sensitivity analysis to determine what would happen if certain aspects of the data or the analysis were changed.[6,15] Sensitivity analyses do not need to be quantitative, and instead could include statements defending the choices made throughout the process (such as the chosen statistical mode or inclusion criteria).[3] In other cases, a sensitivity analysis can use different statistical approaches to assess the influences and biases of components of a study, or a particular study itself.

Cumulative meta-analysis is a method of tracking trends in research on a given topic over time, repeating the analysis whenever a new trial becomes available for inclusion.[24,65] One way to do this is with a Forest plot in which study effects are sorted by year of publication (or report date for unpublished studies). As new studies are added, the average effect size may vary, or converge over time.[51,66] When effects are stable over a series of studies, at a certain point the combined effect may be well established and statistically significant, warranting a change in the established policy or treatment.[67]

Borenstein demonstrated the use of cumulative meta-analysis to assess publication bias or small-sample effects.[66] Instead of sorting by year, studies are sorted by their precision (from most- to least-precise) in a forest plot. If the gradual inclusion of studies with lower precision increases the mean effect estimate, there is evidence of publication bias or small-study effect.[30,66] An alternative to this technique involves a sensitivity analysis where a forest plot is created showing each pooled result, having excluded a study, compared to the pooled result from all studies. In this way, the impact of each individual study on the pooled result can be investigated.[3] Some software programs, like CMA, have the option of systematically calculating a summary effect with a single study removed. In this way, the impact of any individual study can be examined and explored.

When the risks and sources of bias have been evaluated, and the potential effects from sensitivity analyses have been considered, the quality and strength of the evidence and its limitations can then be described and discussed. The applications for evidence-based care, healthcare policy, and avenues of future research are all end goals of a meta-analysis.

Summarizing Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is an internationally-recognized system to classify the evidence yielded from (systematic reviews and) meta-analyses.[68] Within this transparent and structured process, a summary effect for every outcome in the meta-analysis is generated, and then the quality of the evidence is rated for each outcome, across all the studies; a series of articles describing the system have been published by the GRADE Working Group. The categories include: study limitations,[69] imprecision,[48] inconsistency of results,[70] indirectness of evidence,[71] and likelihood of publication bias.[72] RCTs start with a high rating and various threats to the quality of evidence warrant downgrades of the rating (high>moderate>low>very low), until a final rating is reported for each outcome across all the studies in the meta-analysis.[68] Guideline developers may later rate the strength of the evidence reported by the meta-analyst, and subsequently provide those recommendations to clinicians and patients, strengthening the foundation of evidence-based care.[73]

Conclusion

When the process minimizes bias and contains an adequate number of studies for reliable comparison, systematic reviews and meta-analyses are far superior methods to review and synthesize scientific literature.[28] Research findings from a large number of studies can be summarized and presented in a more organized and sophisticated manner than traditional narrative reviews and vote counting.[18,22] Not only can they keep people up-to-date on topics, but they can estimate the average effect of an intervention, allowing effective treatments to more rapidly reach those who would benefit.[22,28] From the efficacy of medications and vaccines,[74] to the proper way to lay a baby to sleep to prevent Sudden Infant Death Syndrome (SIDS),[30] to calculating the speed of light in a vacuum,[75] systematic reviews and meta-analyses provide a panoramic view of the research landscape in a variety of fields.[23]

CHAPTER 2:

THE EFFECT OF MACRONUTRIENT DISTRIBUTION ON THE LIPID PROFILE IN ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

PLAIN LANGUAGE SUMMARY

When it comes to improving a blood lipid panel, what we eat may be more important than how much.

For individuals who want to reduce their "bad" LDL cholesterol, reducing saturated fat is generally seen as the first dietary measure. However, it is not clear what people should replace the saturated fat with, and most people choose carbohydrates. Research over the years has suggested that this choice may cause people to eat more total calories (since they become hungry sooner than if they had eaten fat), and the introduction of carbohydrates (particularly from refined sources like sugars that lack dietary fiber) may increase blood triglyceride levels and decrease the "good" HDL cholesterol. It turns out that even when LDL levels are at or below recommended treatment goals, elevated levels of triglycerides and/or decreased concentrations of HDL are independent risk factors associated with coronary heart disease.

There are a set of published guidelines that recommend acceptable ranges for the percent of macronutrients (i.e. total fat, total protein, and total carbohydrate) that individuals should consume to reduce their risk of chronic disease, while still obtaining all of their essential nutrients. This manuscript sought to examine these guidelines to see if there was perhaps an "optimal" ratio of macronutrients that would demonstrate the greatest improvement in the lipid profile. As it turns out, the quality of the macronutrient plays a larger role in altering the lipid profile than the total amounts of each macronutrient. Generally speaking, reducing total fat saw clinically significant reductions in both total cholesterol and “bad” LDL cholesterol; the results hint that decreasing total carbohydrate intake would reduce levels of triglyceride. Individuals seeking to improve their blood lipid panel may wish to begin at the following distribution of total energy: 28% fat, 18% protein, and 54% carbohydrate. Then, the adoption of a “Mediterranean Diet”, with an emphasis on fresh fruits and vegetables, lean meats, and virgin olive oil will be a good complement to increased physical activity. Fine-tuning of dietary recommendations should be performed under the guidance of a physician and dietitian after considering the risk factors, medications, and preferences of the individual.

An abstract for "The effect of macronutrient distribution on the lipid profile in adults: a systematic review and meta-analysis" by John A. Stroster.

Background
Research supports a reduction in saturated fat to diminish cardiovascular disease risks, such as dyslipidemia. However, the macronutrient that should be substituted for saturated fat in the diet has not been thoroughly investigated.

Objectives
To assess the effect of manipulating macronutrient distribution on the lipid profile of adults, and compare these effects to recommendations regarding macronutrients, such as the Acceptable Macronutrient Distribution Ranges (AMDRs).

Search methods
MEDLINE was searched from January 2002 to December 2010.

Selection criteria
Blinded, randomized controlled trials on human adults that reported macronutrient and lipid profile data from repeated-measure (pre-post) comparisons.

Data collection and analysis
One author assessed trial quality and coded the extracted data in duplicate. To limit bias, one set of articles was "de-identified", using only its unique MEDLINE identifier, while the other set was coded normally. Complete-case analysis was followed to deal with missing data, and studies were excluded if any data pertinent to analyses were missing. Random-effects meta-analysis of raw mean differences (D), meta-regression, subgrouping, sensitivity analyses, and funnel plots were performed.

Main results
Forty-two trials, comprising eighty-six comparisons and 3,144 people were included; 66% of the comparisons were categorized as falling within the AMDRs. The summary effects for the studies in the meta-analysis were:

- ∆Total cholesterol: (-6.40 mg/dL, 95%CI: -8.81 to -3.99, I^2 = 95%)
- ∆LDL cholesterol: (-5.32 mg/dL, 95%CI: -7.45 to -3.18, I^2 = 94%)
- ∆HDL cholesterol: (+ 1.14 mg/dL, 95%CI: 0.39 to 1.88, I^2 = 91%)
- ∆Triglycerides: (-8.22 mg.dL, 95%CI: -11.55 to -4.89, I^2 = 90%)

Subgroup analysis of 9 comparisons (239 subjects) suggested decreasing total fat by at least 3.5% reduced total cholesterol (D: -14.84 mg/dL, 95% CI: -23.05 to -6.64) and LDL cholesterol (D: -13.02 mg/dL, 95%CI: -16.65 to -9.39). Meta-regression indicated that change in LDL cholesterol was estimated to decrease by 0.2mg/dL per unit (mg/dL) increase in pre-treatment LDL, and change in triglycerides was estimated to decrease by 0.2 mg/dL per unit (mg/dL) increase in pre-treatment triglyceride levels.

<u>Author's Conclusions</u>

The Acceptable Macronutrient Distribution Ranges (AMDRs) generally seem to be suitable macronutrient guidelines for the prevention of unfavorable alterations to the lipid profile, although the quality/source of the macronutrients has a larger impact. Decreasing the total amount of dietary fat and replacing it predominantly with carbohydrate was associated with clinically significant reductions in both total and LDL cholesterol. There was insufficient evidence regarding HDL cholesterol and triglycerides, although decreasing total carbohydrate resulted in a decrease in triglycerides that approached clinical significance. An average macronutrient distribution of: 27.6% ±6.7 fat, 17.7% ±3.6 protein, 53.6% ±10.6 carbohydrate may improve total, HDL, and LDL cholesterols.

Summary of findings for effect of macronutrient distribution on the lipid profile.				
	∆TC	∆LDL	∆HDL	∆TG
# of Studies (Design)	42 Blinded RCTs Start: ⊕⊕⊕⊕	42 Blinded RCTs Start: ⊕⊕⊕⊕	42 Blinded RCTs Start: ⊕⊕⊕⊕	42 Blinded RCTs Start: ⊕⊕⊕⊕
Limitations in design	No	No	No	No
Inconsistency	Very Serious (-2) ○○	Very Serious (-2) ○○	Serious (-1) ○	Serious (-1) ○
Indirectness	No	No	No	No
Imprecision	No	No	No	No
Publication bias risk	Unlikely	Unlikely	Uncertain	Uncertain
# of Participants (Comparisons)	3144 subjects (86)	3144 subjects (86)	3144 subjects (86)	3144 subjects (86)
Comparator: Raw Mean Difference (D)	∆ TC (Post-Pre TC)	∆ LDL (Post-Pre LDL)	∆ HDL (Post-Pre HDL)	∆ TG (Post-Pre TG)
Summary Effect	-6.401 mg/dL	-5.317 mg/dL	+1.137 mg/dL	-8.219 mg/dL
95% CI	-8.81 to -3.99	-7.46 to -3.18	+0.39 to +1.88	-11.55 to -4.89
Comments	High level of unexplained heterogeneity I^2 = 95%	High level of unexplained heterogeneity I^2 = 94%	High level of heterogeneity I^2 = 91%	High level of heterogeneity I^2 = 90%
Quality of Evidence (GRADE)	Low ⊕⊕○○	Low ⊕⊕○○	Moderate ⊕⊕⊕○	Moderate ⊕⊕⊕○

PRISMA CHECKLIST

INTRODUCTION

Atherogenic dyslipidemia describes an elevation of blood triglycerides, blood cholesterol (particularly small, dense low-density lipoprotein (LDL) particles that are more easily oxidized), or decreased concentrations of high-density lipoproteins (HDL).[76,77] Non-fasting plasma concentrations of LDL, HDL, and triglycerides (TG) are significant predictors of cardiovascular events in the general population, and even stronger predictors among those with diabetes.[78] For adults 20 years and older, the following are the normal reference ranges for the lipid profile:[79]

- Total cholesterol
    - < 200 mg/dL – Desirable
    - 200-239 mg/dL – Borderline
    - >239 mg/dL – Higher Risk
- LDL Cholesterol
    - < 130 mg/dL – Desirable (<100 mg/dL if individual has CHD)
    - 130-160 mg/dL – Borderline
    - >160 mg/dL – Higher Risk
- HDL Cholesterol
    - >39 mg/dL – Desirable
    - < 39mg/dL – Higher Risk
- Triglycerides
    - < 150 mg/dL – Desirable
    - 150-200 mg/dL – Borderline
    - 200-499 – Higher Risk
    - ≥500 mg/dL – Very High

About 70% of individuals with type 2 diabetes mellitus also possess atherogenic dyslipidemia, and the condition is one of several included within metabolic syndrome.[80-83] Higher intake of saturated fatty acids has been linked to cardiovascular disease and metabolic syndrome; the primary effect is thought to be related to their influence on LDL concentrations.[84,85] Yet even when LDL levels are at or below recommended treatment goals, elevated levels of triglycerides and/or decreased concentrations of HDL are independent risk factors associated with coronary heart disease.[86] Combined pharmaceutical therapy for dyslipidemia has proven effective, but should be used in conjunction with lifestyle modifications, including diet.[86,87] Therefore, dietary advice should be tailored to the risk factors of the individual, in order to maximize the effect of medication therapy, or slow the progression of the condition for those in its early stages.

Evidence from epidemiologic studies, clinical trials, and meta-analyses support a reduction in saturated fat to diminish cardiovascular disease risks, such as dyslipidemia. However, the macronutrient that should be substituted for saturated fat in the diet has not been thoroughly investigated, and the present guidelines from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults state that the range of macronutrients should be tailored to an individual's risk factors.[88] For total fat, the panel recommends a range between 25-35% of total energy for those with lipid disorders, focusing on the higher end of the range for those with metabolic syndrome.[88] The recommendation for carbohydrate is less than 60% of total energy, but for those with metabolic syndrome and altered triglyceride or HDL levels, the target is closer to 50%.[88]

Alternatively, the Institute of Medicine has established Acceptable Macronutrient Distribution Ranges (AMDRs) for energy intake that are associated with reduced risk of chronic disease, while still providing adequate levels of essential nutrients.[89] For adults, the AMDRs are:[89]

- Total fat: 20-35% total energy
- Total carbohydrate: 45-65% total energy
- Total protein: 10-35% total energy

Since the AMDRs are expressed as a percentage of total energy intake, manipulation of one macronutrient beyond its range will ultimately affect one or both of the others, and potentially lead to either dietary inadequacies or the risk for chronic disease.[89] For example, the lower range for carbohydrate intake was set at 45% because it was believed that recommendations below this value would make it difficult for individuals to meet their Adequate Intake (AI) of fiber and certain vitamins.[90] Intake of carbohydrate above 65% of total energy would reduce the intake of fat and/or protein, risking inadequate intake of essential fatty acids and indispensable amino acids, as well as promoting hypertriglyceridemia.[90] The AMDRs assume that individuals will balance their dietary intake and physical activity to maintain energy balance,[89,91] however for decades people have been increasing their total caloric intake and becoming more sedentary.[92] These excess calories typically come from carbohydrate, and often from refined sources that contribute to different, but equally significant health issues when compared to diets high in total and saturated fat.[92,93] Given the absence of convincing evidence to support recommendations for a suitable replacement of saturated fat in the diet of individuals seeking to slow or prevent the progression of atherogenic dyslipidemia,[94] the primary aim of this proposed research is to use a meta-analytic approach to assess the blood lipid response to dietary manipulation of macronutrient distribution and compare the results to established recommendations.

How might the manipulation of macronutrient distribution affect blood lipids?

Determined by complex genetic and environmental factors, dyslipidemia, cardiovascular disease, and metabolic syndrome are inter-related, and their treatments should reflect this.[81,95] Dietary interventions go beyond postprandial changes in lipid concentrations or simple weight gain, because they may induce changes in metabolic and inflammatory processes through modulating genetic expression.[85] Teslovich et al. identified 59 novel loci across the human genome that are associated not only with plasma lipids, but more specifically with coronary artery disease (CAD).[96] Unfortunately, monogenetic disorders of triglyceride metabolism or genome-wide association studies fail to explain more than 10-15% of the risk for developing atherosclerotic dyslipidemia or the independent risk related to increased triglycerides or decreased HDL.[86,97,98] For a more complete understanding of the problem, examinations need to be expanded beyond common variants associated with plasma lipids, and instead consider targeting both modification of the lipoproteins themselves, as well as the dynamic between blood lipids and lifestyle choices.

Target: Weight Loss

Reducing obesity is a frequent goal for the treatment of dyslipidemia, as individuals with adipose tissue disorders, such as abdominal obesity, are more susceptible to metabolic syndrome.[81] Increased adiposity, and its resulting insulin resistance, may alter processes related to lipolysis and lipogenesis.[85] Regardless of issues related to adipose tissue, weight loss in general has been shown to have a positive effect on dyslipidemia. A meta-analysis of seventy studies reviewed the effect of weight loss on blood lipids and reported that each kilogram lost would result in a 1.9 mg/dL decrease in total cholesterol ($P < 0.01$), and a 0.77 mg/dL decrease in LDL ($P<0.001$), but a small decrease in HDL by 0.03 mg/dL ($P \leq 0.05$).[99] While obesity is a contributing factor to metabolic syndrome and heart disease, around 30% of obese individuals seem to be protected from these conditions, highlighting differences in both their phenotype and required treatment, at least compared to those with insulin-resistant obesity.[100,101]

Low-carbohydrate, high-protein, high-fat diets have become popular among individuals seeking to lose weight. While effective for weight loss, research is inconsistent with regard to the effect such diets have on blood lipids. Very low carbohydrate diets seem to have little impact on LDL, but there are more consistent data on improvements to triglyceride and HDL levels, although large variability among individual research subjects has been observed.[102]

Lim et al. compared the effects of three isocaloric diets (1550kcals/d) over a fifteen-month period on 104 subjects (84% female, age 47y ±10).[103] The intervention diets included a very low carbohydrate diet (35% protein, 60% total fat, with 20% saturated fat, 4% carbohydrate); a very low fat diet (20% protein, 10% total fat, with 3% saturated fat, 70% carbohydrate); and a high unsaturated fat diet (20% energy as protein, 30% total fat, with 6% saturated fat and 8% polyunsaturated fat, 50% carbohydrate). Weight change was similar between all dietary groups, with participants gaining weight between the third and fifteenth month. In the very low carbohydrate group, there were increases in LDL cholesterol (11.6 mg/dL, $P< 0.05$), whereas decreases were seen in the other diets. After fifteen months, there were no longer significant differences between any of the three diets with respect to blood lipids.[103]

A similar study was conducted by Tay et al., who compared two isocaloric (1550 kcal/d) diets: a very low carbohydrate/high fat diet (4% carbohydrate, 35% protein, 61% total fat, with 20% saturated fat) and a high carbohydrate/low fat diet (46% carbohydrate, 24% protein, 30% total fat, with < 8% saturated fat) on eighty-eight abdominally obese subjects (65% female, age 51y ±8).[104] After 24 weeks, both groups lost weight, but there was no significant difference in weight reported between the very low carbohydrate and high carbohydrate groups (12.3% ±5.5 versus 10.5% ±5.5, respectively $P = 0.17$). The high carbohydrate diet demonstrated greater reductions for total (-20.9 mg/dL ±30.5, $P<0.05$) and LDL cholesterol (-17.8 mg/dL ±27, $P<0.05$), whereas in the very low carbohydrate group, nearly one-quarter of the subjects showed an increase of their LDL level by at least 10%. The very low carbohydrate group also reported a reduction in triglycerides that was nearly twice that in the comparison group (-56 mg/dL ±54.9 versus -31 mg/dL ±43.4, $P<0.05$).[104] The data from trials such as these often show wide variation, leading some researchers to match the subjects within randomized groups not only on the basis of factors like: age, sex, smoking status and body mass index, but by common genetic polymorphisms related to the condition of interest.[101]

Target: HDL (and TG)

Increasing the concentrations of HDL is often the target of dyslipidemia therapy once LDL levels are normalized. By increasing reverse cholesterol transport, HDL transfers free cholesterol from macrophages and peripheral tissues to the liver to be eliminated through bile in the feces.[105] A high triglyceride-to-HDL ratio has been observed in many individuals with type 2 diabetes,[106] and is believed by some to be related to processes involved in altering the size of LDL particles.[107] In nearly all those with diabetic dyslipidemia, the LDL particles are small and more susceptible to oxidation,[107] and improvement to this ratio has been correlated to delayed progression of atherosclerotic lesions in patients treated with anti-hyperglycemic medications.[108] Researchers and clinicians have utilized the TG-to-HDL ratio as a screening tool to identify potential patients in need of early and aggressive treatment of their dyslipidemia, but the utility of the TG-to-HDL ratio differs with ethnicity, and is not appropriate for all groups, particularly African Americans.[109,110] Through mechanisms that are still widely unknown, for some individuals the HDL is simply not functioning normally, and can even undergo modifications that reduce its protective effect or even allow it to become atherogenic.[111] Therefore absolute concentrations of HDL are less informative than methods adopted to test its functionality.

While medications like statins reduce cardiovascular risk predominantly through the lowering of LDL cholesterol (by up to 40%[112]), they do not effectively treat high triglyceride or low HDL levels, and statin monotherapy only reduces the risk of a cardiovascular event by 25-35%.[105] Given the intolerance and lack of long-term safety data on pharmaceutical options for improving triglycerides and/or HDL,[87] individuals with stabilized LDL, but altered triglycerides and/or HLD levels may benefit the most from low- and very-low carbohydrate diets, despite conflicting results among clinical trials with small sample sizes. Medications intended to improve triglyceride and HDL levels include fibrates that can reduce triglycerides by 30-50%, and niacin, which can raise HDL as much as 30%; the improvement seen from niacin may be difficult to sustain due to intolerance of the drug.[87] Diets that would negatively impact lipid levels effectively undermine pharmaceutical therapy, leading to increased doses and risk for side effects. Among the interventions to help raise HDL levels, the European Society of Cardiology has listed the OmniHeart diet, which can increase HDL concentrations by as much as 4.9%.[86]

The OmniHeart Randomized Trial compared a diet rich in either plant protein (25% total protein, with 12% plant protein, 48% carbohydrate, and 27% total fat) or monounsaturated fat (15% total protein, 48% carbohydrate, and 37% total fat, with 21% monounsaturated fat), with one rich in carbohydrate (15% protein, 58% carbohydrate, 27% total fat).[113] After a two-week run-in period, 164 subjects (45% female, age 53.6y ±10.9) consumed each diet for six weeks, followed by a 2-4 week washout period before randomly crossing over to one of the other diets. Participants were provided all of their food, which was prepared in a research kitchen; one meal was eaten on-site. Weight was measured each weekday and kept stable within 2% of baseline. Both the diets high in plant protein and monounsaturated fat reduced triglycerides more than the high-carbohydrate diet (Prot: -16.4mg/dL, Mono: -9.3mg/dL versus Carb: 0.1mg/dL). The aforementioned protein-rich diet (25% of energy) also reduced both low- and high-density lipoprotein levels (-14.2mg/dL and -2.6mg/dL, respectively), while the diet rich in unsaturated fat (25% of energy) demonstrated similar a change in LDL (-13.1mg/dL), without a change in HDL.[113] The carbohydrate-rich diet used in OmniHeart Trial was similar to that of the Dietary Approaches to Stop Hypertension (DASH) trials, which has been shown to lower blood pressure and LDL, but had no effect on serum triglycerides and decreased HDL cholesterol levels.[114,115] A meta-analysis of nine studies by Garg compared the effects of either a high carbohydrate (49-60% total energy) diet to one with high levels of monounsaturated fat (37-50% total fat, with 22-33% monounsaturated fat). In these studies, the high monounsaturated diet decreased total cholesterol by 3%, triglycerides by 19%, and increased HDL concentrations by 4%, with no effect on LDL cholesterol.[116]

Target: Inflammation

Another common dietary treatment approach for atherogenic dyslipidemia is the Mediterranean diet; its effect is likely due to the anti-inflammatory properties (including polyphenols) of the unsaturated fatty acids contained in the typical foods.[85,117] A meta-analysis of 50 epidemiologic and clinical studies that assessed the effect of Mediterranean diet on metabolic syndrome reported the protective role of the diet by a reduction in mean triglycerides levels by -6.14mg/dL (95%CI: -10.35 to -1.93) and a mean increase in HDL by 1.17mg/dL (95%CI: 0.38 to 1.96).[118] Several studies have attempted to supplement the Mediterranean diet with additional omega-3 fatty acids, but the data are inconsistent, likely due to differences in the treatment effect in specific at-risk populations, as well as the small number of studies that have examined the effect of duration, dosing, efficacy, and safety of omega-3 supplementation.[119]

Elhayany et al. compared a traditional Mediterranean diet (50-55% carbohydrates with a low glycemic index, 30% total fats with an emphasis on high monounsaturated fat, and 15-20% protein); a low carbohydrate version of the Mediterranean diet (35% carbohydrates with a low glycemic index, 45% fats with an emphasis on monounsaturated fat, 15-20% protein); and the 2003 American Diabetic Association (ADA) diet (50-55% carbohydrates, 30% total fat, and 20% protein).[120] One hundred ninety-four subjects (48% female, age 56.3y ±6.2) completed the 12-month trial. While all three diets lowered triglyceride levels, the traditional and low-carbohydrate Mediterranean options showed greater reductions (-129.3 mg/dL ±67 & -134.6 mg/dL ±76, respectively $p<0.001$) versus the American Diabetic Diet (-77.9 mg/dL ±122.2, $p< 0.001$). The low carbohydrate Mediterranean diet was the only one to result in an increase in HDL (+5 mg/dL ±12, $p<0.001$), while the traditional Mediterranean diet showed no change in HDL, and the American Diabetic Association's diet demonstrated a slight decrease (-1.93 mg/dL ±11.2, $p<0.001$). It should be noted that some of the differences seen between the low carbohydrate Mediterranean diet and the other two options may involve the larger amount of weight loss reported in this group (10.1kg lost versus 7.4kg in the traditional diet and 7.7kg in the ADA diet).[120]

Miller et al. compared the Mediterranean South Beach diet to the high-fat, low-carbohydrate Atkins diet, and the high-carbohydrate, low-fat Ornish diet.[121] Eighteen subjects (50% female, age 30.6y ±9.6, BMI < 30kg/m^2) consumed each diet for a four week period. After the dietary intervention, a four week wash-out period was conducted before the subjects were randomly selected to undertake another treatment arm. Weight was measured weekly, and variations of more than 1kg prompted adjustment of their overall energy intake. The Mediterranean-style South Beach diet lowered triglycerides and raised HDL roughly the same amount as the Atkins diet (p=0.95), but demonstrated a decrease in LDL (-11.8mg/dL ±11.7, p=0.003), whereas those on the Atkins diet showed an increase (+8.1 mg/dL±11, p=0.003) Consistent with several other high-carbohydrate diets, the Ornish diet significantly lowered total cholesterol (-22.7 mg/dL ±19.9, p<0.001) and LDL-C (-16.6 mg/dL ±11.7, p<0.001), but also lowered HDL (-8.7 mg/dL±11, p=0.002) and raised triglycerides (+16.2 mg/dL ±35.5, p=0.048).[121]

Target: Macronutrient Quality

Obviously the total amounts of dietary macronutrients do not provide as much insight compared to the quality and sources of those macronutrients. For example, if two diets were isocaloric and even had the same amounts of total and saturated fat, they would produce very different effects on blood lipids if the fat in one diet was predominantly from myristic acid (found in milk products), and the other was rich in stearic acid (from cocoa fat). These two fats produce significantly different effects on blood cholesterol levels, with the prior increasing plasma total and LDL cholesterols, while the latter has very little impact.[85] Whether the source of protein comes from animal or plants is certainly relevant, and amount and quality of any carbohydrate in the diet is also significant. In a meta-analysis of 37 prospective observational studies, diets with either a high glycemic index (GI) or glycemic load (GL) increased the risk of type 2 diabetes (GI RR = 1.40; GL RR = 1.27) and heart disease (GI RR=1.25). The authors predicted that the effect of a low-GI or low-GL diet would be similar to diets emphasizing whole grains or fiber.[122]

A review of dietary trials with CHD end points by Hu and Willett revealed few large studies that explored the effect of substituting different macronutrients for saturated fat[123]. While the largest change in serum cholesterol was shown through the use of polyunsaturated fat, there is still uncertainty as to how the amount and type of protein and carbohydrate interact to influence blood lipids.[123] It is often difficult to assess whether the improvement in blood lipid levels is due to weight loss or from any alterations of the diet. Unfortunately, most studies do not measure the quality of the macronutrients in the diet, instead reporting only the total amounts. Additional factors that can obscure the effect of an intervention include: the impact of exercise,[124] concurrent medication use, and comorbidities. Finally, many published studies have low precision, contain many sources of bias, and do not adequately measure dietary parameters. Taken together, these issues explain much of the inconsistency and variability when trying to explain the effect macronutrient distribution has on blood lipid levels.

Why is it important to do this review?

Previous systematic reviews and meta-analyses related to dietary macronutrients and blood lipids have tended to focus on either one specific macronutrient,[63] its source,[116] or did not focus solely on blinded, randomized controlled trials.[125] Given the inconsistency and variability of past trials and reviews, this systematic review and meta-analysis focused on the general macronutrient distribution, specifically the percent of total energy contributed from total protein, total fat, and total carbohydrate. No distinction was made for the type or source of the macronutrient, as these data are not readily reported. The outcome of interest was the lipid profile, consisting of circulating blood levels of total cholesterol, LDL, HDL, and triglycerides. These analyses were chosen because they are readily reported in clinical literature, and are common diagnostic parameters in the treatment of lipid disorders such as atherosclerotic dyslipidemia. The studies selected for this systematic review and meta-analysis will likely demonstrate lower bias than those in similar meta-analyses, and more effort was taken to ensure the inclusion of adequately-powered studies, and to describe the heterogeneity seen among the studies. To the knowledge of the author, this may be one of the first meta-analyses that examined the Acceptable Macronutrient Distribution Ranges, and therefore this research may implications for our Dietary Reference Intakes (DRIs).

OBJECTIVES

The aim of this systematic review and meta-analysis was to assess the effect of change in dietary macronutrients, which would be expected to result in alterations in the lipid profile, using blinded, randomized controlled trials published in English on MEDLINE.

The primary question of this research project was:

- Does the macronutrient distribution of the diet, specifically the proportion of total energy contributed total dietary fat, total dietary protein, or total dietary carbohydrate alter the primary outcome, the lipid profile (notably total cholesterol, LDL, HDL, and triglycerides)?

Specific questions included:

1. Over the course of a dietary intervention, does changing the percentage of one or more macronutrients alter the primary outcome, the lipid profile (notably total cholesterol, LDL, HDL, and triglycerides)?
2. Do dietary interventions within the Acceptable Macronutrient Distribution Range (defined by energy contributed by total fat between 20-35%, total carbohydrate between 45-65%, and total protein between 10-35%) demonstrate favorable alterations in the lipid profile (specifically decreases in total cholesterol, LDL, triglycerides and increases in HDL)?

3. Does the distribution of macronutrients outside the Acceptable Macronutrient Distribution Range (defined by energy contributed by total fat as <20% or >35% and energy contributed by total carbohydrate as < 45% or >65%) alter the primary outcome, the lipid profile (specifically total cholesterol, LDL, HDL, and triglycerides)?
4. Are effects on the lipid profile moderated by: the pretreatment lipid profile levels, gender, age, duration of the study, or number of subjects in the study?

METHODS

Protocol and Registration

A protocol does not currently exist for this review.

Criteria for considering studies for this review

For inclusion, the studies had to meet all of the following criteria:

1. Randomized controlled trials (RCTs).
2. Single- or double-blinded study design. RCTs that did not explicitly state they were blinded, but provided a sufficient description of the blinding process (e.g. researchers and staff were kept unaware of the treatment allocation for each subject) were included.
3. Dietary interventions performed on human adults, published in English on MEDLINE, between January 2002 and December 2010.
4. Studies reporting single-group or multiple-group repeated-measure (Pre-Post) comparisons.
5. Studies reporting quantitative measures (means and standard deviations) for manipulated dietary components. (Specifically total calories and the percentages of energy from total protein, total fat and total carbohydrate.)
6. Studies reporting quantitative measures (means and standard deviations) for the following parameters within a lipid profile: total cholesterol, HDL cholesterol, LDL Cholesterol, and triglycerides.

Studies were excluded for any of the following reasons:

1. Studies where the allocation was not truly randomized (e.g. semi-randomized or quasi-randomized), or not explicitly stated as randomized.
2. Not performed on adults ($\geq$18 years of age).
3. An English translation of the article could not be acquired.
4. The study did not report means and standard deviations on one or more of the predictor or outcome variables, nor could these values be reliably calculated from reported data.
5. The collected samples for analysis did not originate from a venous source (e.g. cord blood samples, capillary blood, cell cultures).
6. The trial only monitored the effect of a dietary supplement, and did not report data on the complete diet.
7. The length of the study lasted less than one day, and was thereby categorized as a tolerance study or a test meal (e.g. oral fat tolerance test). Trials where the blood samples were drawn less than a week apart were also not included.
8. Pharmaceutical studies that did not have an untreated dietary group free from the effects of the intervention medication.
9. Studies that included individuals who were pregnant or lactating.
10. Cross-over studies were included in the systematic review, but those that did not report data on run-in and/or wash-out phases of the trial were excluded. (Cross-over studies that did not provide within-subject data for each treatment period were not included in the meta-analysis.)

SEARCH METHODS FOR INDIVIDUAL STUDIES

Electronic Searches

Ovid MEDLINE was searched between May and July, 2012 for randomized controlled trials on diet and blood lipids. As shown in Table 1 below, the first step comprised the terms used to seek potential dietary trials. Both medical subject headings (MeSH) and text-word options were included with the Boolean operator "OR" between each collection of terms. Step two followed the same pattern, but sought articles reporting blood lipids. Step 3 combined the two previous searches with the operator "AND", yielding a number of articles that featured both a dietary intervention and blood lipid levels. The articles identified in step 3 were then filtered, limiting the search to blinded RCTs published in English on human adults, between the years 2002 and 2010. The complete search strategy can be found in Appendix A.

Table 1: Simplified search strategy for dietary macronutrients and blood lipids.				
1	Diet (MeSH)	OR	Diet (Text Words) →	Combined Diet
2	Blood Lipids (MeSH)	OR	Blood Lipids (Text Words) →	Combined Blood Lipids
3	Combined Diet	AND	Combined Lipids →	Unfiltered Records

Searching other resources

In addition to the studies retrieved from the MEDLINE search, articles meeting the inclusion criteria were discovered while researching background information on the topic. Our research group also has access to the Howell Database, a collection of MEDLINE studies related to diet therapy and blood lipids that has been maintained for over seventeen years; information about the database has been published previously.[126] In

2006, the database was updated to include information on the macronutrient distribution of the included studies; this work was the subject of a Master's Degree Thesis.[127] This database was used as a source of MEDLINE articles from 1975 to 2002; any database entries that included all dietary macronutrients and lipid profile parameters were screened. (The upper-range of publication was chosen to be 2010 in order to allow sufficient time for medical subject headings to be indexed into MEDLINE.) The original articles were then acquired and compared to the inclusion and exclusion criteria of this systematic review. The macronutrient distributions of these studies meeting the inclusion criteria have not been reported on previously and therefore were included in this systematic review. Additionally, a search for eligible dissertations and theses was undertaken by searching the ProQuest Database, using the Boolean text word search already described. (See Appendix A) Finally, a search of the Journal for Negative Results in Biomedicine (JNRBM.com) was conducted in an effort to minimize reporting bias.

DATA COLLECTION AND ANALYSIS

Selection of studies

Since it was possible that a dietary trial could have performed a lipid profile, but not reported it as a main outcome, articles were only excluded upon initial screening if it could be determined from the title or abstract that it met one of the specified exclusion criteria. (For example, if the title or abstract described how the only participants in the trial were juveniles.) For every other trial, a full text version of the article was screened and compared against the inclusion and exclusion criteria before making a determination. When an electronic version of the article was unavailable, an inter-library loan request was submitted, or a hard copy was acquired via hand-searching.

Data Extraction and Management

For the purpose of coding the articles, a data extraction form was created, which was a form modified from ones used by Howell et al. in 1997,[126] and Hosseinpour in 2006.[127] (The main modification of the form was changing column headings referring to carbohydrate from "CHO" to "CARB", in order to avoid data related to dietary cholesterol being mistakenly entered instead.) Information on the various predictors, outcomes, and demographics of each study group (age, % male, smoking status, etc.) were transcribed from the published study to the form by the primary author of this manuscript (JAS). The database was set up to mirror this form, in order to minimize errors in data entry; a copy of the form can be found as Appendix B.

While it is ideal to have at least two people coding the articles independently, and a third individual available to settle discrepancies, only one individual was available to code articles into this database. In order to reduce potential biases and errors related to a single coder, two hard copies of each article were printed. The first set of articles was "de-identified" through the use of a half sheet of paper to cover the title, author, and journal name; a black marker was used to conceal the name of the author or journal on subsequent pages. The article was then labeled with its unique identifier, a number that is distinct, and used within either MEDLINE (UI) or PubMed (PMID). This set of articles was coded first, and only the unique identifier was provided on the coding form. A month after the first set of articles had been coded, the articles were re-coded, but this time using the second printed set of articles that retained the titles, authors, and journal names. Each of the two piles of articles had been shuffled so the order of the articles would not be remembered by the coder. After both sets were coded, the identity of the first set of coded articles was revealed and compared to the second set. Any discrepancies between the two coding forms led to verification from the original article, where transcription errors were corrected. While this process still permits a single coder to make the same error during both coding efforts, the potential influence that the reputation of a particular author or journal may have on a coder was reduced.

Assessment of Risk for Bias/Assessment of Reporting Biases

The quality of the trials, and their risk for potential bias were assessed by the Cochrane Collaboration's tool for assessment of risk of bias (featured within Review Manager or RevMan 5.2).[31] Including only blinded RCTs, where data were presented for each of the randomized participant groups, reduced selection, performance, and detection biases.[31] The tool was applied to each study and a summary of the overall risk for bias was reported in the systematic review. Contoured enhanced funnel plots were created using STATA's "confunnel" command (STATA v.12) by plotting the effect size of each study against its standard error. Aside from publication bias, asymmetry in funnel plots may be caused by heterogeneity, poor methodological quality, or chance, and these factors were also considered.[58]

Dealing with missing data

An inclusion criterion of this systematic review was the presence of all pre- and post-intervention variables. Without these data, some treatment effects cannot be calculated and subsequent meta-regression cannot be performed on such trials. It is for these reasons that complete-case analysis[15] was chosen, and studies were excluded if any data were missing; no effort was made to contact the original authors. Five studies (eleven comparisons) were excluded from the meta-regression for missing data: Hollis 2009; Mensink 2002; Han 2007; Kasim-Karakas 2009; and Muntungi 2008. When incomplete lipid profiles were reported, for example mean LDL was missing, the Friedewald equation[128] (LDL = Total cholesterol – HDL cholesterol – [Triglycerides/5]) was used to estimate the lone missing parameter, although the reliability of this formula decreases with triglyceride concentrations above 221 mg/dL and disappears at 400 mg/dL. For triglyceride levels between 221-400mg/dL, another formula could be used (LDL = Total cholesterol – HDL cholesterol – (0.16) Triglycerides), although only one study (Chan 2002) required this alternative calculation.

Measures of Treatment Effect

Primary measures of interest were the effect of manipulating macronutrient distribution (percent total energy from total fat, total carbohydrate, and total protein) on the lipid profile, specifically:

1. Change in total cholesterol (mg/dL)
2. Change in LDL cholesterol (mg/dL)
3. Change in HDL cholesterol (mg/dL)
4. Change in triglycerides (mg/dL)

A "comparison" was regarded as an independent group that reported data on all three macronutrients, as well as the outcome parameter of interest within the lipid profile.

Power Analysis

The power of a study is its probability that it will lead to a statistically-significant result; and it is just as important to consider statistical power when performing a meta-analysis. Sometimes the conclusions from meta-analyses may differ from large-scale RCTs, and these differences may be attributable to an insufficient number of studies and/or subjects included in the meta-analysis.[129]

The minimum number of studies for any meta-analysis is two, but the number required to show a significant result will vary between topics. For the random-effects model, the power of a two-tailed test is calculated by:[130]

$$Power = 1 - NORMSDIST(1.96 - \lambda^{*}) + NORMSDIST(-1.96 - \lambda^{*})$$

The normal distribution of the Z test statistic that is not under the null hypothesis can be described by the parameter lambda. Lambda (λ^{*}) is defined as: the mean effect size divided by the square root of the variance of the summary effect.[30]

$$\lambda^* = \frac{true\ mean\ effect\ size\ (\delta^*)}{\sqrt{variance\ of\ the\ true\ mean\ effect\ size\ (V_{\delta^*})}}$$

For random-effects meta-analyses with a high level of heterogeneity, the variance of the summary effect can be estimated as twice the within-study variance, divided by the number of studies:[130] V_{δ^*} = 2.0(Within-study variance (V_Y)/number of studies (k)). Within-study variance is calculated by:

$$V_Y = \frac{\#\ subjects\ per\ group + \#subjects\ per\ group}{\#subjects\ per\ group\ X\ \#subjects\ per\ group} + \frac{true\ mean\ effect\ size^2}{2(\#subjects\ per\ group + \#subjects\ per\ group)}$$

By plugging in the effect size, number of studies, and number of subjects per group (assuming equal groups), lambda can be calculated. After lambda is calculated, the power calculation can be computed with the assistance of Microsoft Excel's *NORMSDIST* function (Microsoft, Corp., 2010). Generally a power of 0.80 or greater is considered suitable for a meta-analysis in healthcare. For a conservative power analysis, the lowest number of subjects (i.e. nine) contained in a single comparison within the meta-analysis was selected, along with twenty-one studies, which represented half the total number of studies actually present in the meta-analysis, and the summary effect (D) for each outcome was used as the effect size (as it turned out these were within intra-personal variation and could be deemed trivial differences). The power analysis for each outcome exceeded the power criterion; therefore 42 studies with an average of thirty-seven subjects per group would be adequately powered to detect trivial differences in the treatment effects. It should be noted that if a standardized mean difference (Cohen's d) was chosen as the effect size index instead, the power for HDL and triglycerides would have failed to meet the 0.80 threshold criterion (36.5% and 60.5%, respectively).

The minimum number of subjects for a meta-analysis is again going to depend on the topic, but review authors are recommended to down-grade their evidence if the total sample size is less than 400 subjects.[48] The optimal information size (OIS), described elsewhere in this manuscript, is another benchmark that can be used. The outcomes for this meta-analysis were measured before and after the experimental intervention, thus constituting a paired (or repeat study) and the sample size was derived from a paired t-test: $n = 2 + C(s/\Delta)^2$. C was a constant dependent on the chosen value of significance (α) and power (1-ß), and was 7.85 for a significance level of 0.05 and a power of 0.80; "s" was the standard deviation of the difference between the two measurements, and Δ was the size of the desired effect.[131]

The power of the moderators used in the meta-regression was estimated by testing the individual regression coefficients. The equation was similar to the one used for the calculating the power of the meta-analysis, and merely substituted lambda for the ratio of the regression coefficient to its standard error.[132] The power for moderators was anticipated to be lower, as the sample size is usually lower than that of the complete meta-analysis.

<u>Unit of Analysis Issues</u>

No cluster randomized trials were identified or included within this systematic review. Factorial designs were included, although the meta-analysis only included the placebo groups, effectively making the design a parallel trial. While cross-over studies were included in the systematic review, these trials reported means and standard deviations from each study period as if they had arose from a parallel design, which is insufficient for a proper meta-analysis.[133] If the studies had reported individual subject data, or at least the mean of the subject-specific differences between the various study periods, a paired t-test could have been used to calculate suitable effect sizes for analysis.[31,133] To avoid unit of analysis errors and "double counting" subjects, only data from the first cross-over period was used in sensitivity analyses. Parallel study designs with multiple groups contributing independent comparisons were treated as separate studies; when studies reported multiple comparisons over time on subjects, the longest follow-up that supplied all necessary data for analysis was selected.[31]

Assessment of Heterogeneity

The Q-statistic was used to test the null hypothesis that the studies in the meta-analysis share a common effect size, and if its p-value is less than 0.05, there is no heterogeneity.[30,31] In words, it is the sum of the product of the weight and square of the effect size, minus the sum of the products of the weight and effect sizes squared, divided by the sum of the weights. It can be defined as the weighted sum of squares, expressed by:

$$Q = \sum_{i=1}^{k} W_i (Y_i - M)^2$$

W_i is the weight of the study (calculated as the inverse of its variance), Y_i is the effect size of the study, M is the summary effect, and k is the number of studies.[30]

To examine what proportion of the total variance represents real differences between the observed effect sizes in the meta-analysis, the I^2 test was calculated, and a value greater than 50% was considered important.[15] I^2 is expressed as:

$I^2 = \left(\frac{Q-df}{Q}\right) \times 100\%$, with df referring to the degrees of freedom (one less than the number of total studies), and Q as the Q-statistic.

One can examine the distribution of the true effect sizes through the prediction interval, as well as predict where the true effect of a new study would fall in 95% of the cases if it was later added to the meta-analysis.

The formula for the prediction interval is:[30]

$$M^* - t_{df}^{\alpha}\sqrt{T^2 + V_M^*}$$

where M* is the mean effect of the sample, T^2 is the sample estimate of the variance of the true effects (Tau-squared), and t_{df}^{α} is the t-value corresponding to a particular alpha level (in this case 95%, or 0.05) where there are df degrees of freedom. Since the equation multiplies the t-value by both Tau-squared and the variance of the mean effect (V_{M*}), the degrees of freedom is the number of studies minus two (k-2).[30] (In Microsoft Excel 2010, the *TINV* function was used to calculate t_{df}^{α}.)

<u>Data Synthesis</u>

The pre-treatment and post-treatment data from the trials were reported as means and standard deviations. Since all the studies reported their outcomes using the same scale and methodology, unstandardized (raw) mean differences (D) were selected as the treatment effect for the synthesis.[30] This has the advantage of retaining the same metric as the original outcome (e.g. mg/dL), and the treatment effect carries clinical significance (e.g. change in mean HDL concentration).[41] The raw mean difference is simply the difference between the two measured time points (D=Post-Pre); the order of the time points was not significant as long as it was consistently followed.[30] A post-treatment mean minus pre-treatment mean calculation had an advantage because the sign of the treatment effect provided information about the direction of change. If S_{Pre} and S_{Post} are the respective standard deviations for the pre- and post-treatment comparisons, then the variance (V_D) can be calculated as: $V_D = S^2_{diff}/n$, where n is the number of subjects, $S_{diff} = (\sqrt{S_{Pre}^2 + S_{Post}^2 - 2 \times r \times S_{Pre} \times S_{Post}})$, and r is the correlation between post-treatment and pre-treatment values.[30] The standard error is merely the square root of the variance: $SE_{D} = \sqrt{V_D}$. The value for r was obtained via the *Correl* function in Microsoft Excel (Microsoft Corp., 2010), but different values were calculated and included in subsequent sensitivity analyses (see supplemental tables at the end of the manuscript).

Since the subjects, treatments, researchers, and various other conditions related to the interventions differed between the studies included in the systematic review, a random-effects model (DerSimonian and Laird Method) was chosen for the meta-analysis, distinguished by use of an asterisk (*) for its variables. The weight assigned to the treatment effects of individual studies (W_i^*) was computed as the inverse of its total variance ($1/V^*_{Yi}$), which included both within-study variation due to random sampling error ($V_{Yi} = S^2/n$) as well as between-study variation, also known as tau-squared

(T^2).[20,30,43] Mathematically, the weights were calculated by:[30] $V^*_{Yi} = V_{Yi} + T^2$, and tau-squared is estimated as $T^2 = (Q – df)/ C$. The Q-statistic has been defined previously, df is the degrees of freedom, and C can be described as the sum of the weights (Wi), minus the sum of the weights squared (W_i^2), divided by the sum of the weights. C can be expressed mathematically using the following equation:

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}$$

For the random-effects model, the weighted mean summary effect size (M^*) was computed as the sum of products of effect size (Y_i) and weight (W_i^*), divided by the sum of the weights.[30] Forest plots were created for each outcome using Comprehensive Meta-Analysis (version 2, BioStat, Inc.), using the following equation:

$$M^* = \frac{\sum_{i=1}^{k} W_i^* Y_i}{\sum_{i=1}^{k} W_i^*}$$

The variance of the estimated summary effect (V_{M*}) was calculated as the inverse of the sum of the weights, and its standard error (SE_{M*}) was the square root of the variance. The 95% confidence intervals were calculated as: $M^* \pm 1.96 \times SE_{M*}$, and the Z-value to test the null hypothesis that the (true) mean effect of the population was zero was computed as $Z^* = M^*/SE_{M*}$, with its two-tailed p-value by: $p^* = 2[1-(\Phi(\lvert Z^* \rvert))]$, where $\Phi(Z^*)$ is the standard normal cumulative distribution.[30]

Subgroup Analysis

The forty-two studies (with eighty-six comparisons) were organized into different subgroups in order to try and explain the substantial amount of heterogeneity within the primary analysis. Each subgroup was treated as if it was an individual study, and the summary plots of these various comparisons were presented in forest plots. (The diamonds usually associated with summary effects were replaced with squares and lines to assess confidence intervals.) Due to this assumption that the subgroups are single studies, the summary effects did not exactly match the value from the preliminary analysis, and these forest plots for subgroups were merely meant to assist in comparing the magnitude of the treatment effect between the subgroups. In order to avoid improper conclusions, any values related to significance testing were removed from figures and tables related to subgroup comparison analyses.

Originally the definition for change in a particular macronutrient was set at five percent, but after considering the research designs of the studies included in the meta-analysis, the threshold was lowered to 3.5% in order to categorize more of the trials that manipulated the quality of a macronutrient, and maintained tight control on change in the total amount of that macronutrient. Therefore, a classification of no change, or a determination that the macronutrient had been “fixed” was set at ±3.5%. Pre-specified subgroups for the primary outcomes included:

- Change in total dietary fat was examined using a mixed-effects analysis, where a random-effects model was used to combine studies within each subgroup, but a fixed-effect model was used to combine the different subgroups to calculate the overall summary effect. The comparison subgroups included:

- Decreased levels: >3.5% decrease
- Fixed (unchanged) levels: between -3.4% to 3.4% change
- Increased levels: >3.5% increase

- Acceptable Macronutrient Distribution Ranges
  - 20-35% Total Fat, 10-35% Total Protein, 45-65% Total Carbohydrate
- High Fat, Moderate Protein, Moderate Carbohydrate
  - >35% Total Fat, 10-35% Total Protein, 45-65% Total Carbohydrate
- High Fat, Moderate Protein, Low Carbohydrate
  - >35% Total Fat, 10-35% Total Protein, <45% Total Carbohydrate

Other macronutrient distribution subgroups had too few comparisons to conduct a reliable analysis. To avoid misleading results and conclusions, only the magnitudes of the treatment effects were compared between subgroups; the statistical significance (p-value) of the different subgroups was not scrutinized.

To compare the mean effect between two subgroups, the subgroups were treated as if they were individual studies and a test for heterogeneity (Q) was performed across the subgroups. The magnitude of the true difference (Diff) between the treatment effects of the subgroups was quantified by subtracting the mean of one subgroup from the other. The 95% confidence interval was estimated by: Diff ± 1.96 (Standard Error of Diff).[30] Since a separate random-effects analysis was initially performed on all the included studies, the combined effect across subgroups was already known.

Random-effects meta-regression using restricted maximum likelihood (reml) was performed using the STATA command “metareg”(STATA version 12), to determine the effect of the following moderators on the primary treatment effects, and develop prediction equations for these moderators:

- Pre-treatment lipid profile parameters (TC, LDL, HDL, TG) in mg/dL
- Mean age (years)
- Sex (% male)
- Study duration (days)
- Number of subjects
- Change in total dietary fat (% total energy)

A random-effects meta-regression may also be referred to as a mixed-effects model when moderators are introduced. (Originally changes in both total protein and total carbohydrate in the diet were selected, but then omitted due to potential confounding, since a change in one of the variables would influence the other two. Change in total fat was chosen because more studies in the database altered their total fat content.)

Since multiple covariates were used in the meta-regression, a Monte Carlo permutation simulation was conducted (via STATA's *permute* command option) for each significant variable to get a "correct" p-value and reduce false-positive findings.[134] Monte Carlo permutation tests use a t-statistic that quantifies how much the estimated covariate varies from the its observed value and from its standard error.[47] In the simulation, the observed t-statistic for every covariate is compared to the largest t-statistic generated in each random permutation. Over many permutations (e.g. 20,000), the probability of observing a t-statistic that is as extreme or more extreme than the observed value (i.e. the adjusted p-value) can be ascertained.[134]

The permute command uses a random number generator during its simulations, and therefore to ensure reproducibility of results the *set seed* command was used to set the initial value of the random number generator to a consistent value. In order to ensure that the value of the set seed was determined at random, a simple protocol was designed. The author of this manuscript (JAS) obtained a dollar bill and added the digits representing the serial number together until a single digit was obtained. (For example, the serial number was: "L18334457S". After ignoring the leading and trailing letters in the serial number, the numerical values were summed: 1+8+3+3+4+4+5+7 =35. The result was added again until a single digit was obtained: for the value of "35", 3+5=8.) This value obtained from the dollar bill was taken to a random number generator (Random.org), and indicated the number of zeros to input into the maximum value of the random number generator to obtain the set seed value, which was "916993". In order to reproduce the results from the meta-regressions in this manuscript, the value "916993" will need to be specified in the *set seed* command of STATA.

A comparison of the random-effects model with the moderators versus the model without them was performed, and the proportion of the total between-study variance explained by the model was calculated by the following equation:[30]

$$R^2 = 1 - \left(\frac{T^2_{Unexplained}}{T^2_{Total}}\right)$$

R^2 is the true explained variance, which is similar to the analogous index used in primary studies; however for meta-analyses the index includes both the variance within studies and between studies. $T^2_{Unexplained}$ was generated from the meta-regression (reml method), and T^2_{Total} was from the random-effects meta-analysis (also using the REML method in this case). In order to directly compare the results of the random-effects meta-regression with the random-effects meta-analysis, the studies that were missing values for any of the moderators were excluded from both analyses. The index can then be compared to the total between-study variance (I^2), and the amount of variation explained by the significant moderators can be described (see Table 2).[30]

<table>
<tr><td colspan="3">Table 2: Sample table for proportion of variance explained by moderators</td></tr>
<tr><td colspan="3">Total Study Variation
[Sampling error + I-squared]</td></tr>
<tr><td>Within-study variation
(Sampling error)</td><td colspan="2">The total between-study variation
(I-squared)
[Within-group + R^2]</td></tr>
<tr><td></td><td>% within-group variation</td><td>% variation explained by moderators (R^2)</td></tr>
</table>

An effort was made to group trials that reported clinically-significant results, defined as a reported effect size that was clearly beyond the estimated mean intra-personal variation for that particular outcome parameter. Differences in treatment effects from these comparisons were deemed more likely to provide clear information on the effect of macronutrient distribution on the lipid profile.

<u>Sensitivity Analysis</u>

Sensitivity analyses were conducted on primary outcomes to determine the impact of certain decisions that were made during the systematic review and/or meta-analysis. The more quantitative analyses included:

1. Using a fixed-effect model instead of a random-effects model.
2. Including the studies using a cross-over design, but only using the data from the first cross-over period.
3. Performing a synthesis that determined the summary effect if individual studies were removed, thus assessing the impact of any single study.
4. To calculate the standard deviation of the difference in lipid profile results, the pre- and post-treatment correlation for each outcome was estimated using the dataset (*CORREL* function in Excel 2010). For a sensitivity analysis, a range of plausible values (r = 0.50, 0.75, 0.99) were calculated and compared to the primary analyses.
5. To assess the risk of publication bias, alternative analyses were utilized in sensitivity analyses:

To roughly determine the number of unpublished studies that would be required to make the P-value for the summary effect non-significant, the classic fail-safe (Rosenthal) N was computed via the following equation:[15]

$$\sum_{i=1}^{k} Z_i/\sqrt{k}$$

Where Z_i is the combination of normal *z*-scores, and *k* is the number of studies.

As a sensitivity analysis, additional funnel plots were created (using CMA, v.2) for the primary outcomes to assess the risk of publication bias, particularly from small trials.[24] The "trim and fill" procedure was utilized to impute studies potentially missing from the analysis.[59] The Egger's test[24] was used to evaluate asymmetry in the funnel plots by the following equation: $SND = a + b \times SE^{-1}$. SND is the standard normal deviate, a is the intercept, b is the slope, and SE is the standard error of the weighted effect size.[135] If there is no publication bias, the intercept will have an expected value of zero, whereas if the test is estimated to be significantly different from zero ($P<0.05$), publication bias may be evident.[3] A negative intercept indicates smaller studies are associated with larger effects, and positive levels trend towards increased accuracy in smaller studies.[135,136]

Summarizing Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to classify the evidence yielded from this systematic review and meta-analysis.[68]

RESULTS AND INTERPRETATION

Description of Studies

Information about the studies included in the systematic review and meta-analysis can be found below in Table 3. Sixty-Five studies were included in the systematic review; the majority was conducted in either North America or Europe, used a double-blind design, and included both men and women. Table 4A and 4B list variables that may have impacted the lipid profile for studies included in the meta-analysis.

Results of the Search

The flow of information through the different phases of the systematic review is shown schematically in Figure 6, and is part of the PRISMA statement.[17] Five hundred forty records were initially identified using the search strategy already described. (See Appendix A.) The next step in the process is usually the removal of duplicate records, and this would have been applicable if additional databases besides MEDLINE were searched. Eight records published in languages other than English were excluded, leaving five hundred thirty-two full-text articles to be assessed for their eligibility based on the aforementioned inclusion and exclusion criteria. Every eligible article was acquired, and systematically checked to ensure that it met every inclusion criteria before being deemed worthy for coding and analysis. Four hundred and eighty-eight articles were excluded, and the rationale for their exclusion was recorded. (See Appendix E) The remaining forty-four articles were then included in the systematic review (qualitative synthesis).

Table 3: Demographics of the included studies.			
	Studies Included in Systematic Review (N = 65)	Studies included in Meta-Analysis (N=42)	Studies Excluded from Meta-Analysis Due to Cross-over Design (N=23)
Included Subjects:			
Number of Subjects	3876	3144	732
Mean Age of Subjects	46.5±13 years	45.5±8 years	49.8±24 years
Percentage of Subjects Who Were Male	50.6%	49.2%	55.0%
Blinding of Studies:			
Double-Blinded Studies	39 (60%)	26 (62%)	13 (57%)
Single-Blinded Studies	26 (40%)	16 (38%)	10 (43%)
Gender of Included Subjects:			
Included only male subjects	14 (22%)	10 (24%)	4 (17%)
Included only female subjects	9 (14%)	7 (17%)	2 (9%)
Included both male and female subjects	42 (64%)	25 (59%)	17 (74%)
Continent Where Research was Conducted:			
Asia	4 (6%)	4 (10%)	0 (0%)
Europe	27 (42%)	13 (31%)	14 (61%)
North America	26 (40%)	22 (52%)	4 (17%)
Oceania	6 (9%)	2 (5%)	4 (17%)
South America	2 (3%)	1 (2%)	1 (5%)
Year Published:			
1990s	7	3	4
2002	8	4	4
2003	4	3	1
2004	8	4	4
2005	4	3	1
2006	6	5	1
2007	6	4	2
2008	7	5	2
2009	6	4	2
2010	9	7	2

Table 4A. Table of variables that may impact the lipid profile.

Study Name (Comparison Group)	Duration (days)	Group Size	∆Tkcals	∆Tkcals SD	Information About Exercise	Smoking Status
Adler 1997	84	11	63	112.72	Uncertain	No data
Alhassan 2006	28	17	131	659.52	No exercise	Non-smoking
Assuncao 2009A	84	20	-187	225.38	50min walking 4d/wk	n=4; 20%
Assuncao 2009B	84	20	-197	259.77	50min walking 4d/wk	n=5; 25%
Beavers 2010A	28	16	188	516.59	Active, but not specified	Non-smoking
Beavers 2010B	28	16	142	653.08	Active, but not specified	Non-smoking
Chan 2002A	42	13	-119	467.88	Expended/d: 1533 kcal±777	n=2 for study
Chan 2002B	42	12	-7	389.87	Expended/d: 1898kcal ±481	n=2 for study
Diaz 2008A	84	16	21	474.77	30min walking/d x 5d/wk	No data
Diaz 2008B	84	19	-19	600.49	30min walking/d x 5d/wk	No data
Dodin 2005A	365	85	-37	505.45	Active >3d/wk: n=57; 67%	n=6; 8%
Dodin 2005B	365	94	-135	584.75	Active >3d/wk: n=71; 76%	n=5; 6%
Esposito 2004	730	55	-390	265.05	Physical Activity: 195±36 min/wk	n=15; 27%
Esposito 2004A	730	90	-170	252.13	Physical activity: 84±36 min/wk	Non-smoking
Esposito 2004B	730	90	-70	263.59	Physical activity: 81±38 min/wk	Non-smoking
Fakhrzadeh 2010	182	62	8	353.28	Uncertain	n=9; 17.9%
Gardner 2007A	60	77	-507	617.39	EE: 31.6±2.1 kcal/kg/d	n=2; 3%
Gardner 2007B	60	79	-520	732.66	EE: 34.5±2.4 kcal/kg/d	n=4; 5%
Gardner 2007C	60	79	-449	711.70	EE: 34.8±2.4 kcal/kg/d	n=4; 5%
Gardner 2007D	60	76	-442	705.61	EE: 34.7±2.3 kcal/kg/d	n=3; 4%
Goyens 2006A	42	13	96	627.15	Not specified	No data
Goyens 2006B	42	14	-286	507.70	Not specified	No data
Gylling 2010A	70	24	-71	682.22	Not specified	No data
Gylling 2010B	70	25	167	675.99	Not specified	No data

Table 4A. (continued)						
Study Name (Comparison Group)	Duration (days)	Group Size	ΔTkcals	ΔTkcals SD	Information About Exercise	Smoking Status
Han 2007A	90	20	-159	498.14	Not specified	No data
Han 2007B	90	20	168	641.95	Not specified	No data
Hjerkinn 2005	1095	244	-192	676.85	Not specified	34%
Hollis 2009A	84	25	-239	932.69	Not specified	Non-smoking
Hollis 2009B	84	26	-338	973.09	Not specified	Non-smoking
Hollis 2009C	84	25	-272	977.97	Not specified	Non-smoking
Kasai 2003A	84	42	60	304.87	Mild to medium levels of activity	No data
Kasai 2003B	84	40	41	492.85	Mild to medium levels of activity	No data
Kasim-Karakas 2009A	60	11	-790	154.83	Not specified	Non-smoking
Kasim-Karakas 2009B	60	13	-550	177.50	Not specified	Non-smoking
Kawashima 2008A	365	150	-29	629.59	PAL: 1.41±0.11	No data
Kawashima 2008B	365	153	-48	660.33	PAL: 1.41±0.11	No data
Kelley 2007A	90	17	11	948.89	Not specified	n=2; 12%
Kelley 2007B	90	17	-269	669.22	Not specified	n=1; 6%
Levin 1990	112	28	-17	508.02	Not specified	No data
Maki 2005A	42	30	-151	925.26	MET-hrs/wk: 281.6± 41	No data
Maki 2005B	42	27	80	1086.83	MET-hrs/wk: 283.04± 43	No data
Malpuech-Brugere 2010A	21	36	41	509.49	Not specified	Non-smoking
Malpuech-Brugere 2010B	21	35	6	573.17	Not specified	Non-smoking
Malpuech-Brugere 2010C	21	36	65	516.91	Not specified	Non-smoking
Melanson 2004	168	22	-626	933.43	Walked 5d/wk at moderate pace	Non-smoking
Mensink 2002A	28	30	-71	845.70	Not specified	7 total smoked

Table 4A. (continued)

Study Name (Comparison Group)	Duration (days)	Group Size	ΔTkcals	ΔTkcals SD	Information About Exercise	Smoking Status
Mensink 2002B	28	30	-143	710.75	Not specified	7 total smoked
Mutungi 2008A	84	15	-582	1151.40	Not reported	No data
Mutungi 2008B	84	13	-497	1107.86	Not reported	No data
Pins 2006A	42	15	47	365.43	6 (40%) individuals reported any activity	Non-smoking
Pins 2006B	42	15	50	383.62	7 (47%) individuals reported any activity	Non-smoking
Polagruto 2006A	42	32	96	739.63	Not specified	No data
Polagruto 2006B	42	35	-71	591.14	Not specified	No data
Price 2010A	28	39	8	710.98	Low activity	Non-smoking
Price 2010B	28	40	-48	845.28	Low activity	Non-smoking
Santo 2008A	28	9	593	1190.04	Not specified	Non-smoking
Santo 2008B	28	11	-314	1333.92	Not specified	Non-smoking
Santo 2008C	28	10	122	645.43	Not specified	Non-smoking
Schwab 2002A	84	20	-565	592.01	2-3 times/wk	No data
Schwab 2002B	84	22	-500	657.87	2-3 times/wk	No data
Schwab 2006A	84	22	81	476.61	Not specified	No data
Schwab 2006B	84	22	123	751.52	Not specified	No data
Schwab 2006C	84	22	39	594.13	Not specified	No data
Smith 2003A	112	25	-72	761.04	Less than 20 min, 3d/wk	n=7; 28%
Smith 2003B	112	23	-24	557.46	Less than 20 min, 3d/wk	n=7; 30%
Smith 2008A	42	45	-1	653.39	Not specified	Non-smoking
Smith 2008B	42	45	-173	733.28	Not specified	Non-smoking
Stendell-Hollis 2010A	182	23	-262	906.03	EE: 2126± 366 kcal/d	Non-smoking
Stendell-Hollis 2010B	182	16	9	736.26	EE: 2101± 262 kcal/d	Non-smoking

Table 4A. (continued)						
Study Name (Comparison Group)	Duration (days)	Group Size	∆Tkcals	∆Tkcals SD	Information About Exercise	Smoking Status
Szapary 2003	56	30	-127	1779.21	Not specified	No data
Tanumihardjo 2009A	90	21	-350	750.60	180 min/wk	No data
Tanumihardjo 2009B	90	23	-342	700.69	180 min/wk	No data
Tapsell 2004A	182	20	92	437.32	Not specified	No data
Tapsell 2004B	182	19	-113	709.94	Not specified	No data
Tapsell 2004C	182	16	-18	763.94	Not specified	No data
Tighe 2010A	84	63	44	826.29	Not specified	No data
Tighe 2010B	84	73	6	807.06	Not specified	No data
Tighe 2010C	84	70	27	738.14	Not specified	No data
Tonstad 2002A	84	34	-239	908.71	Not specified	No data
Tonstad 2002B	84	36	-359	832.29	Not specified	No data
Tonstad 2002C	84	31	-406	988.56	Not specified	No data
Tonstad 2002D	84	29	-406	722.80	Not specified	No data
Wardlaw 1991A	77	15	-24	119	Not specified	No data
Wardlaw 1991B	77	16	119	153	Not specified	No data
Wood 2007A	84	14	-738	778.01	Not specified	No data
Wood 2007B	84	15	-678	940.71	Not specified	No data
Abbreviations: PAL = Physical Activity Level; EE: Energy Expenditure; MET: Metabolic Equivalents of Task						

Table 4B. Table of variables that may impact the lipid profile.

Study Name	Lipid-altering Medications	Fasting Labs	Pre-treatment weight (kg)	Pre-treatment weight S.D.	Δ Weight (kg)	Δ Weight S.D.
Adler 1997	No lipid medications	Fasting	85.00	11.30	0.10	14.20
Alhassan 2006	No lipid medications	Fasting	74.90	13.61	0.80	19.54
Assuncao 2009A	Not specified	Fasting	76.00	9.00	-1.00	12.80
Assuncao 2009B	Not specified	Fasting	73.20	9.00	-1.10	12.80
Beavers 2010A	Not specified	Fasting	*	*	*	*
Beavers 2010B	Not specified	Fasting	*	*	*	*
Chan 2002A	No lipid medications	Fasting	102.00	10.10	-1.60	13.30
Chan 2002B	No lipid medications	Fasting	107.00	16.28	-1.40	25.06
Diaz 2008A	No lipid medications	Fasting	73.40	6.40	-2.50	9.94
Diaz 2008B	No lipid medications	Fasting	75.40	10.03	-2.60	14.81
Dodin 2005A	No lipid medications	Fasting	64.70	11.40	0.60	15.98
Dodin 2005B	No lipid medications	Fasting	68.30	11.30	1.20	16.56
Esposito 2004	Not specified	Unclear	103.00	9.40	-15.00	12.67
Esposito 2004A	No lipid medications	Fasting	78.00	8.00	-4.00	10.63
Esposito 2004B	No lipid medications	Fasting	77.00	8.00	-1.20	10.63
Fakhrzadeh 2010	Not specified	Fasting	62.53	14.80	*	*
Gardner 2007A	Not specified	Fasting	86.00	13.00	*	*
Gardner 2007B	Not specified	Fasting	84.00	12.00	*	*
Gardner 2007C	Not specified	Fasting	85.00	14.00	*	*
Gardner 2007D	Not specified	Fasting	86.00	10.00	*	*
Goyens 2006A	Not specified	Fasting	*	*	0.10	1.20
Goyens 2006B	Not specified	Fasting	*	*	0.50	0.60
Gylling 2010A	Not specified	Fasting	*	*	*	*
Gylling 2010B	Not specified	Fasting	*	*	*	*

Table 4B. (continued)						
Study Name	Lipid-altering Medications	Fasting Labs	Pre-treatment weight (kg)	Pre-treatment weight S.D.	Δ Weight (kg)	Δ Weight S.D.
Han 2007A	No lipid medications	Fasting	60.02	11.48	-1.56	15.27
Han 2007B	No lipid medications	Fasting	61.69	10.62	0.28	14.70
Hjerkinn 2005	27% on statins	Fasting	*	*	*	*
Hollis 2009A	No lipid medications	Fasting	79.00	42.00	0.70	63.41
Hollis 2009B	No lipid medications	Fasting	79.00	54.56	1.60	78.98
Hollis 2009C	No lipid medications	Fasting	77.60	51.50	0.10	71.09
Kasai 2003A	No lipid medications	Fasting	71.20	9.07	-3.30	11.95
Kasai 2003B	No lipid medications	Fasting	71.90	8.85	-4.60	11.26
Kasim-Karakas 2009A	Not specified	Fasting	106.60	18.90	-3.40	26.97
Kasim-Karakas 2009B	Not specified	Fasting	95.30	19.83	-1.10	28.30
Kawashima 2008A	No lipid medications	Fasting	72.50	12.10	-0.60	12.28
Kawashima 2008B	No lipid medications	Fasting	71.90	10.90	0.40	15.63
Kelley 2007A	No lipid medications	Fasting	*	*	*	*
Kelley 2007B	No lipid medications	Fasting	*	*	*	*
Levin 1990	No lipid medications	Fasting	76.10	14.29	-1.70	19.47
Maki 2005A	No lipid medications	Fasting	87.70	20.81	0.80	*
Maki 2005B	No lipid medications	Fasting	85.50	16.63	0.80	*
Malpuech-Brugere 2010A	Not specified	Fasting	*	*	*	*
Malpuech-Brugere 2010B	Not specified	Fasting	*	*	*	*
Malpuech-Brugere 2010C	Not specified	Fasting	*	*	*	*
Melanson 2004	Not specified	Fasting	88.80	15.48	-7.10	20.61
Mensink 2002A	No lipid medications	Fasting	*	*	*	*
Mensink 2002B	No lipid medications	Fasting	*	*	*	*
Mutungi 2008A	Not specified	Fasting	98.90	15.30	-6.70	19.88

Table 4B. (continued)						
Study Name	Lipid-altering Medications	Fasting Labs	Pre-treatment weight (kg)	Pre-treatment weight S.D.	Δ Weight (kg)	Δ Weight S.D.
Mutungi 2008B	Not specified	Fasting	97.60	19.90	-5.90	25.35
Pins 2006A	No lipid medications	Fasting	81.10	22.00	-0.20	31.11
Pins 2006B	No lipid medications	Fasting	80.50	20.00	0.70	29.00
Polagruto 2006A	No lipid medications	Fasting	76.90	18.10	*	*
Polagruto 2006B	No lipid medications	Fasting	71.00	*	*	*
Price 2010A	No lipid medications	Fasting	*	*	*	*
Price 2010B	No lipid medications	Fasting	*	*	*	*
Santo 2008A	No lipid medications	Fasting	73.80	*	0.80	12.90
Santo 2008B	No lipid medications	Fasting	78.00	18.57	1.00	26.27
Santo 2008C	No lipid medications	Fasting	69.90	11.70	0.40	16.55
Schwab 2002A	No lipid medications	Fasting	94.60	9.90	-3.50	13.18
Schwab 2002B	No lipid medications	Fasting	95.70	11.30	-2.20	15.84
Schwab 2006A	No lipid medications	Fasting	79.80	11.30	-1.20	15.49
Schwab 2006B	No lipid medications	Fasting	80.10	12.80	-0.70	18.24
Schwab 2006C	No lipid medications	Fasting	83.30	10.50	-0.20	14.78
Smith 2003A	No lipid medications	Fasting	66.00	10.80	*	*
Smith 2003B	No lipid medications	Fasting	64.20	10.20	*	*
Smith 2008A	No lipid medications	Fasting	73.60	12.00	-0.41	0.27
Smith 2008B	No lipid medications	Fasting	74.80	15.00	0.37	0.16
Stendell-Hollis 2010A	No lipid medications	Fasting	81.90	15.30	-1.20	4.10
Stendell-Hollis 2010B	No lipid medications	Fasting	77.80	9.80	0.20	2.50
Szapary 2003	No lipid medications	Fasting	77.10	14.60	0.40	20.23
Tanumihardjo 2009A	Not specified	Fasting	94.20	14.90	*	*
Tanumihardjo 2009B	Not specified	Fasting	96.00	17.10	*	*

Table 4B. (continued)						
Study Name	Lipid-altering Medications	Fasting Labs	Pre-treatment weight (kg)	Pre-treatment weight S.D.	Δ Weight (kg)	Δ Weight S.D.
Tapsell 2004A	Not specified	Not specified	81.87	11.19	0.40	11.31
Tapsell 2004B	Not specified	Not specified	84.55	4.31	-0.19	14.72
Tapsell 2004C	Not specified	Not specified	87.61	12.83	-1.28	18.31
Tighe 2010A	No lipid medications	Fasting	*	*	*	*
Tighe 2010B	No lipid medications	Fasting	*	*	*	*
Tighe 2010C	No lipid medications	Fasting	*	*	*	*
Tonstad 2002A	No lipid medications	Fasting	*	*	*	*
Tonstad 2002B	No lipid medications	Fasting	*	*	*	*
Tonstad 2002C	No lipid medications	Fasting	*	*	*	*
Tonstad 2002D	No lipid medications	Fasting	*	*	*	*
Wardlaw 1991A	Not specified	Fasting	82.20	10.46	0.00	16.22
Wardlaw 1991B	Not specified	Fasting	87.70	14.40	-0.50	20.36
Wood 2007A	No lipid medications	Fasting	93.60	12.20	-7.40	3.10
Wood 2007B	No lipid medications	Fasting	93.00	16.00	-7.50	1.80
* = Data not Reported						

Due to inadequate reporting, many of the covariables were not included in subsequent meta-regression. Referring to Tables 4A &B, the average duration of the trials included in the meta-analysis was 123.5 days; the studies ranged from three weeks to three years in length. The subjects in the interventions decreased their total caloric intake by 136 kcals on average (range: -790 kcals to 593 kcals), and the average group size was 37 subjects (range: 9 to 244 individuals). Concerning exercise, most of the study protocols instructed their subjects to maintain their current level of activity, but did not measure it, even at baseline. The majority of trials did not track or report smoking status or history of their subjects, and those that did include smokers had enrollments as high as 34% of the sample size. The majority of studies excluded subjects who were taking lipid-altering medications, particularly statins; the rest of the studies did not describe medication usage, and one study (Hjerkinn, 2005) had 27% of their sample on statins. Considering the weight of the subjects, most of the studies recorded a baseline weight, but some did not weight the subjects during the trial, or they included the weight in calculations of BMI, but did not report it separately for direct comparison (with standard deviation). For many of the studies, the weight change was not very significant, although Esposito, 2004 reported a decrease in weight of fifteen kilograms from baseline. If these studies follow the example presented in the meta-analysis by Dattilo and Kris-Etherton, then for every kilogram lost by these subjects, one could expect the following changes to the lipid profile: -1.9 mg/dL for total cholesterol, -0.77 mg/dL for LDL cholesterol, and -0.03 mg/dL for HDL.[99]

In addition to the articles retrieved from the MEDLINE search, fourteen articles meeting the inclusion criteria were found while researching background information on the topic. The Howell Database yielded seven more articles meeting all the inclusion criteria, bringing the total number of studies in the systematic review to sixty-five. No eligible documents were found after searching either the ProQuest Database or the Journal for Negative Results in Biomedicine.

Twenty-three cross-over studies were excluded from the primary meta-analysis due to reporting of results in a manner that would permit appropriate synthesis.[133] Data from the first cross-over period were included in subsequent sensitivity analyses, and while this decision may help with instances of carry-over bias, it can create a biased subset of all first period data.[31] With the exclusion of the cross-over studies, forty-three studies were eligible for meta-analysis (quantitative synthesis).

Excluded Studies

Four hundred and eighty-eight studies were excluded from the systematic review; a list of these studies, with the rationale for their exclusion can be found in Appendix E.

Risk of Bias in Included Studies

The risk of bias in the individual studies included in the systematic review is presented in Appendix D, along with the author’s judgments, and the summary across all studies is shown in Figure 7 (created with Cochrane’s RevMan 5.2).

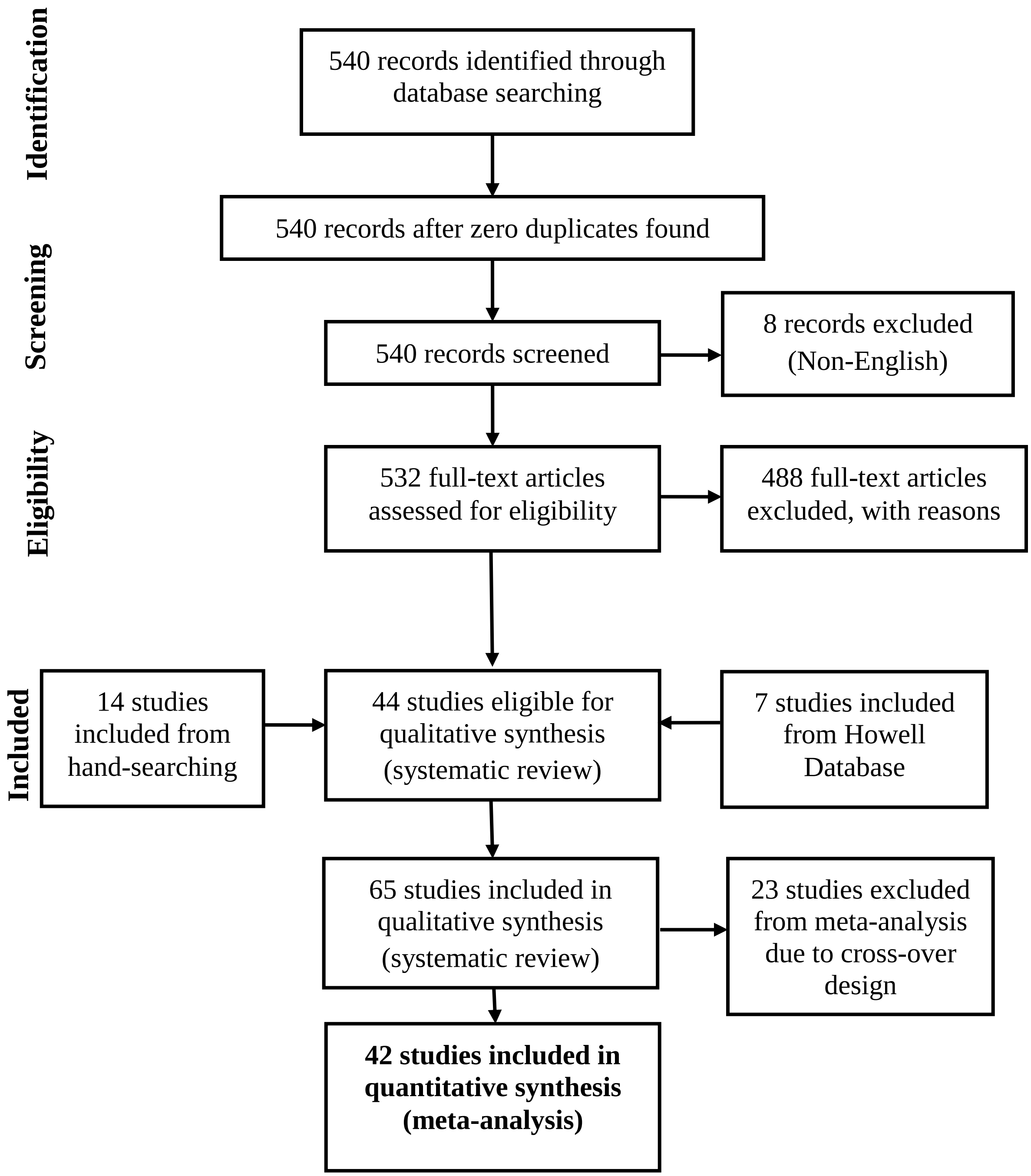


Figure 6. PRISMA four-phase flow diagram – macronutrient distribution and lipid profile.[17]

Allocation

Since all the studies in the systematic review were reportedly randomized controlled trials (RCTs), it was assumed that the generation of group sequence was done randomly. Any studies that used a quasi-random method to assign groups, such as assigning subjects by the first letter in their surname, were excluded. However, very few studies described the specific method of allocation in great detail, and only 12 studies sufficiently reported the methods to conceal the allocation sequence (Esposito 2004; Esposito 2004A; Ewers 2009; Gardner 2007; Goyens 2006; Gylling 2010; Kasim-Karakas 2009; Melanson 2004; Stendell-Hollis 2010; Szapary 2003; Uusitupa 1994; Wong 2010).

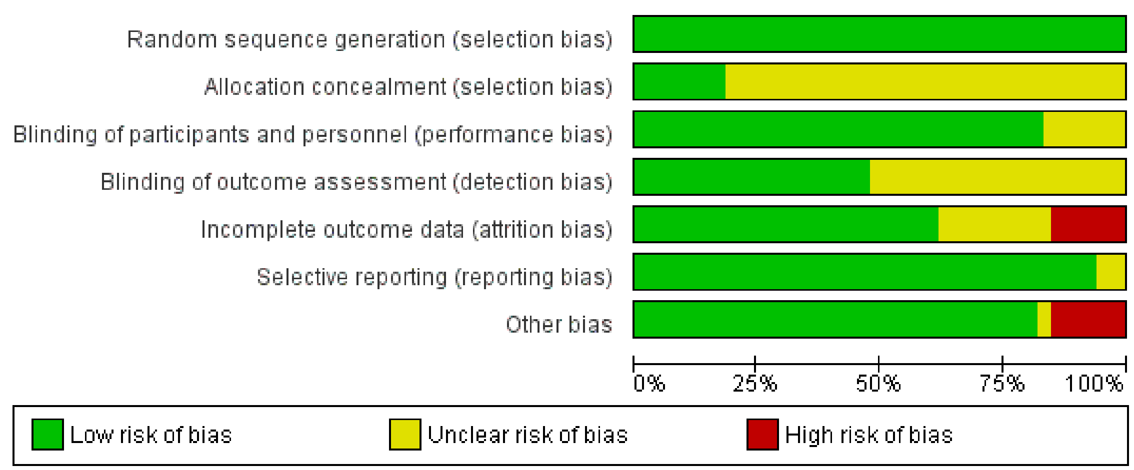
Blinding

While all of the included RCTs utilized a blinded design, with 60% being double-blinded, very few studies described the measures used to blind participants, research staff, and/or outcome assessors. Double-blind studies were judged to have less risk for performance and detection biases than single-blind trials, but only two studies provided detailed information relating to the effectiveness of the blinding procedure (Adler 1997; Stendell-Hollis 2010).

Incomplete Outcome Data

The number of subjects in each intervention group was compared to the total number of subjects randomized to assess the risk for attrition bias. When there was a large difference between the attrition of two groups, this was deemed high risk; some studies did not report from which group the withdrawals originated, and the risk was judged to be unclear. Studies with more than 10% attrition in any group were judged as unclear, while those with greater than 20% attrition were judged to have a high risk for attrition bias (Alhassan 2006; Diaz 2008; Ewers 2009; Melanson 2004; Sheridan 2007; Tapola 2004; Tighe 2010; Tonstad 2002; Wong 2010) .

Figure 7. Risk of bias graph for systematic review.
(Created with Review Manager (RevMan) version 5.2, The Cochrane IMS.)



Selective Reporting

The selective reporting of some outcomes, but not others, was assessed by confirming that all the outcomes proposed by the authors were reported in the results section of the article. It is possible that some researchers could have measured additional outcomes during their experiments, but removed any mention of them from their publications if the results were unfavorable. Finding evidence of such events is highly unlikely, even if the authors were contacted, and therefore if the authors reported all of their proposed outcomes, the risk for selective reporting was judged to be low.

Other Bias

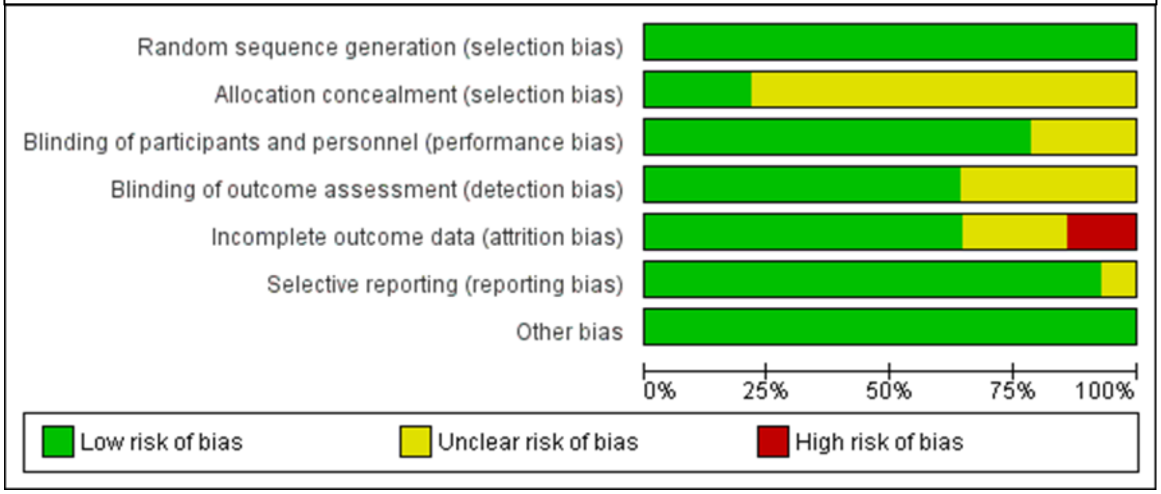
Forms of bias not covered in other areas of the tool mainly included carryover bias from cross-over studies that did not implement adequate wash-out periods, and the bias introduced by small sample sizes. Since cross-over studies were not included in the meta-analysis, carryover bias was not an issue. However, since individual data were not available from the published trials, aggregation (or ecological) bias was a concern during meta-regression.[6,137]

PRIMARY OUTCOME: THE LIPID PROFILE

Study Limitations/Risk of Bias

Since the primary outcome was the lipid profile, the quality of the evidence regarding study limitations was organized at this level, while other evidence rating categories were described in the context of the specific laboratory parameter (i.e. total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides). The risk of bias graph below (Figure 8) displays the review author's judgments about each risk of bias item presented as percentages across all included studies in the meta-analysis.

Figure 8: Risk of bias graph for meta-analysis (crossover studies removed). (Created with Review Manager (RevMan) version 5.2, The Cochrane IMS.)



All the studies included in the meta-analysis were RCTs, so random sequence generation was not a major concern, even though few studies described the process used to randomly assign subjects to groups. The act of randomization guarantees the results from any analysis of these data are subject to the laws of probability, so screened studies with a quasi-randomized design were excluded.[138] While the majority of authors did not provide details related to the methods of allocation concealment, all the studies were at least single-blinded RCTs, so this process was likely conducted, but not explicitly reported. The risk of selection bias was therefore deemed to be low.

Regarding blinding, 62% of the included trials were double-blinded, and the remaining 38% were single-blinded. Blinding of subjects to their dietary treatment may be difficult in some situations if the intervention focuses on one or more food items that are easily recognizable to the subjects, such as almonds. Considering that the research staff and those who were assessing outcomes were blinded in the large majority of studies, performance and detection biases should have been minimized. The main outcome in this meta-analysis was the lipid profile, which cannot be altered merely upon knowledge of the treatment by the subjects; the natural intra-individual variation in the blood lipid levels,[139] or the differences seen during analysis[140] will overshadow any risk of bias introduced by the single-blinded designs.

Incomplete accounting of patients and outcomes were the greatest source of bias in this sample of studies. There were some studies that reported much higher attrition rates in one group over another, and five studies broke the intention-to-treat analysis by excluding individuals from the analysis who deviated from the study protocol. In some cases it was not reported if there were significant differences between those who withdrew from the study and those who completed it, and so both the sheer numbers of withdrawals, as well as the comparison between the groups were examined. Even with these considerations, the majority of studies, including those that contributed more to the summary effect, demonstrated low risk of attrition bias.

Most of the authors seemed to report on all proposed and measured outcomes, limiting the risk of reporting bias. There were no reported instances of stopping the trials early for benefit, or for invalidated outcome measures. Since crossover trials and cluster-randomized trials were not included in the primary meta-analysis, carryover or recruitment biases were not concerns. Considering the information across the studies, as well as for those studies contributing higher weight to the meta-analysis, it was determined that any plausible bias was unlikely to seriously alter the results. The quality assessment for study limitations was therefore: "No serious limitations, do not downgrade".

<u>Identified Subgroups</u>

One subgroup theme that was pursued related to the identification of clinically-significant results. A coefficient of variation (C_V), or relative error, has been defined for each parameter of the lipid profile by the NCEP Laboratory Standardization Panel.[141] Coefficients of variation are dimensionless units, reported as percentages, and are calculated as the ratio of the standard deviation to the mean. Intra-personal variation of the parameters of the lipid profile is comprised of two components: biological fluctuations (C_B) and variations due to analysis (C_A); these values are often reported separately. Since these two uncertainties are not inter-related, they can be combined via summation in quadrature to obtain the total coefficient of variation (C_T) for each outcome: $C_T = \sqrt{C_A^2 + C_B^2}$. The following estimates were used to approximate the total intra-individual variations:

- Total cholesterol = 6.6%[141]
- LDL = 9.1%[141]
- HDL = 8.0%[142]
- TG = 23.9%[143]

The magnitude of intra-individual variation has significant consequences with respect to screening, diagnosis, and treatment of conditions.[141] Many clinical trials describe their results as "clear evidence", even when they are well within the intra-personal variation of the average study subject. Therefore, this meta-analysis will define clinical significance as a reported treatment effect outside the intra-personal variation.

The pre-treatment value for each observation was multiplied by its respective (C_T) value, to produce a predicted range of variation. The post-treatment value for the parameter was then compared to this range, and if it fell outside, the treatment effect was deemed clinically significant, and a separate meta-analysis was performed to explore any meaningful associations.

The relative change in the macronutrient content of the diet was a second subgroup theme. Of the 86 comparisons included in the meta-analysis, 21% manipulated the percentage of fat in their dietary interventions: nine comparisons (239 subjects) decreased fat content in the diet and nine (206 subjects) increased it. The remaining comparisons (2,699 subjects) reported no appreciable changes total dietary fat contributions over the course of the intervention. The change in total fat for these trials was deemed “fixed” or negligible, and defined as a change in dietary fat within 3.5%. A test for heterogeneity ($Q = 19.968$, $df = 2$, $p <0.001$) supports that the subgroups related to change in total fat do not share a common treatment effect between them.

Regarding protein, 15% manipulated the percentage of protein in their dietary interventions, with all of these trials (325 subjects) demonstrating an increase in protein. The remaining comparisons (2,819 subjects) reported no appreciable changes in total protein over the course of their dietary interventions. The change in protein for these dietary trials was deemed “fixed” or negligible, and defined as a change within 3.5% total energy. A test for heterogeneity ($Q = 0.033$, $df = 1$, $p =0.856$) did not reject the possibility that the change in protein subgroups could have the same treatment effect between them.

Concerning carbohydrate, 24.4% of the comparisons manipulated this macronutrient, with eleven reporting decreased carbohydrate intake, and ten increased it. The remaining comparisons (2,557 subjects) reported no appreciable changes in total carbohydrate over the course of their respective dietary interventions. The change in carbohydrate for these dietary trials was deemed "fixed" or negligible, and defined as a change within 3.5% total energy. A test for heterogeneity ($Q = 4.248$, $df = 2$, $p = 0.120$) did not reject the possibility that the change in carbohydrate subgroups could have the same treatment effect between them. None of subgroups related to carbohydrate reported a treatment that was beyond intra-personal variation.

After examining subgroups related to change in the macronutrients over the course of the dietary interventions, the studies in the meta-analysis were re-categorized into subgroups that compared their macronutrient distributions to the Acceptable Macronutrient Distribution Ranges (AMDRs). The following distinctions were used:

- Any parameter within the AMDR was designated as "Moderate"
  - Moderate Fat (MF) = 20-35% total energy
  - Moderate Protein (MP) = 10-35% total energy
  - Moderate Carbohydrate (MC) = 45-65% total energy
- Any parameter that was above the AMDR was designated as "High"
  - High Fat (HF) >35% total energy
  - High Protein (HP) >35% total energy
  - High Carbohydrate (HC) >65% total energy
- Any parameter that was below the AMDR was designated as "Low"
  - Low Fat (LF) <20% total energy
  - Low Protein (LP) <10% total energy
  - Low Carbohydrate (LC) <45% total energy
- Using these guidelines, the following dietary profiles were defined:
  - AMDR: Fat = 20-35%, Protein = 10-35%, Carbohydrate = 45-65%
  - HF/MP/LC: Fat>35%, Protein = 10-35%, Carbohydrate <45%
  - HF/MP/MC: Fat>35%, Protein = 10-35%, Carbohydrate = 45-65%

<u>TOTAL CHOLESTEROL CHANGE (∆TC)</u>

As described in Table 5 below, the studies of this meta-analysis showed a decrease in total cholesterol. The effects of individual studies can be seen in the forest plot in Figure 9, which is sorted from greatest reduction to greatest increase in total cholesterol, with a summary effect of -6.401 mg/dL displayed at the bottom. The intra-personal variation (C_T) for total cholesterol was estimated at 6.6%.

Comparisons that reported changes in total cholesterol more than the estimated intra-personal variation for the parameter were combined into a separate analysis that can be seen in Figure 11. For the studies that reported a clear decrease in total cholesterol, the summary effect was -20.726 mg/dL (95%CI: -24.177 mg/dL to -17.274 mg/dL). There were only two trials that reported a clear increase in total cholesterol, and the overall summary effect of both groups combined was -9.329mg/dL (95%CI: -12.262 to -6.397).

Table 5: Summary effect – change in total cholesterol (Random effects model/raw mean difference) 42 studies (86 comparisons, 3144 subjects; Average power of included studies: 0.9987)							
Effect size and 95% confidence interval						Test of null (2-Tail)	
	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
∆TC (mg/dL)	-6.401	1.231	1.515	-8.813	-3.988	-5.200	<0.001

Macronutrient Distribution & Change in TC (mg/dL)

Study name	Macronutrient Distribution (F/P/C)	Statistics for each study: Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
Kasim-Karakas 2009A	26/34/40	-33.000	1.368	1.872	-35.681	-30.319	-24.121	0.000	1.27	
Kasai 2003B	27/15/56	-32.100	2.424	5.877	-36.851	-27.349	-13.241	0.000	1.23	
Wardlaw 1991B	39/13/47	-31.710	3.315	10.991	-38.208	-25.212	-9.565	0.000	1.18	
Pins 2006A	34/21/45	-29.200	4.665	21.765	-38.344	-20.056	-6.259	0.000	1.09	
Gylling 2010B	31/16/45	-29.000	2.410	5.808	-33.724	-24.276	-12.033	0.000	1.23	
Han 2007A	23/18/59	-26.680	4.626	21.397	-35.746	-17.614	-5.768	0.000	1.09	
Kasai 2003A	27/15/56	-26.300	2.065	4.263	-30.347	-22.253	-12.738	0.000	1.25	
Tonstad 2002C	29/18/50	-23.980	2.368	5.605	-28.620	-19.340	-10.129	0.000	1.23	
Tonstad 2002A	30/18/47	-23.970	2.078	4.317	-28.042	-19.898	-11.536	0.000	1.24	
Stendell-Hollis 2010B	28/18/54	-23.200	6.980	48.720	-36.880	-9.520	-3.324	0.001	0.91	
Tanumihardjo 2009B	24/21/55	-20.110	3.926	15.411	-27.804	-12.416	-5.123	0.000	1.14	
Alhassan 2006	39/17/44	-20.000	3.553	12.622	-26.963	-13.037	-5.629	0.000	1.16	
Wardlaw 1991A	40/13/47	-18.170	2.846	8.098	-23.748	-12.592	-6.385	0.000	1.21	
Wood 2007A	59/27/13	-17.790	3.464	12.002	-24.580	-11.000	-5.135	0.000	1.17	
Santo 2008A	22/20/57	-17.400	7.195	51.768	-31.502	-3.298	-2.418	0.016	0.90	
Tanumihardjo 2009A	29/17/54	-17.020	3.842	14.765	-24.551	-9.489	-4.429	0.000	1.15	
Chan 2002B	34/22/40	-15.470	3.863	14.927	-23.042	-7.898	-4.004	0.000	1.14	
Smith 2003A	40/11/48	-15.460	3.133	9.816	-21.601	-9.319	-4.935	0.000	1.19	
Gardner 2007C	30/20/49	-14.580	2.760	7.616	-19.989	-9.171	-5.283	0.000	1.21	
Mensink 2002B	29/16/53	-13.930	2.564	6.574	-18.955	-8.905	-5.433	0.000	1.22	
Gardner 2007D	21/17/63	-13.200	2.738	7.494	-18.565	-7.835	-4.822	0.000	1.21	
Melanson 2004	28/21/53	-13.200	4.172	17.408	-21.378	-5.022	-3.164	0.002	1.12	
Smith 2003B	37/11/50	-12.760	2.886	8.328	-18.416	-7.104	-4.422	0.000	1.20	
Polagruto 2006A	34/16/50	-12.500	2.321	5.386	-17.049	-7.951	-5.386	0.000	1.23	
Tonstad 2002D	31/17/49	-12.370	1.739	3.023	-15.778	-8.962	-7.115	0.000	1.26	
Schwab 2002A	27/18/51	-11.600	3.231	10.438	-17.932	-5.268	-3.590	0.000	1.18	
Stendell-Hollis 2010A	32/16/53	-11.600	3.672	13.482	-18.797	-4.403	-3.159	0.002	1.16	
Schwab 2006A	26/19/53	-11.220	3.768	14.197	-18.605	-3.835	-2.978	0.003	1.15	
Esposito 2004	29/16/55	-11.000	2.015	4.059	-14.949	-7.051	-5.460	0.000	1.25	
Esposito 2004A	28/14/58	-11.000	1.597	2.550	-14.130	-7.870	-6.889	0.000	1.26	
Wood 2007B	59/27/13	-10.830	5.402	29.178	-21.417	-0.243	-2.005	0.045	1.03	
Gardner 2007B	35/24/42	-10.760	3.151	9.927	-16.935	-4.585	-3.415	0.001	1.19	
Goyens 2006A	41/13/44	-9.280	4.663	21.741	-18.419	-0.141	-1.990	0.047	1.09	
Gardner 2007A	55/28/18	-8.600	3.212	10.315	-14.895	-2.305	-2.678	0.007	1.19	
Chan 2002A	36/20/38	-7.740	4.172	17.408	-15.917	0.437	-1.855	0.064	1.12	
Tonstad 2002B	31/18/49	-7.730	2.058	4.234	-11.763	-3.697	-3.757	0.000	1.25	
Tighe 2010A	35/16/47	-7.350	2.222	4.935	-11.704	-2.996	-3.309	0.001	1.24	
Schwab 2006C	28/18/51	-6.570	4.606	21.216	-15.598	2.458	-1.426	0.154	1.09	
Diaz 2008B	27/19/56	-6.190	5.421	29.391	-16.816	4.436	-1.142	0.254	1.03	
Schwab 2006B	28/19/51	-6.190	3.198	10.224	-12.457	0.077	-1.936	0.053	1.19	
Malpuech-Brugere 2010B	39/15/45	-5.030	2.875	8.263	-10.664	0.604	-1.750	0.080	1.21	
Hjerkinn 2005	28/17/52	-3.870	1.218	1.483	-6.257	-1.483	-3.178	0.001	1.27	
Pins 2006B	35/21/44	-3.600	4.768	22.731	-12.945	5.745	-0.755	0.450	1.08	
Kelley 2007B	34/15/50	-3.480	4.120	16.975	-11.555	4.595	-0.845	0.398	1.13	
Tapsell 2004C	32/22/44	-3.480	3.498	12.237	-10.336	3.376	-0.995	0.320	1.17	
Price 2010B	33/18/47	-2.710	3.121	9.743	-8.828	3.408	-0.868	0.385	1.19	
Smith 2008B	30/16/54	-2.700	2.176	4.734	-6.964	1.564	-1.241	0.215	1.24	
Szapary 2003	33/14/52	-2.450	2.138	4.572	-6.641	1.741	-1.146	0.252	1.24	
Gylling 2010A	42/14/43	-2.320	2.214	4.902	-6.659	2.019	-1.048	0.295	1.24	
Esposito 2004B	30/14/57	-2.000	1.502	2.256	-4.944	0.944	-1.331	0.183	1.27	
Kasim-Karakas 2009B	26/17/57	-2.000	0.864	0.747	-3.694	-0.306	-2.314	0.021	1.28	
Malpuech-Brugere 2010C	39/15/47	-1.940	2.916	8.506	-7.656	3.776	-0.665	0.506	1.20	
Diaz 2008A	23/16/65	-1.930	9.136	83.465	-19.836	15.976	-0.211	0.833	0.75	
Price 2010A	35/18/47	-1.930	2.820	7.951	-7.457	3.597	-0.684	0.494	1.21	
Tighe 2010C	35/16/45	-1.930	2.011	4.044	-5.872	2.012	-0.960	0.337	1.25	
Han 2007B	28/18/55	-1.160	5.116	26.176	-11.188	8.868	-0.227	0.821	1.06	
Mutungi 2008B	55/25/20	-1.000	4.881	23.821	-10.566	8.566	-0.205	0.838	1.07	
Polagruto 2006B	31/17/54	-0.400	2.550	6.500	-5.397	4.597	-0.157	0.875	1.22	
Dodin 2005A	35/17/47	-0.390	1.409	1.985	-3.152	2.372	-0.277	0.782	1.27	
Fakhrzadeh 2010	35/13/53	-0.300	2.765	7.648	-5.720	5.120	-0.108	0.914	1.21	
Adler 1997	31/17/50	-0.200	3.200	10.240	-6.472	6.072	-0.062	0.950	1.19	
Santo 2008B	24/21/54	0.100	6.351	40.339	-12.348	12.548	0.016	0.987	0.96	
Smith 2008A	32/16/52	0.300	2.047	4.191	-3.712	4.312	0.147	0.883	1.25	
Kawashima 2008A	27/14/51	0.780	1.230	1.512	-1.630	3.190	0.634	0.526	1.27	
Levin 1990	26/18/57	2.000	2.671	7.133	-3.235	7.235	0.749	0.454	1.22	
Maki 2005A	35/16/50	2.700	3.875	15.016	-4.895	10.295	0.697	0.486	1.14	
Mensink 2002A	32/15/50	2.700	2.589	6.703	-2.374	7.774	1.043	0.297	1.22	
Kawashima 2008B	28/14/50	2.710	1.156	1.337	0.444	4.976	2.344	0.019	1.28	
Schwab 2002B	27/18/52	3.860	4.084	16.677	-4.144	11.864	0.945	0.345	1.13	
Malpuech-Brugere 2010A	38/15/47	3.870	2.546	6.484	-1.121	8.861	1.520	0.129	1.22	
Mutungi 2008A	56/27/15	3.900	4.933	24.334	-5.768	13.568	0.791	0.429	1.07	
Tapsell 2004A	33/21/43	4.250	4.334	18.780	-4.244	12.744	0.981	0.327	1.11	
Beavers 2010A	34/21/47	4.380	3.975	15.797	-3.410	12.170	1.102	0.270	1.14	
Goyens 2006B	42/14/43	4.640	5.773	33.328	-6.675	15.955	0.804	0.422	1.00	
Beavers 2010B	38/20/47	5.370	5.505	30.302	-5.419	16.159	0.976	0.329	1.03	
Assuncao 2009B	21/15/64	5.600	4.111	16.902	-2.458	13.658	1.362	0.173	1.13	
Hollis 2009C	34/16/50	6.570	2.927	8.567	0.833	12.307	2.245	0.025	1.20	
Dodin 2005B	33/17/50	6.960	1.299	1.688	4.414	9.506	5.357	0.000	1.27	
Hollis 2009B	35/16/48	6.960	2.892	8.366	1.291	12.629	2.406	0.016	1.20	
Tighe 2010B	34/17/48	7.340	2.295	5.269	2.841	11.839	3.198	0.001	1.23	
Hollis 2009A	35/15/50	7.350	2.659	7.069	2.139	12.561	2.764	0.006	1.22	
Tapsell 2004B	33/23/41	9.660	3.895	15.168	2.027	17.293	2.480	0.013	1.14	
Kelley 2007A	36/16/48	10.050	3.715	13.804	2.768	17.332	2.705	0.007	1.15	
Maki 2005B	35/15/52	12.400	2.996	8.979	6.527	18.273	4.138	0.000	1.20	
Assuncao 2009A	21/15/64	19.800	2.923	8.545	14.071	25.529	6.774	0.000	1.20	
Santo 2008C	23/20/57	27.100	11.710	137.132	4.148	50.052	2.314	0.021	0.60	
		-6.401	1.231	1.515	-8.813	-3.988	-5.200	0.000		

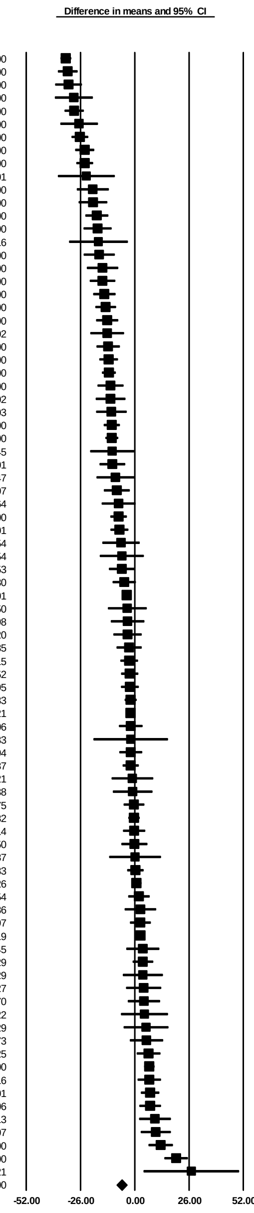


Figure 9. Forest plot – macronutrient distribution and change in total cholesterol.
86 comparisons (3144 subjects)
Macronutrient distribution format (% total energy): Fat/Protein/Carbohydrate
(Values may not add up to 100% due to rounding)

Study Limitations

Refer to the section related to the study limitations for the overall lipid profile.

Inconsistency

The unexplained heterogeneity and inconsistent results related to the outcome of change in total cholesterol were summarized in Table 6.

Table 6: Heterogeneity table – change in total cholesterol. 42 Studies (86 comparisons, 3144 subjects)								
Heterogeneity								
	Q-Statistic			I-Squared	Tau-squared			
	Q	df (Q)	P-value	I^2	T^2	Standard Error	Variance	Tau (T)
ΔTC	1716.579	85	<0.001	95.048%	117.415	28.205	795.518	10.836

- For change in total cholesterol, the effect sizes varied widely across the studies, and there were inconsistent results for both large and small trials; some studies reported decreases in total cholesterol and others reported increases.
    - The confidence intervals for the various studies frequently overlapped. (See supplemental figure S5.)
- The p-value associated with the Q-statistic was <0.001, suggesting these studies did not share a common treatment effect.
- The Q-statistic was larger than the degrees of freedom (Q>df), indicating that additional evidence from an increasing number of studies would only strengthen the case that the excess dispersion is not zero, thus further supporting no common effect size.

- The value for I-squared (I^2) was 95.048%, indicating nearly all of the variation is real, and strongly supported further subgroup analysis and/or meta-regression.
- Tau-squared (T^2) was calculated as 117.415, and reflected the estimated between-study variance of the true effects. The positive nature of the result was based on the amount of excess variation (Q-df >0) and the metric of the effect size.
- The estimated standard deviation of the true effect size, Tau (T), was 10.836. This value can be used to predict, with 95% accuracy, where a new study would be placed in the meta-analysis.
    - The 95% prediction interval was calculated as: -23.327 to 20.047.
- The unexplained between-study variance (R^2) could not be resolved by any of the moderators listed in the meta-regression.

For change in total cholesterol, the studies included in this meta-analysis met all four assessment criteria for inconsistency in results: the magnitude of the treatment effects varied widely across studies, the confidence intervals overlapped, the statistical tests for heterogeneity rejected the null hypothesis that the studies share a common treatment effect, and the I^2 test quantified that nearly all the heterogeneity was real.[70] Since subgroup analyses and meta-regression failed to identify the sources of heterogeneity, the quality assessment of the evidence related to inconsistency was therefore deemed: "Very serious, downgrade two levels".

<u>Indirectness/Differences in Populations</u>

Total cholesterol is measured enzymatically in serum or plasma in a series of biochemical reactions that result in the byproduct of hydrogen peroxide, which is measured quantitatively in a catalyzed reaction that produces a color and its absorbance is measured at 500 nm.[144] Since the concentration of cholesterol is directly proportional to the color intensity, this analysis could technically be considered an indirect measurement of total cholesterol; however the consistent and widespread application of this technique will not be justification for rating down the evidence.

- Only subjects and interventions meeting the eligibility criteria were included in the systematic review, so evidence regarding them was direct by nature.[71]
- There were no compelling reasons to rate down based on population differences, because any suspected differences were unlikely to substantially impact the summary effect.

The quality assessment of the evidence related to indirectness was therefore deemed: “No serious limitations, do not downgrade”.

<u>Imprecision</u>

For change in total cholesterol, a conservative estimate of the optimal information size (OIS) was calculated: the significance (α) was set at 0.05, the power (1-ß) was 0.90, the difference to be detected (Δ) was set at 3mg/dL, and the standard deviation of the effect was estimated at ±36.

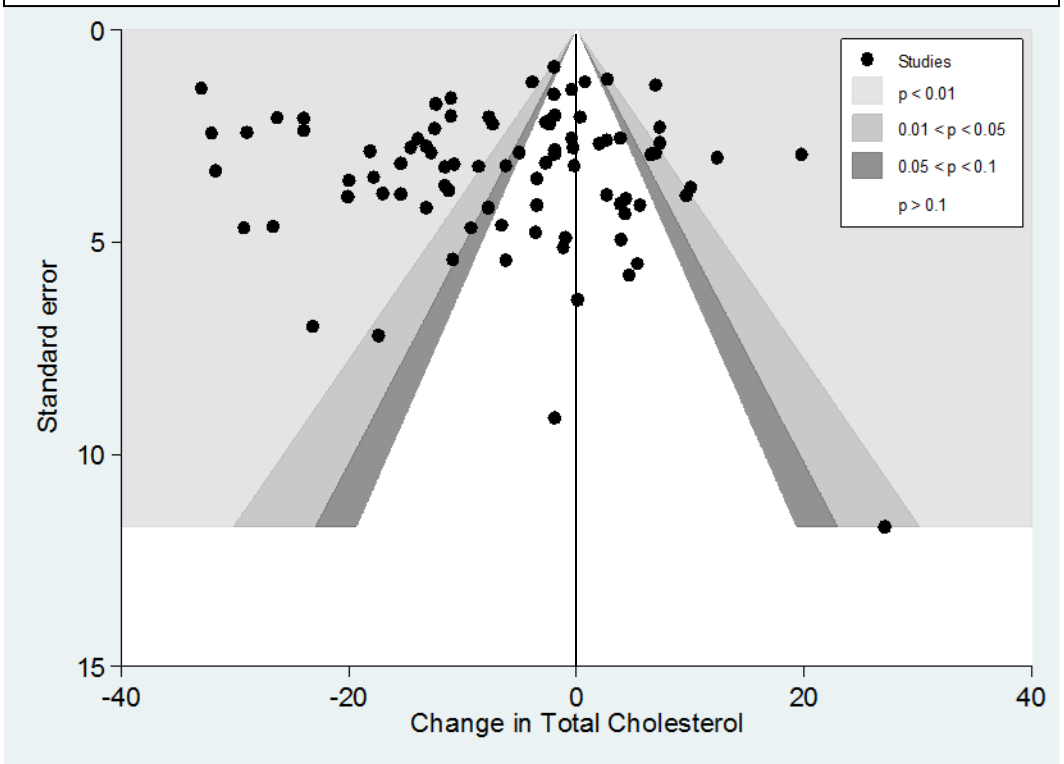
- The OIS was calculated to be 2145 subjects, and the number of subjects in the meta-analysis was 3144, meeting the OIS criterion (OIS< number of studies in systematic review/meta-analysis).
- Comparing the lower and upper boundaries for the 95% CI (-8.813 mg/dL to -3.988 mg/dL) would not have changed the recommendation of the summary effect, since they both indicate a decrease in the change of total cholesterol; the CI around the summary effect was also sufficiently narrow.

The quality assessment of the evidence related to imprecision was therefore deemed: "Not serious, do not downgrade".

Publication Bias Likelihood

- Visual inspection of the contour enhanced funnel plot (Figure 10) indicated asymmetry, but the horizontal scatter suggested heterogeneity may be one possible source the asymmetry, since bias from small studies would have been shown towards the bottom of the funnel. There did not appear to be areas of missing studies within the statistically-insignificant region, making the publication bias unlikely.

Figure 10: Contour funnel plot – change in total cholesterol.



- A precision-focused cumulative meta-analysis did not indicate a substantial shift in the point estimate due to large effects contributed by small studies. (See supplemental figure S3.)
- There may have been some potential time-lag bias, as indicated by continuously diminishing point estimates on the cumulative display sorted by publication year. The point estimate (change in total cholesterol) ranged from -11.146 mg/dL in the year 2002 to -6.401 mg/dL in 2010. (See supplemental figure S4.)
- Only eight studies (1.5%) identified during the systematic review process were excluded for being published in a language other than English. (See Appendix G.)

Considering the significant heterogeneity present, the horizontal scatter of the funnel plot, and the results of the more reliable and transparent cumulative meta-analyses, the likelihood for publication bias was deemed: “Unlikely, do not downgrade”.

Referring to Figure 11, reported impacts beyond intra-personal variation were:

- An overall decrease in total cholesterol of -11.00 mg/dL (95%CI: -13.812 to -8.194), p(Q)<0.001, I^2= 94%.
    - The overall estimate included twenty-two comparisons that decreased total cholesterol, with a summary effect of -21.713 mg/dL (95%CI: -24.968 to -18.458).
        - The average macronutrient distribution of these studies was calculated to be 32% fat, 18% protein, 50% carbohydrate, and was within the AMDRs, although wide variations were noted.
    - This overall estimate also included two studies that raised total cholesterol (MD: +20.23 mg/dL, 95%CI: 14.670 to 25.787).
        - The average macronutrient distribution of these two studies was calculated to be 22% fat, 18% protein, 60% carbohydrate, and was also within the AMDRs, although wide variations were noted.

Macronutrient Distribution Impact on Change in TC (mg/dL)

Group by Comparison	Study name	Macronutrient Distribution (F/P/C)	Impact on TC	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Decreased	Kasim-Karakas 2009A	26/34/40 - MF/MP/LC	Decreased	-33.000	1.368	1.872	-35.681	-30.319	-24.121	0.000
Decreased	Kasai 2003B	27/15/56 - AMDR	Decreased	-32.100	2.424	5.877	-36.851	-27.349	-13.241	0.000
Decreased	Wardlaw 1991B	39/13/47 - HF/MP/MC	Decreased	-31.710	3.315	10.991	-38.208	-25.212	-9.565	0.000
Decreased	Pins 2006A	34/21/45 - MF/MP/LC	Decreased	-29.200	4.665	21.765	-38.344	-20.056	-6.259	0.000
Decreased	Gylling 2010B	31/16/45 - AMDR	Decreased	-29.000	2.410	5.808	-33.724	-24.276	-12.033	0.000
Decreased	Han 2007A	23/18/59 - AMDR	Decreased	-26.680	4.626	21.397	-35.746	-17.614	-5.768	0.000
Decreased	Kasai 2003A	27/15/56 - AMDR	Decreased	-26.300	2.065	4.263	-30.347	-22.253	-12.738	0.000
Decreased	Tonstad 2002C	29/18/50 - AMDR	Decreased	-23.980	2.368	5.605	-28.620	-19.340	-10.129	0.000
Decreased	Tonstad 2002A	30/18/47 - AMDR	Decreased	-23.970	2.078	4.317	-28.042	-19.898	-11.536	0.000
Decreased	Stendell-Hollis 2010B	28/18/54 - AMDR	Decreased	-23.200	6.980	48.720	-36.880	-9.520	-3.324	0.001
Decreased	Tanumihardjo 2009B	24/21/55 - AMDR	Decreased	-20.110	3.926	15.411	-27.804	-12.416	-5.123	0.000
Decreased	Alhassan 2006	39/17/44 - HF/MP/LC	Decreased	-20.000	3.553	12.622	-26.963	-13.037	-5.629	0.000
Decreased	Wardlaw 1991A	40/13/47 - HF/MP/MC	Decreased	-18.170	2.846	8.098	-23.748	-12.592	-6.385	0.000
Decreased	Wood 2007A	59/27/13 - HF/MP/LC	Decreased	-17.790	3.464	12.002	-24.580	-11.000	-5.135	0.000
Decreased	Santo 2008A	22/20/57 - AMDR	Decreased	-17.400	7.195	51.768	-31.502	-3.298	-2.418	0.016
Decreased	Tanumihardjo 2009A	29/17/54 - AMDR	Decreased	-17.020	3.842	14.765	-24.551	-9.489	-4.429	0.000
Decreased	Chan 2002B	34/22/40 - MF/LP/LC	Decreased	-15.470	3.863	14.927	-23.042	-7.898	-4.004	0.000
Decreased	Smith 2003A	40/11/48 - HF/MP/MC	Decreased	-15.460	3.133	9.816	-21.601	-9.319	-4.935	0.000
Decreased	Gardner 2007C	30/20/49 - AMDR	Decreased	-14.580	2.760	7.616	-19.989	-9.171	-5.283	0.000
Decreased	Mensink 2002B	29/16/53 - AMDR	Decreased	-13.930	2.564	6.574	-18.955	-8.905	-5.433	0.000
Decreased	Gardner 2007D	21/17/63 - AMDR	Decreased	-13.200	2.738	7.494	-18.565	-7.835	-4.822	0.000
Decreased	Smith 2003B	37/11/50 - HF/MP/MC	Decreased	-12.760	2.886	8.328	-18.416	-7.104	-4.422	0.000
Decreased				-21.713	1.661	2.758	-24.968	-18.458	-13.074	0.000
Increased	Assuncao 2009A	21/15/64 - AMDR	Increased	19.800	2.923	8.545	14.071	25.529	6.774	0.000
Increased	Santo 2008C	23/20/57 - AMDR	Increased	27.100	11.710	137.132	4.148	50.052	2.314	0.021
Increased				20.228	2.836	8.043	14.670	25.787	7.132	0.000
Overall				-11.003	1.433	2.054	-13.812	-8.194	-7.677	0.000

Difference in means and 95% CI

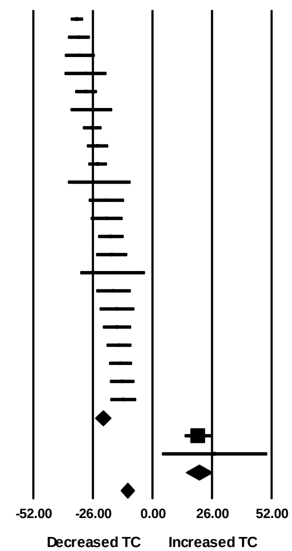
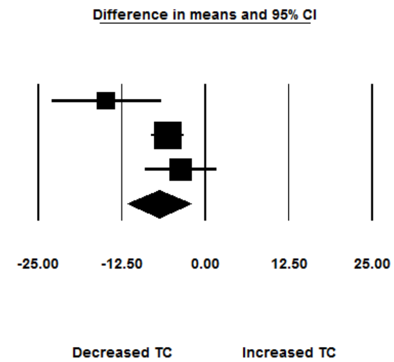


Figure 11. Forest plot – macronutrient distribution and change in total cholesterol (effects beyond intra-personal variation). [Q=150.495, df=1, p<0.001]
Macronutrient distribution format (% total energy): Fat/Protein/Carbohydrate
Definitions & Abbreviations: Decreased TC: >5mg/dL reduction in total cholesterol; AMDR: Acceptable Macronutrient Distribution Ranges, HF: High-Fat, MP: Moderate-Protein, LC: Low-Carbohydrate, MF: Moderate-Fat, HC: High-Carbohydrate, LC: Low-Carbohydrate, HC: High-Carbohydrate, MC: Moderate-Carbohydrate. Ranking of dietary profiles: Low < AMDR (Moderate) < High

Subgroup Analysis/Meta-Regression

Change in Total Fat (Subgroup) & Change in TC (mg/dL)

Study name	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
Decreased Fat	9	-14.844	4.186	17.523	-23.048	-6.640
Fixed Fat	68	-5.657	1.256	1.578	-8.119	-3.195
Increased Fat	9	-3.671	2.739	7.502	-9.039	1.697
		-6.906	2.395	5.737	-11.600	-2.211



Decreased: < -3.4%, Fixed: -3.4 to 3.4%, Increased: >+3.4%

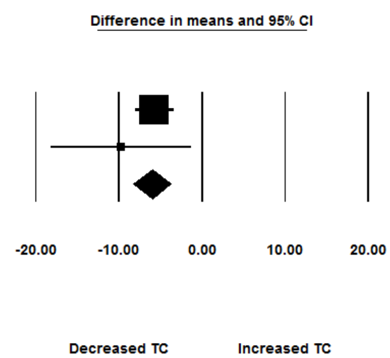
Figure 12: Subgroup forest plot – change in fat and change in total cholesterol.

- With respect to change in total fat, a decrease in overall fat consumption appeared to contribute a significant reduction in total cholesterol beyond what could be attributed to intra-personal variation (-14.844mg/dL, 95%CI: -23.048 to -6.640).
  - However, the small number of comparisons (239 subjects) and relatively low weight of this subgroup warrants more evidence before a more definitive conclusion can be made.
- Those sixty-eight comparisons that did not change the fat contribution in their dietary trials (or the change was deemed to be negligible at ±3.4%) also demonstrated a decrease in total cholesterol that was more reliable.

- The subgroup that increased total fat intake had a confidence interval that crossed both effects, and included only nine comparisons (206 subjects).
    - The true difference between the effect in the decreased fat subgroup studies, as opposed to the fixed fat studies, probably falls in the range of 0.6204mg/dL to 17.754mg/dL. (See supplemental table S14.)

Change in Total Prot (Subgroup) & Change in TC (mg/dL)

Study name	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
Fixed Protein	73	-5.745	1.182	1.397	-8.062	-3.428
Increased Protein	13	-9.790	4.306	18.542	-18.230	-1.350
		-6.028	1.140	1.299	-8.262	-3.794



Decreased: < -3.4%, Fixed: -3.4 to 3.4%, Increased: >+3.4%

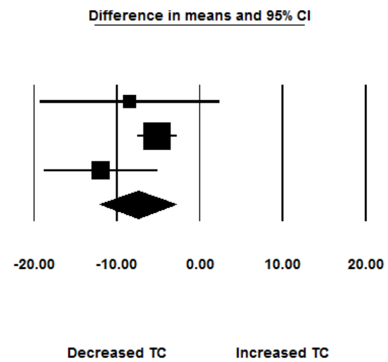
Figure 13: Subgroup forest plot – change in protein and change in total cholesterol.

With respect to change in total protein, the studies in the meta-analysis could only be categorized into two subgroups: increased and fixed protein. This is likely due to the notion that protein has only limited impact on blood lipid levels, and so interventions either leave it unchanged, while manipulating the remaining macronutrients, or increase its amount to provide macronutrient balance (see Figure 13). There was no clear indication as to how change in protein impacted total cholesterol, as the summary effects were within the range of intra-personal variation.

- Studies that increased the amount of total protein in the diet seemed to have the potential for decreasing total cholesterol, but the decrease was within intra-personal variation (Summary effect: -9.790 mg/dL, 95%CI: -18.230 to -1.350, versus -5.745 mg/dL, 95%CI: -8.062 to -3.428 for no change dietary in protein percentage).
    - Once again, the thirteen comparisons featured within this subgroup is a relatively small number (325 subjects), although the wide confidence interval did not cross the null.
    - The true difference between the effect in the fixed protein subgroups, as opposed to the increased protein subgroup, probably falls in the range of 12.796 mg/dL to 4.706 mg/dL. (See supplemental table S14.)

Change in Total Carb (Subgroup) & Change in TC(mg/dL)

Study name	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
Decreased Carb	11	-8.517	5.548	30.780	-19.391	2.357
Fixed Carb	65	-5.184	1.220	1.488	-7.575	-2.793
Increased Carb	10	-11.987	3.508	12.306	-18.863	-5.111
		-7.499	2.333	5.445	-12.073	-2.926



Decreased: < -3.4%, Fixed: -3.4 to 3.4%, Increased: >+3.4%

Figure 14. Subgroup forest plot – change in carbohydrate and change in total cholesterol.

There was no clear indication as to how the carbohydrate subgroups influence changes in total cholesterol, as the summary effects for all three subgroups were within the intra-personal variation for total cholesterol.

- Those interventions that did not alter the mean carbohydrate intake of the diet demonstrated a decrease in total cholesterol that approached clinical significance (summary effect: -5.184mg/dL, 95%CI: -7.575 to -2.793).
- Those that increased carbohydrate intake reported an even larger, but less precise value (Summary effect: -11.987mg/dL, 95% CI: -18.863 to -5.111).
    - The true difference between the effect in the fixed carbohydrate studies, as opposed to the increased carbohydrate studies, probably falls in the range of -14.084mg/dL to 0.478mg/dL. (See supplemental table S14.)

- The subgroup that decreased carbohydrate intake also reported a decrease in total cholesterol, but its confidence interval was sufficiently wide and crossed the null.
  - The true difference between the effect in the fixed carbohydrate studies, as opposed to the decreased carbohydrate studies, probably falls in the range of -12.796 mg/dL to 4.706 mg/dL. (See supplemental table S14.)

Macronutrient Distribution (Subgroups) & Change in TC (mg/dL)

	Observations	Statistics for each study				
		Difference in means	Standard error	Variance	Lower limit	Upper limit
AMDR	57	-5.843	1.345	1.809	-8.479	-3.207
HF/MP/LC	10	-7.610	2.612	6.823	-12.729	-2.491
HF/MP/MC	13	-3.876	3.077	9.468	-9.907	2.155
MF/LP/LC	1	-15.470	3.863	14.923	-23.041	-7.899
MF/MP/HC	1	-1.930	9.136	83.466	-19.836	15.976
MF/MP/LC	4	-19.147	7.964	63.425	-34.756	-3.538
		-7.783	1.851	3.425	-11.411	-4.156

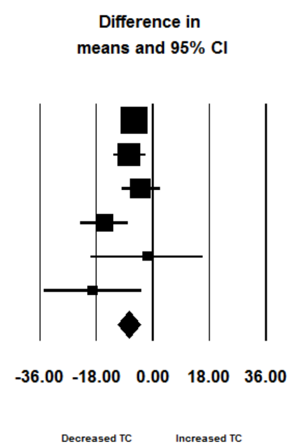


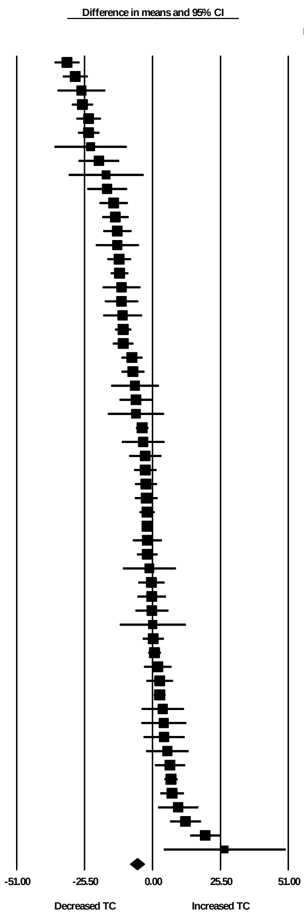
Figure 15. Subgroup forest plot – dietary profiles and change in total cholesterol.

Based on these definitions, the meta-analysis did not include any studies that implemented dietary interventions that would qualify as "Low Fat". About two-thirds of the studies (57 comparisons) were within the AMDRs; twenty-three were designated as "High Fat", and ten would be classified as "High-Fat versus Low-Carbohydrate" diets. Only six comparisons (149 subjects) were not categorized as "High Fat", and due to the low number of trials, these subgroups were not included in most comparison analyses, although their values are presented in Figure 15 for transparency purposes and to inspire future research.

- The AMDR subgroup (2404 subjects) demonstrated a reduction in total cholesterol (-5.843 mg/dL, 95% CI: -8.479 to -3.207), but this was within intra-personal variation.
    - This reduction is similar to the summary effect from complete meta-analysis, likely because the majority of the studies in the meta-analysis followed dietary interventions that were within the AMDRs.
    - The contribution on change in total cholesterol by the various studies within the AMDRs is illustrated in Figure 16.
- The HF/MP/LC subgroup showed a greater decrease in total cholesterol (-7.610 mg/dL, 95%CI: -12.729 to -2.491) compared to AMDR, but had far fewer subjects (206 subjects), a slightly wider confidence interval, and still was not clinically significant.
    - The true difference between the effect in the AMDR studies, as opposed to the HF/MP/LC studies, probably falls in the range of -7.524 mg/dL to 3.990 mg/dL. (See supplemental table S14.)
- The HF/MP/MC subgroup showed a smaller impact on change in total cholesterol (-3.876 mg/dL), and its confidence interval crossed the null (95% CI: -9.907 mg/dL to 2.155 mg/dL).

AMDR & Change in TC (mg/dL)

Studyname	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
	Statistics for each study								
Kasai 2003B	-32.100	2.424	5.877	-36.851	-27.349	-13.241	0.000	1.85	
Gylling 2010B	-29.000	2.410	5.808	-33.724	-24.276	-12.033	0.000	1.85	
Han 2007A	-26.680	4.626	21.397	-35.746	-17.614	-5.768	0.000	1.60	
Kasai 2003A	-26.300	2.065	4.263	-30.347	-22.253	-12.738	0.000	1.88	
Tonstad 2002C	-23.980	2.368	5.605	-28.620	-19.340	-10.129	0.000	1.86	
Tonstad 2002A	-23.970	2.078	4.317	-28.042	-19.898	-11.536	0.000	1.88	
Stendell-Hollis 2010B	-23.200	6.980	48.720	-36.880	-9.520	-3.324	0.001	1.29	
Tanumihardjo 2009B	-20.110	3.926	15.411	-27.804	-12.416	-5.123	0.000	1.69	
Santo 2008A	-17.400	7.195	51.768	-31.502	-3.298	-2.418	0.016	1.26	
Tanumihardjo 2009A	-17.020	3.842	14.765	-24.551	-9.489	-4.429	0.000	1.70	
Gardner 2007C	-14.580	2.760	7.616	-19.989	-9.171	-5.283	0.000	1.82	
Mensink 2002B	-13.930	2.564	6.574	-18.955	-8.905	-5.433	0.000	1.84	
Gardner 2007D	-13.200	2.738	7.494	-18.565	-7.835	-4.822	0.000	1.82	
Melanson 2004	-13.200	4.172	17.408	-21.378	-5.022	-3.164	0.002	1.66	
Polagruto 2006A	-12.500	2.321	5.386	-17.049	-7.951	-5.386	0.000	1.86	
Tonstad 2002D	-12.370	1.739	3.023	-15.778	-8.962	-7.115	0.000	1.91	
Stendell-Hollis 2010A	-11.600	3.672	13.482	-18.797	-4.403	-3.159	0.002	1.72	
Schwab 2002A	-11.600	3.231	10.438	-17.932	-5.268	-3.590	0.000	1.77	
Schwab 2006A	-11.220	3.768	14.197	-18.605	-3.835	-2.978	0.003	1.71	
Esposito 2004A	-11.000	1.597	2.550	-14.130	-7.870	-6.889	0.000	1.92	
Esposito 2004	-11.000	2.015	4.059	-14.949	-7.051	-5.460	0.000	1.89	
Tonstad 2002B	-7.730	2.058	4.234	-11.763	-3.697	-3.757	0.000	1.88	
Tighe 2010A	-7.350	2.222	4.935	-11.704	-2.996	-3.309	0.001	1.87	
Schwab 2006C	-6.570	4.606	21.216	-15.598	2.458	-1.426	0.154	1.60	
Schwab 2006B	-6.190	3.198	10.224	-12.457	0.077	-1.936	0.053	1.77	
Diaz 2008B	-6.190	5.421	29.391	-16.816	4.436	-1.142	0.254	1.49	
Hjerkinn 2005	-3.870	1.218	1.483	-6.257	-1.483	-3.178	0.001	1.94	
Kelley 2007B	-3.480	4.120	16.975	-11.555	4.595	-0.845	0.398	1.66	
Price 2010B	-2.710	3.121	9.743	-8.828	3.408	-0.868	0.385	1.78	
Smith 2008B	-2.700	2.176	4.734	-6.964	1.564	-1.241	0.215	1.87	
Szapary 2003	-2.450	2.138	4.572	-6.641	1.741	-1.146	0.252	1.88	
Gylling 2010A	-2.320	2.214	4.902	-6.659	2.019	-1.048	0.295	1.87	
Esposito 2004B	-2.000	1.502	2.256	-4.944	0.944	-1.331	0.183	1.92	
Kasim-Karakas 2009B	-2.000	0.864	0.747	-3.694	-0.306	-2.314	0.021	1.95	
Price 2010A	-1.930	2.820	7.951	-7.457	3.597	-0.684	0.494	1.81	
Tighe 2010C	-1.930	2.011	4.044	-5.872	2.012	-0.960	0.337	1.89	
Han 2007B	-1.160	5.116	26.176	-11.188	8.868	-0.227	0.821	1.53	
Polagruto 2006B	-0.400	2.550	6.500	-5.397	4.597	-0.157	0.875	1.84	
Fakhrzadeh 2010	-0.300	2.765	7.648	-5.720	5.120	-0.108	0.914	1.82	
Adler 1997	-0.200	3.200	10.240	-6.472	6.072	-0.062	0.950	1.77	
Santo 2008B	0.100	6.351	40.339	-12.348	12.548	0.016	0.987	1.37	
Smith 2008A	0.300	2.047	4.191	-3.712	4.312	0.147	0.883	1.88	
Kawashima 2008A	0.780	1.230	1.512	-1.630	3.190	0.634	0.526	1.94	
Levin 1990	2.000	2.671	7.133	-3.235	7.235	0.749	0.454	1.83	
Mensink 2002A	2.700	2.589	6.703	-2.374	7.774	1.043	0.297	1.84	
Kawashima 2008B	2.710	1.156	1.337	0.444	4.976	2.344	0.019	1.94	
Schwab 2002B	3.860	4.084	16.677	-4.144	11.864	0.945	0.345	1.67	
Tapsell 2004A	4.250	4.334	18.780	-4.244	12.744	0.981	0.327	1.63	
Beavers 2010A	4.380	3.975	15.797	-3.410	12.170	1.102	0.270	1.68	
Assuncao 2009B	5.600	4.111	16.902	-2.458	13.658	1.362	0.173	1.66	
Hollis 2009C	6.570	2.927	8.567	0.833	12.307	2.245	0.025	1.80	
Dodin 2005B	6.960	1.299	1.688	4.414	9.506	5.357	0.000	1.93	
Tighe 2010B	7.340	2.295	5.269	2.841	11.839	3.198	0.001	1.86	
Tapsell 2004B	9.660	3.895	15.168	2.027	17.293	2.480	0.013	1.69	
Maki 2005B	12.400	2.996	8.979	6.527	18.273	4.138	0.000	1.79	
Assuncao 2009A	19.800	2.923	8.545	14.071	25.529	6.774	0.000	1.80	
Santo 2008C	27.100	11.710	137.132	4.148	50.052	2.314	0.021	0.79	
	-5.843	1.345	1.808	-8.478	-3.207	-4.346	0.000		



AMDRs (% Total Energy): Fat = 20-35%, Protein = 10-35%, Carbohydrate = 45-65%

Figure 16. Subgroup forest plot – AMDR and change in total cholesterol.

Random-effects Meta-Regression (restricted maximum likelihood (REML)) was conducted for change in total cholesterol using the six moderators featured in Table 7, and the proportion of between-study variation explained (adjusted R^2) was 6.74%, but no single moderator achieved significance.

Table 7: Meta-regression table – total cholesterol.						
No of comparisons = 75. Tau-squared estimate ($T^2_{Unexplained}$) = 102.6 (REML method). Adjusted p-value computed with Monte Carlo permutation test (set seed to 916993); permutations = 20,000. I-squared (I^2) = 92.04%. Adjusted R^2 = 6.74%						
	Coefficient	Std. Error	p>|t|	p adjusted	[95% Conf. Interval]	
Pct_male	-6.634226	4.08133	0.109	0.333	-14.77843	1.509901
Age	0.2114119	0.1302328	0.109	0.362	-0.0484636	0.4712874
Duration	-0.0010732	0.0099576	0.914	1.000	-0.0209433	0.0187969
Subjects	0.0287426	0.0483989	0.555	0.978	-0.0678359	0.1253211
Fat_Chg	0.1396597	0.2568899	0.588	0.984	-0.372956	0.6522754
TC_Pre	-0.096824	0.0600403	0.111	0.407	-0.2166326	0.0229846
Constant	6.196045	10.82297	0.569		-15.40087	27.79295
The proportion of between-study variation explained (adjusted R^2) was 6.74%, but no single moderator achieved significance. No covariates met the 0.80 power criterion.						

- 75 comparisons were included in the model, and 20,000 permutations were performed to help eliminate false positives that may arise during analysis of multiple covariates; the adjusted p-values are to be viewed as the “correct” p-values.
    - For change in total cholesterol, there were no differences between the moderators that were “flagged” before and after permutation testing, as none of the moderators demonstrated significance ($p<0.05$)
- The between-trial variance (T^2) was calculated to be 102.6.

- The estimated treatment effect given particular values of the covariates can be derived from the following regression equation:
    - Change in Total Cholesterol = 6. 196045 – 6.63 (% male as decimal) + 0.21 (age in years) – 0.001 (duration of study in days) + 0.03 (number of subjects) + 0.14 (the percent change in total dietary fat) - 0.10 (pre-treatment cholesterol level).

<u>Sensitivity Analyses</u>

- The summary effect using a fixed-effect model was similar to the result reported through random-effects (-5.893mg/dL F.E. versus -6.401mg/dL R.E.), and as expected, its 95% confidence interval was more narrow due to the fewer sources of variation accounted for by the model (-6.411 to -5.375 F.E. versus -8.813 to -3.988 R.E). (See supplemental table S2.)
- The results after the addition of the 23 crossover studies originally excluded from the meta-analysis did not differ substantially with respect to summary effect, statistical significance, or tests of heterogeneity (see Table 8). It should be noted that only the data from the first period of each crossover trial was used in order to minimize unit-of-analysis errors, however this decision may increase bias because reporting of data from solely the first period may be dependent on the researchers having found significant carry-over in their respective study designs.

- Since there were no significant differences between the two options, and the meta-analysis was significantly powered without the crossover trials, their exclusion was appropriate due to the risk of injecting additional biases into the meta-analysis.

Table 8: Sensitivity analysis – effect of crossover trials on change in total cholesterol.
Outcome: Change in Total Cholesterol (mg/dL)
Original Analysis: 42 studies (86 comparisons, 3144 subjects)
With Cross-overs: 65 studies (111 comparisons, 3876 subjects)

Summary Effects (Random Effects Model/Raw Mean Difference)							
Effect size and 95% confidence interval						Test of null (2-Tail)	
ΔTC	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
Original Analysis	-6.401	1.231	1.515	-8.813	-3.988	-5.200	<0.001
With Crossovers	-6.693	1.028	1.056	-8.708	-4.679	-6.512	<0.001

Heterogeneity								
	Q-Statistic			I-Squared	Tau-squared			
ΔTC	Q-value	df (Q)	P-value	I-squared (I^2)	Tau-squared (T^2)	Standard Error	Variance	Tau (T)
Original Analysis	1716.6	85	<0.001	95.0%	117.4	28.205	795.518	10.8
With Cross-overs	2202.2	110	<0.001	95.0%	105.1	26.137	683.150	10.3

- The “one study removed” analysis showed no significant impact of any individual study on the summary effect. (See supplemental figure S6.)

- The use of different pre- and post-treatment correlations when calculating the effect sizes did not impact the summary effect by more than one-tenth of one unit of measurement (mg/dL). It essentially did not matter what value was chosen (from $r = 0.5$ to 0.99), and the results from the Excel's *Correrl* function provided decent approximation. (See supplemental table S3.)
- Sensitivity analyses for publication bias did not conflict with the primary assessment methods:
  - Trim-and-fill also supported asymmetry, imputing 13 studies, which would support a greater decrease in total cholesterol. If asymmetry was due to bias, the analysis suggests that the adjusted effect would be between -11.59 mg/dL to -6.60 mg/dL. (See supplemental figure S2 and supplemental table S1.)
  - The Egger's regression intercept was negative (-0.80460), supporting the notion that smaller studies had larger than average effects; but the p-value was not significant [p= 0.457; 95%CI: -2.94814 to 1.33893)]. (See supplemental table S1)
  - Classic Fail-safe N indicated there would need to be 174 studies with a mean effect of zero before the summary effect became non-significant. (See supplemental table S1.)

LOW-DENSITY LIPOPROTEIN (LDL) CHANGE

As shown in Table 9 below, the studies in the meta-analysis showed a reduction in LDL cholesterol, and the effects of individual studies can be observed in the forest plot in Figure 17. The studies were sorted from greatest reduction in LDL to greatest increase in LDL, with the summary effect of -5.317 mg/dL presented on the bottom line.

Comparisons that reported changes in LDL cholesterol more than the estimated intra-personal variation for the parameter were combined into a separate analysis that can be seen in Figure 19. For the studies that reported a clear decrease in LDL cholesterol, the summary effect was -18.516 mg/dL (95%CI: -21.087 mg/dL to -15.946 mg/dL). There were only five trials that reported a clear increase in LDL cholesterol, and the overall summary effect of both groups combined was -9.021 mg/dL (95%CI: -11.235 mg/dL to -6.806 mg/dL).

Table 9. Summary effect – change in LDL cholesterol
(Random effects model/raw mean difference)
42 studies (86 comparisons, 3144 subjects; Average power of included studies: 0.9981)

	Effect size and 95% confidence interval					Test of null (2-Tail)	
	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
∆LDL (mg/dL)	-5.317	1.093	1.195	-7.460	-3.175	-4.864	<0.001

Study Limitations

Refer to the section related to the study limitations for the overall lipid profile.

Macronutrient Distribution & Change in LDL (mg/dL)

Study name	Macronutrient Distribution (F/P/C)	Statistics for each study								
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
Stendell-Hollis 2010B	28/18/54	-30.940	5.974	35.686	-42.648	-19.232	-5.179	0.000	0.95	
Wardlaw 1991B	39/13/47	-29.000	3.376	11.397	-35.617	-22.383	-8.590	0.000	1.18	
Kasai 2003B	27/15/56	-27.070	2.878	8.282	-32.710	-21.430	-9.407	0.000	1.22	
Tonstad 2002C	29/18/50	-25.910	1.877	3.522	-29.588	-22.232	-13.806	0.000	1.28	
Tonstad 2002A	30/18/47	-23.970	1.751	3.065	-27.402	-20.538	-13.691	0.000	1.28	
Gylling 2010B	31/16/45	-23.200	2.206	4.868	-27.524	-18.876	-10.515	0.000	1.26	
Kasim-Karakas 2009A	26/34/40	-22.600	1.917	3.674	-26.357	-18.843	-11.790	0.000	1.28	
Han 2007A	23/18/59	-22.040	4.123	16.999	-30.121	-13.959	-5.346	0.000	1.12	
Kasai 2003A	27/15/56	-22.040	2.211	4.887	-26.373	-17.707	-9.969	0.000	1.26	
Pins 2006A	34/21/45	-17.600	4.139	17.132	-25.712	-9.488	-4.252	0.000	1.12	
Alhassan 2006	39/17/44	-17.000	3.427	11.745	-23.717	-10.283	-4.961	0.000	1.17	
Wardlaw 1991A	40/13/47	-16.630	3.051	9.311	-22.611	-10.649	-5.450	0.000	1.20	
Esposito 2004	29/16/55	-16.200	2.732	7.462	-21.554	-10.846	-5.931	0.000	1.23	
Stendell-Hollis 2010A	32/16/53	-15.470	4.242	17.991	-23.783	-7.157	-3.647	0.000	1.11	
Tonstad 2002D	31/17/49	-15.080	1.739	3.026	-18.489	-11.671	-8.669	0.000	1.28	
Santo 2008B	24/21/54	-14.800	6.667	44.454	-27.868	-1.732	-2.220	0.026	0.89	
Tanumihardjo 2009B	24/21/55	-14.700	3.273	10.711	-21.114	-8.286	-4.492	0.000	1.19	
Tanumihardjo 2009A	29/17/54	-14.690	3.019	9.116	-20.608	-8.772	-4.865	0.000	1.21	
Wood 2007A	59/27/13	-14.310	3.638	13.235	-21.440	-7.180	-3.934	0.000	1.16	
Santo 2008A	22/20/57	-14.000	5.920	35.052	-25.604	-2.396	-2.365	0.018	0.96	
Schwab 2006A	26/19/53	-13.920	3.090	9.550	-19.977	-7.863	-4.504	0.000	1.20	
Schwab 2002A	27/18/51	-11.600	2.472	6.109	-16.444	-6.756	-4.693	0.000	1.24	
Smith 2003A	40/11/48	-11.600	2.903	8.427	-17.289	-5.911	-3.996	0.000	1.21	
Esposito 2004A	28/14/58	-11.400	2.170	4.707	-15.652	-7.148	-5.255	0.000	1.26	
Polagruto 2006A	34/16/50	-11.300	2.345	5.497	-15.895	-6.705	-4.820	0.000	1.25	
Schwab 2006B	28/19/51	-11.220	3.128	9.783	-17.350	-5.090	-3.587	0.000	1.20	
Tonstad 2002B	31/18/49	-10.440	2.032	4.130	-14.423	-6.457	-5.137	0.000	1.27	
Gardner 2007D	21/17/63	-10.100	1.844	3.401	-13.715	-6.485	-5.477	0.000	1.28	
Smith 2003B	37/11/50	-9.670	2.435	5.929	-14.442	-4.898	-3.971	0.000	1.25	
Mensink 2002B	29/16/53	-9.290	2.918	8.512	-15.008	-3.572	-3.184	0.001	1.21	
Chan 2002B	34/22/40	-9.290	4.118	16.958	-17.361	-1.219	-2.256	0.024	1.12	
Schwab 2006C	28/18/51	-8.900	4.239	17.969	-17.208	-0.592	-2.100	0.036	1.11	
Goyens 2006A	41/13/44	-8.890	4.380	19.184	-17.474	-0.306	-2.030	0.042	1.09	
Tapsell 2004C	32/22/44	-8.500	7.160	51.273	-22.534	5.534	-1.187	0.235	0.85	
Gardner 2007C	30/20/49	-7.300	1.924	3.701	-11.071	-3.529	-3.795	0.000	1.28	
Melanson 2004	28/21/53	-6.600	3.655	13.361	-13.764	0.564	-1.806	0.071	1.16	
Wood 2007B	59/27/13	-6.580	5.537	30.662	-17.433	4.273	-1.188	0.235	0.99	
Tighe 2010A	35/16/47	-6.190	2.013	4.051	-10.135	-2.245	-3.075	0.002	1.27	
Chan 2002A	36/20/38	-5.540	23.518	553.075	-51.634	40.554	-0.236	0.814	0.19	
Malpuech-Brugere 2010B	39/15/45	-5.410	2.826	7.988	-10.950	0.130	-1.914	0.056	1.22	
Smith 2008B	30/16/54	-5.400	2.117	4.483	-9.550	-1.250	-2.550	0.011	1.26	
Gardner 2007B	35/24/42	-5.300	1.952	3.812	-9.127	-1.473	-2.715	0.007	1.27	
Szapary 2003	33/14/52	-4.930	2.645	6.994	-10.113	0.253	-1.864	0.062	1.23	
Levin 1990	26/18/57	-4.000	2.435	5.931	-8.773	0.773	-1.642	0.101	1.25	
Diaz 2008B	27/19/56	-3.870	3.879	15.046	-11.473	3.733	-0.998	0.318	1.14	
Tighe 2010C	35/16/45	-3.870	1.987	3.947	-7.764	0.024	-1.948	0.051	1.27	
Esposito 2004B	30/14/57	-3.200	2.080	4.326	-7.277	0.877	-1.538	0.124	1.27	
Malpuech-Brugere 2010C	39/15/47	-2.710	3.030	9.182	-8.649	3.229	-0.894	0.371	1.20	
Price 2010A	35/18/47	-2.710	2.270	5.155	-7.160	1.740	-1.194	0.233	1.26	
Pins 2006B	35/21/44	-2.500	4.305	18.532	-10.937	5.937	-0.581	0.561	1.10	
Adler 1997	31/17/50	-2.400	1.735	3.011	-5.801	1.001	-1.383	0.167	1.28	
Hjerkinn 2005	28/17/52	-1.890	1.693	2.867	-5.209	1.429	-1.116	0.264	1.29	
Santo 2008C	23/20/57	-1.100	10.876	118.282	-22.416	20.216	-0.101	0.919	0.57	
Kasim-Karakas 2009B	26/17/57	-1.000	0.964	0.930	-2.890	0.890	-1.037	0.300	1.31	
Tapsell 2004A	33/21/43	-0.390	6.474	41.908	-13.078	12.298	-0.060	0.952	0.91	
Kelley 2007B	34/15/50	-0.380	4.236	17.945	-8.683	7.923	-0.090	0.929	1.11	
Polagruto 2006B	31/17/54	-0.300	2.476	6.133	-5.154	4.554	-0.121	0.904	1.24	
Gylling 2010A	42/14/43	0.000	1.646	2.710	-3.227	3.227	0.000	1.000	1.29	
Fakhrzadeh 2010	35/13/53	0.400	1.717	2.947	-2.964	3.764	0.233	0.816	1.29	
Dodin 2005A	35/17/47	0.770	1.397	1.951	-1.968	3.508	0.551	0.581	1.30	
Price 2010B	33/18/47	1.160	2.630	6.919	-3.996	6.316	0.441	0.659	1.23	
Smith 2008A	32/16/52	1.600	2.121	4.499	-2.557	5.757	0.754	0.451	1.26	
Gardner 2007A	55/28/18	2.300	2.062	4.253	-1.742	6.342	1.115	0.265	1.27	
Tighe 2010B	34/17/48	2.320	1.991	3.966	-1.583	6.223	1.165	0.244	1.27	
Mensink 2002A	32/15/50	2.320	3.003	9.018	-3.566	8.206	0.773	0.440	1.21	
Kawashima 2008A	27/14/51	2.700	1.181	1.396	0.384	5.016	2.285	0.022	1.31	
Hollis 2009C	34/16/50	3.090	3.350	11.223	-3.476	9.656	0.922	0.356	1.18	
Maki 2005A	35/16/50	3.400	3.611	13.041	-3.678	10.478	0.941	0.346	1.16	
Han 2007B	28/18/55	3.870	3.838	14.728	-3.652	11.392	1.008	0.313	1.14	
Assuncao 2009B	21/15/64	3.900	4.084	16.677	-4.104	11.904	0.955	0.340	1.12	
Malpuech-Brugere 2010A	38/15/47	4.250	2.574	6.625	-0.795	9.295	1.651	0.099	1.24	
Hollis 2009B	35/16/48	4.640	2.912	8.481	-1.068	10.348	1.593	0.111	1.21	
Beavers 2010A	34/21/47	4.880	3.656	13.365	-2.285	12.045	1.335	0.182	1.16	
Kawashima 2008B	28/14/50	5.020	1.164	1.355	2.739	7.301	4.313	0.000	1.31	
Diaz 2008A	23/16/65	5.030	5.742	32.973	-6.224	16.284	0.876	0.381	0.97	
Dodin 2005B	33/17/50	5.420	1.283	1.645	2.906	7.934	4.226	0.000	1.30	
Tapsell 2004B	33/23/41	5.800	5.490	30.136	-4.959	16.559	1.057	0.291	0.99	
Goyens 2006B	42/14/43	6.190	5.995	35.940	-5.560	17.940	1.033	0.302	0.95	
Hollis 2009A	35/15/50	6.190	2.977	8.864	0.355	12.025	2.079	0.038	1.21	
Beavers 2010B	38/20/47	6.940	4.595	21.115	-2.066	15.946	1.510	0.131	1.08	
Schwab 2002B	27/18/52	7.740	3.964	15.717	-0.030	15.510	1.952	0.051	1.13	
Mutungi 2008B	55/25/20	10.700	5.565	30.972	-0.208	21.608	1.923	0.055	0.99	
Maki 2005B	35/15/52	16.600	2.890	8.349	10.937	22.263	5.745	0.000	1.21	
Mutungi 2008A	56/27/15	16.800	5.558	30.892	5.906	27.694	3.023	0.003	0.99	
Kelley 2007A	36/16/48	18.560	3.686	13.590	11.335	25.785	5.035	0.000	1.15	
Assuncao 2009A	21/15/64	25.500	3.694	13.646	18.260	32.740	6.903	0.000	1.15	
		-5.317	1.093	1.195	-7.460	-3.175	-4.864	0.000		

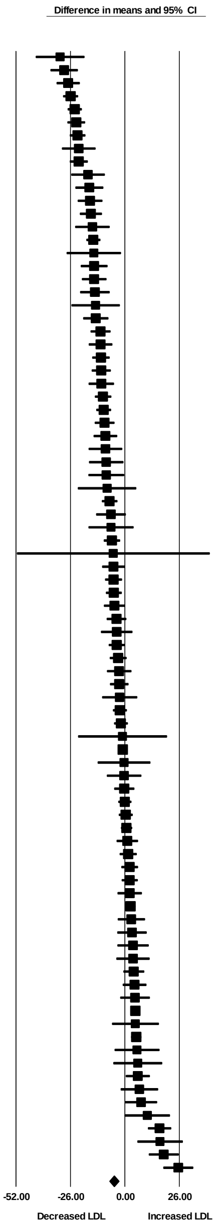


Figure 17. Forest plot – macronutrient distribution and change in LDL cholesterol. 42 studies, 86 comparisons (3144 subjects)
Macronutrient distribution format (% total energy): Fat/Protein/Carbohydrate
(Values may not add up to 100% due to rounding)

<u>Inconsistency</u>

The unexplained heterogeneity and inconsistent results related to the outcome of change in LDL cholesterol were summarized in Table 10.

Table 10: Heterogeneity table – change in LDL cholesterol.
42 Studies (86 comparisons, 3144 subjects)

	Heterogeneity							
	Q-Statistic			I-Squared	Tau-squared			
	Q	df (Q)	P-value	I^2	T^2	Standard Error	Variance	Tau (T)
ΔLDL	1365.779	85	<0.001	93.776%	90.010	20.221	408.902	9.487

- For change in LDL cholesterol, the effect sizes varied widely across the studies, and there were inconsistent results for both large and small studies; some reported decreases in LDL cholesterol and some reported increases in comparable magnitudes.
    - The confidence intervals for the various studies did not overlap significantly. (See supplemental figure S11.)
- The p-value associated with the Q-statistic was <0.001, suggesting the studies did not share a common effect size.
- The Q-statistic was larger than the degrees of freedom (Q>df), indicating that additional evidence from an increasing number of studies would only strengthen the case that the excess dispersion is not zero, thus further supporting no common effect size.

- The value of I^2 was 93.776% indicating nearly all of the variation is real, and strongly supported subgroup analysis and/or meta-regression.
- Tau-squared (T^2) was calculated as 90.010, and reflected the estimated between-study variance of the true effects. The positive nature of the result was based on the amount of excess variation (Q-df >0) and the metric of the effect size.
- The estimated standard deviation of the true effect size, Tau (T), was 9.487. This value can be used to predict, with 95% accuracy, where a new study would fit in the meta-analysis.
  - The 95% prediction interval was calculated as (-24.308 mg/dL to 13.674 mg/dL).
- 22.4% of the unexplained between-study variance (R^2) could be explained by the covariates in the meta-regression.
  - Pre-treatment LDL in mg/dL was the covariate shown to significantly moderate change in LDL. (To see a bubble plot of this moderator, see supplemental figure S25.)

For change in LDL cholesterol, the confidence intervals did not overlap, but the studies included in this meta-analysis met three of the four assessment criteria for inconsistency in results: the magnitude of the treatment effects varied widely across studies, the statistical tests for heterogeneity rejected the null hypothesis that the studies share a common treatment effect, and the I^2 test quantified that nearly all the heterogeneity was real.[70] Subgroup analyses and meta-regression failed to identify more than one-quarter of the heterogeneity, and so the quality assessment of the evidence related to inconsistency was therefore deemed: "Very Serious, downgrade two levels".

Indirectness (Differences in Populations)

- Only subjects and interventions meeting the eligibility criteria were included in the systematic review, so evidence regarding them was direct by nature.[71]
- A direct LDL assay uses detergents and other chemicals to either block or solubilize specific lipoprotein classes to achieve specificity for LDL. LDL is then measured enzymatically using methods similar to those described for total cholesterol.[144]
    - Since the concentration of cholesterol is directly proportional to the measured color intensity, even a "direct" measurement of LDL could technically be considered an indirect approach; however the consistent and widespread application of this technique will not be justification for rating down the evidence, as the method isn't considered a substitute or surrogate endpoint.
- If total cholesterol, HDL, and triglycerides are all measured, the Friedewald equation (LDL = Total cholesterol – HDL cholesterol – [Triglycerides/5]) can be used to estimate LDL, although the reliability of this formula decreases with triglyceride concentrations above 221 mg/dL and disappears at 400 mg/dL.[145]
    - (For triglyceride levels between 221-400mg/dL, another formula could be used: LDL = Total cholesterol – HDL cholesterol – (0.16) Triglycerides.)[145]

  - There were two studies that reported mean triglyceride levels above 220 mg/dL: Chan, 2002 and Kelly, 2007; the maximum triglyceride reported was 265.5 mg/dL. Kelly, 2007 utilized NMR to directly measure the LDL, whereas Chan, 2002 used the Friedewald equation.
  - The LDL level was corrected for the elevated triglycerides for the study Chan, 2002, and this had the effect of substantially increasing the standard deviation of LDL, since the triglycerides had a reported standard deviation of ±425.16. (The Friedewald equation should have reported a similar standard deviation.)
- Most of the forty-two studies included the meta-analysis estimated LDL via the Friedewald equation (twenty-two studies reported using this calculation and three had it calculated by the systematic reviewer).
  - Four studies measured LDL directly through enzymatic methods, one used electrophoresis, one used NMR, and two used ultracentrifugation.
  - Nine studies did not specify the method used.

The differences between the methods used to measure LDL in the meta-analysis are worth mentioning. The Friedewald equation tends to underestimate LDL if the analyzed specimen was not from a subject who fasted a minimum of 8 hours, and optimally >12 hours.[145] One of the major disadvantages of calculating LDL is the variation seen in routine clinical laboratories. Many clinical trials send their blood chemistry samples to a local laboratory, perhaps at an area hospital, but the relative standard deviation in a routine lab can be as high as 12%, as opposed 4% in a certified reference lab. That means that any LDL calculations based on such varied analyses are going to be even more varied, especially compared to LDL results obtained from reliable methods to measure the parameter directly.[145] The Friedewald equation itself is relatively reliable compared to the accepted reference method (i.e. ß-quantification method), producing 86-92% agreement in subjects with fasting triglycerides <200mg/dL,[145] but the agreement decreases to 75% when fasting triglycerides are between 201-300mg/dL.

These issues will not significantly impact the results of this meta-analysis, since only five comparisons had pre-treatment triglycerides above 200mg/dL, and only two with values over 220mg/dL. This may be an area of concern for researchers wishing to study dyslipidemic individuals. Since there were no serious differences in the population or the methodology, quality assessment of the evidence related to indirectness was: "No serious limitations, do not downgrade".

Imprecision

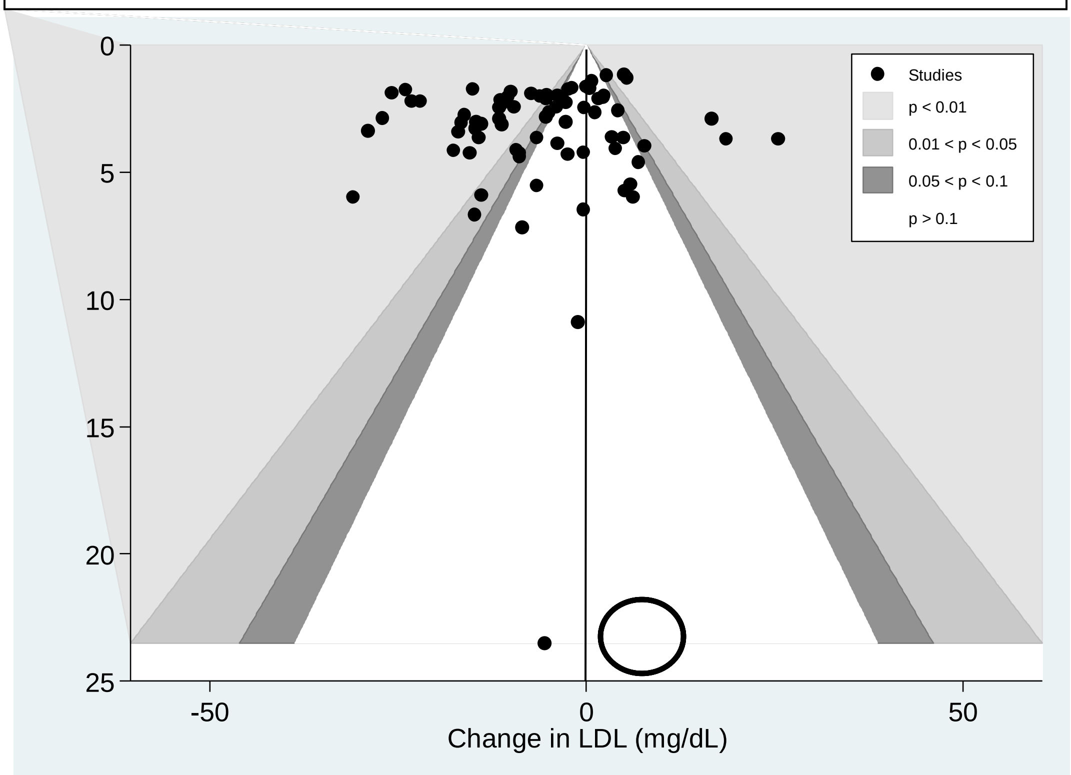
- Since LDL was usually calculated from the other three lipid profile parameters, the 3144 subjects in the meta-analysis should be adequate for the OIS criterion, since it was adequate for total cholesterol, HDL, and triglycerides.
- Comparing the lower and upper boundaries for the 95% CI (-7.460 to -3.175) would not have changed the recommendation of the summary effect, since they both indicate a decrease in the change of LDL cholesterol.

The quality assessment of the evidence related to imprecision was therefore deemed: "Not serious, do not downgrade".

Publication Bias

- Visual inspection of the contour enhanced funnel plot indicated asymmetry, but the horizontal scatter suggested heterogeneity may be a possible source, since bias from small studies would be shown towards the bottom of the funnel. There was one spot where a study may have been missing, indicated by the ring in Figure 18, but this area would likely constitute a treatment effect that was not clinically significant.

Figure 18. Contour funnel plot – change in LDL cholesterol.



- A precision-focused cumulative meta-analysis did not indicate a substantial shift in the point estimate due to large effects from small studies. (See supplemental figure S9.)
- There may have been some potential time-lag bias, as indicated by continuously diminishing point estimates on the cumulative display sorted by publication year. The point estimate (change in LDL cholesterol) ranged from -12.426 mg/dL in the year 2002 to -5.317 mg/dL in 2010. (See supplemental figure S10.)

<u>Subgroup Analysis/Meta-Regression</u>

Referring to Figure 11, reported impacts beyond intra-personal variation were:

- An overall decrease in LDL cholesterol of -9.02 mg/dL (95%CI: -11.235 to -6.806), p(Q)<0.001, I^2= 95%.
  - The overall estimate included twenty-three comparisons that decreased LDL cholesterol, with a summary effect of -18.52 mg/dL (95%CI: -21.087 to -15.946).
  - The average macronutrient distribution of these studies was calculated to be 31% fat, 18% protein, 51% carbohydrate, and was within the AMDRs, although wide variations were noted.

- This overall estimate also included five studies that raised LDL cholesterol (MD: +18.33 mg/dL, 95%CI: 13.966 to 22.692).
    - The average macronutrient distribution of these five studies was calculated to be 41% fat, 20% protein, 39% carbohydrate, and compared to the AMDRs would be categorized as high-fat, low-carbohydrate (HF/MP/LC), although wide variations were noted.

Macronutrient Distribution Impact & Change in LDL (mg/dL)

Group by Comparison	Study name	Macronutrient Distribution (F/P/C)	Impact on LDL	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Decreased	Stendell-Hollis 2010B	28/18/54 - AMDR	Decreased	-30.940	5.974	35.686	-42.648	-19.232	-5.179	0.000
Decreased	Wardlaw 1991B	39/13/47 - HF/MP/MC	Decreased	-29.000	3.376	11.397	-35.617	-22.383	-8.590	0.000
Decreased	Kasai 2003B	27/15/56 - AMDR	Decreased	-27.070	2.878	8.282	-32.710	-21.430	-9.407	0.000
Decreased	Tonstad 2002C	29/18/50 - AMDR	Decreased	-25.910	1.877	3.522	-29.588	-22.232	-13.806	0.000
Decreased	Tonstad 2002A	30/18/47 - AMDR	Decreased	-23.970	1.751	3.065	-27.402	-20.538	-13.691	0.000
Decreased	Gylling 2010B	31/16/45 - AMDR	Decreased	-23.200	2.206	4.868	-27.524	-18.876	-10.515	0.000
Decreased	Kasim-Karakas 2009A	26/34/40 - MF/MP/LC	Decreased	-22.600	1.917	3.674	-26.357	-18.843	-11.790	0.000
Decreased	Han 2007A	23/18/59 - AMDR	Decreased	-22.040	4.123	16.999	-30.121	-13.959	-5.346	0.000
Decreased	Kasai 2003A	27/15/56 - AMDR	Decreased	-22.040	2.211	4.887	-26.373	-17.707	-9.969	0.000
Decreased	Alhassan 2006	39/17/44 - HF/MP/LC	Decreased	-17.000	3.427	11.745	-23.717	-10.283	-4.961	0.000
Decreased	Wardlaw 1991A	40/13/47 - HF/MP/MC	Decreased	-16.630	3.051	9.311	-22.611	-10.649	-5.450	0.000
Decreased	Esposito 2004	29/16/55 - AMDR	Decreased	-16.200	2.732	7.462	-21.554	-10.846	-5.931	0.000
Decreased	Stendell-Hollis 2010A	32/16/53 - AMDR	Decreased	-15.470	4.242	17.991	-23.783	-7.157	-3.647	0.000
Decreased	Santo 2008B	24/21/54 - AMDR	Decreased	-14.800	6.667	44.454	-27.868	-1.732	-2.220	0.026
Decreased	Tanumihardjo 2009B	24/21/55 - AMDR	Decreased	-14.700	3.273	10.711	-21.114	-8.286	-4.492	0.000
Decreased	Tanumihardjo 2009A	29/17/54 - AMDR	Decreased	-14.690	3.019	9.116	-20.608	-8.772	-4.865	0.000
Decreased	Wood 2007A	59/27/13 - HF/MP/LC	Decreased	-14.310	3.638	13.235	-21.440	-7.180	-3.934	0.000
Decreased	Santo 2008A	22/20/57 - AMDR	Decreased	-14.000	5.920	35.052	-25.604	-2.396	-2.365	0.018
Decreased	Schwab 2006A	26/19/53 - AMDR	Decreased	-13.920	3.090	9.550	-19.977	-7.863	-4.504	0.000
Decreased	Smith 2003A	40/11/48 - HF/MP/MC	Decreased	-11.600	2.903	8.427	-17.289	-5.911	-3.996	0.000
Decreased	Esposito 2004A	28/14/58 - AMDR	Decreased	-11.400	2.170	4.707	-15.652	-7.148	-5.255	0.000
Decreased	Smith 2003B	37/11/50 - HF/MP/MC	Decreased	-9.670	2.435	5.929	-14.442	-4.898	-3.971	0.000
Decreased	Tapsell 2004C	32/22/44 - MF/MP/LC	Decreased	-8.500	7.160	51.273	-22.534	5.534	-1.187	0.235
Decreased				-18.516	1.312	1.720	-21.087	-15.946	-14.118	0.000
Increased	Mutungi 2008B	55/25/20 - HF/MP/LC	Increased	10.700	5.565	30.972	-0.208	21.608	1.923	0.055
Increased	Maki 2005B	35/15/52 - AMDR	Increased	16.600	2.890	8.349	10.937	22.263	5.745	0.000
Increased	Mutungi 2008A	56/27/15 - HF/MP/LC	Increased	16.800	5.558	30.892	5.906	27.694	3.023	0.003
Increased	Kelley 2007A	36/16/48 - HF/MP/MC	Increased	18.560	3.686	13.590	11.335	25.785	5.035	0.000
Increased	Assuncao 2009A	21/15/64 - AMDR	Increased	25.500	3.694	13.646	18.260	32.740	6.903	0.000
Increased				18.329	2.226	4.955	13.966	22.692	8.235	0.000
Overall				-9.021	1.130	1.277	-11.235	-6.806	-7.983	0.000

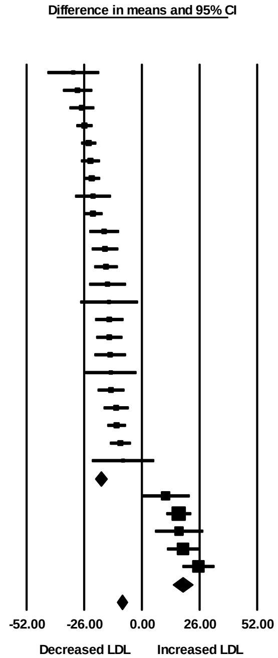


Figure 19. Forest plot – macronutrient distribution and change in LDL cholesterol (effects beyond intra-personal variation). [Q=203.390, df=1, p<0.001]
Macronutrient distribution format (% total energy): Fat/Protein/Carbohydrate
<u>Definitions & Abbreviations:</u> Decreased LDL: >5mg/dL reduction; AMDR: Acceptable Macronutrient Distribution Ranges, HF: High-Fat, MP: Moderate-Protein, LC: Low-Carbohydrate, MF: Moderate-Fat, HC: High-Carbohydrate, LC: Low-Carbohydrate, HC: High-Carbohydrate, MC: Moderate-Carbohydrate.
Ranking of dietary profiles: Low < AMDR (Moderate) < High

Change in Total Fat (Subgroups) & Change in LDL (mg/dL)

Subgroup	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
Decreased Fat	9	-13.019	1.851	3.426	-16.647	-9.391
Fixed Fat	68	-5.065	1.218	1.484	-7.452	-2.678
Increased Fat	9	1.195	3.093	9.567	-4.867	7.257
		-5.962	3.503	12.273	-12.829	0.904

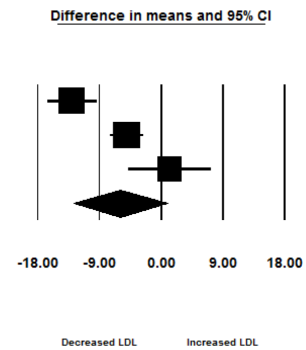


Figure 20. Subgroup forest plot – change in fat and change in LDL cholesterol.

- Comparisons that decreased fat (more than a 3.5%) showed a significant decrease in LDL concentrations beyond what could be explained by intra-personal variation: raw mean difference was -13.019 mg/dL, with a 95% CI of -16.646 mg/dL to -9.391 mg/dL.
    - The small number of comparisons and wider confidence interval require more studies in this subgroup before definitive conclusions can be made.
    - The true difference between the decreased fat subgroup and those comparisons categorized as fixed probably falls within this range for LDL (95% confidence interval): 3.61 mg/dL to 12.3 mg/dL. (See supplemental table S16.)
- Comparisons that increased fat did not show a clear effect on change in LDL, because while the summary effect supports the notion that the trials that increased fat increased LDL concentrations by 1.195 mg/dL, the confidence interval was sufficiently wide and crosses the null (95% CI: -4.866 mg/dL to 7.257 mg/dL).

- The true difference between the increased fat subgroup and those comparisons categorized as fixed probably falls within this range for LDL (95% confidence interval): -0.25 mg/dL to 12.8 mg/dL. (See supplemental table S16.)
- The true difference between the increased fat and decreased fat subgroups probably falls within this range for LDL (95% confidence interval): 7.1 mg/dL to 21.3 mg/dL. (See supplemental table S16.)

Change in Total Protein (Subgroups) & Change in LDL (mg/dL)

Subgroup	Observations	Statistics for each study				
		Difference in means	Standard error	Variance	Lower limit	Upper limit
Fixed Protein	73	-5.388	1.168	1.364	-7.677	-3.099
Increased Protein	13	-4.758	3.261	10.634	-11.149	1.633
		-5.316	1.100	1.209	-7.472	-3.161

Difference in means and 95% CI

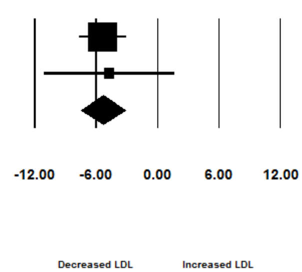


Figure 21. Subgroup forest plot – change in protein and change in LDL cholesterol

- Comparisons that increased protein (more than 3.5%) did not show a clear effect on LDL concentrations beyond intra-personal variation. This subgroup reported a decrease in the treatment effect (change in LDL) of -4.759 mg/dL, but there were few comparisons contained in the subgroup (325 subjects), the confidence interval was sufficiently wide (-11.150 mg/dL to 1.632 mg/dL), and it included the null.

- The true difference between the increased protein subgroup and those comparisons categorized as fixed probably falls within this range for LDL (95% confidence interval): -6.2 mg/dL to 7.5 mg/dL. (See supplemental table S16.)

Change in Total Carbohydrate (Subgroups) & Change in LDL (mg/dL)

Subgroup	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
		Statistics for each study				
Decreased Carb	11	-2.413	4.684	21.940	-11.593	6.767
Fixed Carb	65	-4.886	1.187	1.409	-7.212	-2.560
Increased Carb	10	-10.652	2.731	7.458	-16.005	-5.299
		-6.301	2.164	4.683	-10.542	-2.059

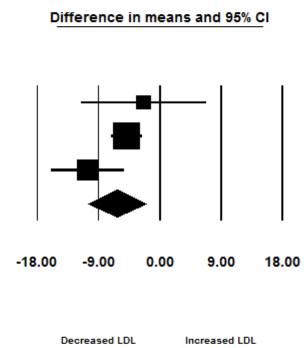


Figure 22. Subgroup forest plot – change in carbohydrate and change in LDL cholesterol.

- Comparisons that decreased carbohydrate (more than 3.5%) did not show a clear effect on LDL concentrations. This subgroup reported a decrease in the treatment effect (change in LDL) of -2.413 mg/dL, but there were few comparisons in the subgroup (310 subjects), the confidence interval was sufficiently wide (95%CI: -11.595 mg/dL to 6.768 mg/dL), and it included the null.

    - The true difference between the decreased carbohydrate subgroup and those comparisons categorized as fixed probably falls within this range for LDL (95% confidence interval): -11.9 mg/dL to 7.0 mg/dL. (See supplemental table S16.)

- The subgroup that increased carbohydrate (more than 3.5%) reported a decrease in LDL (-10.652 mg/dL) that approached clinical significance. Again, the small number of comparisons (277 subjects), requires caution when interpreting these results, but the confidence interval (95%CI: -16.004 mg/dL to -5.301 mg/dL) did not cross the null.
    - The true difference between the increased carbohydrate subgroup and those comparisons categorized as fixed probably falls within this range for LDL (95% confidence interval): -11.6 mg/dL to 0.07 mg/dL. (See supplemental table S16.)
    - The true difference between the increased carbohydrate and decreased carbohydrate subgroups probably falls within this range for LDL (95% confidence interval): -18.9 mg/dL to 2.4 mg/dL. (See supplemental table S16.)

AMDR (Subgroups) & Change in LDL (mg/dL)

Subgroup	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
AMDR	57	-5.969	1.312	1.721	-8.540	-3.398
HF/MP/LC	10	-2.067	3.531	12.468	-8.988	4.854
HF/MP/MC	13	-2.425	2.894	8.375	-8.097	3.247
MF/LP/LC	1	-9.290	4.118	16.958	-17.361	-1.219
MF/MP/HC	1	5.030	5.842	34.129	-6.420	16.480
MF/MP/LC	4	-13.806	5.453	29.735	-24.494	-3.118
		-4.899	1.767	3.121	-8.361	-1.436

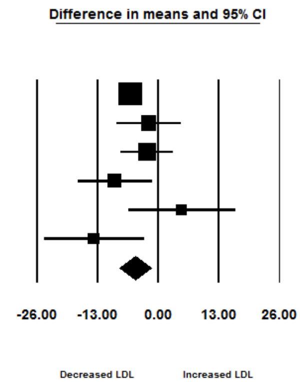


Figure 23. Subgroup forest plot – dietary profiles and change in LDL cholesterol.

Re-categorizing the 86 comparisons into subgroups based on the AMDR qualifications revealed that no studies included in the meta-analysis followed a "low-fat" (LF) intervention, defined as total dietary fat being less than twenty percent of total energy (see Figure 24). Low-carbohydrate groups were also poorly represented in the meta-analysis, so the results from these groups should be interpreted with care. A test for heterogeneity ($Q = 8.693$, $df = 5$, $p = 0.122$) did not reject the possibility that the subgroups related to AMDR could have the same treatment effect between them.

- 66.3% of the comparisons were categorized as being within the AMDRs. This subgroup (2404 subjects) showed a decrease in LDL, with a summary effect of -5.969 mg/dL (95% CI: -8.539 mg/dL to -3.398 mg/dL), but this was not clinically significant.
    - Dietary trials focusing on the AMDRs can be found in Figure 24.

- 11.6% of the comparisons were categorized as “high-fat, low-carbohydrate” diets, and there was no clear effect on LDL concentration. The summary effect was -2.067 mg/dL, but there were few comparisons (206 subjects), and the confidence interval crossed the null.
    - The true difference between the HF/MP/LC subgroup and those comparisons that were within the AMDRs probably falls within this range for LDL (95% confidence interval): -3.5 mg/dL to 11.3 mg/dL. (See supplemental table S16.)

AMDR Fat Percentage & Change in LDL (mg/dL)

Study name	Fat %	Statistics for each study						
		Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Stendell-Hollis 2010B	27.6	-30.940	5.974	35.686	-42.648	-19.232	-5.179	0.000
Kasai 2003B	26.6	-27.070	2.878	8.282	-32.710	-21.430	-9.407	0.000
Tonstad 2002C	28.6	-25.910	1.877	3.522	-29.588	-22.232	-13.806	0.000
Tonstad 2002A	29.6	-23.970	1.751	3.065	-27.402	-20.538	-13.691	0.000
Gylling 2010B	30.9	-23.200	2.206	4.868	-27.524	-18.876	-10.515	0.000
Han 2007A	22.8	-22.040	4.123	16.999	-30.121	-13.959	-5.346	0.000
Kasai 2003A	26.6	-22.040	2.211	4.887	-26.373	-17.707	-9.969	0.000
Esposito 2004	29.0	-16.200	2.732	7.462	-21.554	-10.846	-5.931	0.000
Stendell-Hollis 2010A	32.0	-15.470	4.242	17.991	-23.783	-7.157	-3.647	0.000
Tonstad 2002D	30.8	-15.080	1.739	3.026	-18.489	-11.671	-8.669	0.000
Santo 2008B	23.6	-14.800	6.667	44.454	-27.868	-1.732	-2.220	0.026
Tanumihardjo 2009B	23.7	-14.700	3.273	10.711	-21.114	-8.286	-4.492	0.000
Tanumihardjo 2009A	28.6	-14.690	3.019	9.116	-20.608	-8.772	-4.865	0.000
Santo 2008A	21.5	-14.000	5.920	35.052	-25.604	-2.396	-2.365	0.018
Schwab 2006A	26.3	-13.920	3.090	9.550	-19.977	-7.863	-4.504	0.000
Schwab 2002A	27.4	-11.600	2.472	6.109	-16.444	-6.756	-4.693	0.000
Esposito 2004A	28.0	-11.400	2.170	4.707	-15.652	-7.148	-5.255	0.000
Polagruto 2006A	34.1	-11.300	2.345	5.497	-15.895	-6.705	-4.820	0.000
Schwab 2006B	27.8	-11.220	3.128	9.783	-17.350	-5.090	-3.587	0.000
Tonstad 2002B	30.8	-10.440	2.032	4.130	-14.423	-6.457	-5.137	0.000
Gardner 2007D	21.1	-10.100	1.844	3.401	-13.715	-6.485	-5.477	0.000
Mensink 2002B	29.1	-9.290	2.918	8.512	-15.008	-3.572	-3.184	0.001
Schwab 2006C	28.4	-8.900	4.239	17.969	-17.208	-0.592	-2.100	0.036
Gardner 2007C	30.2	-7.300	1.924	3.701	-11.071	-3.529	-3.795	0.000
Melanson 2004	28.0	-6.600	3.655	13.361	-13.764	0.564	-1.806	0.071
Tighe 2010A	34.6	-6.190	2.013	4.051	-10.135	-2.245	-3.075	0.002
Smith 2008B	29.7	-5.400	2.117	4.483	-9.550	-1.250	-2.550	0.011
Szapary 2003	32.8	-4.930	2.645	6.994	-10.113	0.253	-1.864	0.062
Levin 1990	25.5	-4.000	2.435	5.931	-8.773	0.773	-1.642	0.101
Diaz 2008B	27.2	-3.870	3.879	15.046	-11.473	3.733	-0.998	0.318
Tighe 2010C	34.5	-3.870	1.987	3.947	-7.764	0.024	-1.948	0.051
Esposito 2004B	30.0	-3.200	2.080	4.326	-7.277	0.877	-1.538	0.124
Price 2010A	35.0	-2.710	2.270	5.155	-7.160	1.740	-1.194	0.233
Adler 1997	30.9	-2.400	1.732	3.000	-5.795	0.995	-1.386	0.166
Hjerkinn 2005	27.6	-1.890	1.693	2.867	-5.209	1.429	-1.116	0.264
Santo 2008C	22.6	-1.100	10.876	118.282	-22.416	20.216	-0.101	0.919
Kasim-Karakas 2009B	25.9	-1.000	0.964	0.930	-2.890	0.890	-1.037	0.300
Tapsell 2004A	32.6	-0.390	6.474	41.908	-13.078	12.298	-0.060	0.952
Kelley 2007B	33.8	-0.380	4.236	17.945	-8.683	7.923	-0.090	0.929
Polagruto 2006B	31.1	-0.300	2.476	6.133	-5.154	4.554	-0.121	0.904
Gylling 2010A	32.3	0.000	1.646	2.710	-3.227	3.227	0.000	1.000
Fakhrzadeh 2010	34.5	0.400	1.717	2.947	-2.964	3.764	0.233	0.816
Price 2010B	32.8	1.160	2.630	6.919	-3.996	6.316	0.441	0.659
Smith 2008A	32.3	1.600	2.121	4.499	-2.557	5.757	0.754	0.451
Tighe 2010B	33.8	2.320	1.991	3.966	-1.583	6.223	1.165	0.244
Mensink 2002A	31.7	2.320	3.003	9.018	-3.566	8.206	0.773	0.440
Kawashima 2008A	26.9	2.700	1.181	1.396	0.384	5.016	2.285	0.022
Hollis 2009C	33.7	3.090	3.350	11.223	-3.476	9.656	0.922	0.356
Han 2007B	27.6	3.870	3.838	14.728	-3.652	11.392	1.008	0.313
Assuncao 2009B	21.1	3.900	4.084	16.677	-4.104	11.904	0.955	0.340
Beavers 2010A	34.2	4.880	3.656	13.365	-2.285	12.045	1.335	0.182
Kawashima 2008B	28.4	5.020	1.164	1.355	2.739	7.301	4.313	0.000
Dodin 2005B	32.9	5.420	1.283	1.645	2.906	7.934	4.226	0.000
Tapsell 2004B	32.7	5.800	5.490	30.136	-4.959	16.559	1.057	0.291
Schwab 2002B	27.4	7.740	3.964	15.717	-0.030	15.510	1.952	0.051
Maki 2005B	34.8	16.600	2.890	8.349	10.937	22.263	5.745	0.000
Assuncao 2009A	21.3	25.500	3.694	13.646	18.260	32.740	6.903	0.000
		-5.969	1.312	1.720	-8.539	-3.398	-4.551	0.000

Difference in means and 95% CI

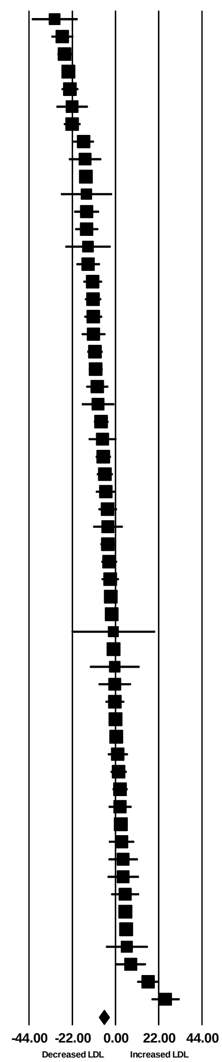


Figure 24. Subgroup forest plot – AMDR and change in LDL cholesterol.

- 15.1% of the comparisons were high fat diets, with their protein and carbohydrate percentages falling in line with the AMDRs. This subgroup had a similar number of comparisons (385 subjects) compared to the “high-fat, low carbohydrate” subgroup, and reported a similar summary effect of -2.425 mg/dL. Like with the previous group, the HF/MP/MC subgroup had a confidence interval that crossed the null (95% CI: -8.098mg/dL to 3.247 mg/dL)
    - The true difference between the HF/MP/MC subgroup and those comparisons that were within the AMDRs probably falls within this range for LDL (95% confidence interval): -2.7 mg/dL to 9.8 mg/dL. (See supplemental table S16.)
    - The true difference between the HF/MP/MC subgroup and those comparisons that were within the HF/MP/MC subgroup probably falls within this range for LDL (95% confidence interval): -9.3 mg/dL to 8.6 mg/dL. (See supplemental table S16.)

Random-effects meta-regression (restricted maximum likelihood (REML)) was conducted for change in LDL cholesterol using the six moderators featured in Table 11, and the proportion of the between-study variation explained (adjusted R^2) was 22.4%, with pre-treatment LDL (LDL_Pre) concentrations being the significant covariate. The between-study variance (T^2) was calculated to be 78.8.

Table 11: Meta-regression table – LDL cholesterol.						
Macronutrient Distribution and Change in LDL (mg/dL) No of comparisons = 75. Tau-squared estimate ($T^2_{Unexplained}$) = 78.8 (REML method). Adjusted p-value computed with Monte Carlo permutation test (set seed to 916993); permutations = 20,000. I-squared (I^2) = 90.9%						
	Coefficient	Std. Error	p>|t|	p adjusted	[95% Conf. Interval]	
Pct_male	-6.63697	3.676357	0.075	0.292	-13.97303	0.6990868
Age	0.2208821	0.1094336	0.047	0.194	0.0025107	0.4392535
Duration	-0.0076928	0.0086999	0.380	0.912	-0.0250532	0.0096676
Subjects	0.0578575	0.0422688	0.176	0.596	-0.0264887	0.1422036
Fat_Chg	0.2149374	0.2235141	0.340	0.856	-0.231078	0.6609528
LDL_Pre*	-0.1641607	0.0546433	0.004	0.014	-0.2731998	-0.055122
Constant	7.594007	6.746033	0.264		-5.867493	21.05551
22.4% of the unexplained between-study variance (R^2) could be explained by: pre-treatment LDL levels in mg/dL. Power of the moderator "LDL_Pre" = 0.8518. *The change in LDL is estimated to decrease by 0.2 mg/dL per unit (mg/dL) increase in pre-treatment LDL.						

- The change in LDL is estimated to decrease by 0.2 mg/dL per unit (mg/dL) increase in pre-treatment LDL.
  - Pre-treatment LDL did meet the 0.80 power criterion (0.8518).
- 75 comparisons were included in the model, and 20,000 permutations were performed to help eliminate false positives that may arise during the analysis of multiple covariates; the adjusted p-values are to be viewed as the "correct" p-values.
  - Before permutation testing, sex (% male), age, and pre-treatment LDL were all "flagged" as demonstrating statistical significance ($p<0.05$).

  - After the permutation test, only pre-treatment levels remained significant, making % male and age false positives.
    - A bubble plot of the pre-treatment LDL moderator can be seen on supplemental figure S25.
- The estimated treatment effect given particular values of the covariates can be derived from the following regression equation:
  - Change in LDL Cholesterol = 7.594007 – 6.64 (% male as decimal) + 0.22 (age in years) – 0.008 (duration of study in days) + 0.06 (number of subjects) + 0.21 (the percent change in total dietary fat) – 0.16 (pre-treatment LDL level)

<u>Sensitivity Analyses</u>

- The summary effect using a fixed-effect model was similar to the result reported through random effects (-4.611 mg/dL F.E. versus -5.237 mg/dL R.E.), and as expected, its 95% confidence interval was more narrow due to the fewer sources of variation accounted for by the model (-5.121 to -4.101 F.E. versus -7.362 to -3.113 R.E). (See supplemental table S5.)
- The results after the addition of the 23 crossover studies originally excluded from the meta-analysis did not differ substantially with respect to summary effect, statistical significance, or tests of heterogeneity (see Table 12). It should be noted that only the data from the first period of each crossover trial was used in order to minimize unit-of-analysis errors, however this decision may increase bias because

reporting of data from solely the first period may be dependent on the researchers having found significant carry-over in their respective study designs.

- Since there were no significant differences between the two options, and the meta-analysis was significantly powered without the crossover trials, their exclusion was appropriate due to the risk of injecting additional biases into the meta-analysis.

Table 12: Sensitivity analysis – effect of crossover trials on change in LDL cholesterol.
Outcome: Change in LDL Cholesterol (mg/dL)
Original Analysis: 42 studies (86 comparisons, 3144 subjects)
With Cross-overs: 65 studies (111 comparisons, 3876 subjects)

Summary Effects (Random Effects Model/Raw Mean Difference)

	Effect size and 95% confidence interval					Test of null (2-Tail)	
ΔLDL	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
Original Analysis	-5.317	1.093	1.195	-7.460	-3.175	-4.864	<0.001
With Crossovers	-5.424	0.874	0.763	-7.137	-3.712	-6.208	<0.001

Heterogeneity

	Q-Statistic			I-Squared	Tau-squared			
ΔLDL	Q	df (Q)	P-value	(I^2)	(T^2)	Standard Error	Variance	Tau (T)
Original Analysis	1365.779	85	<0.001	93.8%	90.010	20.221	408.90	9.487
With Cross-overs	1702.271	110	<0.001	93.5%	74.047	19.969	398.761	8.605

- The “one study removed” analysis showed no significant impact of any individual study on the summary effect. (See supplemental figure S12.)

- The use of different pre- and post-treatment correlations when calculating the effect sizes did not impact the summary effect by more than one-tenth of one unit of measurement (mg/dL). It essentially did not matter what value was chosen (from r = 0.5 to 0.99), and the results from the Excel's *Correrl* function provided decent approximation. (See supplemental table S6.)
- Sensitivity analyses for publication bias did not conflict with the primary assessment methods:
    - Trim and fill also supported asymmetry, imputing 12 studies, which would support a greater decrease in LDL cholesterol. If asymmetry was due to bias, the analysis suggests that the adjusted effect would be between -10.05 mg/dL and -5.56 mg/dL. (See supplemental figure S8 and supplemental table S4.)
    - The Egger's regression intercept was negative (-1.13964), supporting the notion that smaller studies had larger than average effects; the p-value was not significant [p= 0.25953; 95%CI: (-3.13607 to 0.85679)]. (See supplemental table S4.)
    - Classic Fail-safe N indicated there would need to be 7238 studies with a mean effect of zero before the summary effect became non-significant. (See supplemental table S4.)

HIGH-DENSITY LIPOPROTEIN (HDL) CHANGE

As shown in Table 13 below, the studies in the meta-analysis showed a marginal increase in HDL cholesterol, and the effects of individual studies can be observed in the forest plot in Figure 25. The studies were sorted from greatest increase in HDL to greatest decrease in HDL, with the summary effect of +1.137 mg/dL presented on the bottom line.

Observations that reported changes in HDL cholesterol more than the estimated intra-personal variation for the parameter were combined into a separate analysis that can be seen in Figure 27. For the studies that reported a clear increase in HDL cholesterol, the summary effect was +6.775 mg/dL (95%CI: 5.261 mg/dL to 8.289 mg/dL). There were only four trials that reported a clear decrease in HDL cholesterol, and the overall summary effect of both groups combined was +2.163 mg/dL (95%CI: 0.956 mg/dL to -3.371 mg/dL).

Table 13. Summary effect – change in HDL cholesterol.
(Random effects model/raw mean difference)
42 studies (86 observations, 3144 subjects)

Effect size and 95% confidence interval						Test of null (2-Tail)	
	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
ΔHDL (mg/dL)	1.137	0.380	0.144	0.393	1.881	2.994	0.003

Study Limitations

Refer to the section related to the study limitations for the overall lipid profile.

Macronutrient Distribution & Change in HDL (mg/dL)

Study name	Macronutrient Distribution (F/P/C) - Dietary Profile	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
		Statistics for each study						
Santo 2008C	23/20/57 - AMDR	27.300	3.722	13.853	20.005	34.595	7.335	0.000
Santo 2008B	24/21/54 - AMDR	12.700	2.209	4.881	8.370	17.030	5.748	0.000
Mutungi 2008A	56/27/15 - HF/MP/LC	9.500	2.107	4.439	5.371	13.629	4.509	0.000
Esposito 2004	29/16/55 - AMDR	9.000	0.704	0.496	7.620	10.380	12.779	0.000
Tapsell 2004B	33/23/41 - AMDR	8.900	1.109	1.229	6.727	11.073	8.028	0.000
Stendell-Hollis 2010B	28/18/54 - AMDR	7.730	2.090	4.368	3.634	11.826	3.699	0.000
Tapsell 2004C	32/22/44 - MF/MP/LC	7.730	4.191	17.567	-0.485	15.945	1.844	0.065
Wood 2007B	59/27/13 - HF/MP/LC	5.800	1.844	3.400	2.186	9.414	3.145	0.002
Tapsell 2004A	33/21/43 - AMDR	5.420	1.218	1.483	3.033	7.807	4.450	0.000
Tonstad 2002C	29/18/50 - AMDR	4.640	1.310	1.716	2.072	7.208	3.542	0.000
Hjerkinn 2005	28/17/52 - AMDR	4.450	0.541	0.293	3.390	5.510	8.227	0.000
Tonstad 2002B	31/18/49 - AMDR	4.260	1.342	1.801	1.630	6.890	3.174	0.002
Han 2007B	28/18/55 - AMDR	4.250	2.122	4.503	0.091	8.409	2.003	0.045
Esposito 2004A	28/14/58 - AMDR	4.000	0.551	0.303	2.921	5.079	7.265	0.000
Maki 2005B	35/15/52 - AMDR	3.900	0.675	0.456	2.577	5.223	5.778	0.000
Stendell-Hollis 2010A	32/16/53 - AMDR	3.870	1.723	2.968	0.493	7.247	2.246	0.025
Tonstad 2002D	31/17/49 - AMDR	3.860	1.387	1.925	1.141	6.579	2.782	0.005
Wood 2007A	59/27/13 - HF/MP/LC	3.860	1.726	2.977	0.478	7.242	2.237	0.025
Assuncao 2009B	21/15/64 - AMDR	3.200	1.163	1.353	0.920	5.480	2.751	0.006
Kelley 2007A	36/16/48 - HF/MP/MC	3.090	1.415	2.001	0.317	5.863	2.184	0.029
Levin 1990	26/18/57 - AMDR	3.000	1.082	1.172	0.878	5.122	2.771	0.006
Schwab 2006C	28/18/51 - AMDR	2.710	1.081	1.169	0.591	4.829	2.507	0.012
Tonstad 2002A	30/18/47 - AMDR	2.710	1.570	2.466	-0.368	5.788	1.726	0.084
Schwab 2006B	28/19/51 - AMDR	2.700	1.511	2.283	-0.261	5.661	1.787	0.074
Adler 1997	31/17/50 - AMDR	2.300	0.678	0.460	0.971	3.629	3.392	0.001
Maki 2005A	35/16/50 - HF/MP/MC	2.200	0.675	0.455	0.878	3.522	3.262	0.001
Hollis 2009A	35/15/50 - HF/MP/MC	1.940	1.263	1.594	-0.535	4.415	1.536	0.124
Malpuech-Brugere 2010B	39/15/45 - HF/MP/MC	1.930	1.864	3.474	-1.723	5.583	1.036	0.300
Polagruto 2006A	34/16/50 - AMDR	1.900	2.233	4.988	-2.477	6.277	0.851	0.395
Goyens 2006B	42/14/43 - HF/MP/LC	1.540	2.485	6.175	-3.330	6.410	0.620	0.535
Hollis 2009B	35/16/48 - HF/MP/MC	1.540	1.394	1.942	-1.191	4.271	1.105	0.269
Tighe 2010B	34/17/48 - AMDR	1.540	0.969	0.940	-0.360	3.440	1.589	0.112
Szapary 2003	33/14/52 - AMDR	1.430	1.662	2.763	-1.828	4.688	0.860	0.390
Beavers 2010B	38/20/47 - HF/MP/MC	1.320	2.244	5.035	-3.078	5.718	0.588	0.556
Pins 2006A	34/21/45 - MF/MP/LC	1.200	1.353	1.832	-1.453	3.853	0.887	0.375
Dodin 2005B	33/17/50 - AMDR	1.160	0.831	0.690	-0.468	2.788	1.397	0.162
Gylling 2010B	31/16/45 - AMDR	1.160	1.815	3.293	-2.397	4.717	0.639	0.523
Kawashima 2008A	27/14/51 - AMDR	1.160	0.589	0.347	0.005	2.315	1.968	0.049
Kawashima 2008B	28/14/50 - AMDR	1.160	0.533	0.284	0.115	2.205	2.177	0.030
Kelley 2007B	34/15/50 - AMDR	1.160	0.797	0.635	-0.401	2.721	1.456	0.145
Schwab 2006A	26/19/53 - AMDR	1.160	1.405	1.975	-1.595	3.915	0.825	0.409
Pins 2006B	35/21/44 - HF/MP/LC	1.100	1.488	2.214	-1.816	4.016	0.739	0.460
Alhassan 2006	39/17/44 - HF/MP/LC	1.000	1.625	2.641	-2.185	4.185	0.615	0.538
Esposito 2004B	30/14/57 - AMDR	1.000	0.513	0.263	-0.005	2.005	1.951	0.051
Smith 2008B	30/16/54 - AMDR	0.800	0.967	0.934	-1.095	2.695	0.828	0.408
Tighe 2010C	35/16/45 - AMDR	0.770	1.024	1.048	-1.236	2.776	0.752	0.452
Chan 2002B	34/22/40 - MF/LP/LC	0.390	1.297	1.681	-2.151	2.931	0.301	0.764
Malpuech-Brugere 2010A	38/15/47 - HF/MP/MC	0.390	1.595	2.544	-2.736	3.516	0.245	0.807
Price 2010A	35/18/47 - AMDR	0.390	1.193	1.423	-1.948	2.728	0.327	0.744
Wardlaw 1991A	40/13/47 - HF/MP/MC	0.390	1.079	1.163	-1.724	2.504	0.362	0.718
Mensink 2002A	32/15/50 - AMDR	0.380	1.220	1.489	-2.012	2.772	0.311	0.756
Melanson 2004	28/21/53 - AMDR	0.300	1.298	1.686	-2.245	2.845	0.231	0.817
Goyens 2006A	41/13/44 - HF/MP/LC	0.000	3.307	10.937	-6.482	6.482	0.000	1.000
Hollis 2009C	34/16/50 - AMDR	0.000	1.421	2.020	-2.785	2.785	0.000	1.000
Malpuech-Brugere 2010C	39/15/47 - HF/MP/MC	0.000	1.181	1.395	-2.315	2.315	0.000	1.000
Schwab 2002A	27/18/51 - AMDR	0.000	1.435	2.058	-2.812	2.812	0.000	1.000
Schwab 2002B	27/18/52 - AMDR	0.000	1.336	1.786	-2.619	2.619	0.000	1.000
Polagruto 2006B	31/17/54 - AMDR	-0.300	1.574	2.478	-3.385	2.785	-0.191	0.849
Beavers 2010A	34/21/47 - AMDR	-0.370	1.736	3.015	-3.773	3.033	-0.213	0.831
Gylling 2010A	42/14/43 - AMDR	-0.380	2.229	4.969	-4.749	3.989	-0.170	0.865
Gardner 2007A	55/28/18 - HF/MP/LC	-0.400	0.949	0.901	-2.261	1.461	-0.421	0.674
Gardner 2007B	35/24/42 - MF/MP/LC	-0.500	0.722	0.521	-1.915	0.915	-0.692	0.489
Mensink 2002B	29/16/53 - AMDR	-0.770	1.332	1.774	-3.380	1.840	-0.578	0.563
Chan 2002A	36/20/38 - HF/MP/LC	-0.780	1.275	1.627	-3.280	1.720	-0.612	0.541
Tighe 2010A	35/16/47 - AMDR	-0.780	1.132	1.282	-2.999	1.439	-0.689	0.491
Kasim-Karakas 2009B	26/17/57 - AMDR	-1.000	0.349	0.122	-1.684	-0.316	-2.865	0.004
Smith 2008A	32/16/52 - AMDR	-1.000	1.128	1.272	-3.210	1.210	-0.887	0.375
Price 2010B	33/18/47 - AMDR	-1.160	1.057	1.117	-3.231	0.911	-1.098	0.272
Wardlaw 1991B	39/13/47 - HF/MP/MC	-1.160	0.836	0.699	-2.799	0.479	-1.387	0.165
Mutungi 2008B	55/25/20 - HF/MP/LC	-1.200	1.407	1.980	-3.958	1.558	-0.853	0.394
Dodin 2005A	35/17/47 - HF/MP/MC	-1.540	0.775	0.600	-3.058	-0.022	-1.988	0.047
Kasai 2003B	27/15/56 - AMDR	-1.550	1.027	1.055	-3.564	0.464	-1.509	0.131
Diaz 2008A	23/16/65 - MF/MP/HC	-1.930	3.517	12.370	-8.823	4.963	-0.549	0.583
Tanumihardjo 2009B	24/21/55 - AMDR	-1.930	1.468	2.155	-4.807	0.947	-1.315	0.189
Diaz 2008B	27/19/56 - AMDR	-1.940	1.918	3.678	-5.699	1.819	-1.012	0.312
Santo 2008A	22/20/57 - AMDR	-2.000	2.983	8.896	-7.846	3.846	-0.671	0.503
Kasai 2003A	27/15/56 - AMDR	-2.320	1.257	1.581	-4.784	0.144	-1.845	0.065
Tanumihardjo 2009A	29/17/54 - AMDR	-2.320	1.723	2.969	-5.697	1.057	-1.346	0.178
Fakhrzadeh 2010	35/13/53 - AMDR	-2.500	0.667	0.445	-3.808	-1.192	-3.746	0.000
Smith 2003A	40/11/48 - HF/MP/MC	-3.090	1.360	1.850	-5.756	-0.424	-2.272	0.023
Smith 2003B	37/11/50 - HF/MP/MC	-3.480	1.386	1.920	-6.196	-0.764	-2.511	0.012
Gardner 2007C	30/20/49 - AMDR	-3.800	0.738	0.545	-5.247	-2.353	-5.149	0.000
Kasim-Karakas 2009A	26/34/40 - MF/MP/LC	-4.000	0.326	0.106	-4.639	-3.361	-12.275	0.000
Gardner 2007D	21/17/63 - AMDR	-5.300	0.857	0.735	-6.980	-3.620	-6.183	0.000
Assuncao 2009A	21/15/64 - AMDR	-6.500	1.336	1.786	-9.119	-3.881	-4.864	0.000
Han 2007A	23/18/59 - AMDR	-8.890	1.308	1.712	-11.455	-6.325	-6.794	0.000
		1.137	0.380	0.144	0.393	1.881	2.994	0.003

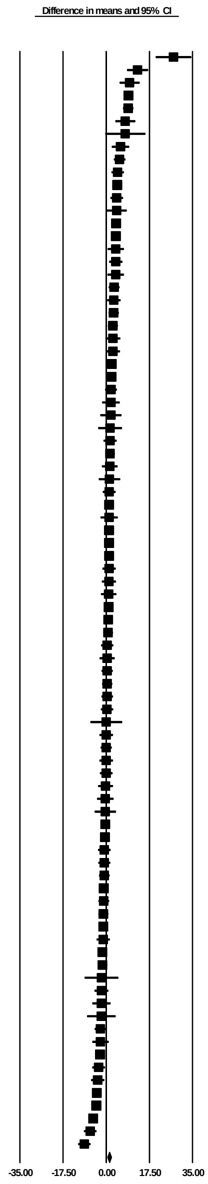


Figure 25. Forest plot – macronutrient distribution and change in HDL cholesterol.
86 observations (3144 subjects)
Macronutrient distribution format (% total energy): Fat/Protein/Carbohydrate
(Values may not add up to 100% due to rounding)

<u>Inconsistency</u>

The unexplained heterogeneity and inconsistent results related to the outcome of change in HDL cholesterol were summarized in Table 14.

Table 14. Heterogeneity table – change in HDL cholesterol.
42 Studies (86 observations, 3144 subjects)

	Heterogeneity							
	Q-Statistic			I-Squared	Tau-squared			
	Q	df (Q)	p-value	I^2	T^2	Standard Error	Variance	Tau (T)
ΔHDL	987.360	85	<0.001	91.391%	10.313	2.724	7.423	3.211

- The changes in HDL tended to be smaller than the other parameters, but the treatment effects and conclusions still varied widely for both small and large trials; some studies reported decreases in HDL cholesterol and others reported increases in comparable magnitudes.
    - The confidence intervals for the various studies showed minimal overlap. (See supplemental figure S17.)
- The p-value associated with the Q-statistic was <0.001, suggesting the studies did not share a common effect size.
- The Q-statistic was larger than the degrees of freedom (Q>df), indicating that additional evidence from an increasing number of studies would only strengthen the case that the excess dispersion is not zero, thus further supporting no common effect size.

- The value of I^2 was 91.391%, indicating nearly all of the variation is real, and strongly supported subgroup analysis and/or meta-regression.
- Tau-squared (T^2) was calculated as 10.313, and reflected the estimated between-study variance of the true effects. The positive nature of the result was based on the amount of excess variation (Q-df >0) and the metric of the effect size.
- The estimated standard deviation of the true effect size, Tau (T), was 3.211. This value can be used to predict, with 95% accuracy, where a new study would fit in the meta-analysis.
    - The 95% prediction interval was calculated as (-5.294 mg/dL to 7.568 mg/dL).
- 39.5% of the unexplained between-study variance (R^2) could be explained by the covariates in the meta-regression.
    - Study duration was the covariate shown to significantly moderate change in HDL.

For change in HDL cholesterol, there was a small number of overlapping confidence intervals, and the treatment effect varied widely across studies. In addition, the statistical tests for heterogeneity rejected the null hypothesis that the studies share a common treatment effect, and the I^2 test quantified that nearly all the heterogeneity was real. Subgroup analyses and meta-regression managed to identify and explain nearly 40% of the variation, and so the quality of the assessment of the evidence related to inconsistency was therefore deemed: “Serious, downgrade one level”.

<u>Indirectness (Differences in Populations)</u>

- Only subjects and interventions meeting the eligibility criteria were included in the systematic review, so evidence regarding them was direct by nature.
- To measure HDL cholesterol, the apoB-containing lipoproteins (including chylomicrons and HDL) in the serum or plasma are introduced to a blocking agent that makes them non-reactive with the enzymatic conditions seen in the total cholesterol assay. With the apoB effectively excluded from analysis, only the HDL cholesterol is detected.
    - Even though the amount of HDL is being measured more directly, the concentration is still directly proportional to the color intensity (absorbance is at 600nm) produced by the reaction during the assay, however the consistent and widespread application of this technique will not be justification for rating down the evidence, as the method isn't considered a substitute or surrogate endpoint.

Since there were no serious differences in the population or the methodology, quality assessment of the evidence related to indirectness was: "No serious limitations, do not downgrade".

<u>Imprecision</u>

For change in HDL cholesterol, a conservative estimate of the optimal information size (OIS) was calculated: the significance (α) was set at 0.05, the power (1-ß) was 0.90, the Δ was set at 1mg/dL, and the standard deviation of the effect was ±13.

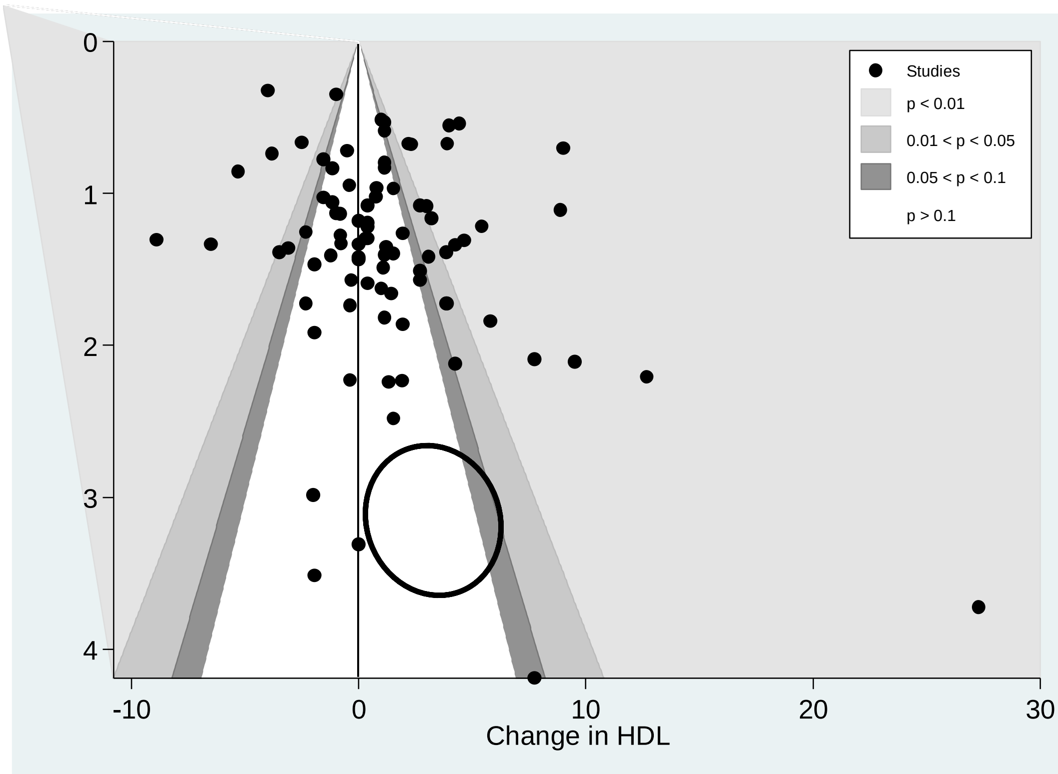
- The OIS was calculated to be 2517 subjects, and the number of subjects in the meta-analysis was 3144, meeting the OIS criterion (OIS< number of studies in systematic review/meta-analysis).
- Comparing the lower and upper boundaries for the 95% CI (+0.393 mg/dL to +1.881 mg/dL) would not have changed the recommendation of the summary effect, since they both indicate an increase in the change of HDL cholesterol; the CI around the summary effect was also narrow

The quality assessment of the evidence related to imprecision was therefore deemed: “Not serious, do not downgrade”.

Publication Bias

- HDL cholesterol: visual inspection of the contour enhanced funnel plot indicated asymmetry, and the empty area near the bottom-right of the plot may indicate publication bias in addition to the influences of heterogeneity.
    - There is some horizontal scatter, which may be the result of the high level of heterogeneity between the studies.
    - The area where missing studies may exist is shown with a ring on Figure 26, although studies in this area probably would not report clinically-significant treatment effects.

Figure 26. Contour funnel plot – change in HDL cholesterol.



- A precision-focused cumulative meta-analysis did not indicate a substantial shift in the point estimate due to large effects from small studies. (See supplemental figure S15.)
- The cumulative display sorted by publication year did not indicate time-lag bias. (See supplemental figure S16.)

While there may be an area with some missing studies, given the abundant heterogeneity present, the horizontal scatter of the funnel plot, and the results of the more reliable and transparent cumulative meta-analyses, the likelihood for publication bias was deemed: "Uncertain risk, but do not downgrade".

Macronutrient Distribution Impact on Change in HDL (mg/dL)

Group by Comparison	Study name	Macronutrient Distribution (F/P/C)	Impact on HDL	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Decreased	Kasim-Karakas 2009A	26/34/40 - MF/MP/LC	Decreased	-4.000	0.326	0.106	-4.639	-3.361	-12.275	0.000
Decreased	Gardner 2007D	21/17/63 - AMDR	Decreased	-5.300	0.857	0.735	-6.980	-3.620	-6.183	0.000
Decreased	Assuncao 2009A	21/15/64 - AMDR	Decreased	-6.500	1.336	1.786	-9.119	-3.881	-4.864	0.000
Decreased	Han 2007A	23/18/59 - AMDR	Decreased	-8.890	1.308	1.712	-11.455	-6.325	-6.794	0.000
Decreased				-5.903	1.022	1.044	-7.905	-3.900	-5.778	0.000
Increased	Santo 2008C	23/20/57 - AMDR	Increased	27.300	3.722	13.853	20.005	34.595	7.335	0.000
Increased	Santo 2008B	24/21/54 - AMDR	Increased	12.700	2.209	4.881	8.370	17.030	5.748	0.000
Increased	Mutungi 2008A	56/27/15 - HF/MP/LC	Increased	9.500	2.107	4.439	5.371	13.629	4.509	0.000
Increased	Esposito 2004	29/16/55 - AMDR	Increased	9.000	0.704	0.496	7.620	10.380	12.779	0.000
Increased	Tapsell 2004B	33/23/41 - AMDR	Increased	8.900	1.109	1.229	6.727	11.073	8.028	0.000
Increased	Stendell-Hollis 2010B	28/18/54 - AMDR	Increased	7.730	2.090	4.368	3.634	11.826	3.699	0.000
Increased	Tapsell 2004C	32/22/44 - MF/MP/LC	Increased	7.730	4.191	17.567	-0.485	15.945	1.844	0.065
Increased	Wood 2007B	59/27/13 - HF/MP/LC	Increased	5.800	1.844	3.400	2.186	9.414	3.145	0.002
Increased	Tapsell 2004A	33/21/43 - AMDR	Increased	5.420	1.218	1.483	3.033	7.807	4.450	0.000
Increased	Tonstad 2002C	29/18/50 - AMDR	Increased	4.640	1.310	1.716	2.072	7.208	3.542	0.000
Increased	Hjerkinn 2005	28/17/52 - AMDR	Increased	4.450	0.541	0.293	3.390	5.510	8.227	0.000
Increased	Tonstad 2002B	31/18/49 - AMDR	Increased	4.260	1.342	1.801	1.630	6.890	3.174	0.002
Increased	Han 2007B	28/18/55 - AMDR	Increased	4.250	2.122	4.503	0.091	8.409	2.003	0.045
Increased	Esposito 2004A	28/14/58 - AMDR	Increased	4.000	0.551	0.303	2.921	5.079	7.265	0.000
Increased	Maki 2005B	35/15/52 - AMDR	Increased	3.900	0.675	0.456	2.577	5.223	5.778	0.000
Increased	Wood 2007A	59/27/13 - HF/MP/LC	Increased	3.860	1.726	2.977	0.478	7.242	2.237	0.025
Increased				6.775	0.772	0.597	5.261	8.289	8.771	0.000
Overall				2.163	0.616	0.380	0.956	3.371	3.511	0.000

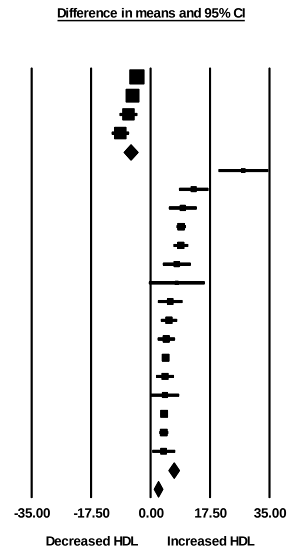


Figure 27. Forest plot – macronutrient distribution and change in HDL cholesterol (effects beyond intra-personal variation). [Q = 97.983, df = 1, p<0.001]
Macronutrient distribution format (% total energy): Fat/Protein/Carbohydrate
<u>Definitions & Abbreviations:</u>
Decreased HDL: >5mg/dL reduction; AMDR: Acceptable Macronutrient Distribution Ranges, HF: High-Fat, MP: Moderate-Protein, LC: Low-Carbohydrate, MF: Moderate-Fat, HC: High-Carbohydrate, LC: Low-Carbohydrate, HC: High-Carbohydrate, MC: Moderate-Carbohydrate.
Ranking of dietary profiles: Low < AMDR (Moderate) < High

Subgroup Analysis/Meta-Regression

Referring to Figure 27, reported impacts beyond intra-personal variation were:

- An overall increase in HDL cholesterol of +2.16 mg/dL (95%CI: 0.956 to 3.371), $p(Q)<0.001$, $I^2 = 98\%$.
    - The overall estimate included sixteen observations that increased HDL cholesterol, with a summary effect of +6.78 mg/dL (95%CI: 5.261 to 8.289).
        - The average macronutrient distribution of these studies was calculated to be 35% fat, 20% protein, 45% carbohydrate, and this was barely within the AMDRs for fat and carbohydrate, although wide variations were noted.
    - This overall estimate also included four studies that lowered HDL cholesterol (MD: -5.90 mg/dL, 95%CI: -7.905 to -3.900).
        - The average macronutrient distribution of these five studies was calculated to be 23% fat, 21% protein, 56% carbohydrate, and was within the AMDRs, although wide variations were noted with respect to protein and carbohydrates.

Change in Total Fat (Subgroups) & Change in HDL (mg/dL)

	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
		Statistics for each study				
Decreased Fat	9	-0.841	1.076	1.158	-2.950	1.268
Fixed Fat	68	1.097	0.392	0.154	0.329	1.865
Increased Fat	9	3.651	1.258	1.583	1.185	6.117
		1.193	0.987	0.974	-0.741	3.128

Difference in means and 95% CI

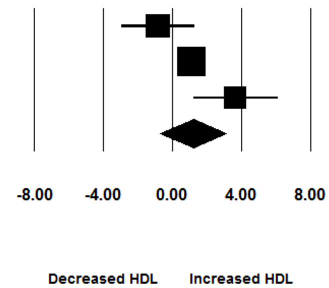


Figure 28. Subgroup forest plot – change in fat and change in HDL cholesterol.

- A test for heterogeneity (Q = 7.364, df = 2, p = 0.025) supported that the subgroups related to change in total fat do not share a common treatment effect between them. None of the subgroups reported summary effects that were beyond intra-personal variation.
- Observations that decreased fat (more than 3.5%) did not demonstrate a clear effect on change in HDL.
    - Summary effect was -0.841 mg/dL (95%CI: -2.950 mg/dL to 1.268 mg/dL). The confidence interval is wide and crosses the null.
    - The true difference between the decreased fat subgroup and those observations categorized as fixed probably falls within this range for HDL (95% confidence interval): -0.31 mg/dL to 4.18 mg/dL. (See supplemental table S18.)

- The increased fat subgroup reported a summary effect of +3.651 mg/dL, with a confidence interval of 1.185 mg/dL to 6.117 mg/dL.
    - The true difference between the increased fat subgroup and those observations categorized as fixed probably falls within this range for HDL (95% confidence interval): -0.03 mg/dL to 5.14 mg/dL. (See supplemental table S18.)
    - The true difference between the increased fat and decreased fat subgroups probably falls within this range for HDL (95% confidence interval): 1.25 mg/dL to 7.74 mg/dL. (See supplemental table S18.)

Change in Total Protein (Subgroups) & Change in HDL (mg/dL)

Study name	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
Fixed Protein	73	0.975	0.380	0.144	0.230	1.720
Increased Protein	13	2.345	1.219	1.486	-0.044	4.734
		1.170	0.479	0.229	0.231	2.109

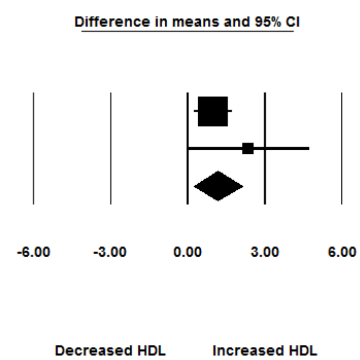


Figure 29. Subgroup forest plot – change in protein and change in HDL

Regarding the protein subgroups, a test for heterogeneity (Q = 1.151, df = 1, p = 0.283) did not reject the possibility that the subgroups shared a common treatment effect. None of the subgroups reported treatment effects that were beyond intra-personal variation.

- Observations that increased protein (more than 3.5%) did not show a clear effect on HDL concentrations. This subgroup reported an increase in the treatment effect (change in HDL) of 0.975 mg/dL, but there were few observations contained in the subgroup (325 subjects), the confidence interval was sufficiently wide (-0.044 mg/dL to 4.734 mg/dL), and it included the null.
  - The true difference between the increased protein subgroup and those observations categorized as fixed probably falls within this range for HDL (95% confidence interval): -1.13 mg/dL to 3.87 mg/dL. (See supplemental table S18.)

Change in Total Carbohydrate & Change in HDL (mg/dL)

Subgroup	Observations	Statistics for each study				
		Difference in means	Standard error	Variance	Lower limit	Upper limit
Decreased Carb	11	0.920	1.184	1.402	-1.401	3.241
Fixed Carb	65	1.462	0.410	0.168	0.658	2.266
Increased Carb	10	-0.818	0.826	0.682	-2.437	0.801
		0.600	0.778	0.605	-0.925	2.125

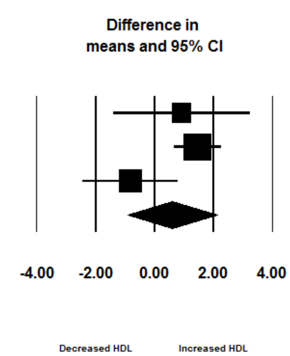


Figure 30. Subgroup forest plot – change in carbohydrate and change in HDL cholesterol.

Concerning carbohydrate, a test for heterogeneity (Q = 6.120, df = 2, p = 0.047) supported that the subgroups related to change in total carbohydrate do not share a common treatment effect between them. None of the subgroups reported summary effects that were beyond intra-personal variation.

- Observations that decreased carbohydrate (more than 3.5%) did not show a clear effect on HDL concentrations. This subgroup reported an increase in the treatment effect (change in HDL) of 0.920 mg/dL, but there were few observations in the subgroup (310 subjects), the confidence interval was sufficiently wide (95%CI: -1.401 mg/dL to 3.241 mg/dL), and it included the null.
    - The true difference between the decreased carbohydrate subgroup and those observations categorized as fixed probably falls within this range for HDL (95% confidence interval): -1.91 mg/dL to 3.00 mg/dL. (See supplemental table S18.)
- The subgroup that increased carbohydrate (more than 3.5%) did not report a clear effect on HDL concentration, reporting a summary effect of -0.818 mg/dL, and the confidence interval (95%CI: -2.438 mg/dL to 0.801 mg/dL) crossed the null.
    - The true difference between the increased carbohydrate subgroup and those observations categorized as fixed probably falls within this range for HDL (95% confidence interval): -4.09 mg/dL to -0.47 mg/dL. (See supplemental table S18.)

- ○ The true difference between the increased carbohydrate and decreased carbohydrate subgroups probably falls within this range for HDL (95% confidence interval): -4.57 mg/dL to 1.09 mg/dL. (See supplemental table S18.)

AMDR (Subgroups) & Change in HDL (mg/dL)

Study name	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
AMDR	57	1.350	0.465	0.216	0.439	2.261
HF/MP/LC	10	1.865	0.987	0.974	-0.069	3.799
HF/MP/MC	13	0.187	0.582	0.339	-0.954	1.328
MF/LP/LC	1	0.390	1.297	1.682	-2.152	2.932
MF/MP/HC	1	-1.930	3.517	12.369	-8.823	4.963
MF/MP/LC	4	-0.317	1.638	2.683	-3.527	2.893
		0.898	0.322	0.104	0.267	1.529

(Statistics for each study)

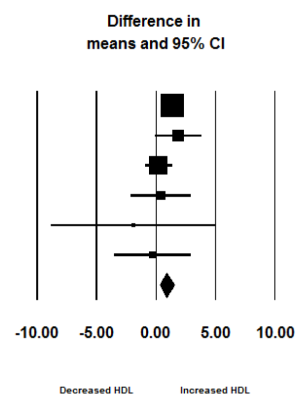


Figure 31. Subgroup forest plot – dietary profiles and change in HDL cholesterol.

A test for heterogeneity (Q = 4.745, df = 5, p = 0.448) did not reject the possibility that the subgroups related to AMDR could have the same treatment effect between them. None of the subgroups reported summary effects beyond intra-personal variation for HDL.

- The AMDR subgroup (2404 subjects) showed an increase in HDL, with a summary effect of +1.350 mg/dL (95% CI: 0.439 mg/dL to 2.261 mg/dL).
  - ○ Dietary trials focusing on the AMDRs can be found in Figure 32.

- The observations that were categorized as “high-fat, low-carbohydrate” diets (HF/MP/LC), showed no clear effect on HDL concentration. The summary effect was +1.865 mg/dL, but there were few observations (206 subjects), and the confidence interval crossed the null.
    - The true difference between the HF/MP/LC subgroup and those observations that were within the AMDRs probably falls within this range for HDL (95% confidence interval): -1.6 mg/dL to 2.7 mg/dL. (See supplemental table S18.)
- Thirteen observations were categorized as high fat diets, with their protein and carbohydrate percentages falling in line with the AMDRs (HF/MP/MC). This subgroup had a similar number of observations (385 subjects) compared to the “high-fat, low carbohydrate” subgroup, but reported a lower summary effect of +0.187 mg/dL. Like with the previous group, the HF/MP/MC subgroup had a confidence interval that crossed the null (95% CI: -0.955 mg/dL to 1.328 mg/dL).
    - The true difference between the HF/MP/MC subgroup and those observations that were within the AMDRs probably falls within this range for HDL (95% confidence interval): -2.6 mg/dL to 0.3 mg/dL. (See supplemental table S18.)

AMDR Carbohydrate & Change in HDL (mg/dL)

Study name	% Carb	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
Santo 2008C	56.6	27.30	3.72	13.85	20.01	34.59	7.33	0.00	0.89	
Santo 2008B	53.5	12.70	2.21	4.88	8.37	17.03	5.75	0.00	1.41	
Esposito 2004	55.0	9.00	0.70	0.50	7.62	10.38	12.78	0.00	1.97	
Tapsell 2004B	41.4	8.90	1.11	1.23	6.73	11.07	8.03	0.00	1.84	
Stendell-Hollis 2010B	54.3	7.73	2.09	4.37	3.63	11.83	3.70	0.00	1.45	
Tapsell 2004A	43.1	5.42	1.22	1.48	3.03	7.81	4.45	0.00	1.80	
Tonstad 2002C	50.0	4.64	1.31	1.72	2.07	7.21	3.54	0.00	1.77	
Hjerkinn 2005	51.7	4.45	0.54	0.29	3.39	5.51	8.23	0.00	2.00	
Tonstad 2002B	48.7	4.26	1.34	1.80	1.63	6.89	3.17	0.00	1.76	
Han 2007B	54.8	4.25	2.12	4.50	0.09	8.41	2.00	0.05	1.44	
Esposito 2004A	58.0	4.00	0.55	0.30	2.92	5.08	7.27	0.00	2.00	
Maki 2005B	51.9	3.90	0.67	0.46	2.58	5.22	5.78	0.00	1.97	
Stendell-Hollis 2010A	53.0	3.87	1.72	2.97	0.49	7.25	2.25	0.02	1.61	
Tonstad 2002D	49.3	3.86	1.39	1.92	1.14	6.58	2.78	0.01	1.74	
Assuncao 2009B	64.3	3.20	1.16	1.35	0.92	5.48	2.75	0.01	1.82	
Levin 1990	57.1	3.00	1.08	1.17	0.88	5.12	2.77	0.01	1.85	
Schwab 2006C	51.3	2.71	1.08	1.17	0.59	4.83	2.51	0.01	1.85	
Tonstad 2002A	47.3	2.71	1.57	2.47	-0.37	5.79	1.73	0.08	1.67	
Schwab 2006B	51.3	2.70	1.51	2.28	-0.26	5.66	1.79	0.07	1.69	
Adler 1997	50.2	2.30	0.68	0.46	0.97	3.63	3.39	0.00	1.97	
Polagruto 2006A	49.8	1.90	2.23	4.99	-2.48	6.28	0.85	0.39	1.40	
Tighe 2010B	47.7	1.54	0.97	0.94	-0.36	3.44	1.59	0.11	1.89	
Szapary 2003	52.4	1.43	1.66	2.76	-1.83	4.69	0.86	0.39	1.63	
Dodin 2005B	49.8	1.16	0.83	0.69	-0.47	2.79	1.40	0.16	1.93	
Gylling 2010B	45.4	1.16	1.81	3.29	-2.40	4.72	0.64	0.52	1.57	
Kawashima 2008A	50.5	1.16	0.59	0.35	0.00	2.32	1.97	0.05	1.99	
Kawashima 2008B	50.2	1.16	0.53	0.28	0.12	2.20	2.18	0.03	2.01	
Kelley 2007B	50.0	1.16	0.80	0.63	-0.40	2.72	1.46	0.15	1.94	
Schwab 2006A	53.2	1.16	1.41	1.98	-1.59	3.91	0.83	0.41	1.73	
Esposito 2004B	57.1	1.00	0.51	0.26	-0.00	2.00	1.95	0.05	2.01	
Smith 2008B	53.9	0.80	0.97	0.93	-1.09	2.69	0.83	0.41	1.89	
Tighe 2010C	45.4	0.77	1.02	1.05	-1.24	2.78	0.75	0.45	1.87	
Price 2010A	47.0	0.39	1.19	1.42	-1.95	2.73	0.33	0.74	1.81	
Mensink 2002A	50.1	0.38	1.22	1.49	-2.01	2.77	0.31	0.76	1.80	
Melanson 2004	53.2	0.30	1.30	1.69	-2.24	2.84	0.23	0.82	1.77	
Hollis 2009C	49.7	0.00	1.42	2.02	-2.79	2.79	0.00	1.00	1.73	
Schwab 2002A	51.4	0.00	1.43	2.06	-2.81	2.81	0.00	1.00	1.72	
Schwab 2002B	52.1	0.00	1.34	1.79	-2.62	2.62	0.00	1.00	1.76	
Polagruto 2006B	54.2	-0.30	1.57	2.48	-3.39	2.79	-0.19	0.85	1.67	
Beavers 2010A	47.2	-0.37	1.74	3.02	-3.77	3.03	-0.21	0.83	1.60	
Gylling 2010A	45.6	-0.38	2.23	4.97	-4.75	3.99	-0.17	0.86	1.40	
Mensink 2002B	52.6	-0.77	1.33	1.77	-3.38	1.84	-0.58	0.56	1.76	
Tighe 2010A	47.1	-0.78	1.13	1.28	-3.00	1.44	-0.69	0.49	1.84	
Kasim-Karakas 2009B	56.7	-1.00	0.35	0.12	-1.68	-0.32	-2.86	0.00	2.04	
Smith 2008A	51.8	-1.00	1.13	1.27	-3.21	1.21	-0.89	0.38	1.84	
Price 2010B	47.4	-1.16	1.06	1.12	-3.23	0.91	-1.10	0.27	1.86	
Kasai 2003B	56.2	-1.55	1.03	1.06	-3.56	0.46	-1.51	0.13	1.87	
Tanumihardjo 2009B	55.4	-1.93	1.47	2.15	-4.81	0.95	-1.31	0.19	1.71	
Diaz 2008B	56.3	-1.94	1.92	3.68	-5.70	1.82	-1.01	0.31	1.53	
Santo 2008A	57.4	-2.00	2.98	8.90	-7.85	3.85	-0.67	0.50	1.12	
Kasai 2003A	56.3	-2.32	1.26	1.58	-4.78	0.14	-1.85	0.07	1.79	
Tanumihardjo 2009A	54.3	-2.32	1.72	2.97	-5.70	1.06	-1.35	0.18	1.61	
Fakhrzadeh 2010	52.7	-2.50	0.67	0.45	-3.81	-1.19	-3.75	0.00	1.98	
Gardner 2007C	49.3	-3.80	0.74	0.54	-5.25	-2.35	-5.15	0.00	1.96	
Gardner 2007D	63.1	-5.30	0.86	0.73	-6.98	-3.62	-6.18	0.00	1.92	
Assuncao 2009A	64.0	-6.50	1.34	1.79	-9.12	-3.88	-4.86	0.00	1.76	
Han 2007A	59.3	-8.89	1.31	1.71	-11.45	-6.33	-6.79	0.00	1.77	
		1.35	0.47	0.22	0.44	2.26	2.90	0.00		

Statistics for each study

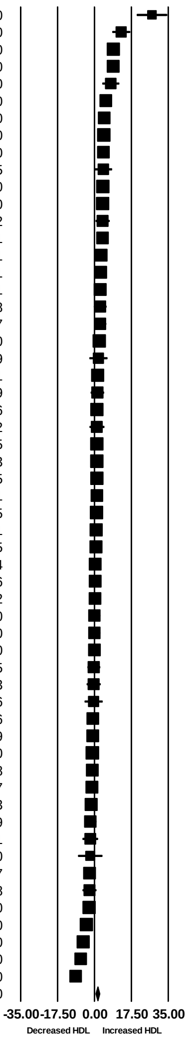


Figure 32. Subgroup forest plot – AMDR and change in HDL cholesterol.
[AMDRs (% total energy):
Fat = 20-35%, Protein = 10-35%, Carbohydrate = 45-65%]

- The true difference between the HF/MP/MC subgroup and those observations that were within the HF/MP/MC subgroup probably falls within this range for HDL (95% confidence interval): -3.9 mg/dL to 0.6 mg/dL. (See supplemental table S18.)

Random-effects meta-regression (restricted maximum likelihood (REML)) was conducted for change in HDL cholesterol using the six moderators featured in Table 15, and the proportion of the between-study variation explained (adjusted R^2) was 39.5%, with duration of the study (Duration) being the only significant covariate. The estimate for the between-study variation (T^2) was 6.268.

Table 15: Meta-regression table – HDL cholesterol.

Macronutrient Distribution and Change in HDL (mg/dL)
No of observations = 75. Tau-squared estimate ($T^2_{Unexplained}$) = 6.268 (REML method).
Adjusted p-value computed with Monte Carlo permutation test (set seed to 916993); permutations = 20,000. I-squared (I^2) = 82.26%

	Coefficient	Std. Error	p>|t|	p adjusted	[95% Conf. Interval]	
Pct_male	2.438209	1.278087	0.061	0.195	-0.1121744	4.988592
Age	0.0486976	0.0341621	0.159	0.450	-0.0194719	0.116867
Duration*	0.0073604	0.0030134	0.017	0.046	0.0013471	0.0133736
Subjects	-0.0297902	0.0154382	0.058	0.175	-0.0605966	0.0010162
Fat_Chg	0.1269806	0.0758326	0.099	0.302	-0.024341	0.2783022
HDL_Pre	-0.0427325	0.0554191	0.443	0.927	-0.1533197	0.0678546
Constant	0.1521271	3.493798	0.965		-6.819638	7.123892

39.5% of the unexplained between-study variance (R^2) could be explained by: the duration of the study in days.
The power of the moderator “Duration” = 0.6853
*The change in HDL is estimated to increase by 0.01 mg/dL per day increase in study duration.

- The change in HDL is estimated to increase by 0.01 mg/dL per day increase in study duration.
  - Study duration did not meet the 0.80 power criterion (0.6853).
- 75 observations were included in the model, and 20,000 permutations were performed to help eliminate false positives that may arise during the analysis of multiple covariates; the adjusted p-values are to be viewed as the "correct" p-values.
  - For change in HDL cholesterol, there were no differences between the moderators that were "flagged" before and after permutation testing, as study duration was the only covariate that demonstrated significance ($p<0.05$).
  - For a bubble plot of the moderator "Duration", see supplemental figure S26.
- The estimated treatment effect given particular values of the covariates can be derived from the following regression equation:
  - Change in HDL Cholesterol = 0.1521271 + 2.44 (% male as decimal) + 0.05 (age in years) + 0.007 (duration of study in days) - 0.03 (number of subjects) + 0.13 (the percent change in total dietary fat) – 0.04 (pre-treatment HDL level).

Sensitivity Analyses

- The summary effect using a fixed-effect model was similar to the result reported through random-effects (+0.448 mg/dL F.E. versus +1.137 mg/dL R.E.), and as expected, its 95% confidence interval was more narrow due to the fewer sources of variation accounted for by the model (0.242 mg/dL to 0.654mg/dL F.E. versus 0.393 mg/dL to 1.881 mg/dL R.E). (See supplemental table S8.)
- The results after the addition of the 23 crossover studies originally excluded from the meta-analysis did not differ substantially with respect to summary effect, statistical significance, or tests of heterogeneity (see Table 16). It should be noted that only the data from the first period of each crossover trial was used in order to minimize unit-of-analysis errors, however this decision may increase bias because reporting of data from solely the first period may be dependent on the researchers having found significant carry-over in their respective study designs.
    - Since there were no significant differences between the two options, and the meta-analysis was significantly powered without the crossover trials, their exclusion was appropriate due to the risk of injecting additional biases into the meta-analysis.

Table 16: Sensitivity analysis – effect of crossover trials on change in HDL cholesterol.
Outcome: Change in HDL Cholesterol (mg/dL)
Original Analysis: 42 Studies (86 observations, 3144 Subjects)
With Cross-overs: 65 Studies (111 Observations, 3876 Subjects)

Summary Effects (Random Effects Model/Raw Mean Difference)

	Effect size and 95% confidence interval					Test of null (2-Tail)	
ΔHDL	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
Original Analysis	+1.137	0.380	0.144	0.393	1.881	2.994	0.003
With Crossovers	+0.824	0.308	0.095	0.220	1.429	2.672	0.008

Heterogeneity

	Q-Statistic			I-Squared	Tau-squared			
ΔHDL	Q	df (Q)	P-value	(I^2)	(T^2)	Standard Error	Variance	Tau (T)
Original Analysis	987.360	85	<0.001	91.39%	10.313	2.724	7.423	3.211
With Cross-overs	1076.479	110	<0.001	89.78%	8.328	2.206	4.867	2.886

- The “one study removed” analysis showed no significant impact of any individual study on the summary effect. (See supplemental figure S18.)
- The use of different pre- and post-treatment correlations when calculating the effect sizes did not impact the summary effect by more than one-tenth of one unit of measurement (mg/dL). It essentially did not matter what value was chosen (from r = 0.5 to 0.99), and the results from the Excel’s *Correl* function provided decent approximation. (See supplemental table S9.)

- Sensitivity analyses for publication bias supported the primary assessment methods, describing the unclear risk of publication bias:
    - Trim and fill also supported asymmetry and publication bias, imputing 19 studies, which would support a greater increase in HDL cholesterol. If asymmetry was due to bias, the analysis suggests that the adjusted effect would be between +1.50 mg/dL to 3.21 mg/dL. (See supplemental figure S14 and supplemental table S7.)
    - The Egger's regression intercept was positive (+1.69154), supporting the trend towards increased accuracy in smaller studies. The p-value was significant [p=0.02502; 95%CI: (0.21745 to 3.16564)], which supported that there was evidence of publication bias. (See supplemental table S7.)
    - Classic Fail-safe N indicated there would need to be 1143 studies with a mean effect of zero before the summary effect became non-significant. (See supplemental table S7.)

TRIGLYCERIDE CHANGE (ΔTG)

As shown in Table 17 below, the studies in the meta-analysis reported a decrease in triglycerides, and the effects of individual studies can be observed in the forest plot in Figure 33. The studies were sorted from greatest decrease in triglycerides to greatest increase in triglycerides, with the summary effect of -8.219 mg/dL presented on the bottom line.

Eight comparisons that reported changes in triglycerides more than the estimated intra-personal variation for the parameter were combined into a separate analysis that can be seen in Figure 35. For the studies that reported a clear decrease in triglyceride levels, the summary effect was -45.767 mg/dL (95%CI: -51.210 mg/dL to -40.325 mg/dL); there were no trials that reported a clear increase in triglycerides.

Study Limitations

Refer to the section related to the study limitations for the overall lipid profile.

Table 17. Summary effect – change in triglycerides.
(Random effects model/raw mean difference)
42 studies (86 comparisons, 3144 subjects; Average power of included studies: 0.9992)

	Effect size and 95% confidence interval					Test of null (2-Tail)	
	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
ΔTG (mg/dL)	-8.219	1.700	2.888	-11.550	-4.888	-4.836	<0.001

Macronutrient Distribution & Change in TG (mg/dL)

Study name	Macronutrient Distribution (F/P/C) - Dietary Profile	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
		Statistics for each study								
Kelley 2007A	36/16/48 - HF/MP/MC	-60.230	13.284	176.459	-86.266	-34.194	-4.534	0.000	0.77	
Gardner 2007A	55/28/18 - HF/MP/LC	-52.300	5.578	31.112	-63.232	-41.368	-9.376	0.000	1.27	
Wood 2007B	59/27/13 - HF/MP/LC	-50.490	9.204	84.705	-68.529	-32.451	-5.486	0.000	1.03	
Mutungi 2008B	55/25/20 - HF/MP/LC	-49.400	11.882	141.188	-72.689	-26.111	-4.157	0.000	0.85	
Chan 2002B	34/22/40 - MF/LP/LC	-44.290	16.495	272.082	-76.619	-11.961	-2.685	0.007	0.62	
Mutungi 2008A	56/27/15 - HF/MP/LC	-44.100	8.355	69.800	-60.475	-27.725	-5.279	0.000	1.08	
Maki 2005B	35/15/52 - AMDR	-42.900	7.451	55.520	-57.504	-28.296	-5.757	0.000	1.14	
Wood 2007A	59/27/13 - HF/MP/LC	-39.860	4.893	23.942	-49.450	-30.270	-8.146	0.000	1.31	
Melanson 2004	28/21/53 - AMDR	-38.400	8.699	75.674	-55.450	-21.350	-4.414	0.000	1.06	
Hjerkinn 2005	28/17/52 - AMDR	-32.330	2.226	4.956	-36.693	-27.967	-14.523	0.000	1.43	
Kasim-Karakas 2009A	26/34/40 - MF/MP/LC	-32.000	2.642	6.978	-37.178	-26.822	-12.114	0.000	1.42	
Diaz 2008A	23/16/65 - MF/MP/HC	-27.460	7.946	63.136	-43.034	-11.886	-3.456	0.001	1.11	
Gardner 2007B	35/24/42 - MF/MP/LC	-24.800	5.757	33.138	-36.083	-13.517	-4.308	0.000	1.26	
Tanumihardjo 2009B	24/21/55 - AMDR	-23.910	7.904	62.477	-39.402	-8.418	-3.025	0.002	1.11	
Alhassan 2006	39/17/44 - HF/MP/LC	-22.000	7.282	53.030	-36.273	-7.727	-3.021	0.003	1.16	
Kelley 2007B	34/15/50 - AMDR	-20.370	10.179	103.608	-40.320	-0.420	-2.001	0.045	0.96	
Esposito 2004	29/16/55 - AMDR	-19.000	3.523	12.413	-25.905	-12.095	-5.393	0.000	1.38	
Polagruto 2006A	34/16/50 - AMDR	-18.700	5.540	30.689	-29.558	-7.842	-3.376	0.001	1.27	
Tapsell 2004B	33/23/41 - AMDR	-18.600	7.644	58.438	-33.583	-3.617	-2.433	0.015	1.13	
Esposito 2004A	28/14/58 - AMDR	-18.000	2.762	7.628	-23.413	-12.587	-6.517	0.000	1.41	
Stendell-Hollis 2010B	28/18/54 - AMDR	-17.720	9.143	83.603	-35.641	0.201	-1.938	0.053	1.03	
Stendell-Hollis 2010A	32/16/53 - AMDR	-17.710	23.926	572.470	-64.605	29.185	-0.740	0.459	0.38	
Tapsell 2004C	32/22/44 - MF/MP/LC	-17.710	7.534	56.755	-32.476	-2.944	-2.351	0.019	1.14	
Gardner 2007C	30/20/49 - AMDR	-17.400	4.573	20.915	-26.364	-8.436	-3.805	0.000	1.33	
Goyens 2006B	42/14/43 - HF/MP/LC	-15.940	6.434	41.392	-28.550	-3.330	-2.478	0.013	1.21	
Han 2007A	23/18/59 - AMDR	-15.940	18.552	344.191	-52.302	20.422	-0.859	0.390	0.53	
Tonstad 2002C	29/18/50 - AMDR	-15.940	5.152	26.546	-26.038	-5.842	-3.094	0.002	1.29	
Price 2010B	33/18/47 - AMDR	-14.170	7.211	52.001	-28.304	-0.036	-1.965	0.049	1.16	
Tonstad 2002A	30/18/47 - AMDR	-14.170	2.997	8.983	-20.044	-8.296	-4.728	0.000	1.40	
Wardlaw 1991B	39/13/47 - HF/MP/MC	-14.170	8.130	66.093	-30.104	1.764	-1.743	0.081	1.10	
Maki 2005A	35/16/50 - HF/MP/MC	-14.100	5.772	33.312	-25.412	-2.788	-2.443	0.015	1.26	
Pins 2006B	35/21/44 - HF/MP/LC	-10.700	7.737	59.864	-25.865	4.465	-1.383	0.167	1.13	
Wardlaw 1991A	40/13/47 - HF/MP/MC	-10.630	7.332	53.762	-25.001	3.741	-1.450	0.147	1.15	
Kasai 2003B	27/15/56 - AMDR	-9.740	3.779	14.282	-17.147	-2.333	-2.577	0.010	1.37	
Tonstad 2002B	31/18/49 - AMDR	-9.740	5.148	26.503	-19.830	0.350	-1.892	0.058	1.29	
Kawashima 2008B	28/14/50 - AMDR	-9.740	4.993	24.935	-19.527	0.047	-1.951	0.051	1.30	
Chan 2002A	36/20/38 - HF/MP/LC	-8.860	55.672	3099.354	-117.975	100.255	-0.159	0.874	0.09	
Schwab 2002A	27/18/51 - AMDR	-8.860	6.375	40.644	-21.355	3.635	-1.390	0.165	1.22	
Schwab 2002B	27/18/52 - AMDR	-8.860	7.993	63.887	-24.526	6.806	-1.108	0.268	1.11	
Malpuech-Brugere 2010B	39/15/45 - HF/MP/MC	-8.860	5.001	25.014	-18.663	0.943	-1.771	0.076	1.30	
Kawashima 2008A	27/14/51 - AMDR	-7.970	4.267	18.207	-16.333	0.393	-1.868	0.062	1.34	
Santo 2008A	22/20/57 - AMDR	-7.600	10.711	114.731	-28.594	13.394	-0.710	0.478	0.93	
Tonstad 2002D	31/17/49 - AMDR	-6.200	5.587	31.218	-17.151	4.751	-1.110	0.267	1.27	
Pins 2006A	34/21/45 - MF/MP/LC	-5.600	6.996	48.951	-19.313	8.113	-0.800	0.423	1.18	
Kasai 2003A	27/15/56 - AMDR	-5.320	3.742	14.005	-12.655	2.015	-1.422	0.155	1.37	
Tapsell 2004A	33/21/43 - AMDR	-4.430	7.460	55.650	-19.051	10.191	-0.594	0.553	1.14	
Tighe 2010A	35/16/47 - AMDR	-3.550	4.629	21.432	-12.624	5.524	-0.767	0.443	1.32	
Goyens 2006A	41/13/44 - HF/MP/LC	-3.540	6.198	38.411	-15.687	8.607	-0.571	0.568	1.23	
Tighe 2010B	34/17/48 - AMDR	-3.540	3.092	9.562	-9.601	2.521	-1.145	0.252	1.40	
Mensink 2002B	29/16/53 - AMDR	-1.770	3.249	10.554	-8.137	4.597	-0.545	0.586	1.39	
Smith 2008A	32/16/52 - AMDR	-1.000	4.730	22.372	-10.270	8.270	-0.211	0.833	1.32	
Adler 1997	31/17/50 - AMDR	-0.900	6.328	40.045	-13.303	11.503	-0.142	0.887	1.22	
Beavers 2010B	38/20/47 - HF/MP/MC	-0.870	9.843	96.882	-20.162	18.422	-0.088	0.930	0.98	
Diaz 2008B	27/19/56 - AMDR	0.000	9.649	93.103	-18.912	18.912	0.000	1.000	1.00	
Levin 1990	26/18/57 - AMDR	0.000	3.301	10.898	-6.470	6.470	0.000	1.000	1.39	
Dodin 2005B	33/17/50 - AMDR	0.880	3.084	9.511	-5.165	6.925	0.285	0.775	1.40	
Mensink 2002A	32/15/50 - AMDR	0.880	3.907	15.262	-6.777	8.537	0.225	0.822	1.36	
Smith 2003A	40/11/48 - HF/MP/MC	0.880	2.764	7.639	-4.537	6.297	0.318	0.750	1.41	
Schwab 2006C	28/18/51 - AMDR	0.890	18.780	352.681	-35.918	37.698	0.047	0.962	0.53	
Assuncao 2009A	21/15/64 - AMDR	1.000	7.728	59.717	-14.146	16.146	0.129	0.897	1.13	
Esposito 2004B	30/14/57 - AMDR	1.000	2.664	7.099	-4.222	6.222	0.375	0.707	1.42	
Kasim-Karakas 2009B	26/17/57 - AMDR	2.000	1.530	2.340	-0.998	4.998	1.307	0.191	1.45	
Beavers 2010A	34/21/47 - AMDR	2.440	9.119	83.155	-15.433	20.313	0.268	0.789	1.03	
Dodin 2005A	35/17/47 - HF/MP/MC	2.660	2.344	5.496	-1.935	7.255	1.135	0.257	1.43	
Polagruto 2006B	31/17/54 - AMDR	3.300	4.086	16.696	-4.709	11.309	0.808	0.419	1.35	
Price 2010A	35/18/47 - AMDR	3.540	11.474	131.651	-18.949	26.029	0.309	0.758	0.88	
Malpuech-Brugere 2010C	39/15/47 - HF/MP/MC	3.540	3.452	11.918	-3.226	10.306	1.025	0.305	1.38	
Santo 2008C	23/20/57 - AMDR	4.200	13.962	194.935	-23.165	31.565	0.301	0.764	0.74	
Malpuech-Brugere 2010A	38/15/47 - HF/MP/MC	4.430	2.891	8.356	-1.236	10.096	1.533	0.125	1.41	
Assuncao 2009B	21/15/64 - AMDR	6.900	9.673	93.570	-12.059	25.859	0.713	0.476	0.99	
Gylling 2010A	42/14/43 - AMDR	7.090	6.733	45.336	-6.107	20.287	1.053	0.292	1.19	
Tanumihardjo 2009A	29/17/54 - AMDR	7.090	8.486	72.016	-9.543	23.723	0.835	0.403	1.07	
Tighe 2010C	35/16/45 - AMDR	7.090	2.774	7.696	1.653	12.527	2.556	0.011	1.41	
Han 2007B	28/18/55 - AMDR	7.970	12.583	158.339	-16.693	32.633	0.633	0.526	0.81	
Gylling 2010B	31/16/45 - AMDR	8.860	3.345	11.192	2.303	15.417	2.648	0.008	1.39	
Szapary 2003	33/14/52 - AMDR	8.880	5.922	35.070	-2.727	20.487	1.499	0.134	1.25	
Santo 2008B	24/21/54 - AMDR	9.500	8.435	71.145	-7.032	26.032	1.126	0.260	1.08	
Schwab 2006A	26/19/53 - AMDR	10.620	14.248	202.999	-17.305	38.545	0.745	0.456	0.72	
Smith 2003B	37/11/50 - HF/MP/MC	10.630	5.462	29.837	-0.076	21.336	1.946	0.052	1.27	
Gardner 2007D	21/17/63 - AMDR	10.900	4.563	20.822	1.956	19.844	2.389	0.017	1.33	
Smith 2008B	30/16/54 - AMDR	12.000	3.193	10.197	5.741	18.259	3.758	0.000	1.40	
Hollis 2009A	35/15/50 - HF/MP/MC	13.290	6.063	36.761	1.407	25.173	2.192	0.028	1.24	
Schwab 2006B	28/19/51 - AMDR	14.170	6.562	43.055	1.310	27.030	2.160	0.031	1.20	
Hollis 2009B	35/16/48 - HF/MP/MC	16.830	5.939	35.269	5.190	28.470	2.834	0.005	1.24	
Hollis 2009C	34/16/50 - AMDR	18.600	5.462	29.838	7.894	29.306	3.405	0.001	1.27	
Fakhrzadeh 2010	35/13/53 - AMDR	24.600	7.243	52.458	10.404	38.796	3.396	0.001	1.16	
		-8.219	1.700	2.888	-11.550	-4.888	-4.836	0.000		

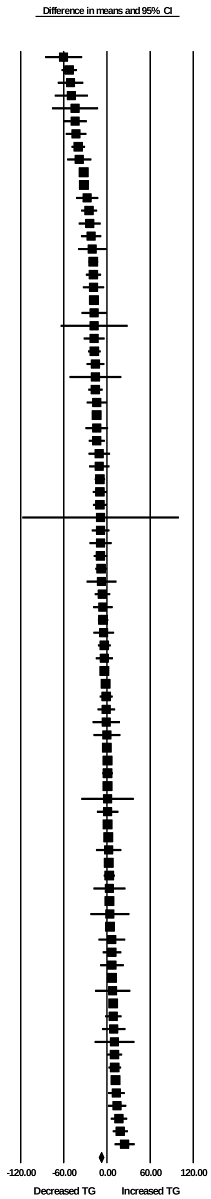


Figure 33. Forest plot – macronutrient distribution and change in triglycerides.
86 comparisons (3144 subjects)
Macronutrient distribution format (% total energy): Fat/Protein/Carbohydrate
(Values may not add up to 100% due to rounding)

<u>Inconsistency</u>

The unexplained heterogeneity and inconsistent results related to the outcome of change in triglycerides were summarized in Table 18.

Table 18. Heterogeneity table – change in triglycerides.
42 Studies (86 comparisons, 3144 subjects)

Heterogeneity								
	Q-Statistic			I-Squared	Tau-squared			
	Q	df (Q)	P-value	I^2	T^2	Standard Error	Variance	Tau (T)
ΔTG	863.284	85	<0.001	90.154%	196.787	49.882	2488.201	14.028

- Change in triglycerides varied more widely across the studies than the other parameters; the most notable differences were between large and small studies.
    - The confidence intervals for the various studies showed minimal overlap. (See supplemental figure S23.)
- The p-value associated with the Q-statistic was <0.001, suggesting the studies do not share a common effect size.
- The Q-statistic was larger than the degrees of freedom (Q>df), indicating that additional evidence from an increasing number of studies would only strengthen the case that the excess dispersion is not zero, thus supporting no common effect size.
- The value for I^2 was 90.154%, indicating most of the variation is real, and strongly supported subgroup analysis and/or meta-regression.

- Tau-squared (T^2) was calculated as 196.787, and reflected the estimated between-study variance of the true effects. The positive nature of the result was based on the amount of excess variation (Q-df >0) and the metric of the effect size.
- The estimated standard deviation of the true effect size, Tau (T), was 14.028. This value can be used to predict, with 95% accuracy, where a new study would fit in the meta-analysis.
    - The 95% prediction interval was calculated as (-36.291 mg/dL to 19.853 mg/dL).
- 33.99% of the unexplained between-study variance (R^2) could be explained by the covariates in the meta-regression.
    - Pre-treatment levels of triglyceride and the percent change of dietary fat were the covariates shown to significantly moderate change in triglycerides.

For change in triglycerides, there was a small number of overlapping confidence intervals, and the reported treatment effect varied widely across studies. In addition, the statistical tests for heterogeneity rejected the null hypothesis that the studies share a common treatment effect, and the I^2 test quantified that nearly all the heterogeneity was real. Subgroup analyses and meta-regression managed to identify and explain nearly 34% of the variation, and so the quality of the assessment of the evidence related to inconsistency was therefore deemed: “Serious, downgrade one level”.

<u>Indirectness (Differences in Populations)</u>

- Only subjects and interventions meeting the eligibility criteria were included in the systematic review, so evidence regarding them was direct by nature.
- Triglycerides are measured enzymatically in serum or plasma in a series of biochemical reactions that eventually result in the byproduct of hydrogen peroxide, which is measured quantitatively in a catalyzed reaction that produces a color and its absorbance is measured at 500 nm. Since the concentration of triglycerides is directly proportional to the color intensity, this analysis could be considered an indirect measurement of the parameter.
    - However, the consistent and widespread application of this technique will not be justification for rating down the evidence, as the method isn't considered a substitute or surrogate endpoint.

Since there were no serious differences in the population or the methodology, quality assessment of the evidence related to indirectness was: "No serious limitations, do not downgrade".

<u>Imprecision</u>

For change in triglycerides, a conservative estimate of the optimal information size (OIS) was calculated: the significance (α) was set at 0.05, the power (1-ß) was 0.90, the Δ was set at 6mg/dL, and the standard deviation of the effect was ±13.

- The OIS was calculated to be 2781 subjects, and the number of subjects in the meta-analysis was 3144, meeting the OIS criterion (OIS< number of studies in systematic review/meta-analysis).

- Comparing the lower and upper boundaries for the 95% CI (-11.550 to -4.888) would not have changed the recommendation of the summary effect, since they both indicate a decrease in the change of triglycerides.

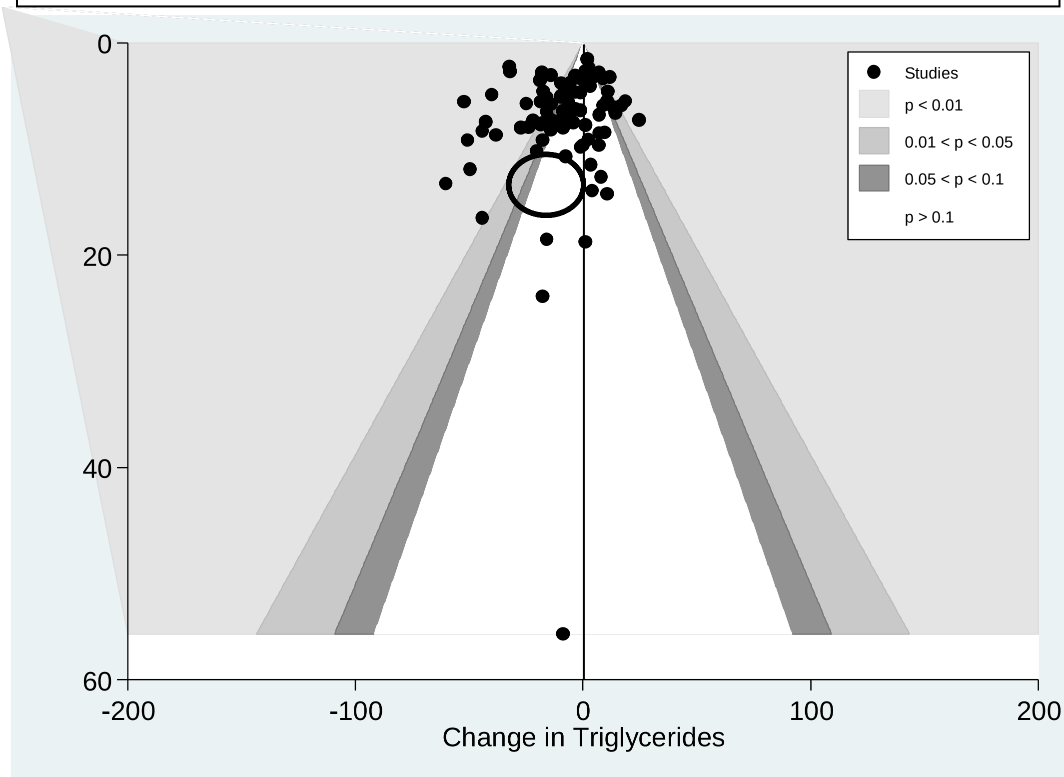
The quality assessment of the evidence related to imprecision was therefore deemed: "Not serious, do not downgrade".

Publication Bias

- Visual inspection of the contour enhanced funnel plot (see Figure 34) indicated asymmetry, and the cluster of points toward the top of the funnel may indicate heterogeneity or other factors than besides publication bias.
    - The area where missing studies may exist is shown with a ring on Figure 34; such studies may report a clinically-significant treatment effect.
- A precision-focused cumulative meta-analysis did not indicate a substantial shift in the point estimate due to large effects from small studies. (See supplemental figure S21.)
- The cumulative meta-analysis sorted by publication year did not indicate time-lag bias. (See supplemental figure S22.)

While the funnel plot indicates that there may be an area with one or more missing studies, given the abundant heterogeneity present, and the results of the more reliable and transparent cumulative meta-analyses, the likelihood for publication bias was deemed: "Uncertain, but do not downgrade".

Figure 34. Contour funnel plot – change in triglycerides.



Subgroup Analysis/Meta-Regression

Referring to Figure 35, reported impacts beyond intra-personal variation were:

- Eight studies reported a significant decrease in triglycerides, for a summary effect of -45.77 mg/dL (95%CI: -51.210 to -40.33), p(Q)=0.643, I^2 = 0%.

Macronutrient Distribution Impact & Change in TG (mg/dL)

Study name	Macronutrient Distribution (F/P/C)	Impact on TG	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Kelley 2007A	36/16/48 - HF/MP/MC	Decreased	-60.230	13.284	176.459	-86.266	-34.194	-4.534	0.000
Gardner 2007A	55/28/18 - HF/MP/LC	Decreased	-52.300	5.578	31.112	-63.232	-41.368	-9.376	0.000
Wood 2007B	59/27/13 - HF/MP/LC	Decreased	-50.490	9.204	84.705	-68.529	-32.451	-5.486	0.000
Mutungi 2008B	55/25/20 - HF/MP/LC	Decreased	-49.400	11.882	141.188	-72.689	-26.111	-4.157	0.000
Chan 2002B	34/22/40 - MF/LP/LC	Decreased	-44.290	16.495	272.082	-76.619	-11.961	-2.685	0.007
Mutungi 2008A	56/27/15 - HF/MP/LC	Decreased	-44.100	8.355	69.800	-60.475	-27.725	-5.279	0.000
Wood 2007A	59/27/13 - HF/MP/LC	Decreased	-39.860	4.893	23.942	-49.450	-30.270	-8.146	0.000
Melanson 2004	28/21/53 - AMDR	Decreased	-38.400	8.699	75.674	-55.450	-21.350	-4.414	0.000
			-45.767	2.777	7.711	-51.210	-40.325	-16.481	0.000

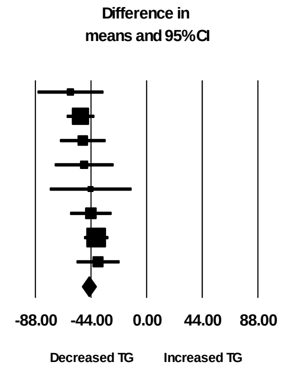


Figure 35. Forest plot – macronutrient distribution and change in triglycerides (effects beyond intra-personal variation). [Q = 5.136, df = 7, p=0.643]; Macronutrient distribution format (% total energy): Fat/Protein/Carbohydrate

<u>Definitions & Abbreviations:</u>

Decreased triglycerides: >5mg/dL reduction; AMDR: Acceptable Macronutrient Distribution Ranges, HF: High-Fat, MP: Moderate-Protein, LC: Low-Carbohydrate, MF: Moderate-Fat, HC: High-Carbohydrate, LC: Low-Carbohydrate, HC: High-Carbohydrate, MC: Moderate-Carbohydrate.

Ranking of dietary profiles: Low < AMDR (Moderate) < High

- There were no studies that reported a significant increase in triglycerides.
  - The average macronutrient distribution of these eight studies was calculated to be 48% fat, 24% protein, 28% carbohydrate, and compared to the AMDRs would be categorized as high-fat, low-carbohydrate (HF/MP/LC), although there was some wide variation between these studies with respect to fat and carbohydrate.

Change in Total Fat (Subgroups) & Change in TG (mg/dL)

Study name	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
		Statistics for each study				
Decreased Fat	9	-7.315	8.137	66.211	-23.263	8.633
Fixed Fat	68	-5.579	1.603	2.570	-8.721	-2.437
Increased Fat	9	-28.602	7.241	52.432	-42.794	-14.410
		-12.963	7.170	51.416	-27.017	1.091

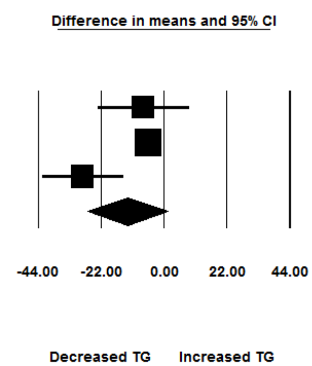


Figure 36. Subgroup forest plot – change in fat and change in triglycerides.

- A test for heterogeneity (Q = 9.644, df = 2, p = 0.008) supported that the subgroups related to change in total fat do not share a common treatment effect between them.
- Comparisons that decreased fat (more than 3.5%) did not demonstrate a clear effect on change in triglycerides.

- The summary effect was –7.315 mg/dL (95%CI: -23.263 mg/dL to 8.633 mg/dL); the confidence interval is wide and crossed the null.
- The true difference between the decreased fat subgroup and those comparisons categorized as fixed probably falls within this range for triglycerides (95% confidence interval): -14.52 mg/dL to 18.00 mg/dL. (See supplemental table S20.)

- The increased fat subgroup reported a summary effect of -28.602 mg/dL that approached clinical significance, with a confidence interval of -42.794 mg/dL to -14.410 mg/dL. The summary effect was still slightly within intra-personal variation, and while its confidence interval did not cross the null, it was sufficiently wide, and more comparisons need to be added to this subgroup before these results can be deemed conclusive.
    - The true difference between the increased fat subgroup and those comparisons categorized as fixed probably falls within this range for triglycerides (95% confidence interval): -37.56 mg/dL to -8.49 mg/dL. (See supplemental table S20.)
    - The true difference between the increased fat and decreased fat subgroups probably falls within this range for triglycerides (95% confidence interval): -42.64 mg/dL to 0.06 mg/dL. (See supplemental table S20.)

Change in Total Protein (Subgroups) & Change in TG (mg/dL)

Study name	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
Fixed Protein	73	-4.534	1.552	2.409	-7.576	-1.492
Increased Protein	13	-29.215	4.368	19.079	-37.776	-20.654
		-16.537	12.336	152.174	-40.715	7.641

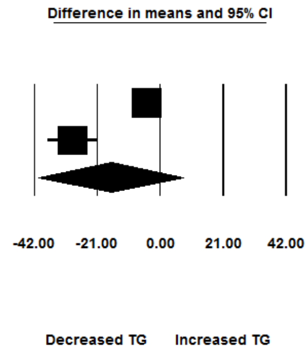


Figure 37. Subgroup forest plot – change in protein and change in triglycerides.

Regarding the protein subgroups, a test for heterogeneity (Q = 28.346, df = 1, p <0.001) supported that the subgroups related to change in total protein do not share a common treatment effect between them.

- Comparisons that increased protein (more than 3.5%) showed an effect on triglyceride concentrations that approached clinical significance. This subgroup reported a decrease in the treatment effect (change in triglyceride) of -29.215 mg/dL, but there were few comparisons contained in the subgroup (325 subjects), contributing to a confidence interval that was somewhat wide (-37.776 mg/dL to -20.654 mg/dL).
    - The true difference between the increased protein subgroup and those comparisons categorized as fixed probably falls within this range for triglycerides (95% confidence interval): -33.77 mg/dL to -15.59 mg/dL. (See supplementary table S20.)

Change in Total Carbohydrate (Subgroups) & Change in TG (mg/dL)

Study name	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
Decreased Carb	11	-30.504	5.225	27.301	-40.745	-20.263
Fixed Carb	65	-5.382	1.721	2.962	-8.755	-2.009
Increased Carb	10	-2.076	3.679	13.535	-9.287	5.135
		-11.871	6.606	43.635	-24.818	1.076

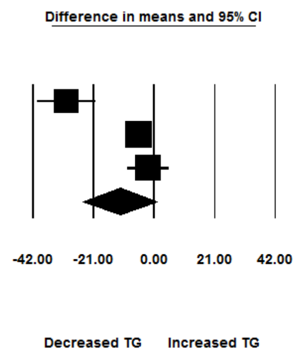


Figure 38. Subgroup forest plot – change in carbohydrate and change in triglycerides.

- Concerning carbohydrate, a test for heterogeneity (Q = 22.906, df = 2, p <0.001) supported that the subgroups related to change in total carbohydrate do not share a common treatment effect between them.
- Comparisons that decreased carbohydrate (more than 3.5%) showed an effect on triglyceride concentrations that approached clinical significance. This subgroup reported a decrease in the treatment effect (change in triglycerides) of -30.504 mg/dL, but there were few comparisons in the subgroup (310 subjects), which contributed to a sufficiently wide confidence interval (95%CI: -40.745 mg/dL to -20.263 mg/dL).

    - The true difference between the decreased carbohydrate subgroup and those comparisons categorized as fixed probably falls within this range for triglycerides (95% confidence interval): 14.34 mg/dL to 35.90 mg/dL. (See supplemental table S20.)

- The subgroup that increased carbohydrate (more than 3.5%) did not report a clear effect on triglyceride concentration, reporting a summary effect of -2.076 mg/dL, the confidence interval (95%CI: -9.287 mg/dL to 5.135 mg/dL) crossed the null, and included both effects.
    - The true difference between the increased carbohydrate subgroup and those comparisons categorized as fixed probably falls within this range for triglycerides (95% confidence interval): -4.65 mg/dL to -11.27 mg/dL. (See supplemental table S20.)
    - The true difference between the increased carbohydrate and decreased carbohydrate subgroups probably falls within this range for triglycerides (95% confidence interval): 15.90 mg/dL to 40.95 mg/dL. (See supplemental table S20.)

AMDR (Subgroups) & Change in TG (mg/dL)

Study name	Observations	Difference in means	Standard error	Variance	Lower limit	Upper limit
AMDR	57	-4.495	1.826	3.334	-8.074	-0.916
HF/MP/LC	10	-31.234	6.359	40.437	-43.697	-18.771
HF/MP/MC	13	-1.033	2.805	7.868	-6.531	4.465
MF/LP/LC	1	-44.290	16.495	272.085	-76.620	-11.960
MF/MP/HC	1	-27.460	7.946	63.139	-43.034	-11.886
MF/MP/LC	4	-21.154	5.966	35.593	-32.847	-9.461
		-17.384	5.182	26.855	-27.541	-7.228

Statistics for each study

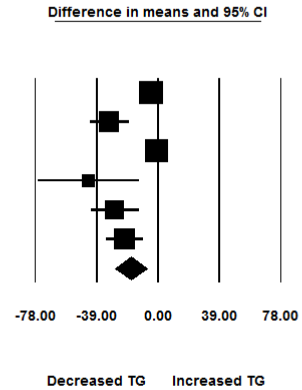


Figure 39. Subgroup forest plot – dietary profiles and change in triglycerides.

A test for heterogeneity (Q = 38.293, df = 5, p <0.001) supported that the subgroups related to AMDRs do not share a common treatment effect between them.

- The AMDR subgroup (2404 subjects) showed a decrease in triglycerides, with a summary effect of -4.495 mg/dL (95% CI: -8.074 mg/dL to -0.917 mg/dL).
    - Dietary trials focusing on the AMDRs and change in triglycerides can be found on Figure 40.
- The comparisons that were categorized as “high-fat, low-carbohydrate” diets (HF/MP/LC), reported a decrease in triglyceride concentration that approached clinical significance. The summary effect was -31.23 mg/dL, but there were few comparisons (206 subjects), and the confidence interval was sufficiently wide (-43.698 mg/dL to -18.770 mg/dL).

  - The true difference between the HF/MP/LC subgroup and those comparisons that were within the AMDRs probably falls within this range for triglycerides (95% confidence interval): -39.71 mg/dL to -13.77 mg/dL. (See supplemental table S20.)

- Thirteen comparisons were categorized as high fat diets, with their protein and carbohydrate percentages falling in line with the AMDRs (HF/MP/MC). This subgroup had a similar number of comparisons (385 subjects) compared to the "high-fat, low carbohydrate" subgroup, but reported a negligible reduction in triglycerides, with a summary effect of -1.033 mg/dL. The HF/MP/MC subgroup had a confidence interval that crossed the null (95% CI: -6.530 mg/dL to 4.465 mg/dL).
  - The true difference between the HF/MP/MC subgroup and those comparisons that were within the AMDRs probably falls within this range for triglycerides (95% confidence interval): -3.1 mg/dL to 10.0 mg/dL. (See supplemental table S20.)
  - The true difference between the HF/MP/MC subgroup and those comparisons that were within the HF/MP/MC subgroup probably falls within this range for triglycerides (95% confidence interval): 16.6 mg/dL to 43.8 mg/dL. (See supplemental table S20.)

AMDR Fat Percentage & Change in TG (mg/dL)

Studyname	Fat%	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
		Statistics for each study								
Maki 2005B	34.8	-42.900	7.451	55.520	-57.504	-28.296	-5.757	0.000	1.67	
Melanson 2004	28.0	-38.400	8.699	75.674	-55.450	-21.350	-4.414	0.000	1.52	
Hjerkinn 2005	27.6	-32.330	2.226	4.956	-36.693	-27.967	-14.523	0.000	2.24	
Tanumihardjo 2009B	23.7	-23.910	7.904	62.477	-39.402	-8.418	-3.025	0.002	1.62	
Kelley 2007B	33.8	-20.370	10.179	103.608	-40.320	-0.420	-2.001	0.045	1.35	
Esposito 2004	29.0	-19.000	3.523	12.413	-25.905	-12.095	-5.393	0.000	2.14	
Polagruto 2006A	34.1	-18.700	5.540	30.689	-29.558	-7.842	-3.376	0.001	1.91	
Tapsell 2004B	32.7	-18.600	7.644	58.438	-33.583	-3.617	-2.433	0.015	1.65	
Esposito 2004A	28.0	-18.000	2.762	7.628	-23.413	-12.587	-6.517	0.000	2.20	
Stendell-Hollis 2010B	27.6	-17.720	9.143	83.603	-35.641	0.201	-1.938	0.053	1.47	
Stendell-Hollis 2010A	32.0	-17.710	23.926	572.470	-64.605	29.185	-0.740	0.459	0.47	
Gardner 2007C	30.2	-17.400	4.573	20.915	-26.364	-8.436	-3.805	0.000	2.03	
Han 2007A	22.8	-15.940	18.552	344.191	-52.302	20.422	-0.859	0.390	0.68	
Tonstad 2002C	28.6	-15.940	5.152	26.546	-26.038	-5.842	-3.094	0.002	1.96	
Price 2010B	32.8	-14.170	7.211	52.001	-28.304	-0.036	-1.965	0.049	1.70	
Tonstad 2002A	29.6	-14.170	2.997	8.983	-20.044	-8.296	-4.728	0.000	2.18	
Kasai 2003B	26.6	-9.740	3.779	14.282	-17.147	-2.333	-2.577	0.010	2.11	
Tonstad 2002B	30.8	-9.740	5.148	26.503	-19.830	0.350	-1.892	0.058	1.96	
Kawashima 2008B	28.4	-9.740	4.993	24.935	-19.527	0.047	-1.951	0.051	1.98	
Schwab 2002A	27.4	-8.860	6.375	40.644	-21.355	3.635	-1.390	0.165	1.81	
Schwab 2002B	27.4	-8.860	7.993	63.887	-24.526	6.806	-1.108	0.268	1.61	
Kawashima 2008A	26.9	-7.970	4.267	18.207	-16.333	0.393	-1.868	0.062	2.06	
Santo 2008A	21.5	-7.600	10.711	114.731	-28.594	13.394	-0.710	0.478	1.29	
Tonstad 2002D	30.8	-6.200	5.587	31.218	-17.151	4.751	-1.110	0.267	1.91	
Kasai 2003A	26.6	-5.320	3.742	14.005	-12.655	2.015	-1.422	0.155	2.11	
Tapsell 2004A	32.6	-4.430	7.460	55.650	-19.051	10.191	-0.594	0.553	1.67	
Tighe 2010A	34.6	-3.550	4.629	21.432	-12.624	5.524	-0.767	0.443	2.02	
Tighe 2010B	33.8	-3.540	3.092	9.562	-9.601	2.521	-1.145	0.252	2.18	
Mensink 2002B	29.1	-1.770	3.249	10.554	-8.137	4.597	-0.545	0.586	2.16	
Smith 2008A	32.3	-1.000	4.730	22.372	-10.270	8.270	-0.211	0.833	2.01	
Adler 1997	30.9	-0.900	6.328	40.045	-13.303	11.503	-0.142	0.887	1.81	
Diaz 2008B	27.2	0.000	9.649	93.103	-18.912	18.912	0.000	1.000	1.41	
Levin 1990	25.5	0.000	3.301	10.898	-6.470	6.470	0.000	1.000	2.16	
Dodin 2005B	32.9	0.880	3.084	9.511	-5.165	6.925	0.285	0.775	2.18	
Mensink 2002A	31.7	0.880	3.907	15.262	-6.777	8.537	0.225	0.822	2.10	
Schwab 2006C	28.4	0.890	18.780	352.681	-35.918	37.698	0.047	0.962	0.67	
Assuncao 2009A	21.3	1.000	7.728	59.717	-14.146	16.146	0.129	0.897	1.64	
Esposito 2004B	30.0	1.000	2.664	7.099	-4.222	6.222	0.375	0.707	2.21	
Kasim-Karakas 2009B	25.9	2.000	1.530	2.340	-0.998	4.998	1.307	0.191	2.28	
Beavers 2010A	34.2	2.440	9.119	83.155	-15.433	20.313	0.268	0.789	1.47	
Polagruto 2006B	31.1	3.300	4.086	16.696	-4.709	11.309	0.808	0.419	2.08	
Price 2010A	35.0	3.540	11.474	131.651	-18.949	26.029	0.309	0.758	1.21	
Santo 2008C	22.6	4.200	13.962	194.935	-23.165	31.565	0.301	0.764	0.98	
Assuncao 2009B	21.1	6.900	9.673	93.570	-12.059	25.859	0.713	0.476	1.41	
Gylling 2010A	32.3	7.090	6.733	45.336	-6.107	20.287	1.053	0.292	1.76	
Tanumihardjo 2009A	28.6	7.090	8.486	72.016	-9.543	23.723	0.835	0.403	1.55	
Tighe 2010C	34.5	7.090	2.774	7.696	1.653	12.527	2.556	0.011	2.20	
Han 2007B	27.6	7.970	12.583	158.339	-16.693	32.633	0.633	0.526	1.10	
Gylling 2010B	30.9	8.860	3.345	11.192	2.303	15.417	2.648	0.008	2.15	
Szapary 2003	32.8	8.880	5.922	35.070	-2.727	20.487	1.499	0.134	1.86	
Santo 2008B	23.6	9.500	8.435	71.145	-7.032	26.032	1.126	0.260	1.55	
Schwab 2006A	26.3	10.620	14.248	202.999	-17.305	38.545	0.745	0.456	0.96	
Gardner 2007D	21.1	10.900	4.563	20.822	1.956	19.844	2.389	0.017	2.03	
Smith 2008B	29.7	12.000	3.193	10.197	5.741	18.259	3.758	0.000	2.17	
Schwab 2006B	27.8	14.170	6.562	43.055	1.310	27.030	2.160	0.031	1.79	
Hollis 2009C	33.7	18.600	5.462	29.838	7.894	29.306	3.405	0.001	1.92	
Fakhrzadeh 2010	34.5	24.600	7.243	52.458	10.404	38.796	3.396	0.001	1.70	
		-4.495	1.826	3.334	-8.074	-0.917	-2.462	0.014		

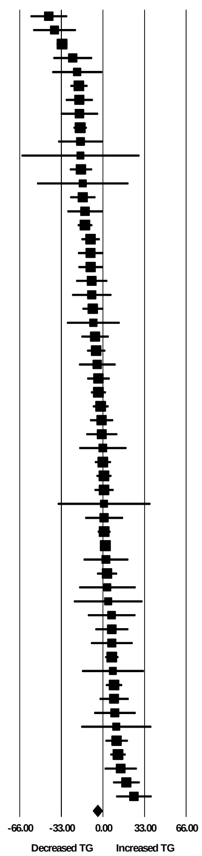


Figure 40. Subgroup forest plot – AMDR and change in triglycerides.

Random-effects meta-regression (restricted maximum likelihood (REML)) was conducted for change in triglycerides using the six moderators featured in Table 19, and the proportion of the between-study variation explained (adjusted R^2) was 33.99%, with percent change in total dietary fat (Fat_Chg) and pre-treatment triglyceride levels (TG_Pre) being the only significant covariates.

Table 19. Meta-regression table – triglycerides.

Macronutrient distribution and change in triglycerides (mg/dL)
No of comparisons = 75. Tau-squared estimate ($T^2_{Unexplained}$) = 133.5 (REML method).
Adjusted p-value computed with Monte Carlo permutation test (set seed to 916993); permutations = 20,000. I-squared (I^2) = 81.03%

	Coefficient	Std. Error	p>|t|	p adjusted	[95% Conf. Interval]	
Pct_male	-2.741428	5.141091	0.596	0.990	-13.0032	7.51746
Age	0.1101944	0.1438198	0.446	0.943	-0.1767935	0.3971822
Duration	0.0021702	0.0124893	0.863	1.000	-0.0227519	0.0270922
Subjects	-0.0532051	0.0604622	0.382	0.891	-0.1738555	0.0674453
Fat_Chg*	-1.313111	0.3130134	<0.001	<0.001	-1.937719	-0.688502
TG_Pre*	-0.1815523	0.0546187	0.001	0.007	-0.2905422	-0.072563
Constant	13.85118	8.572491	0.111		-3.254957	30.95732

33.99% of the unexplained between-study variance (R^2) could be explained by: the change in the percentage of energy contributed by total dietary fat and pre-treatment triglyceride levels in mg/dL.

*The change in triglycerides is estimated to decrease by 1.3mg/dL for every percent increase in total dietary fat, and decrease 0.2mg/dL for each unit (mg/dL) increase in pre-treatment triglycerides.

- The change in triglycerides is estimated to decrease by 1.3mg/dL for every percent increase in total dietary fat, and decrease 0.2mg/dL for each unit (mg/dL) increase in pre-treatment triglycerides.
    - A bubble plot for these moderators can be found on supplemental figures S27 and S28.

- 75 comparisons were included in the model, and 20,000 permutations were performed to help eliminate false positives that may arise during the analysis of multiple covariates; the adjusted p-values are to be viewed as the "correct" p-values.
    - For change in triglycerides, there were no differences between the moderators that were "flagged" before and after permutation testing, as change in total fat and pre-treatment levels were the only covariates that demonstrated significance ($p<0.05$).
- The estimated treatment effect given particular values of the covariates can be derived from the following regression equation:
    - Change in Triglycerides = 13.85118 - 2.74 (% male as decimal) + 0.11 (age in years) + 0.002 (duration of study in days) - 0.05 (number of subjects) – 1.31 (the percent change in total dietary fat) – 0.18 (pre-treatment triglyceride level).

Sensitivity Analyses

- The summary effect using a fixed-effect model was similar to the result reported through random-effects (-6.053 mg/dL F.E. versus -8.219 mg/dL R.E.), and as expected, its 95% confidence interval was more narrow due to the fewer sources of variation accounted for by the model (-7.023 mg/dL to -5.082 mg/dL F.E. versus -11.550 mg/dL to -4.888 mg/dL R.E). (See supplemental table S11.)
- The results after the addition of the 23 crossover studies originally excluded from the meta-analysis did not differ substantially with respect to summary effect,

statistical significance, or tests of heterogeneity (see Table 20). It should be noted that only the data from the first period of each crossover trial was used in order to minimize unit-of-analysis errors, however this decision may increase bias because reporting of data from solely the first period may be dependent on the researchers having found significant carry-over in their respective study designs.

- Since there were no significant differences between the two options, and the meta-analysis was significantly powered without the crossover trials, their exclusion was appropriate due to the risk of injecting additional biases into the meta-analysis.

Table 20: Sensitivity analysis – effect of crossover trials on change in triglycerides.
Outcome: Change in Triglycerides (mg/dL)
Original Analysis: 42 Studies (86 comparisons, 3144 Subjects)
With Cross-overs: 65 Studies (111 comparisons, 3876 Subjects)

Summary Effects (Random Effects Model/Raw Mean Difference)							
Effect size and 95% confidence interval						Test of null (2-Tail)	
ΔTG	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
Original Analysis	-8.219	1.700	2.888	-11.550	-4.888	-4.836	<0.001
With Crossovers	-7.734	1.375	1.890	-10.429	-5.039	-5.625	<0.001

Heterogeneity								
	Q-Statistic			I-Squared	Tau-squared			
ΔTG	Q	df (Q)	P-value	(I^2)	(T^2)	Standard Error	Variance	Tau (T)
Original Analysis	863.28	85	<0.001	90.15%	196.79	49.882	2488.20	14.03
With Cross-overs	1025.6	110	<0.001	89.28%	163.08	37.648	1417.39	12.77

- The “one study removed” analysis showed no significant impact of any individual study on the summary effect. (See supplemental figure S24.)
- The use of different pre- and post-treatment correlations when calculating the effect sizes did not impact the summary effect by more than one-tenth of one unit of measurement (mg/dL). It essentially did not matter what value was chosen (from r = 0.5 to 0.99), and the results from the Excel’s *Correl* function provided decent approximation. (See supplemental table S11.)
- Sensitivity analyses for publication bias supported the primary assessment methods, describing the unclear risk of publication bias:

- Trim and fill also supported asymmetry, imputing 11 studies, which would support a greater decrease in triglycerides. If asymmetry was due to bias, the analysis suggests that the adjusted effect would be between +15.07 mg/dL to -8.16 mg/dL. (See supplemental figure S20 and supplemental table S10.)
- The Egger's regression intercept was negative -0.91902), supporting the notion that smaller studies had larger than average effects; the p-value was not significant [p= 0.18800; 95%CI: (-2.29589 to 0.45786)]. (See supplemental table S10.)
- Fail-safe N indicated there would need to be 3530 studies with a mean effect of zero before the summary effect became non-significant. (See supplemental table S10.)

Summary of Evidence

The summary of the evidence for each of the outcomes in this meta-analysis is summarized in Table 21. The meta-regression did not manage to identify more than 40% of the unexplained heterogeneity in the meta-analysis, and this was the main cause to downgrade the findings. The choice to use the summary effects from the preliminary analysis, as opposed to one of the subgroups, or the "favorable outcomes" analyses was intentionally done to solicit caution when interpreting the results. Since the abundant heterogeneity was present in nearly every subgroup analyzed, reporting the summary effects from one of the subgroups instead was not warranted.

Table 21. Summary of findings for effect of macronutrient distribution on the lipid profile.

	∆TC	∆LDL	∆HDL	∆TG
# of Studies (Design)	42 Blinded RCTs Start: ⊕⊕⊕⊕	42 Blinded RCTs Start: ⊕⊕⊕⊕	42 Blinded RCTs Start: ⊕⊕⊕⊕	42 Blinded RCTs Start: ⊕⊕⊕⊕
Limitations in design	No	No	No	No
Inconsistency	Very Serious (-2) ○○	Very Serious (-2) ○○	Serious (-1) ○	Serious (-1) ○
Indirectness	No	No	No	No
Imprecision	No	No	No	No
Publication bias risk	Unlikely	Unlikely	Uncertain	Uncertain
# of Participants (Comparisons)	3144 subjects (86)	3144 subjects (86)	3144 subjects (86)	3144 subjects (86)
Comparator: Raw Mean Difference (D)	∆ TC (Post-Pre TC)	∆ LDL (Post-Pre LDL)	∆ HDL (Post-Pre HDL)	∆ TG (Post-Pre TG)
Summary Effect (MD)	-6.401 mg/dL	-5.317 mg/dL	+1.137 mg/dL	-8.219 mg/dL
95% CI	-8.81 to -3.99	-7.46 to -3.18	+0.39 to +1.88	-11.55 to -4.89
Comments	High level of unexplained heterogeneity $I^2 = 95\%$	High level of unexplained heterogeneity $I^2 = 94\%$	High level of heterogeneity $I^2 = 91\%$	High level of heterogeneity $I^2 = 90\%$
Quality of Evidence (GRADE)	Low ⊕⊕○○	Low ⊕⊕○○	Moderate ⊕⊕⊕○	Moderate ⊕⊕⊕○

DISCUSSION

Addressing the Specific Questions

> QUESTION: Does the macronutrient distribution of the diet, specifically the proportion of total energy contributed total dietary fat, total dietary protein, or total dietary carbohydrate alter the primary outcome, the lipid profile (notably total cholesterol, LDL, HDL, and triglycerides)?

Forty-two studies were included in this meta-analysis, comprising eighty-six comparisons and representing 3,144 subjects. Each study reported both the proportions of total macronutrients, and complete lipid profiles before and after the dietary interventions, and therefore all were included in the preliminary meta-analysis. The choice to include all the studies in a preliminary analysis provided the opportunity to report a combined effect across all subgroups; this decision was also appropriate since multiple different subgroups of the studies were examined. The results of this combined analysis were reported as separate outcomes corresponding to the four parameters included in the lipid profile, and are summarized in Table 21. For the 86 comparisons, the reported summary effects for the four lipid profile parameters were:

- A decrease in total cholesterol of -6.4 mg/dL (95%CI: -8.81 to -3.99), I^2 = 95%.
- A decrease in LDL of -5.3 mg/dL (95%CI: -7.46 to -3.18), I^2 = 94%.
- An increase in HDL of +1.137 mg/dL (95%CI: +0.39 to +1.88), I^2 = 91%.
- A decrease in triglycerides of -8.219 mg/dL (95%CI: -11.55 to -4.89), I^2 = 90%.

On their own, the summary effects reported from the meta-analysis of all the included studies lacked the appropriate context to address the impact macronutrient distribution had on blood lipids, but they did provide a foundation that were compared to further analyses of the various subgroups. Likewise, future research on macronutrients can build upon these results, expanding to look at macronutrient quality along with the total amounts recommended in an individual's diet. Some avenues for further examination include: the effect of monounsaturated fat in general versus the use of olive oil; revisiting how phytosterol margarines improve the lipid profile; and the carbohydrate content of variations of the Mediterranean Diet.

Given the variations in the subjects, designs, and dietary interventions of these studies, issues with heterogeneity were likely unavoidable. Despite these differences, the subjects included in the meta-analysis were still representative of individuals with alterations in their lipid profile, and neither the interventions, nor the outcome measurements of interest were starkly dissimilar. Therefore, it was deemed more advantageous to explore and examine the clinical differences between these studies through a meta-analysis, as opposed to merely describing them in a systematic review.

Even though efforts were made to utilize a random effects model on blinded RCTs, there was still a substantial amount of heterogeneity reported. Random effects modeling may distort summary effects if there are differences in results between large and smaller, more biased studies.[51] However, funnel plots, cumulative meta-analyses and other sensitivity tests failed to demonstrate clear bias from small studies, and both tests of heterogeneity and the proportion between-study variation deemed to be real (I^2) suggested the use of subgroups and meta-regression to help resolve the observed heterogeneity.

A meta-analysis by Kastorini on the Mediterranean diet and metabolic syndrome reported notable heterogeneity, although not as much as represented by the studies in our database.[118] The Mediterranean diet increased HDL (I^2 = 63.6%) and five of the twenty-nine clinical trials showed a benefit to triglycerides, while the remaining twenty-four showed no difference (I^2 = 55.3).[118] This meta-analysis included both observational studies and some clinical trials, and it is important to judge the quality of the results in this context. The meta-analysis of isoenergetic RCTs of subjects who consumed dietary interventions high in monounsaturated fat by Garg[116] showed favorable results compared to carbohydrate, but the results were within the intra-personal variation of the individuals. Still, a systematic review by Hooper recommended advice on the Mediterranean diet and permanent reductions in fat intake,[146] because even small but favorable impacts to risk factors to cardiovascular disease can have sizeable impacts to morbidity and overall quality of life.

While attempting to identify source of heterogeneity, several potential confounding variables were examined, such as physical activity. Only a few studies in this meta-analysis included reliable information regarding the impact of exercise on the lipid profile. In their meta-analysis of Step I and Step II diets, Yu-Poth et al. reported that exercise resulted in greater decreases in total cholesterol (-24.4 mg/dL), LDL (-18.9 mg/dL), and triglycerides (-15.1 mg/dL), and prevented the decrease in HDL typically seen with low-fat diets.[147] While exercise may demonstrate favorable improvements to the lipid profile that complement dietary interventions, a sixteen-month supervised study of moderate aerobic exercise (45min 5d/week) among seventy-four young men and women showed that exercise did not measurably alter the macronutrient intake of the subjects.[148] The individuals in the exercise group of this study lost an average of 5.2

kilograms (±15.8) of body weight,[148] and this study highlights the importance of reliably estimating energy expenditure, and treating it as an independent factor that impacts the lipid profile. Like with exercise, other potential confounders, such as: the use of lipid-altering medications, weight change, the specific number of hours the subjects were asked to fast, and the history related to tobacco usage all need to be consistently reported in research trials that measure the lipid profile.

In an attempt to identify dietary trials that clearly impacted blood lipids, studies were grouped together if they reported a treatment effect that was clinically significant; this was a sort of "signal-to-noise" adjustment. The aforementioned results highlighted studies that reported treatment effects that could not be explained by intra-individual variation; it does not mean that the results from the primary analysis were less reliable, but rather they could be explained by either the intervention, intra-personal variability in the biochemical parameter, or another factor that escaped detection by the meta-analysis. Considering that a large amount of heterogeneity was still present, even when comparisons were grouped based on very similar outcome magnitudes, it is very unlikely that the changes in the lipid profile can be completely explained by the mere distribution of the macronutrients, and therefore more focused subgroup analyses and meta-regressions were performed.

QUESTION: Over the course of a dietary intervention, does changing the percentage of one or more macronutrients alter the primary outcome, the lipid profile (specifically total cholesterol, LDL, HDL, and triglycerides)?

Most of the studies included in the meta-analysis did not show appreciable changes in the total amounts of macronutrients, and their interventions instead usually compared two different macronutrients (e.g. carbohydrate versus fat), or equal total amounts of the macronutrient, but from different sources (e.g. casein protein versus soy protein). Tests for heterogeneity supported that the subgroups did not share a common treatment effect between them, and the high number of studies categorized as having "fixed" amounts of macronutrients in each subgroup analysis provided a good comparison standard when describing the effects of alterations of that macronutrient.

- Decreasing the amount of total dietary fat was associated with a clinically significant reduction in total cholesterol (9 comparisons, 239 subjects, MD: -14.84 mg/dL, 95%CI: -23.048 to -6.640).
    - The true difference between the effect in the decreased fat subgroup, versus the subgroup where total fat remained unchanged, probably falls within the range of 0.62 mg/dL to 17.75 mg/dL.
- Increasing the amount of total dietary carbohydrate was associated with a decrease in total cholesterol that approached clinical significance (10 comparisons, 277 subjects, MD: -11.99 mg/dL, 95%CI: -18.863 to -5.111).

  - The true difference between the increased carbohydrate subgroup, versus the subgroup where total carbohydrate remained unchanged, probably falls within the range of -12.80 mg/dL to 4.71 mg/dL.

The comparisons in this meta-analysis tended to reduce the total amount of fat, and substitute it with near-identical increases to carbohydrate, which had the effect of reducing total cholesterol when it occurred. Since LDL is the particle that transports cholesterol, similar effects would be expected when the total amount of fat is replaced predominantly with carbohydrate:

- Decreasing the amount of total dietary fat was associated with a clinically significant reduction in LDL cholesterol (9 comparisons, 239 subjects, MD: -13.019 mg/dL, 95%CI: -16.647 to -9.391)
  - The true difference between the decreased fat subgroup, versus the subgroup where total fat remained unchanged, probably falls within the range of 3.61 mg/dL to 12.3 mg/dL.
- Increasing the amount of carbohydrate was associated with a decrease in LDL that approached clinical significance (10 comparisons, 277 subjects, MD: -10.65 mg/dL, 95%CI: -16.00 to -5.30).
  - The true difference between the increased carbohydrate subgroup, versus the subgroup where total carbohydrate remained unchanged, probably falls within the range of -11.6 mg/dL to 0.07 mg/dL.

Making appreciable decreases to total fat, and then balancing the macronutrient distribution with carbohydrate did not tend to favor significant increases to HDL concentrations. The comparisons of macronutrient subgroups did not report any clinically-significant changes to HDL.

A meta-analysis of RCTs by Hooper et al. reported that diets low in fat (<30% total energy) demonstrated decreases to all four parameters of the lipid profile, with no significant change occurring to HDL:[63]

- Total cholesterol: -3.90 mg/dL; 95%CI: -5.41 to -1.93, $I^2 = 0\%$
    - 15 comparisons, 7602 subjects
- LDL cholesterol: -3.87 mg/dL; 95% CI: -5.40 to -1.90, $I^2 = 0\%$
    - 14 comparisons, 6971 subjects
- HDL cholesterol: -0.40 mg/dL; 95%CI: -0.77 to +0.39, $I^2 = 0\%$
    - 15 comparisons, 7082 subjects
- Triglycerides: -23.9 mg/dL; 95%CI: -46.9 to 0, $I^2 = 0\%$
    - 5 comparisons, 706 subjects

Hooper's meta-analysis featured many more subjects and far lower heterogeneity than the low-fat subgroups in this meta-analysis, but none of these results were clinically significant.[63]

While the meta-analysis of Hooper et al. focused on reduction and/or modification of fat, our data suggest that decreases to triglycerides may be due to the removal of carbohydrate, rather than the associated changes to total fat to the diet. Parks and Hellerstein (2000) also took a similar stance, describing that carbohydrate-induced elevations in triglycerides have been shown in fat contents as high as 30%, and replacing as little as 10% of the total fat content may profoundly alter VLDL levels.[93] Concerning triglycerides, these data support the need for more studies examining the manipulation of macronutrients, as none of the subgroups reported clinically significant changes to triglycerides, although some approached clinical significance. The tentative evidence from this analysis supports a decrease in triglycerides by increasing the proportions from total fat and total protein, while decreasing total carbohydrate:

- Increasing total dietary fat was associated with a decrease in triglycerides that approached clinical significance (9 comparisons, 206 subjects, MD: -28.60 mg/dL 95%CI: -42.794 to -14.410)
    - The true difference between the increased fat subgroup, versus the subgroup where total fat remained unchanged, probably falls within the range of -37.56 mg/dL to -8.49 mg/dL.
- Increasing total dietary protein was associated with a decrease in triglycerides that approached clinical significance (13 comparisons, 325 subjects, MD: -29.22 mg/dL, 95%CI: -37.776 to -20.654).
    - The true difference between the increased protein subgroup, versus the subgroup where total protein remained unchanged, probably falls within the range of -33.77 mg/dL to -15.59 mg/dL.
- Decreasing total dietary carbohydrate was associated with a decrease in triglyceride concentration that approached clinical significance (11 comparisons, 310 subjects, MD: -30.50 mg/dL, 95%CI: -40.745 to -20.263)
    - The true difference between the decreased carbohydrate subgroup, versus the subgroup where total carbohydrate remained unchanged, probably falls within the range of 14.34 mg/dL to 35.90 mg/dL.

These results support the notion that decreasing the total amount of carbohydrate, especially refined carbohydrate,[84] is associated with a subsequent decrease in triglycerides. Above 65% the consumption of carbohydrate increases the risk of hypertriglyceridemia,[90] but our data may bring into question this upper range, and we urge more future research on the effects of total carbohydrate intake between 55-65% of total energy on the lipid profile, specifically HDL and triglycerides.

> QUESTION: Do dietary interventions within the Acceptable Macronutrient Distribution Range (defined by energy contributed by total fat between 20-35%, total carbohydrate between 45-65%, and total protein between 10-35%) demonstrate favorable alterations in the lipid profile (specifically decreases in total cholesterol, LDL, triglycerides and increases in HDL)?

This is likely one of the few meta-analyses to-date that examined the Acceptable Macronutrient Distribution Ranges (AMDRs), and the first to our knowledge that focused on the effects of following these macronutrient guidelines on parameters of the lipid profile. It has been suggested that if an individual's diet falls within the AMDRs that their intake is consistent with risk reduction of chronic disease, since this is of the themes of the recommendations.[149] However, our data are more in line with statements made by Nestle that the greater importance are the qualitative differences within each of the three categories of macronutrients.[150] While most of the dietary interventions featuring intake within the AMDRs demonstrated favorable effects on blood lipids, there were some within the AMDRs that produced alterations in the lipid profile that could eventually lead to chronic disease. If recommendations are to be made regarding macronutrients, both the distribution and the sources of the macronutrients need to be taken into consideration.

Fifty-seven of the eighty-six comparisons (66%) in the meta-analysis were categorized as having macronutrient distribution ranges that fell within the AMDRs, as well as within the more narrowly-defined Adult Treatment Panel III Guidelines. The large number of comparisons within this subgroup, comprising 2,404 subjects, provided an opportunity to examine the Acceptable Macronutrient Distribution Ranges through a meta-analytic technique. The average macronutrient distribution for the comparisons in the meta-analysis categorized as within the AMDRs was: 29.2% ±8.5 fat, 17.0% ±4.0 protein, and 52.3% ±11.1 carbohydrate.

At first glance, it did not appear that the AMDR subgroup was associated with clinically significant changes in any of the four parameters:

- Total cholesterol – MD: -5.84 mg/dL (95%CI: -8.48 to -3.21)
- LDL cholesterol – MD: -5.97 mg/dL (95%CI: -8.54 to -3.40)
- HDL cholesterol – MD: +1.35 mg/dL (95%CI: +0.44 to +2.26)
- Triglycerides – MD: -4.50 mg/dL (95%CI: -8.07 to -0.92)

Upon examining the treatment effects for the individual studies, however, it was revealed that the range of each outcome varied considerably (e.g. -30.94 mg/dL to +21.3 mg/dL for LDL), and that any two comparisons with similar total amounts of a macronutrient could have vastly different treatment effects. This further supports the importance of monitoring the quality of the macronutrients. Incidentally, a maximum intake of 25% total energy from refined carbohydrate sources (i.e. sugar) was suggested along with the AMDRs,[92] and this is another topic where more research is required related to reducing excess adiposity and dyslipidemia.[84]

Revisiting the select number of comparisons that reported treatment effects that were beyond intra-personal variation, the majority of favorable outcomes (i.e. decreased TC, LDL, and increased HDL) were reported from comparisons within the AMDRs, as opposed to outside them. The exception to this was triglycerides, where the majority of comparisons that reported decreased concentrations had carbohydrate contributions below 45%.

- For the AMDR comparisons that demonstrated a clinically significant reduction to total cholesterol, the average macronutrient distribution was:
    - 26.9% ±6.3 fat, 17.5% ±3.6 protein, 53.7% ±10.4 carbohydrate
        - The percentage of total energy from fat ranged from 21.1% to 31.7%.
        - The percentage of total energy from protein ranged from 14.9 to 20.9%.
        - The percentage of total energy from carbohydrate ranged from 45.4 to 63.1%.

This macronutrient distribution is similar to one reported by Thomson et al.[151], who fed nineteen overweight breast cancer survivors a reduced-fat diet within the AMDRs. The macronutrient distribution was 25% fat, 15-20% protein, and 55-60% carbohydrate. After six months, total cholesterol was reduced by -5.2 mg/dL ± 31.5, which is within intra-personal variation, but consistent with the summary effect observed from the AMDR subgroup of -5.84 mg/dL (95%CI: -8.48 to -3.21).

- For the AMDR comparisons that demonstrated a clinically significant reduction to LDL, the average macronutrient distribution was:
    - 27.1% ±6.8 fat, 17.4% ±3.6 protein, and 55.5% ±11.2 carbohydrate.
        - The percentage of total energy from fat ranged from 22.6% to 32%.
        - The percentage of total energy from protein ranged from 14 to 20.9%.
        - The percentage of total energy from carbohydrate ranged from 45.4 to 59.3%.

- For the AMDR comparisons that demonstrated a clinically significant increase to HDL, the average macronutrient distribution was:
    - 28.8% ±7.0 fat, 18.1% ±3.5 protein, 51.6% ±10.1 carbohydrate
        - The percentage of total energy from fat ranged from 22.6% to 34.8%.
        - The percentage of total energy from protein ranged from 14.0% to 22.6%.
        - The percentage of total energy from carbohydrate ranged from 41.4% to 58.0%.

- There was only one AMDR observation that reported a clinically significant decrease in triglycerides, and its macronutrient distribution was:
    - 28% fat, 21% protein, and 53% carbohydrate
        - Once again, the average macronutrient distribution for eight comparisons shown to clearly lower triglycerides was outside the AMDRs: 48% fat, 24% protein, 28% carbohydrate.

From the information provided by the studies within the AMDR comparisons, the average macronutrient distribution to promote potential decreases in total cholesterol and LDL, and increases in HDL would be:

- 27.6% ±6.7 fat, 17.7% ±3.6 protein, and 53.6% ±10.6 carbohydrate

There were not enough comparisons to make a suggestion for triglycerides, but given the highest carbohydrate percentage to show a significant reduction in triglycerides was 53%, it is likely that the distribution would need to be modified through a reduction of carbohydrate, and an increase in protein.

- For triglycerides, the suggested distribution would be: 28% fat, >18% protein, <54% carbohydrate.
    - If monounsaturated sources were chosen, the reduction in carbohydrate could be balanced with increases to both fat and protein.

Since the meta-analysis dealt solely with total amounts of macronutrients, the impact that the quality and source of a particular macronutrient has on the lipid profile simply cannot be answered. The only way to answer questions regarding macronutrient quality was to look at an outcome, and then go back to the original study and explore some possible answers. Only one out of the eighty-six comparisons analyzed (Wood, 2007A) reported improvements in all four lipid parameters. The macronutrient distribution was 59% fat, 27% protein, and 13% carbohydrate, and was a carbohydrate-restricted diet that supplemented subjects with soluble fiber (hemicellulose) from the Konjac plant, but this product is not presently approved by the Food and Drug Administration, making the confirmation of the results difficult for American researchers.

> QUESTION: Does the distribution of macronutrients outside the Acceptable Macronutrient Distribution Range (defined by energy contributed by total fat as <20% or >35% and energy contributed by total carbohydrate as < 45% or >65%) alter the primary outcome, the lipid profile (specifically total cholesterol, LDL, HDL, and triglycerides)?

There were not a sufficient number of comparisons in any of the subgroups outside of the AMDRs to make reliable recommendations. Only six comparisons were interventions containing less than 20% total fat, so comparisons of low-fat versus high-fat diets could not be performed. Also, there was only one observation that had a carbohydrate intake above 65%, and therefore comparisons against high-carbohydrate dietary profiles could not be made. Published articles will often designate a diet that is within the AMDRs as either “high-“ or “low-“, but this was not the convention used in this manuscript. Since the definitions for high or low as they pertain to macronutrient distributions are rather arbitrary, using the AMDR as a benchmark was deemed to be somewhat more objective.

A study by Jenkins et al., fed twenty overweight, hyperlipidemic men a low carbohydrate diet consisting of: 43% fat, 30% protein, and 27% carbohydrate (HF/MP/LC). After four weeks: total cholesterol, LDL, and triglycerides were all reduced by clinically significant levels (-52mg/dL, -36mg/dL, and -76mg/dL respectively), while HDL was lowered by -2 mg/dL. The HDL value differed from the HF/MP/LC studies in this meta-analysis, which reported a summary effect of +1.865 mg/dL for HDL.

> QUESTION: Are effects on the lipid profile moderated by the pretreatment lipid profile levels, gender, age, duration of the study, change in percent dietary fat, or number of subjects in the study?

One of the advantages of meta-analysis over other techniques is the ability to assess the consistency of effects and elucidate the impact of covariables.[51] After subgroup analysis failed to sufficiently identify the sources of variation in the meta-analysis, random-effects meta-regression was implemented. From the results of demographic and study design moderators, the following can be stated:

- Total cholesterol did not appear to be moderated by any of the listed covariates.
- Change in LDL cholesterol is estimated to decrease by 0.2mg/dL per unit (mg/dL) increase in pre-treatment LDL.
- Change in HDL is estimated to increase by 0.01 mg/dL for every day increase in study duration.
- Change in triglycerides is estimated to decrease by 1.3mg/dL for every percent increase in the change in total dietary fat, and decrease 0.2 mg/dL per unit (mg/dL) increase in pre-treatment triglyceride levels.
- No outcome appeared to be moderated by age, gender, or study sample size.

Despite the use of permutation testing to arrive at corrected p-values for the covariates, the findings regarding HDL and triglycerides should be interpreted with caution, as they may be the result of aggregation bias. The meta-analysis detects changes that occur between studies, but sometimes there are various differences within individual studies that collectively appear to make logical sense when making between-study comparisons. For example, HDL levels are usually difference for men compared to women, and since the majority of these studies pooled their HDL levels together as a single mean, this may be misrepresented in a meta-regression. Likewise, smoking status can affect HDL levels up to 13%, and if smoking status is not an included moderator, this connection may be missed.[142] (A large number of studies in the meta-analysis did not provide clear information on smoking status; therefore it was not included in the meta-regression.) For triglycerides, the moderator related to change in the percent total fat likely increased in response to decreases in total carbohydrate, although such assumptions made upon mere biologic plausibility should be approached with caution.

Limitations

One of the main limitations of this systematic review and meta-analysis is that the topic may have been too broadly defined. Just because a study manipulates the diet, and then measures pre- and post-treatment lipid profiles, does not mean that the study was designed to detect a change in either. For example, to truly establish an individual's coefficient of variation for LDL, it takes four separate samples, run in duplicate, to achieve a total coefficient of variation of 5%.[141] Setting up such protocols is important in study designs that aim to use each subject as their own control. To complicate the matter, most of the interventions contained in the meta-analysis manipulated the quality of the macronutrient, rather than just the total amounts. For this reason, small changes in the distribution of a macronutrient seemed to have a much greater effect on the outcomes than truly occurred. Like with the diets, the outcome measurements analyzed the total amounts of lipoproteins, as opposed to their functionality or potential atherogenicity (e.g. size of the LDL particle). These data, along with measures of inflammation and glycemia, would be more useful in answering questions regarding atherogenic dyslipidemia and metabolic syndrome.

While the risk from publication bias was assessed to be unlikely, another limitation of the study was that the systematic review was restricted to a single major electronic database, MEDLINE. Currently, EMBASE is not available at the University of Arizona, and the inability to search such databases increases the risk for publication bias. Searching the Cochrane Library would produce titles and abstracts from both these databases, and may be an indirect method to quantify the articles on EMBASE. There were a few articles that were identified through other means (e.g. hand-searching, Google Scholar searches) that could not be located using the developed search strategy, supporting the notion that the sensitivity of the search could be improved somewhat. However, considering that the AMDRs are guidelines developed for the American population, it is unlikely that a substantial number of articles focusing on this particular subgroup of the meta-analysis would be found outside of MEDLINE.

Another limitation related to the pre-treatment levels seen in the subjects included in the meta-analysis, which are organized by quartiles in Table 22 below:

Table 22. Pre-treatment laboratory values for subjects in meta-analysis (by quartile).

Quartile	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)
Q1	158.93 – 189.30	83.91 – 113.59	36.74 – 43.31	72.63 – 106.26
Q2	189.30 – 208.28	113.59 – 128.77	43.31 – 50.14	106.26 – 129.76
Q3	208.28 – 224.28	128.77 – 145.82	50.14 – 56.13	129.76 – 154.89
Q4	224.28 – 266.82	145.82 – 191.80	56.13 – 67.67	154.89 – 265.72

Many of the subjects in the meta-analysis had reasonably favorable lipid profiles at baseline, for example only a portion of the first quartile of HDL was designated as higher risk (<39 mg/dL). Given near-normal levels, one would expect smaller changes during the course of an intervention, and this is supported in some cases through the meta-regression analyses. It may have been more beneficial to include a criterion for risk of dyslipidemia in the inclusion criteria of the systematic review to detect larger changes in blood lipids.

CONCLUSIONS

Implications for Clinical Practice

Recommendations based solely on total amounts of macronutrients will be associated with wide variability in results and high heterogeneity. Decreasing the total amount of dietary fat, and increasing the total amount of dietary carbohydrate were associated with clinically significant reductions in both total cholesterol (GRADE: Low) and LDL cholesterol (GRADE: Low). The evidence is weaker, but approached clinical significance regarding the reduction of total dietary carbohydrate, and increased total amounts of both dietary fat and protein, in their associated reduction to triglyceride concentrations (GRADE: Moderate).

The Acceptable Macronutrient Distribution Ranges (AMDRs) generally seem to be suitable macronutrient guidelines for the prevention of unfavorable alterations to the lipid profile, although the quality/source of the macronutrients has a larger impact. Within the AMDRs, the most favorable impact to total cholesterol (Grade: Low), LDL (GRADE: Low), and HDL (GRADE: Moderate) were observed with an average macronutrient distribution of: 27.6% ±6.7 fat, 17.7% ±3.6 protein, 53.6% ±10.6 carbohydrate (28/18/54). This distribution mirrors recommendations made by the National Cholesterol Education Program: 25-35% fat, and carbohydrate intake closer to 50% if alterations in either HDL or triglycerides are present; it is also similar to the distribution of their Step I & II Diets.[88,147] Again there was insufficient evidence to make a definitive recommendation for reducing triglycerides (GRADE: Moderate), although the macronutrient distribution above would likely have the percentage contributed by carbohydrate lowered, and in its place increases to lean protein and fat, emphasizing monounsaturated sources.

Four recommendations for clinical trials would improve the quality of future meta-analyses:

1. Mandatory prospective registration of all randomized controlled trials would greatly reduce the risk for publication bias.
2. Classifying recruited individuals by genotype/phenotype of interest to better replicate gene-diet interactions.
3. Reporting data on individual subjects will reduce aggregation bias in the meta-regressions and allow for the reliable incorporation of cross-over trials.
4. Finally, the direct measurement of LDL concentrations is critical for accurate recommendations for dyslipidemic individuals.

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APPENDIX A: MEDLINE SEARCH STRATEGY FOR DIETARY MACRONUTRIENTS AND LIPID PROFILE		
Source: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) 1946 to Present.		
Step	Searches	Results
1 (Diet MeSH)	exp Diet Therapy/ or Diet.sh. or Caloric Restriction.sh. or Diabetic Diet.sh. or Diet, Carbohydrate-Restricted.sh. or Dietary carbohydrates.sh. or Diet, Fat-Restricted.sh. or Dietary fats.sh. or Diet, gluten-Free.sh. or Diet, Mediterranean.sh. or Diet, High-Fat.sh. or Diet, Protein-Restricted.sh. or Dietary proteins.sh. or Diet, Reducing.sh. or Diet, Sodium-Restricted.sh. or Diet, Macrobiotic.sh. or Diet, Vegetarian.sh. or Energy Intake.sh. or Fasting.sh. or Diet Fads.sh. or Ketogenic Diet.sh.	233832
2 (Diet Text Words)	(Diet Therapy or Diet or Nutritional Management or Dietary Management or Caloric Restriction or Restriction, Caloric or Low-Calorie Diet or Diets, Low-Calorie or Low Calorie Diet or Low-Calorie Diets or Isocaloric Diet or Isocaloric Diets or Diet, Isocaloric or Diets, Isocaloric or High-Calorie Diet or High-Calorie Diets or High Calorie Diet or High Calorie Diets or Diet, High Calorie or Diets, High Calorie or Diet, High-Calorie or Diets, High-Calorie or Diabetic Diet or Diet, Diabetic or Diabetic Diets or Diets, Diabetic or Diet, Fat-Restricted or Diet, Fat Restricted or Fat-Restricted Diet or Diets, Fat-Restricted or Fat Restricted Diet or Fat Restricted Diets or Diet, Low-Fat or Diet Low Fat or Diets, Low-Fat or Low-Fat Diet or Low-Fat Diets or Diet, Fat-Free or Diet, Fat Free or Diets, Fat Free or Fat-Free Diet or Fat-Free Diets or Dietary Fats or Diet, Gluten-Free or Diet, Gluten Free or Gluten-Free Diet or Diets, Gluten-Free or Gluten Free Diet or Gluten-Free Diets or Diet, Carbohydrate-Restricted or Carbohydrate-Restricted Diet or Carbohydrate-Restricted Diets or Diet, Carbohydrate Restricted or Diets, Carbohydrate-Restricted or Diet, Low Carbohydrate or Carbohydrate Diet, Low or Carbohydrate Diets, Low or Diets, Low Carbohydrate or Low Carbohydrate Diet or Low Carbohydrate Diets or South Beach Diet or Beach Diet, South or Diet, South Beach or Atkins Diet or Diet, Atkins or Dietary Carbohydrates or High Carbohydrate Diet or High Carbohydrate Diets or Diet, High Carbohydrate or Diets, High Carbohydrate or high-Carbohydrate Diet or High-Carbohydrate Diets or Diet, High-Carbohydrate or Diets, High-Carbohydrate or Diet, Mediterranean or Mediterranean Diet or Diets, Mediterranean or Mediterranean Diets or Diet, Protein-Restricted or Diet, Protein Restricted or Protein-Restricted Diet or Diets, Protein-Restricted	205573

(Step 2 cont.)	or Protein Restricted Diet or Protein-Restricted Diets or Diet, Low-Protein or Diet, Low Protein or Diets, Low-Protein or Low-Protein Diets or Low-Protein Diet or Low Protein Diet or Diet, Protein-Free or Diet, Protein Free or Diets, Protein-Free or Protein-Free Diet or Protein-Free Diets or Dietary Proteins or Diet, Reducing or Diets, Reducing or Reducing Diet or Reducing Diets or Weight Reduction Diet or Diet, Weight Reduction or Diets, Weight Reduction or Weight Reduction diets or Weight Loss Diet or Diet, Weight Loss or Diets, Weight Loss or Weight Loss Diet or Diet, Sodium-Restricted or Diet, Sodium Restricted or Diets, Sodium-Restricted or Sodium-Restricted Diet or Sodium-Restricted Diets or Diet, Low-sodium or Diet, Low Sodium or Diets, Low-Sodium or Low-Sodium Diet or Low-Sodium Diets or Diet, Low-Salt or Diet, Low Salt or Diets, Low-Salt or Low-Salt Diet or Diet, Salt-Free or Diet, Salt Free or Diets, Salt-Free or Salt-Free Diet or Salt-Free Diets or Diet, Vegetarian or Diets, Vegetarian or Vegetarian Diets or Vegetarian Diet or Vegetarianism or Diet, Vegan or Diets, Vegan or Vegan Diets or Vegan Diet or Diet, Macrobiotic or Diets, Macrobiotic or Macrobiotic Diet or Macrobiotic Diets or Diet Fads or Ketogenic Diet or Diet, Ketogenic or Diets, Ketogenic or Ketogenic Diets).tw.	
3 (Blood Lipid MeSH)	Cholesterol, LDL.sh. or Cholesterol, LDL/bl or Cholesterol, LDL/du or Cholesterol, LDL/bl, du or Cholesterol, HDL.sh. or Cholesterol, HDL/bl or Cholesterol, HDL/du or Cholesterol, HDL/bl, du or Triglycerides.sh. or Triglycerides/bl or Triglycerides/du or Triglycerides/bl, du or Lipoproteins.sh. or Lipoproteins/bl or Lipoproteins/du or Lipoproteins/bl, du or Dyslipidemias.sh. or Hyperlipidemias.sh. or Lipids/bl or Lipids/du or Lipids/bl, du	145963
4 (Blood Lipids Text Words)	(Lipid Profile or Lipid Panel or Lipid Blood Test or Blood Lipid Analysis or Lipoprotein Analysis or Hyperlipidemia Testing or Dyslipidemia Testing or Hyperlipidemia Analysis or Dyslipidemia Analysis or Hyperlipidemia Panel or Dyslipidemia Panel or Lipoprotein Cholesterol Analysis or Lipoprotein Cholesterol Panel or Lipoprotein Cholesterol Test or Serum Lipids or Serum Lipoproteins or Serum Total Cholesterol or Serum LDL Cholesterol or Serum HDL Cholesterol or Serum Triglycerides or Serum LDL-Cholesterol or Serum HDL-Cholesterol or Serum LDL-C or Serum HDL-C or Serum Triacylglycerol or Serum Triacylglycerols or Plasma Lipids or Plasma Lipoproteins or Plasma Total Cholesterol or Plasma LDL Cholesterol or Plasma HDL Cholesterol or Plasma Triglycerides	160864

Step 4 (cont.)	or Plasma LDL-Cholesterol or Plasma HDL-Cholesterol or Plasma LDL-C or Plasma HDL-C or Plasma Triacylglycerol or Plasma Triacylglycerols or LDL or LDL-C or Low-Density Lipoprotein Cholesterol or Low Density Lipoprotein Cholesterol or Lipoprotein Cholesterol, Low Density or Lipoprotein Cholesterol, Low-Density or Low-Density Lipoprotein or Low-Density Lipoproteins or Low Density Lipoprotein or Low Density Lipoproteins or Cholesterol, LDL or Cholesterol, Low Density or Cholesterol, Low-Density or HDL or HDL-C or High-Density Lipoprotein Cholesterol or High Density Lipoprotein Cholesterol or Lipoprotein Cholesterol, High Density or Lipoprotein Cholesterol, High-Density or High-Density Lipoprotein or High-Density Lipoproteins or High Density Lipoprotein or High Density Lipoproteins or Cholesterol, HDL or Cholesterol, High Density or Cholesterol, High-Density or Triglyceride or Triglycerides or Triacylglycerol or Triacylglycerols or Total Cholesterol or Cholesterol, Total or Total Blood Cholesterol or Blood Cholesterol, Total or Total Blood Lipoproteins).tw	
5	Step 1 OR Step 2	350590
6	Step 3 OR Step 4	225823
7	Step 5 AND Step 6	40653
8	Randomized controlled trial.pt or Randomized Controlled Trial/ or Random Allocation/	397366
9	Double-Blind Method/ or Single-Blind Method/	133503
10	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.	123403
11	Step 9 OR Step 10	168504
12	Step 8 AND Step 11	116980
13	Step 12 AND Step 7	1400
14	Limit Step 13 to (humans and year="2002-2010" and "all adult")	540
15 (Identify Non-English Articles)	limit 14 to (afrikaans or albanian or arabic or armenian or azerbaijani or belorussian or bengali or bosnian or bulgarian or burmese or catalan or chinese or croatian or czech or danish or dutch or esperanto or estonian or finnish or flemish or french or gaelic, scots or georgian or german or greek or hausa or hebrew or hindi or hungarian or icelandic or indonesian or interlingua or italian or japanese or kirghiz or korean or latin or latvian or lithuanian or macedonian or malay or marathi or masai or multilingual or norwegian or persian or polish or portuguese or pushto or rumanian or russian or serbian or slovak or slovene or spanish or swahili or swedish or tagalog or tamil or telugu or thai	11

	or turkish or ukrainian or urdu or vietnamese or welsh)	
16 (# of English Translations Available)	Limit Step 15 to English language	3
17	Limit Step 14 to English	532
Abbreviations: exp = Explode, .sh = Medical Subject Heading (MeSH), /bl = blood, du = diagnostic use, tw = text word, .pt = Publication type, .ti = Title, .ab = Abstract. $ = truncation, adj25 = adjacent to (within 25 words)		

APPENDIX B: MACRONUTRIENT CODING FORM

Study ID:		Macronutrient Coding Form Observation-Point Data for Macronutrients and Lipid Profile
Group:		

Author: Journal: Year: Volume: Pages:

[ ] ↑ Carb [ ] ↑ Fat [ ] ↑ Protein
[ ] ↓ Carb [ ] ↓ Fat [ ] ↓ Protein (AMDRs: Fat = 20-35%, Prot = 10-35%, Carb = 45-65%)

Rx	**Dietary**										
	Dur (d)	kJ	kJ SD	kcal	kcal SD	TFat %	TFat SD	Prot %	Prot SD	Carb %	Carb SD
1											
2											
3											
4											

Study ID:		Macronutrient Coding Form Observation-Point Data for Macronutrients and Lipid Profile
Group:		

Author: Journal: Year: Volume: Pages:

[ ] ↑ Carb [ ] ↑ Fat [ ] ↑ Protein
[ ] ↓ Carb [ ] ↓ Fat [ ] ↓ Protein (AMDRs: Fat = 20-35%, Prot = 10-35%, Carb = 45-65%)

Lipid Profile																
Pre-Treatment: [ ] mg/dL OR [ ] mmol/L								**Rx**	Post-Treatment: [ ] mg/dL OR [ ] mmol/L							
TC	TC SD	HDL	HDL SD	LDL	LDL SD	TRIG	TRIG SD		TC	TC SD	HDL	HDL SD	LDL	LDL SD	TRIG	TRIG SD
								1								
								Δ								
								2								
								Δ								
								3								
								Δ								
								4								
								Δ								

Value	Variable Description
	Location of subjects: 1.) Metabolic Ward 2.) Hospital or other Healthcare Institution 3.) Free-Living 4.) Outpatient with meals taken in Institution 5.) Combination of 1 & 3 6.) Combination 3 & 4
	Total number of subjects for entire study (N)
	Group size
	Percent male (decimal)
	Percent female (decimal)
	Mean Age (years)
	Standard Deviation of Age
	Allocation concealment/Blinding: 1.) Single 2.) Double 3.) Unblinded
Control of confounding variables: 1.) Design 2.) Statistical 3.) No control	
	Apriori control of Body Weight
	Apriori control of Smoking
	Apriori control of Blood Pressure
	Apriori control of Physical Activity
	Apriori control of Calorie Intake
	Body weight controlled during study: 1.) Yes 2.) No
	Percentage attrition of this treatment group
	Percentage attrition of comparison groups
	Compliance to treatment: 1.) good 2.) fair 3.) poor 4.) unknown
	Method of assessing dietary compliance: 1.) Self reported intake records of three days or less 2.) Self reported intake records of 4-6 days 3.) Self reported intake records of 7-10 days 4.) Weighted and/or measured intake records in an institutional setting 5.) Combination intake records and measured/weighed intake 6.) Dietary interview (24 or 48 hour recall) 7.) Observation of measured intake 8.) Unknown 9.) Food Frequency Questionnaire (FFQ)

APPENDIX C: STUDIES INCLUDED IN THE META-ANALYSIS

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APPENDIX D: CHARACTERISTICS OF STUDIES IN THE META-ANALYSIS, WITH RISK OF BIAS

Adler 1997[152]	Study ID: 9022529	
Methods	RCT, blinded, placebo-controlled parallel trial.	
Participants	46 men (age 45.9±11.1y, BMI 26.8±4.1 kg/m^2) without diabetes or CVD, but who had TC >200mg/dL. Participants were excluded if taking lipid-altering, or blood pressure medications or supplements within 4 weeks of the beginning of the study.	
Interventions	After a 3-wk run-in, subjects were randomized into one of four treatment groups for 12 weeks: 1.) 900mg garlic placebo & 12g fish oil placebo; 2.) 900mg garlic & 12g fish oil placebo; 3.) 900mg garlic placebo & 12g fish oil; 4.) 900mg garlic & 12g fish oil.	
Outcomes	Total cholesterol, LDL, triglycerides, tolerance to treatment.	
Notes	Only the double placebo group was used for the meta-analysis.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	Randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Garlic pills were administered in a double-blind fashion, whereas fish oil and oil placebo were administered in a single-blind fashion. The blinding to the supplements and the placebos was checked at the end of the study by use of a questionnaire.
Blinding – All Outcomes (Detection Bias)	Low	Blinded, but information about the blinding of the outcome assessors not reported.
Incomplete outcome data (Attrition Bias)	Low	50 were originally randomized, and 46 completed the study (8% attrition). One subject withdrew from group 1, one from group 2, and two from group 3; all reported withdrawals were for personal reasons or unrelated medical reasons.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes, although compliance was measured through pill counts and serum phospholipid analyses, and no subjective questionnaire was administered to gauge tolerability of the treatments.
Other Bias	Low	None observed.

Free of systematic difference in treatment?	Low	All groups seemed to receive similar treatment.
Free of dietary differences other than macronutrients?	Low	Since the supplements would have effects independent of the macronutrient distribution, the double placebo group was chosen for the meta-analysis.

Alhassan, 2006[153]	Study ID: 16546486	
Methods	RCT, Double-blind, placebo-controlled parallel design	
Participants	26 healthy, sedentary subjects (14 men, 12 women), aged 53±8y, BMI 27±1 kg/m^2. Nonsmokers, not taking medications known to alter lipids, capable of exercise, TC of 240mg/dL or less or TG of 200mg/dL or less.	
Interventions	Intervention group received a plant sterol ester (PSE) margarine or a placebo margarine, with or without exercise. Participants consumed the margarine over 4 weeks, and measurements were taken during the following week, while still consuming the product. Exercise was then conducted over the next 4 weeks, while still taking the spread.	
Outcomes	Independent and combined effects of PSE and aerobic exercise on blood lipids. Activities of lipoprotein lipase and cholesterol ester transfer protein.	
Notes	Exercise group (MS + EX) was not included in analyses, as the focus was the effect of dietary change.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment (Selection Bias)	Unclear	Gender-stratification was the only information reported about the allocation.
Blinding – All Outcomes (Performance Bias and Detection Bias)	Low	Double-blinded study, although the description of the procedure was not reported. The study used a placebo.
Blinding – All Outcomes (Detection Bias)	Low	Double-blind, but information about the blinding of the outcome assessors not reported.
Incomplete outcome data (Attrition Bias)	High	39 initially randomized (23 Intervention, 16 Placebo) 26.1% attrition in Treatment versus 43.8% Placebo. 3 withdrew from treatment, 3 removed from intervention. 1 withdrew from placebo, 6 were

		removed.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	None observed.
Free of systematic difference in treatment?	Low	Both groups seemed to get similar treatment.
Free of dietary differences other than macronutrients?	High	The main interventions dealt with PSE and/or exercise, either of which could affect blood lipids beyond the effect of changes in dietary macronutrients.

Assuncao,2009(A/B)[154]	Study ID: 19437058	
Methods	RCT, Double-blinded, parallel design	
Participants	40 abdominally-obese non-pregnant women from Brazil, between the ages of 20-40y (28.5±6.7y Soybean and 31.0±6.4y coconut). Low socioeconomic status, non-menopausal.	
Interventions	40 women randomized into two equal groups: Soybean or Coconut oil capsules. The treatment period was 12 weeks.	
Outcomes	Anthropometric data, lipid profile, as well as insulin, glucose, and some inflammatory parameters.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT, paired according to BMI
Allocation Concealment Selection Bias	Unclear	Randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind, placebo-controlled. Both treatment and placebo capsules were similar in color, odor, and flavor, and presented to subjects in identical containers. From report: “Both the physical trainer and the nutritionist were not aware of the distribution of the individuals between study groups.”
Blinding – All Outcomes Detection Bias	Low	Double-blind, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data	Low	No withdrawals were reported.

(Attrition Bias)		
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	None observed.
Free of systematic difference in treatment?	Low	No differences in treatment could be detected.
Free of dietary differences other than macronutrients?	High	Different oils, with different effects on blood lipids aside from the effects seen from total macronutrients.

Beavers, 2010(A/B)[155]	Study ID: 20521988	
Methods	RCT, Single-blinded, parallel study.	
Participants	32 active postmenopausal women (53.88±3.65y soy group & 54.87±3.05y dairy group) with a BMI between 19-35kg/m^2. No HRT, underlying health problems, or smoking, no supplements aside from multivitamins.	
Interventions	After a 2-week run-in, subjects were randomly assigned to either a soymilk or dairy milk group for 4 weeks, with 4-d intake records.	
Outcomes	Blood lipid profile.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. Participants were matched based on baseline protein intake and cardiopulmonary fitness level, which was tested before randomization.
Allocation Concealment Selection Bias	Unclear	Randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Single-blinded. From report: “The milk was provided to participants in black bags…in such a way that investigators were blinded to treatment order.” Even if participants knew dietary treatment, unlikely they could manipulate a biomarker like lipid profile.
Blinding – All Outcomes (Detection Bias)	Low	Single-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data	Low	32 subjects randomized, and 32 completed study.

(Attrition Bias)		
Selective Reporting (Reporting Bias)	Low	Authors reported data on all proposed outcomes.
Other Bias	Low	No other biases observed.
Free of systematic difference in treatment?	Low	No differences detected.
Free of dietary differences other than macronutrients?	High	Different types of protein and fat that could impact the blood lipids aside from total macronutrient distribution.

Chan, 2002(A/B)[156]	Study ID:12059988	
Methods	RCT, double-blind placebo-controlled 2X2 factorial design	
Participants	49 obese men (BMI >29kg/m^2, waist circumference >100cm, aged 50±2.5y for placebo group, 58±2.2y for fish oil group.) without diabetes, abnormal renal or hepatic conditions, or consumed fish oil supplements.	
Interventions	After a 3 week run-in, individuals were randomized into either fish oil, corn oil placebo, statin + placebo, or statin + fish oil for 6 weeks. Habitual diets kept weight from varying more than 2%, and assessed via 24hr recall.	
Outcomes	Lipids and lipoproteins, RLP-C and apoC-III.	
Notes	Atorvastatin (n=14) or Atorvastatin + fish oil (n=12) groups were not included in the meta-analysis.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but method of allocation concealment not reported.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind, but description of the blinding procedure was not reported.
Blinding – All Outcomes (Detection Bias)	Low	Double-blind, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	52 originally randomized, 49 completed study; no reasons were given for withdrawals. Losses were similar between groups: 1 lost in Fish oil, one in Atrovastatin, one in Atrovastatin + fish oil.)

Selective Reporting (Reporting Bias)	Low	Authors reported all proposed outcomes.
Other Bias	Low	No additional bias detected.
Free of systematic difference in treatment?	Low	No differences in treatment observed.
Free of dietary differences other than macronutrients?	High	Corn oil versus fish oil supplements could impact the lipid profile independent of effect of dietary macronutrients.

Diaz, 2008(A/B)[157]	Study ID: 17531459	
Methods	RCT, double-blind, placebo-controlled parallel trial.	
Participants	38 generally healthy, overweight, premenopausal women (age 36±5.9y, BMI 28.0±0.5kg/m^2).	
Interventions	There was a 2-wk "baseline" period and 12-wk intervention consisting of diet, supplementation and exercise. During the baseline, women remained sedentary, and did not consume any supplements. During the 12-wk intervention, subjects received dietary counseling, provided either a placebo or a combined chromium picolinate and conjugated linoleic acid supplement, and instructed to perform moderate exercise (30 min of walking or jogging 5/d a week). The macronutrient distribution was: 15-20% Pro, 50-55% carbohydrate, and 30-35% fat.	
Outcomes	Body weight, body composition, indices of metabolic and cardiovascular health.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	From report: "Randomized assignments to the placebo group or the CP-CLA supplement group were made based on the date the women qualified to participate in the study. The subjects were not matched based on any physical, metabolic or lifestyle characteristics at the time of randomization."
Blinding – All Outcomes (Performance Bias)	Low	Double-blind design. From report: "The CP-CLA and placebo capsules were…placed in coded bottles by a technician otherwise not involved in the research project and provided to staff in a blinded fashion."

Blinding – All Outcomes (Detection Bias)	Low	From report: "All other research staff remained blinded with respect to the subject's group assignment until after all testing and sample analyses were completed."
Incomplete outcome data (Attrition Bias)	High	59 subjects were randomized into the study, and 38 completed the trial (36% attrition). There were twice as many dropouts in the placebo group (14) compared to the treatment group (7). 5 subjects cited not having enough time to complete the trial, 2 wished to get pregnant, 1 dropped out at her physician's request, 1 withdrew due to personal issues, 1 left due to nausea, and 6 withdrew for unspecified reasons. Data from 3 women were excluded because they exercised too much.
Selective Reporting (Reporting Bias)	Low	Authors reported all proposed outcomes.
Other Bias	Low	No other biases observed.
Free of systematic difference in treatment?	Low	No differences were observed between the groups.
Free of dietary differences other than macronutrients?	Unclear	The supplementation and the exercise may have an effect on lipid profile independent of the macronutrient distribution.

Dodin, 2005(A/B)[158]	Study ID:15613422	
Methods	RCT, double-blinded parallel trial.	
Participants	179 healthy menopausal women (85 in flaxseed group, aged 54.0±4; 94 in wheat germ group, aged 55.4±4.5) having a serum FSH $\geq$40. Excluded for history of major chronic illness, regularly consumed soy or flaxseed, took medications that affected lignin absorption, or had an allergy to flaxseed.	
Interventions	Subjects were randomized to consume either 40g of flaxseed or wheat germ for one year. Dietary intake was measured using FFQ and 3d diary.	
Outcomes	Lipid profile, bone mineral density symptoms, anthropometrics, and BP.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	From report: "The randomization schedule was prepared by the clinical unit of the research center…using computer-generated randomization in blocks of 4 to 8.
Allocation	Unclear	RCT, but while the specific method of allocation

Concealment Selection Bias		concealment was not described, the study was randomized and double-blinded.
Blinding – All Outcomes (Performance Bias)	Low	Double-blinded. From report: "Subjects, investigators, and staff were blinded to dietary assignments for the duration of the study."
Blinding – All Outcomes (Detection Bias)	Low	Double-blinded. From report: "…staff and statisticians were blinded to the dietary assignments for the duration of the study."
Incomplete outcome data (Attrition Bias)	High	199 randomized and 179 completed the study: 85 flax (15.8% attrition) and 94 placebo (4.1%). More were lost in treatment arm: 16 lost to follow-up and 10 discontinued but had an endpoint. For the placebo: 4 were lost to follow-up and 13 discontinued, but had an endpoint. Reasons were given for all lost subjects.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	No other biases noted.
Free of systematic difference in treatment?	Low	No differences in treatment noted.
Free of dietary differences other than macronutrients?	High	The flaxseed intervention may have an impact on blood lipids beyond the mere change in macronutrients.

Esposito, 2004[159]	Study ID:15213209	
Methods	RCT, single-blind parallel trial.	
Participants	110 sedentary obese men (43.5±4.8y; BMI: 36.9±2.5kg/m^2) with erectile dysfunction. Exclusions: any glucose intolerance, hypertension, CVD, or other serious disorders, drug or alcohol abuse.	
Interventions	Intervention group was given detailed advice to reduce body weight by 10%. Dietary advice was tailored to each man based on 3 food diaries, and the intervention lasted 2yr. The control group only received general information.	
Outcomes	Long-term weight reduction, increase in physical activity, endothelial function (like lipid profile) and erectile function.	
Notes	Only the intervention group was used in the meta-analysis.	
Risk of Bias		
Random sequence generation	Low	RCT, from report: "Men were randomly assigned to either the intervention or control group using a

(Selection Bias)		computer-generated random number sequence."
Allocation Concealment Selection Bias	Low	From report: "Allocation was concealed in sealed study folders that were maintained at a central secure location until informed consent was obtained."
Blinding – All Outcomes (Performance Bias)	Low	Single-blinded design. From report: "The nurses who scheduled the study visits did not have access to the randomization list." However, the staff members involved in the intervention had to know the group assignments, and the participants likely knew what intervention they were assigned to, but given the inclusion criteria and outcomes, it is unlikely that knowledge of the treatment would affect lipid profile.
Blinding – All Outcomes (Detection Bias)	Low	Single-blinded design. From report: "Laboratory staff did not know participants' group assignments."
Incomplete outcome data (Attrition Bias)	Low	110 total subjects were randomized (55 to each group); 3 withdrew and declined follow-up from each group (5.5% attrition), but all 6 who withdrew were still included in analysis because they happened after 24 weeks of follow-up.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	No other biases observed.
Free of systematic difference in treatment?	High	The intervention inherently would lead to differences between treatment and control groups.
Free of dietary differences other than macronutrients?	Unclear	More detailed dietary data would be needed to ascertain whether any components within the diets (especially the control group) would affect the lipid profile beyond the macronutrients distribution.

Esposito, 2004(A/B)[160]	Study ID:15383514
Methods	RCT, single-blind parallel trial.
Participants	180 sedentary, weight stable nonsmokers with metabolic syndrome. Exclusions: CVD, psychiatric disorders, alcohol abuse, or use of any medication. 90 subjects (54% male) in intervention group, aged 44.3±6.4y; 90 subjects (56% male) in control group, aged 43.5 ±5.9y.
Interventions	Randomized to either a Mediterranean diet or a control prudent diet. Both diets had similar macronutrient composition, but the

	intervention diet focused on increased consumption of fruits, vegetables, whole grains and walnuts. Diets were assessed by 3d food records. The control group received more generalized advice.	
Outcomes	Endothelial function and vascular inflammation related to metabolic syndrome, including lipid profile.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT, from report: “Patients were randomly assigned to either the intervention or control group using a computer-generated random number sequence.”
Allocation Concealment Selection Bias	Low	From report: “Allocation was concealed in sealed study folders that were maintained at a central secure location until informed consent was obtained.”
Blinding – All Outcomes (Performance Bias)	Low	Single-blinded design. From report: “The nurses who scheduled the study visits did not have access to the randomization list.” However, the staff members involved in the intervention knew group assignments, and participants likely knew assigned intervention, but given the inclusion criteria and outcomes, it is unlikely that knowledge of the treatment would affect lipid profile.
Blinding – All Outcomes (Detection Bias)	Low	Single-blinded design. From report: “Laboratory staff did not know participants’ group assignments.”
Incomplete outcome data (Attrition Bias)	Low	180 randomized 90 to each group. 8 subjects in each group withdrew (8.9% attrition), but were still included in analyses because this occurred after 24 weeks of follow-up.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	No other biases observed.
Free of systematic difference in treatment?	High	There were differences between the advice related to diet and exercise between the two groups, but this was intended.
Free of dietary differences other than macronutrients?	Unclear	Since the diets did not contain any medications or supplements, only the quality of the macronutrients (walnuts) might impact the blood lipids differently.

Fakhrzadeh, 2010[161]	Study ID: 20803425	
Methods	RCT, double-blinded, placebo-controlled parallel trial.	
Participants	124 Iranian elderly subjects (41.1% male, age 74.8±9.4y, BMI 25.5±5.8 kg/m^2, 18% were smokers, 14% had diabetes). Exclusion criteria were liver disease, cardiac and renal disease, coagulation disorders, or allergies to fish.	
Interventions	Subjects were randomized to one of two groups: a treatment group who received 1g fish oil capsule per day (180mg EPA, 120mg DHA, 300mg n-3) or 1g MCT oil placebo for 6 months. They were asked to keep their diet and other lifestyle patterns the same. Diet was measured with 3-d recalls.	
Outcomes	Lipid profile, lipoprotein subtypes, glucose, insulin, and insulin resistance.	
Notes	Only the placebo group was included in the meta-analysis.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blinded. From report: "Subjects and investigators were blinded to the intervention."
Blinding – All Outcomes (Detection Bias)	Low	Double-blinded design, but specifics regarding the blinding of outcome assessors not reported.
Incomplete outcome data (Attrition Bias)	Low	134 subjects were randomized into the study, and 124 completed the trial (7.7% attrition). Ten persons refused to complete the trial, but no mention as to specific reasons or group assignment was reported.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No differences between the groups were detected.
Free of dietary differences other than macronutrients?	Low	Since the fish oil supplements would alter the lipid profile independently from the macronutrient distribution, only the placebo group was included in the meta-analysis.

Gardner, 2007(A-D)[162]	Study ID: 17341711	
Methods	RCT, single-blind, parallel trial.	
Participants	311 healthy, overweight or obese, premenopausal women (age 41±6y, BMI 32±4 kg/m^2). Subjects were excluded if they had a history of hypertension, diabetes, heart, renal, or liver disease, cancer, uncontrolled thyroid disorders, consumed excessive alcohol, were pregnant, lactating, or took any medications known to affect weight.	
Interventions	Subjects were randomized to one of four dietary plans: 1.) Atkins 2.) Zone 3.)LEARN 4.) Ornish for one year. Each diet group received a 1hr class regarding the diet, and data was recorded a baseline, 2, 6, and 12 months. Dietary intake was measured by unannounced 3-day, 24-hour recalls.	
Outcomes	Weight loss and related metabolic variables, including lipid profile.	
Notes	The 2-month data were used, since this provided the greatest number of subjects for the lipid profile analysis.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Low	From report: "Randomization was conducted in blocks of 24 (6 per treatment group) and occurred by having a blinded technician select folded pieces of paper with group assignments from an opaque envelope.
Blinding – All Outcomes (Performance Bias)	Low	Single-blinded design, where the researchers were not informed what diet the subjects were on, but each participant received a book detailing their respective diet.
Blinding – All Outcomes (Detection Bias)	Unclear	It is unclear how those who were involved in outcome assessment remained blinded during the course of the trial, especially since the participants knew what diet they were on.
Incomplete outcome data (Attrition Bias)	Low	At the 2 month mark, 24 subjects had withdrawn from the study (7.7% attrition), leaving 287. The reasons for withdrawals and the group assignments were reported by the authors, and did not differ greatly at 2-months. (Incidentally, 249 completed the full 12-month intervention, with 20% attrition.)
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.

Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No major differences were seen between the treatments.
Free of dietary differences other than macronutrients?	Low	The intervention compared different diets that focus primarily on different levels of carbohydrate intake.
Goyens, 2006(A/B)[163]	Study ID:16482073	
Methods	RCT, double-blind parallel trial.	
Participants	37 subjects (64.7±4.2y, 37.8% male) who had TC <8.0 mmol/L, TG <3.0mmol/L, free of medications or specialized diets known to affect parameters of interest.	
Interventions	Subjects followed a run-in diet rich in oleic acid for three weeks. Participants were then randomized to either the ALA group (n=14), EPA/DHA group (n=13), or to continue on the Oleic acid (n=10).	
Outcomes	Lipid profile, coagulation and fibrinolytic factors, and endothelial function.	
Notes	Oleic to ALA, and Oleic to DHA/EPA were recorded, as these were the only two interventions that changed the diet.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT, stratified for gender.
Allocation Concealment Selection Bias	Low	From report: "Subjects were randomly allocated…as was described previously."
Blinding – All Outcomes (Performance Bias)	Low	Double-blind, but description of the blinding procedure was not reported. All dietary fats came in the form of experimental shortenings, and assessment was made with food diaries.
Blinding – All Outcomes (Detection Bias)	Low	Double-blind, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	41 subjects randomized, 37 completed the trial and were analyzed (9.8%). Two were excluded due to medication use, one withdrew due to personal reasons, one had incomplete data.
Selective Reporting (Reporting Bias)	Low	Authors reported data on all proposed outcomes.
Other Bias	Low	No other biases observed.

Free of systematic difference in treatment?	Low	No differences in treatment observed.
Free of dietary differences other than macronutrients?	High	Since the difference between the treatments was related to the type of fat, there were additional factors that would influence blood lipids beyond the macronutrient distribution.

Gylling, 2010(A/B)[164]	Study ID:19709787	
Methods	RCT, double-blind, placebo-controlled parallel design.	
Participants	49 healthy subjects (35% male, aged 61.8±7.9y), with TC 4.5-7.5mmol/L, free of medications known to lower lipids.	
Interventions	25 individuals comprising the intervention group consumed vegetable oil-based spreads and consumed oat-based drinks enriched with PSE for 10 wks; the 24 people in the control group consumed the same plant products, without the PSE. 3d food records.	
Outcomes	Serum total cholesterol and safety outcomes related to high PSE consumption.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. From report: "The 1/1 randomization was performed according to a computer generated randomization list."
Allocation Concealment Selection Bias	Low	RCT and information about the allocation was not made available to researchers until after the study.
Blinding – All Outcomes (Performance Bias)	Low	Double-blinded. From report: "The products were received blinded with computer generated different colors…and the color codes were opened after all analyses were performed."
Blinding – All Outcomes (Detection Bias)	Low	Double-blinded, but information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	51 randomized, and 49 completed (3.9% attrition). One subject from each group withdrew due to refusal to drink test drink, and because cholesterol meds were started.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	No other biases observed.

Free of systematic difference in treatment?	Low	No differences in treatments observed.
Free of dietary differences other than macronutrients?	High	PSE content in intervention group may have an impact beyond macronutrient distribution.

Han, 2007(A/B)[165]	Study ID: 17570262	
Methods	RCT, single-blinded, placebo-controlled trial.	
Participants	40 subjects from China (20% male, between the ages of 45-65y) with diabetes, stable body weight, free from HTN, CVD, or other systemic diseases. Participants maintained any prescribed medications.	
Interventions	Subjects were randomized into two groups: one group received 18g/d MCT oil and the other received 18g/d corn (LCT) oil for 90 days.	
Outcomes	Body weight, insulin sensitivity, and serum lipid profile.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. Subjects were randomized based on medications, medical conditions, age, sex, and initial body weight.
Allocation Concealment Selection Bias	Unclear	RCT, but information about the allocation was not made available to researchers until after the study.
Blinding – All Outcomes (Performance Bias)	Unclear	Single-blinded. From report: "The subjects were not informed of the nature of the oil…" No information about the blinding of the research personnel was provided.
Blinding – All Outcomes (Detection Bias)	Unclear	Single-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	40 subjects were randomized, and 40 completed the study.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	No other forms of bias were observed.
Free of systematic difference in treatment?	Low	No significant differences between the groups were noted.
Free of dietary	High	Since the difference between the interventions is

differences other than macronutrients?		the quality of the oil in the supplement, there would be influences beyond the total amount of fat in the diets.

Hjerkinn, 2005[166]	Study ID:15755826	
Methods	RCT, single-blinded 2X2 factorial design.	
Participants	487 elderly dyslipidemic men (~70y). Excluded if thought to have illness that would affect longevity, study compliance, or had to travel a great distance.	
Interventions	282 subjects randomly assigned to receive n-3, and 281 received a corn oil placebo for 3 years, and 281 with or without dietary counseling. Four groups: control group (no diet advice, on placebo), diet + placebo, no diet + n-3, diet + n-3. FFQ was used to assess dietary intake.	
Outcomes	Markers of endothelial activation.	
Notes		
Risk of Bias	Pooled lipid levels for the groups diet + n-3 and diet + placebo, since the dietary data were pooled.	
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Unclear	Single-blinded, subjects were blinded for the n-3 supplementation. No mention of methods used to blind study personnel.
Blinding – All Outcomes (Detection Bias)	Unclear	Single-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Unclear	563 randomized, 487 completed trial (13.5% attrition). 38 had died, 29 dropped out due to disease states interfering with study follow-up, and 9 were unwilling to complete.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	No other biases observed.
Free of systematic difference in treatment?	High	One of the interventions was dietary counseling, so differences in treatment were introduced by design.
Free of dietary	High	Supplementation with n-3 may affect lipid profile

differences other than macronutrients?		independently of macronutrient distribution.

Hollis, 2009(A-C)[167]	Study ID:20439553	
Methods	RCT, double-blinded parallel trial.	
Participants	76 generally healthy, non-smoking, non-obese adults 18-50y. Excluded if regularly consumed red wine or grape products or dietary supplements that would alter outcomes.	
Interventions	Randomly assigned to 1 of 3 groups: Concord grape juice, a polyphenol-free grape drink, and a no-treatment control group. There was a 1 week run-in, followed by a 12wk intervention.	
Outcomes	Body weight, markers of metabolic syndrome, and antioxidant capacity.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind. From report: “The participants and investigators were blinded to the identity of the beverages.”
Blinding – All Outcomes (Detection Bias)	Low	Double-blind, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Unclear	86 recruited, and 76 completed the study (11.6% attrition), but unclear from which groups the withdrawals came or how many had been randomized.
Selective Reporting (Reporting Bias)	Unclear	The list of outcomes was vague, and while weight and biochemical parameters related to metabolic syndrome were measured and reported, parameters like blood pressure were not.
Other Bias	Low	No other biases observed.
Free of systematic difference in treatment?	Unclear	The control group was given no dietary advice by design.
Free of dietary	Unclear	The polyphenols in the grape juice may have an

differences other than macronutrients?		independent effect on blood lipids aside from changes in macronutrient distribution.

Kasai, 2003(A/B)[168]	Study ID:12810404	
Methods	RCT, double-blinded parallel trial.	
Participants	82 non-obese, generally healthy adults (75 men, 7 women) who were somewhat physically active.	
Interventions	Subjects were randomly assigned to either a LCT diet or MLCT diet for 12 weeks, while maintaining their present level of physical activity. Diet was assessed by daily diaries throughout the study.	
Outcomes	Body fat	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blinded, but description of the blinding procedure was not reported.
Blinding – All Outcomes (Detection Bias)	Low	Double-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Unclear	93 subjects randomized, and 82 completed the trial (11.8% attrition). 10 subjects were unable to consume their specified meal for 3 consecutive days and were excluded, and one opted out of the study; the group assignments for the withdrawals were not reported.
Selective Reporting (Reporting Bias)	Low	The authors reported additional outcomes compared to study aims.
Other Bias (Carryover bias, etc.)	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No difference in treatment was observed.
Free of dietary differences other than	High	The difference in fat quality between the two diets may have an affect aside from the macronutrient

macronutrients?		distribution.

Kasim-Karakas, 2009(A/B)[169]	Study ID:18691705	
Methods	RCT, Single-blinded parallel design.	
Participants	24 female subjects, aged 18-45, with polycystic ovary disease. Excluded if taking medications or supplements that may alter weight or insulin sensitivity within the last 2 months or had chronic illness or excessively consumed alcohol.	
Interventions	The subjects were randomized to one of two hypocaloric diets: a simple sugar group (n=13) and a protein group (n=11) for 2 months. 7 day food records were used to assess diet.	
Outcomes	Changes in body composition, leptin, adiponectin, plasma lipids, glucose homeostasis, and CRP.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Low	From report: "…subjects were randomized using a block design provided by the Research Randomizer (program)."
Blinding – All Outcomes (Performance Bias)	Low	Single-blinded. The dietitians were blinded to the randomization scheme, and the daily servings were packaged to look identical to subjects.
Blinding – All Outcomes (Detection Bias)	Unclear	Single-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Unclear	33 subjects were randomized and 24 completed the trial (18.75% attrition in simple sugar group and 17.6% in protein group). The reason for each withdrawal was clearly reported, but the total number of withdrawals compared to those originally randomized may introduce some bias.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias (Carryover bias, etc.)	Low	No other biases observed.
Free of systematic difference in treatment?	Low	No significant differences in treatment observed.

Free of dietary differences other than macronutrients?	Low	The difference in the treatments was related to macronutrients.

Kawashima,2008(A/B)[170]	Study ID:18155990	
Methods	RCT, double-blind, placebo-controlled, parallel design.	
Participants	277 obese subjects (BMI ≥25; 55% men, age 47.8±10.3y), with either hypertension and/or elevated TG (≥150mg/dL). Excluded if on medications or a diet that would affect weight and/or serum TG.	
Interventions	Subjects were randomized into either a diacylglycerol or triacylglycerol group, using the test oil for cooking for 12 months.	
Outcomes	Body weight and serum TG.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blinded. From report: "Test oils were bottled in unlabeled (plastic) containers. Taste and appearance of the (DG and TG) oils were similar and participants could not distinguish between them."
Blinding – All Outcomes (Detection Bias)	Low	Double-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Unclear	312 subjects randomized and 277 completed the trial; 21 lost in the DG (16.8% lost) and 14 in TG (11.5% lost). 9 subjects failed to submit a baseline dietary record, and 303 participants included in intention-to-treat analysis.
Selective Reporting (Reporting Bias)	Low	Authors reported more than stated primary outcomes.
Other Bias (Carryover bias, etc.)	Low	No other biases detected.
Free of systematic difference in treatment?	Low	No significant differences between the two treatments observed.

Free of dietary differences other than macronutrients?	Unclear	Not certain how the differences between the two fats would affect blood lipids beyond their contribution as total fat in the diet.

Kelley, 2007(A/B)[171]	Study ID:17684201	
Methods	RCT, double-blind placebo-controlled study.	
Participants	34 moderately hyperlipidemic men (aged 54.1±1.6y); excluded if taking medications or supplements known to alter lipids	
Interventions	Subjects maintained their normal diet and were randomly assigned to either a DHA group or a control group using olive oil for 90 days. 24 hour recalls were used to assess diet.	
Outcomes	Blood lipids	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blinded, but description of the blinding procedure was not reported.
Blinding – All Outcomes (Detection Bias)	Low	Double-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	40 subjects were randomized and 34 completed the study. Three subjects withdrew from each group; their reasons were also similar between groups.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias (Carryover bias, etc.)	Low	No other biases observed.
Free of systematic difference in treatment?	Low	No differences between treatments observed.
Free of dietary differences other than macronutrients?	High	The study design compared two different oils, which may impact lipid profile independently than macronutrient distribution.

Levin, 1990[172]	Study ID: 2203322	
Methods	RCT, double-blinded, placebo-controlled parallel trial.	
Participants	58 overweight men and women (aged 32-70y, 81% male), with total cholesterol >200mg/dL and TG <3.39mmol/L. Subjects were excluded if they had significant acute or chronic disease, took fish oil supplements, soluble fibers, or other medication known to affect blood lipids.	
Interventions	Subjects were placed on an 8-wk stabilization period with the AHA Step-I diet, and then randomized to either a psyllium fiber group, or a placebo of cellulose. Subjects consumed 5.1g of fiber in 240mL of water twice a day for 16 weeks. Compliance was measured by counting unopened packets. 3-day food records were used to assess diet.	
Outcomes	Plasma lipid/lipoproteins, glucose, iron, ferritin levels and coagulation studies.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind design. From report: “Both test products were provided to subjects in identical foil packets…”
Blinding – All Outcomes (Detection Bias)	Low	Double-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	62 subjects were randomized into the study, and 58 completed the trial (6.5% attrition). However, the reasons and group assignments for these individuals were not reported.
Selective Reporting (Reporting Bias)	Low	Authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No other differences between the
Free of dietary differences other than	Low	The psyllium fiber group was sugar free, and the placebo group was indigestible cellulose, so there

macronutrients?		was little else to influence blood lipids.

Maki, 2005(A/B)[173]	Study ID: 15930485	
Methods	RCT, double-blind, placebo-controlled parallel trial.	
Participants	57 subjects (age 53.6±11.8y, 54% male, BMI ~30kg/m^2) who were in generally good health but had reduced HDL levels. Subjects were excluded if BMI >40, total cholesterol >300mg/dL, TG >350mg/dL.	
Interventions	Subjects were randomized to receive either capsules containing DHA-rich algal oil or control capsules of olive oil for six weeks. 3-d diet records were used to monitor intake.	
Outcomes	Fasting lipid and lipoprotein response.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind design. From report: “Study products…were indistinguishable from one another in appearance and odor.” Subjects were given a questionnaire related to side effects and the nature of the supplement they took.
Blinding – All Outcomes (Detection Bias)	Low	Double-blind design. From report: “All assessments were completed prior to breaking the treatment code, thus without knowledge of treatment assignment.”
Incomplete outcome data (Attrition Bias)	Low	61 subjects randomized, and the results from 57 were included in analysis. 2 subjects did not complete the treatment; one was lost to follow-up and the other had an abnormal baseline lab but was mistakenly randomized. Two others had excessive weight gain, and were excluded before breaking the treatment code.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	Treatment groups seemed to be treated the same.

Free of dietary differences other than macronutrients?	High	The quality of the oil will affect blood lipids independently of the total fat contained in the diets.

Malpuech-Brugere, 2010(A-C)[174]	Study ID: 20485306	
Methods	RCT, double-blinded, controlled parallel trial.	
Participants	107 healthy non-smoking subjects (50.5% male, age 26.3±11.7y, BMI ~22kg/m^2) with HDL>1mmol/L, LDL<4.1mmol/L, TG <1.7mmol/L.	
Interventions	Subjects consumed an experimental product during a 1-wk run-in period. They were then randomized to one of three groups for 3 weeks: 1.) to stay on the run-in diet (72% SFA), 2.) to consume a product with 63.3% SFA 3.) to consume a product with 56.6% SFA. Dietary intake was assessed by 5-day records.	
Outcomes	CVD risk factors, including lipid profile.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. Volunteers were stratified based on gender.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind trial. Subjects would not be able to tell the fatty acid composition of the test products. However, specific details related to the blinding of research subjects or personnel were not reported.
Blinding – All Outcomes (Detection Bias)	Low	Double-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	111 subjects were randomized and 107 completed the trial (3.6% attrition). The reasons for the withdrawals were not reported.
Selective Reporting (Reporting Bias)	Unclear	The proposed criteria of “CVD risk factors” were vague, and while lipids and fibrinogen was reported on, no markers of inflammation or coagulation were performed.
Other Bias	Low	No other biases were observed.

Free of systematic difference in treatment?	Low	No differences between the treatment groups were observed.
Free of dietary differences other than macronutrients?	High	The differences between the treatment groups were based primarily on their saturated fat content, and this would likely impact blood lipids differently, despite the total fat percentages being nearly identical.

Melanson,2004(A/B)[175]	Study ID: 15474871	
Methods	RCT, single-blinded parallel trial.	
Participants	90 non-smoking, sedentary subjects (14.4% male, age 42.6±6.0y, BMI 31.5±2.8kg/m^2) who were free of major diseases.	
Interventions	Subjects were randomly assigned to either an exercise-only group, or one that combined diet plus exercise for 12 weeks. The macronutrient composition of the diet was approximately 50% CHO, 25% Prot, and 25% fat; intake was assessed through 3-day food records.	
Outcomes	Body composition, fitness, plasma lipids, weight loss, quality of life, and mood.	
Notes	Only included the diet plus exercise group in the meta-analysis.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Low	From report: "To ensure unbiased group placement, an off-site statistician randomized subjects blindly through a computer-generated program after controlling for sex distribution."
Blinding – All Outcomes (Performance Bias)	Unclear	The subjects would have known if they were in the exercise only group or the diet and exercise group. No specific details regarding the blinding of research personnel were described.
Blinding – All Outcomes (Detection Bias)	Unclear	Information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	High	90 subjects were randomized, and 28 were lost in the exercise only group, while 21 were lost in the diet and exercise group (48.8% attrition). The reasons for the withdrawals were not reported, and

		the large number of withdrawals may introduce bias.
Selective Reporting (Reporting Bias)	Low	The authors reported on all the proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	There was difference with respect to the dietary recommendations given to the diet and exercise group, but this was intended.
Free of dietary differences other than macronutrients?	Low	While the impact of exercise cannot be parsed from the dietary treatment, there were no other dietary factors that would influence lipid profile.

Mensink,2002(A/B)[140]	Study ID: 11755939	
Methods	RCT, double-blind, placebo-controlled, parallel trial.	
Participants	60 relatively healthy subjects (26.7% male, age 36±14y, BMI 23.3±2.7kg/m^2) with mean fasting total cholesterol <251mg/dL, TG <266mg/dL, BMI <30, BP <160/95mmHg. Exclusions included: medications affecting lipids, abuse of drugs or alcohol, no known allergy to dairy products.	
Interventions	Subjects consumed 150mls of placebo yogurt three times a day for three weeks, before being randomized to either: 1.) continue consuming the placebo yogurt or 2.) consuming an experimental yogurt with plant stanol esters for four weeks. FFQs were used to assess diet.	
Outcomes	Blood lipid levels.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	Double-blind RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind design. From report: “The placebo and experimental (yogurts) were similar in (color), taste, absorbable fat content, and caloric value to preserve the double-blind design of the study.”
Blinding – All Outcomes (Detection Bias)	Unclear	Information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome	Low	60 subjects were randomized, and 60 subjects

data (Attrition Bias)		completed the study.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No difference between the treatments was observed.
Free of dietary differences other than macronutrients?	High	The plant stanol esters contained in the experimental yogurt may have an impact on blood lipids independent of the macronutrient composition of the diet.

Mutungi, 2008(A/B)[176]	Study ID: 18203890	
Methods	RCT, single-blinded, placebo-controlled parallel trial.	
Participants	28 overweight/obese male subjects (age 40-70y, BMI 25-37kg/m^2) who had no documented thyroid or heart conditions, diabetes, gout, or allergy to eggs.	
Interventions	Subjects were randomized to consume a carbohydrate-reduced diet (10-15% CHO, 25-30% prot, 55-60% fat) that contained either: 1.) liquid whole eggs or 2.) liquid egg substitute for 12 weeks. 3-d weighted food records and 5-d food records were used to assess dietary intake.	
Outcomes	Variables of metabolic syndrome, including lipid profile.	
Notes	Table 1 lists energy in kJ, but the values conflict with values given in abstract, and it was assumed these values were actually kcals, since the diet was not an energy-restricted on.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Unclear	Single-blinded design, and the experimental and control products are likely similar enough that subjects could not discern their identity, however details related to the blinding of research subjects and personnel was not provided.
Blinding – All Outcomes (Detection Bias)	Unclear	Information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of

		the blinding procedure.
Incomplete outcome data (Attrition Bias)	Unclear	31 subjects were randomized and 28 completed the trial (9.6% attrition). Compliance issues were the reasons for withdrawal, but the group assignment was not provided.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant differences in the treatment were noted.
Free of dietary differences other than macronutrients?	Low	The main differences between the two treatments are related to macronutrients.

Pins, 2006(A/B)[177]	Study ID: 17086017	
Methods	RCT, double-blinded, placebo-controlled parallel trial.	
Participants	30 generally healthy, non-smoking adults (47% male, age 46.1±13.7y, BMI 29±4.5kg/m^2) with mild hypertension. Excluded if had diabetes, cancer, CVD, or other chronic medical condition, were pregnant, lactating, or had a BMI>40.	
Interventions	Subjects were randomly assigned to consume either: 1.) control protein (unmodified whey protein) or 2.) active protein (hydrolyzed wheat protein) for 6 weeks, along with their usual diet. 3-d food records were used to measure dietary intake.	
Outcomes	Primary outcome was blood pressure, but lipid profile was also measured.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind design. From report: “The final protein products were identical in weight, appearance, and texture, and were packaged in individual serving packets that were labeled either group A or group B to indicate the respective treatment groups. Study investigators and research staff were blinded to the study treatments.”

Blinding – All Outcomes (Detection Bias)	Low	All research staff was blinded to the study treatments, although the method of blinding was not specified.
Incomplete outcome data (Attrition Bias)	Low	30 subjects were randomized, and 30 completed the trial.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant differences between the treatments were observed.
Free of dietary differences other than macronutrients?	Unclear	It is not certain how the hydrolyzing of a protein could impact blood lipids, independent of the macronutrient distribution of the diet.

Polagruto,2006(A/B)[178]	Study ID: 17081832	
Methods	RCT, double-blind, placebo-controlled parallel trial.	
Participants	67 subjects (29.8% male, age 52.5±11.6y, BMI ~26.4kg/m^2) with a fasting serum total cholesterol level >200mg/dL. Excluded if were taking any medications known to alter lipids or consuming any phytosterol-enriched foods.	
Interventions	Subjects were randomized to consume either 2 snack bars per day that contained 1.5g of phytosterol or a control product that contained no phytosterols for 6 weeks. 3-day diet records were used to measure dietary intake. All subjects maintained their level of physical activity, and received nutrition-related information each week.	
Outcomes	Serum cholesterol levels.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind design. From report: "There was no difference in taste of product composition between phytosterol-enriched product and placebo product, other than the inclusion of sterol esters and cocoa flavanols…To ensure blinding to both investigators and study participants, products were

		labeled with a numerical code."
Blinding – All Outcomes (Detection Bias)	Low	Double-blind design, although information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	72 subjects were randomized to the study, and 70 completed the trial; the two subjects dropped out for personal reasons. An additional three subjects failed to provide food diaries at the end of the study and were excluded from analyses, yielding 67 subjects (6.9% attrition).
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant differences between the treatments were observed.
Free of dietary differences other than macronutrients?	High	The effect of phytoesters on blood lipids will be independent of the macronutrient distribution of the diet.

Price, 2010(A/B)[179]	Study ID: 20980654	
Methods	RCT, single-blinded, placebo-controlled, parallel trial.	
Participants	80 healthy, nonsmoking subjects (50.5% male, age 51.7±5.1y, BMI 28.9±3.5kg/m^2) with no serious illnesses, and taking no medication or supplements.	
Interventions	Participants were randomly assigned to receive either alerone-rich cereal products or control cereal products for 4-weeks. 4-d food diaries were used to measure dietary intake.	
Outcomes	Plasma betaine and related biomarkers, including lipid profile.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. Subjects were stratified by sex and age.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Unclear	Single-blinded design. From report: "The control bread and RTE cereal products were formulated with similar energy, macronutrient, and fiber

		contents…The RTE cereal was portioned into individual packages for distribution to participants.”
Blinding – All Outcomes (Detection Bias)	Unclear	Information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	80 subjects were recruited, and 79 completed the trial (1.3% attrition).
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant difference was observed between the treatments.
Free of dietary differences other than macronutrients?	High	Since the macronutrient composition of the test and placebo products was the same, any influence on the lipid profile would be independent to total macronutrient distribution.

Santo, 2008(A-C)[180]	Study ID: 18461102	
Methods	RCT, double-blinded, placebo-controlled, parallel trial.	
Participants	30 nonsmoking, sedentary males (age 24.2±4.4y, BMI 23.9±6.3kg/m^2) who were not taking any medications that would influence cholesterol levels or consuming a diet rich in soy.	
Interventions	Subjects were randomized to consume either: 1.) milk protein isolate as a control, 2.) isoflavone-poor soy protein isolate, 3.) isoflavone-rich soy protein isolate for 4-weeks. 3-d dietary records were used to measure intake.	
Outcomes	Lipid profile, lipoprotein particle size and number, apoplipoprotein and lipase concentrations.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. From report: “Each participant was randomly assigned by a trained research assistant to 1 of 3 protein supplement groups…”
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All	Low	Double-blind design. From report: “Protein packets

Outcomes (Performance Bias)		were placed in large envelopes labeled 1, 2, or 3 without the presence of the principle investigator to ensure that the study was blinded."
Blinding – All Outcomes (Detection Bias)	Unclear	Double-blind design, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Unclear	35 subjects were randomized, and 30 were included in the final analysis (14.3% attrition). Five subjects were eliminated due to poor study compliance and data outliers.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant difference was noted between treatments.
Free of dietary differences other than macronutrients?	High	The quality of the macronutrients differed between the groups.

Schwab, 2002(A/B)[181]	Study ID: 12399266	
Methods	RCT, double-blinded, placebo-controlled, parallel trial.	
Participants	42 obese subjects (33.3% male, age 44.2±8.9y, BMI 33.5±3.1kg/m^2) without any chronic disease, and normal liver, kidney, and thyroid function.	
Interventions	Subjects participated in a 4-wk run-in period where they 2 daily servings of orange juice with some grapefruit juice mixed in. Then they began a 12-wk intervention period, being randomized into one of two groups: 1.) a group who consumed 2 servings of orange juice with 6g/d of betaine 2.) a control group who consumed 100g of orange juice twice a day. 4-day food diaries were used to measure intake.	
Outcomes	Body weight, body composition, resting energy expenditure, homocysteine, lipid profile, and blood pressure.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. The subjects were matched based on sex, BMI, and menopausal status.
Allocation Concealment	Unclear	RCT, but randomization method not clearly described.

Selection Bias		
Blinding – All Outcomes (Performance Bias)	Low	Double-blind design. From report: "The laboratory personnel were unaware of the randomization group."
Blinding – All Outcomes (Detection Bias)	Low	Double-blind design, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	46 subjects were recruited, but three were lost during the run-in period, leaving 43 to be randomized and all but one completed the study (2.3% attrition). The subject reportedly withdrew due to a lack of motivation.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant difference between the treatments was observed.
Free of dietary differences other than macronutrients?	High	Betaine may impact blood lipids independently from the distribution of macronutrients.

Schwab, 2006(A-C)[182]	Study ID: 16523204	
Methods	RCT, double-blinded, placebo-controlled, parallel trial.	
Participants	66 subjects (43.9% male, age 53±8y, BMI 28.9±3.4 kg/m^2) with normal liver, kidney, and thyroid functions who had impaired glucose metabolism. Excluded if taking medications that would affect glycemia or blood lipids.	
Interventions	Subjects were randomized to a group that consumed a drink that contained either: 1.) sugar beet pectin 2.) polydextrose 3.) control group without fiber enhancement for 12 weeks. Subjects were given nutrition counseling and asked to follow an isocaloric diet that would promote weight maintenance. 4-d food records were used to monitor intake.	
Outcomes	Plasma glucose and lipid profile.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT

Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blind design. Aside from the ingredient of interest, all three drinks had the same composition.
Blinding – All Outcomes (Detection Bias)	Low	Double-blind design, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	70 subjects were randomized, and 66 completed the trial (5.7% attrition). One subject dropped out due to lack of motivation, another had unspecified skin issues. A subject withdrew due to excessive alcohol consumption, and another dropped out due to scheduling issues.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant differences between the treatments were observed.
Free of dietary differences other than macronutrients?	High	The difference between the treatments is the quality of the fiber.

Smith, 2003(A/B)[183]	Study ID: 13129466	
Methods	RCT, single-blinded, parallel trial	
Participants	48 healthy, normolipemic subjects (51% male, age 20±2.5y, BMI 22.4±2.7kg/m^2) who were not following a diet or taking medications or supplements that would affect blood lipids or coagulation factors.	
Interventions	Subjects consumed a SFA-rich diet as a run-in period for 8 weeks. Afterwards, subjects were randomized to either a diet moderate in MUFA or rich in MUFA for 16 weeks. 4-d food diaries were used to measure intake.	
Outcomes	Lipoprotein risk markers, including lipid profile, and thrombogenic risk markers.	
Notes		
Risk of Bias		
Random sequence	Low	RCT. Groups were stratified based on gender,

generation (Selection Bias)		fasting TC and TG.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Unclear	Single-blinded design, but details regarding the blinding were not specified.
Blinding – All Outcomes (Detection Bias)	Unclear	Single-blind design, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	51 were recruited, and 48 subjects completed the trial (5.9% attrition).
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant differences between treatments were observed.
Free of dietary differences other than macronutrients?	High	Since the difference between the interventions is the amount of MUFA, there would be influences beyond the total amount of fat in the diets.

Smith, 2008(A/B)[184]	Study ID: 18838533
Methods	RCT, double-blinded, parallel trial
Participants	90 healthy, nonsmoking subjects (29% male, age 44.6±13.5y, BMI 26.4±3.7kg/m^2) who had TC>200mg/dL. Exluded if BMI>30, CVD, chronic inflammatory diseases, cancer, renal or hepatic disease, drug or alcohol abuse, recent excessive weight loss, or medications for dyslipidemia, hypertension, or inflammation.
Interventions	Subjects were randomized to either a low- or high-molecular weight barley ß-glucan (6g/d) group for 6 weeks, while maintaining their usual diet. The supplements were administered as a powder and mixed with a beverage to be consumed twice a day. 3-d diet records were used to measure intake.
Outcomes	Cardiovascular biomarkers, including lipid profile, and body weight.

Notes	The lipid profile results were listed as mmol/L, but the magnitude of the values was indicative of mg/dL, and therefore this was the unit chosen.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. Subjects were stratified based on age and sex.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Unclear	Double-blind design, but very few details were provided.
Blinding – All Outcomes (Detection Bias)	Unclear	Double-blinded, but information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure. Almost no information about the blinding procedure was reported.
Incomplete outcome data (Attrition Bias)	Low	90 subjects were randomized, and 90 completed the trial.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant differences between the treatments were observed.
Free of dietary differences other than macronutrients?	High	The ß-glucan products may have an impact on the blood lipids that would not be detected based on mere changes of the dietary macronutrient distribution.

Stendell-Hollis, 2010(A/B)[185]	Study ID: 20807303
Methods	RCT, double-blind, placebo-controlled, parallel pilot study.
Participants	54 overweight, nonsmoker female survivors of breast cancer (age 57.1±8.2y, BMI 30.1±4.2kg/m^2), free of other chronic illnesses, and medications that would influence glycemia or blood lipids.
Interventions	Participants were required to complete a 2-wk run in consisting

	of daily intake of herbal tea. Subjects were then randomized to receive either 960ml of decaffeinated green tea or herbal placebo tea daily for six months. FFQ was used to estimate dietary intake.	
Outcomes	Body weight and composition, metabolic parameters and lipids.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT.
Allocation Concealment Selection Bias	Low	From report: "(Randomization) was completed using a table of random numbers, independent of study personnel…"
Blinding – All Outcomes (Performance Bias)	Low	Double-blinded design. From report: "The investigators and subjects were blinded to the tea compositions until all subjects had completed the trial and data analysis was underway."
Blinding – All Outcomes (Detection Bias)	Low	From report: "The investigators and subjects were blinded to the tea compositions until all subjects had completed the trial and data analysis was underway…Blinded taste testing prior to study initiation showed that people (n=6) were unable to correctly differentiate green tea from herbal tea product."
Incomplete outcome data (Attrition Bias)	Unclear	54 completed the run-in period and were randomized. 15 women (6 from treatment, 9 from placebo) were lost to follow-up (27.8% attrition). Intolerance or dislike of the product was reported by 4 subjects, while scheduling conflicts were reported by 3 individuals, difficulty retrieving samples, and no specific reasons were given by the remainder. There were no statistically significant differences between completers and non-completers with respect to clinical, demographic, and lifestyle data."
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were detected.
Free of systematic difference in treatment?	Low	No significant difference between treatments was seen.
Free of dietary	High	The influence of green tea on blood lipids would be

differences other than macronutrients?		independent of the distribution of total macronutrients.

Szapary, 2003[186]	Study ID: 12915429	
Methods	RCT, double-blinded, placebo-controlled parallel trial.	
Participants	36 subjects (47% male, age 48.9±15.8y) with LDL between 130-200mg/dL and TG<400mg/dL. Excluded if had history of CVD, DM, thyroid or liver disorder, pregnancy, lactation, or medication/supplements that would affect blood lipids.	
Interventions	Subjects were screened to one of three groups: 1.) standard dose herbal extract guggulipid (1000mg), 2.) high-dose guggulipid (2000mg), or 3.) placebo. All subjects were instructed to maintain their usual diet; FFQ was used to estimate diet.	
Outcomes	LDL cholesterol.	
Notes	Only the placebo group was included in the meta-analysis, and the information regarding participants reflects the placebo group.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT.
Allocation Concealment Selection Bias	Low	From report: "Randomization was performed by an unblended investigational pharmacist using a random-number generator."
Blinding – All Outcomes (Performance Bias)	Low	Double-blind design. The two supplement capsules were identical in shape, color, texture, and taste.
Blinding – All Outcomes (Detection Bias)	Low	From report: "All study personnel were blinded to treatment assignment and block size. Masking was assessed by questionnaires at the conclusion of the study."
Incomplete outcome data (Attrition Bias)	Unclear	103 total subjects were randomized, 36 into the placebo group, and 30 completed the trial (16.7% attrition). 4 individuals had an adverse event, and 2 withdrew for personal reasons. From report: "Participants who dropped out did not differ significantly from the rest of the participants in terms of demographics, medical history, and baseline characteristics."
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.

Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	No significant difference between the treatments noted.
Free of dietary differences other than macronutrients?	Low	Since only the placebo group was included in the meta-analysis, no outside influences on lipid profile would be anticipated.

Tanumihardjo, 2009(A/B)[187]	Study ID: 19234056	
Methods	RCT, Single-blinded, parallel trial	
Participants	60 obese subjects (26.7% male, age 33.6±8.1y, BMI 33.5±3.7kg/m^2) free of serious medical or mental illness and not taking medications or supplements that would influence weight loss.	
Interventions	Subjects were randomly assigned to either: 1.) a high-vegetable group, consuming 8 servings of vegetables and 2-3 servings of fruit per day or 2.) a reduction group that reduced caloric intake by 500 kcal and consume <25% energy from fat. 3-d diet records were used to measure intake.	
Outcomes	Body weight and composition, serum chemistry profile, serum lipid profile, insulin, glucose, hematocrit, and CRP.	
Notes	The 3-month period was included, as it included the most subjects with completed outcomes.	
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. Subjects were stratified by gender and BMI.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Single-blinded. From report: "It was not possible to blind subjects to their own treatment. However, the subjects were not aware of the other treatment…Similarly, it was not possible to blind researchers assisting with food distribution…However, researchers and consultants who analyzed blood samples were unaware of treatment assignments."
Blinding – All Outcomes (Detection Bias)	Unclear	However, researchers and consultants who analyzed blood samples were unaware of treatment assignments.

Incomplete outcome data (Attrition Bias)	Low	60 subjects were randomized, and 26 completed the 3-month time point (6.7% attrition). One subject in the HiVeg group used a contraindicated medication. In the reduction group, one became pregnant, one declined participation, and one lost to follow-up.
Selective Reporting (Reporting Bias)	Unclear	Some of the secondary outcomes were not reported at the end of treatment periods.
Other Bias	Low	No other biases were detected.
Free of systematic difference in treatment?	Unclear	There were differences with respect to the dietary advice.
Free of dietary differences other than macronutrients?	Low	The diets differed through the emphasis of fruits, vegetables, and dietary fat.

Tapsell, 2004(A-C)[188]	Study ID: 15562184	
Methods	RCT, single-blinded, parallel controlled trial.	
Participants	58 generally healthy subjects (43.9% male, age 59.3±8.1y, BMI 29.7±3.7kg/m^2) with type 2 diabetes. Excluded if on insulin therapy, AbA1C>9%, BMI>35, had major illness or had food allergies incompatible with study treatment.	
Interventions	Subjects were randomized into one of three diet groups focusing on <30% energy as fat: 1.) low fat control 2.) low fat/modified fat 3.) walnut inclusive (30g of walnuts/d) for 6 months. 3-day diet records measured intake.	
Outcomes	Blood lipid profiles.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Unclear	Two dietitians undertook all dietary assessments, while there were additional dietitians who provided only advice to the different groups. The dietitian for the control group was blinded to the intervention diets.
Blinding – All Outcomes (Detection Bias)	Unclear	Information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of

		the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	58 subjects were randomized and 55 completed the trial (5.2% attrition). One subject dropped out from each group, but no reasons were reported.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were observed.
Free of systematic difference in treatment?	Low	There seemed to be little difference between the treatments.
Free of dietary differences other than macronutrients?	High	Since all three diets attempted to achieve <30% total fat consumption, the difference between them was the quality of fat.

Tighe, 2010(A-C)[189]	Study ID: 20685951	
Methods	RCT, single-blinded, parallel trial.	
Participants	206 subjects (50.5% male, age 51.8±6.9, BMI 27.7±3.9) at high risk for CVD. Excluded if had CVD, hyperglycemia, hypertension, thyroid disorder, or medications or supplements known to affect outcome variables.	
Interventions	Subjects consumed a refined diet for 4-wks, and then were randomized to one of three groups: 1.) refined diet control 2.) wheat 3.) wheat + oats for 12 weeks. There was no major alteration to the lifestyle of the subject. 7-d food diaries were used to measure intake.	
Outcomes	Total cholesterol, LDL, insulin sensitivity, inflammation, BP.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. Subject groups were stratified by sex, age, and BMI.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Unclear	Single-blinded, but no details provided.
Blinding – All Outcomes (Detection Bias)	Unclear	Information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.

Incomplete outcome data (Attrition Bias)	High	226 subjects were randomized, 206 completed the trial (8.8% attrition). 13 subjects withdrew or were excluded from the control group, versus 4 and 3 from the wheat and wheat + oats groups, respectively.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases noted.
Free of systematic difference in treatment?	Low	No significant differences between treatments were noted.
Free of dietary differences other than macronutrients?	High	The macronutrient intakes did not change, and the differences between the trials were related to the quality of the starch.

Tonstad, 2002(A-D)[190]	Study ID: 12081819	
Methods	RCT, double-blinded, parallel trial	
Participants	130 subjects (83.1% male, age 52.5±8.6y, BMI 25.0±2.1kg/m^2) with TC >5.8mmol/L and TG <4.5mmol/L. Excluded if had significant cardiovascular, renal, hepatic, GI, or endocrine diseases; BMI>30, uncontrolled hypertension, excessive alcohol, taking lipid-lowering drugs, or n-3 supplements.	
Interventions	Subjects consumed a run-in diet similar to the Step I diet for between 4-24 weeks. Participants were then randomized to one of four treatments for 16 weeks: 1.) 30g isolated soy protein and 10g cotyledon fiber 2.) 50g isolated soy protein and 16.6g cotyledon fiber 3.) 30g casein and 10g cellulose 4.) 50g casein and 16.6g cellulose. 3-d weighted dietary records were used to measure diet.	
Outcomes	Lipid, lipoprotein, and homocysteine concentrations.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Double-blinded. From report: “Subjects and investigators were blinded to the source of test product during the course of the trial, but because

		of different sizes of boxes containing the test products, the study coordinator and dietitian were not blinded to whether low or high doses were assigned."
Blinding – All Outcomes (Detection Bias)	Unclear	Information about the blinding of the outcome assessors was not reported, nor was any information provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	High	159 subjects were randomized, and 130 completed the trial (18.2% attrition). The attrition from groups 1-4 were respectively: 13%, 10%, 23%, and 28%.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were noted.
Free of systematic difference in treatment?	Low	No significant differences between the treatments were noted.
Free of dietary differences other than macronutrients?	High	The differences between the diets were the quality of the protein and fiber.

Wardlaw, 1991(A/B)[191]	Study ID: 1905474	
Methods	RCT, single-blinded, parallel trial.	
Participants	31 male subjects (age 33±8y, BMI 27.3±4.6kg/m^2) who had TC >5.17mmol/L.	
Interventions	Subjects were placed on a 3-wk baseline diet that was similar to the American diet. Participants were then randomized to either a diet high in mono- or polyunsaturated fats for 8 weeks. Subjects were encouraged to maintain their weight and were weighed daily.	
Outcomes	Serum lipid and apolipoprotein concentrations.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. Subjects were stratified based on BMI, TC, and age.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All Outcomes (Performance Bias)	Low	Single-blinded. From report: "Two investigators supervised the feeding of subjects and were blinded to the changes in serum chemistry values."

Blinding – All Outcomes (Detection Bias)	Low	From report: "The other investigators supervised or performed all laboratory analyses and were blinded to dietary assignments." No information was provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	34 subjects were randomized, and 32 completed the trial (5.9% attrition). One subject was taking an exclusionary medication, another missed a blood draw and one was dropped from the analysis because his TC was outside inclusion.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were noted.
Free of systematic difference in treatment?	Low	No significant differences were noted between the treatments.
Free of dietary differences other than macronutrients?	High	All diets provided between 63-42% total fat, but the quality of fat differed between the dietary treatments.

Wood, 2007(A/B)[192]	Study ID: 17161227	
Methods	RCT, double-blinded, placebo-controlled parallel trial.	
Participants	29 overweight and obese men (age 38.8±14.4y, BMI 29.7±3.46kg/m^2). Excluded if took lipid-lowering drugs or supplements, history of CVD, DM, or thyroid disease, recently experienced more than 2.5kg weight loss or was on a CRD.	
Interventions	Subjects were placed on a carbohydrate-restricted diet and asked to supplement their intake with either: 1.) soluble fiber (Konjac-mannan, 3g/d) or 2.) placebo (maltodextrin). 7-d weighted food records were used to measure intake.	
Outcomes	Plasma lipids, anthropometrics, body composition, BP, and intake.	
Notes		
Risk of Bias		
Random sequence generation (Selection Bias)	Low	RCT. Subjects were matched based on BMI and age.
Allocation Concealment Selection Bias	Unclear	RCT, but randomization method not clearly described.
Blinding – All	Low	Double-blind design. All researchers administering

Outcomes (Performance Bias)		the interventions were blinded to group assignment.
Blinding – All Outcomes (Detection Bias)	Low	From report: "…those assessing the outcomes were blinded to group assignment." No information was provided regarding the effectiveness of the blinding procedure.
Incomplete outcome data (Attrition Bias)	Low	30 subjects were randomized, and 29 completed the trial (3.3% attrition). The subject discontinued due to military obligations.
Selective Reporting (Reporting Bias)	Low	The authors reported on all proposed outcomes.
Other Bias	Low	No other biases were noted.
Free of systematic difference in treatment?	Low	No significant differences between treatments were noted.
Free of dietary differences other than macronutrients?	High	The difference between the treatments related to the quality of the fiber.

APPENDIX E: LIST OF STUDIES EXCLUDED FROM THE SYSTEMATIC REVIEW, WITH REASONS

Study (By Year)	Reason for Exclusion
Li, 2010	Incomplete macronutrient data
Santo, 2010	Test meal; data presented as area under the curve (AUC)
Rhodes, 2010	Pregnant subjects, not blinded
Sodergren, 2010	Incomplete macronutrient data/Incomplete lipid profile
Ohlsson, 2010	Duration <1d/Test meal
Rhee, 2010	Incomplete lipid profile
Fisher-Wellman, 2010	Duration <1d/Test meal
Gagliardi, 2010	Lipids reported as medians (no means/S.D.)
Van Mierlo, 2010	Incomplete macronutrient data
Wolever, 2010	Incomplete lipid profile
Rontoyanni, 2010	Duration <1d/Test meal
Pal, 2010	Lacking standard deviations(S.D.)/presented lipids as AUC
Schwartz, 2010	Drug study that did not have an unaffected diet group
Fukumitsu, 2010	No dietary macronutrients/supplement study
Hirota, 2010	Incomplete macronutrient data
Venkatramanan, 2010	Incomplete macronutrient data
Sola, 2010	Lacking standard deviations for macronutrients
Fountaine, 2010	Incomplete macronutrient data
Yeung, 2010	Incomplete lipid profile/ Lacking S.D. for macronutrients
Burton-Freeman, 2010	Incomplete macronutrient data
Boxer, 2010	Incomplete macronutrient data
Holub, 2010	Lacking S.D. for macronutrients
Marini, 2010	Lacking S.D. for macronutrients
Schroder, 2010	Incomplete macronutrient data
Bitto, 2010	Incomplete macronutrient data
Malaguarnera, 2010	Incomplete macronutrient data
Hiatt, 2010	Incomplete macronutrient data / Drug study
Maki, 2010	Incomplete macronutrient data
Huyen, 2010	Incomplete macronutrient data/ Supplement trial
Jorde, 2010	Incomplete macronutrient data
Chirinos, 2010	Drug study that did not have an unaffected diet group
Khoury, 2010	Lacking S.D. for macronutrients
Koska, 2010	Lacking S.D. for macronutrients
Snel, 2010	Incomplete macronutrient data/AUC/Supplement study
Siener, 2010	Incomplete macronutrient data
Fenercioglu, 2010	Incomplete macronutrient data
Carpentier, 2010	No diet intervention (IV bolus of MCT oil)
Goldfine, 2010	Incomplete macronutrient data/Drug study
Boesch-Saadatmandi, 2010	Samples were cell cultures/Drug study

Study (By Year)	Reason for Exclusion
Almoosawi, 2010	Incomplete macronutrient data
Kuate, 2010	Incomplete macronutrient data
Aghdassi, 2010	Incomplete macronutrient data/Supplement study
Kondo, 2010	Drug study that did not have an unaffected diet group
Otta, 2010	Incomplete macronutrient data
Cheng, 2010	Incomplete macronutrient data/Supplement study
Gylling, 2010	Incomplete macronutrient data
Weisse, 2010	Incomplete macronutrient data
Klafke, 2010	Incomplete macronutrient data
Cugnet-Anceau, 2010	Incomplete macronutrient data
Vrolix, 2010	Excluded data on habitual data for wahout/run-in
Legrand, 2010	Lacking S.D. for macronutrients
Roth, 2010	Drug study that did not have an unaffected diet group
Ma, 2010	Washout diet data not reported
Teng, 2010	Washout diet data not reported
De Castro, 2009	Drug study that did not have an unaffected diet group
Chevassus, 2009	Incomplete macronutrient data
Masson, 2009	Incomplete macronutrient data
Shikany, 2009	No blinding information
Sivaprakaspillai, 2009	Incomplete macronutrient data
Vega-Lopez, 2009	Lacking S.D. for macronutrients
Heufelder, 2009	Incomplete macronutrient data
Krishna, 2009	Drug study that did not have an unaffected diet group
Hadley, 2009	Incomplete macronutrient data/Supplement study
Egert, 2009	Incomplete macronutrient data
Lecerf, 2009	Lacking S.D. for macronutrients
Watanabe, 2009	Incomplete macronutrient data
Patenaude, 2009	Incomplete macronutrient data
Haugaard, 2009	Incomplete macronutrient data
Teas, 2009	Incomplete macronutrient data
Mori, 2009	Incomplete macronutrient data
Pipe, 2009	Incomplete macronutrient data
Brackenridge, 2009	Incomplete macronutrient data
Kar, 2009	Incomplete macronutrient data
Di Pierro, 2009	Incomplete macronutrient data/AUC
Bregar, 2009	Lacking S.D. for macronutrients
Gastaldelli, 2009	Lacking S.D. for macronutrients
Gatta, 2009	Lacking S.D. for macronutrients/AUC
Damsgaard, 2009	Incomplete macronutrient data
Schiepers, 2009	Incomplete macronutrient data
Madsen, 2009	Incomplete macronutrient data

Study (By Year)	Reason for Exclusion
Tuomilehto, 2009	Incomplete macronutrient data
Krikken, 2009	Lacking S.D. for macronutrients
Liatis, 2009	Incomplete macronutrient data
Houweling, 2009	Incomplete macronutrient data
Ataie-Jafari, 2009	Incomplete macronutrient data
Dai, 2009	Incomplete macronutrient data
Maljaars, 2009	Incomplete macronutrient data
Carabin, 2009	Incomplete macronutrient data
Ngondi, 2009	Lacking S.D. for macronutrients
Chen, 2009	Lacking S.D. for macronutrients
Hursel, 2009	Incomplete macronutrient data
Wright, 2009	Incomplete macronutrient data
Coates, 2009	Incomplete macronutrient data
Krandish, 2009	Incomplete macronutrient data
Solomon, 2009	Only one diet set reported (no pre & post)
Ruiu, 2009	Incomplete macronutrient data
Pohl, 2009	Incomplete diet (enteral supplement)
Khandelwal, 2009	No post-diet data reported
Sanchez-Muniz, 2009	Incomplete macronutrient data
Westpahl, 2009	Incomplete macronutrient data
Kajiyama, 2008	Incomplete macronutrient data
Hibi, 2008	Incomplete macronutrient data
Hajer. 2008	Drug study that did not have an unaffected diet group
Sattler, 2008	Incomplete macronutrient data
Weidner, 2008	Incomplete macronutrient data
DeFronzo, 2008	Drug study that did not have an unaffected diet group
Derosa, 2008	Incomplete macronutrient data
Li, 2008	No post-treatment diet data reported
Rudkowska, 2008	Lacking S.D. for macronutrients
Teplan, 2008	Incomplete macronutrient data
Lutjohann, 2008	Drug study that did not have an unaffected diet group
Kobayashi, 2008	Incomplete macronutrient data
Treyzon, 2008	Incomplete macronutrient data
Lopez, 2008	Incomplete macronutrient data
Olijhoek, 2008	Drug study that did not have an unaffected diet group
Svensson, 2008	Incomplete macronutrient data
Devaraj, 2008	Incomplete macronutrient data
Thorp, 2008	No baseline diet reported.
Shepherd, 2008	Drug study that did not have an unaffected diet group
Newsom, 2008	Incomplete macronutrient data
Kools, 2008	Not conducted on adults

Study (By Year)	Reason for Exclusion
Van Gaal, 2008	Incomplete macronutrient data
Gunnarsdottir, 2008	Incomplete macronutrient data
Maki, 2008	Incomplete macronutrient data
Musliner, 2008	Drug study that did not have an unaffected diet group
Keogh, 2008	Incomplete macronutrient data
Ramel, 2008	Incomplete macronutrient data
Francini-Pesenti, 2008	Incomplete macronutrient data
Roynette, 2008	Incomplete macronutrient data
Rosenson, 2008	Drug study that did not have an unaffected diet group
Micallef, 2008	No post-treatment lipid profile reported
Sorensen, 2008	Test meal/Not full diet
Bloedon, 2008	Incomplete macronutrient data
Mensink, 2008	Lacking S.D. for macronutrients
Vogt, 2008	Incomplete macronutrient data
Armah, 2008	Incomplete macronutrient data
Salvas-Salvado, 2008	Incomplete macronutrient data
Shepherd, 2008	Drug study that did not have an unaffected diet group
Hughes, 2008	Incomplete diet (only reported lunch and dinner)
Milte, 2008	Incomplete macronutrient data
Nissen, 2008	Drug study that did not have an unaffected diet group
Fassett, 2008	Incomplete macronutrient data
Magnoni, 2008	Incomplete macronutrient data
Ravn-Haren, 2008	Incomplete macronutrient data
Francini-Pesenti, 2008	Incomplete macronutrient data
Lithander, 2008	No post-treatment lipid profile reported
Raff, 2008	Incomplete macronutrient data
Damsgaard, 2008	No washout diet data reported
Allen, 2008	Did not report lipids for crossover group/no washout
Kassis, 2008	Incomplete macronutrient data
Shimizu, 2008	Incomplete macronutrient data
Hall, 2008	Incomplete macronutrient data
Lund, 2008	Drug study that did not have an unaffected diet group/AUC
Albarracin, 2008	Incomplete macronutrient data
Reyes, 2008	Reported TGs as medians and not means
Motard-Belanger, 2008	Washout diet data not reported
Reiner, 2007	No lipid profile/Supplement trial
Gill, 2007	No washout diet data reported
Sola, 2007	Washout diet data not reported
Ose, 2007	Drug study that did not have an unaffected diet group
Berglund, 2007	Incomplete diet/No total kcals reported
Wang, 2007	No baseline diet reported

Study (By Year)	Reason for Exclusion
Dekker, 2007	Not complete diet/Fat tolerance test
Nagao, 2007	Incomplete macronutrient data
Shepherd, 2007	Drug study that did not have an unaffected diet group
Schnell, 2007	Incomplete macronutrient data
Zimbroff, 2007	Drug study that did not have an unaffected diet group
Vidarsdottir, 2007	Incomplete macronutrient data
Seppo, 2007	Incomplete macronutrient data
Jiang, 2007	Incomplete macronutrient data
Lambert, 2007	Incomplete macronutrient data
Kobayashi, 2007	Incomplete macronutrient data
Singh, 2007	Incomplete macronutrient data
Atteritano, 2007	Lacking S.D. for macronutrients
Liu, 2007	Drug study that did not have an unaffected diet group
Forcheron, 2007	Incomplete diet reported/Energy reported in kcal/kg only
Neyestani, 2007	No lipid profile
Lim, 2007	Incomplete macronutrient data
Spangler, 2007	Incomplete macronutrient data
Cazzola, 2007	Incomplete macronutrient data
Mieszczanska, 2007	Drug study that did not have an unaffected diet group
Steck, 2007	Incomplete macronutrient data
Shrestha, 2007	Incomplete macronutrient data
Bovet, 2007	Incomplete macronutrient data
Erondu, 2007	Incomplete macronutrient data
Dejager, 2007	Drug study; no lipid profile
Murphy, 2007	Incomplete macronutrient data
Tuomasjukka, 2007	Trial <1d, test meal.
Chonchol, 2007	Incomplete macronutrient data
De Truchis, 2007	Incomplete macronutrient data
Kopelman, 2007	Incomplete macronutrient data
Inoue, 2007	Incomplete macronutrient data
Hininger-Favier, 2007	Incomplete macronutrient data
Gaullier, 2007	Incomplete macronutrient data
Khoury, 2007	No lipid profile
Rosenstock, 2007	Incomplete macronutrient data
Nazare, 2007	Incomplete macronutrient data
Hollander, 2007	Incomplete macronutrient data
Carrero, 2007	Incomplete macronutrient data
Anderson, 2007	Incomplete macronutrient data
Major, 2007	Incomplete macronutrient data
Grunberger, 2007	Incomplete macronutrient data
Guimaraes, 2006	Incomplete macronutrient data

Study (By Year)	Reason for Exclusion
van Wijk, 2006	Incomplete macronutrient data
Fassett, 2006	Incomplete macronutrient data
Demonty, 2006	Incomplete macronutrient data
Knopp, 2006	Drug study that did not have an unaffected diet group
Kassis, 2006	Incomplete macronutrient data
Jauhaiainen, 2006	Incomplete macronutrient data
Opala, 2006	Supplement; no lipid profile
Devaraj, 2006	No total kcals reported
Hackman, 2006	Incomplete macronutrient data
Krebs, 2006	Incomplete macronutrient data
Anderson, 2006	Incomplete macronutrient data
Castro Cabezas, 2006	Incomplete macronutrient data
Oben, 2006	Incomplete macronutrient data
Suomela, 2006	Incomplete macronutrient data
Hallikainen, 2006	Incomplete macronutrient data
Ahuja, 2006	Incomplete macronutrient data
Hart, 2006	Incomplete macronutrient data
Derosa, 2006	Incomplete macronutrient data
Vaisman, 2006	Incomplete macronutrient data
Chardigny, 2006	Incomplete macronutrient data
Feillet-Coudray, 2006	Incomplete macronutrient data
Satoh, 2006	Incomplete macronutrient data
Chou, 2006	Incomplete lipid profile
Berthold, 2006	Incomplete macronutrient data
Gruendel, 2006	Incomplete macronutrient data
Mang, 2006	Incomplete macronutrient data
Gonzalez-Ortiz, 2006	Incomplete macronutrient data
Mallon, 2006	Incomplete macronutrient data
Ahn, 2006	Incomplete macronutrient data
Geppart, 2006	Incomplete macronutrient data
Sorof, 2006	Incomplete macronutrient data
Weickert, 2006	Incomplete macronutrient data
AbuMweiss, 2006	Incomplete macronutrient data
Raff, 2006	Incomplete macronutrient data
Wu, 2006	Incomplete macronutrient data
Doornbos, 2006	Incomplete macronutrient data
Christ, 2006	Incomplete macronutrient data
Al Majali, 2006	Incomplete macronutrient data
Pi-Sunyer, 2006	Incomplete macronutrient data
Chen, 2006	Values based on body weight (g/kg), but wt. not reported
Tholstrup, 2006	Incomplete macronutrient data

Study (By Year)	Reason for Exclusion
Lustig, 2006	Incomplete macronutrient data
Tomonobu, 2006	Test meal; duration <1d
Saito, 2006	Incomplete macronutrient data
Yamamoto, 2006	Incomplete macronutrient data
Derosa, 2006	Incomplete macronutrient data
Goldberg, 2006	Incomplete macronutrient data
Diepvens, 2006	Incomplete macronutrient data
Boshtam, 2005	Incomplete macronutrient data
Ceballos, 2005	Drug study that did not have an unaffected diet group
Paniagua, 2005	Incomplete macronutrient data
Lofgren, 2005	Incomplete macronutrient data
Hidalgo, 2005	Incomplete macronutrient data
Neri, 2005	Incomplete macronutrient data
Preuss, 2005	Incomplete macronutrient data
Barrios, 2005	Incomplete macronutrient data
Patch, 2005	Incomplete macronutrient data
Ashraf, 2005	Incomplete macronutrient data
Chen, 2005	Incomplete macronutrient data
Despres, 2005	Incomplete macronutrient data
Jakulj, 2005	Incomplete macronutrient data
Lefevre, 2005	No mean total kcals reported
Ziai, 2005	Incomplete macronutrient data
Zelissen, 2005	Incomplete macronutrient data
Mamo, 2005	Incomplete macronutrient data
Buse, 2005	Incomplete macronutrient data
Gostner, 2005	Incomplete macronutrient data
Breier, 2005	Incomplete macronutrient data
Lofgren, 2005	No mean total kcals reported
Davidson, 2005	Incomplete macronutrient data
Burdge, 2005	Incomplete macronutrient data
Bugel, 2005	Incomplete macronutrient data
Fontani, 2005	Incomplete macronutrient data
Castano, 2005	Incomplete macronutrient data
Ngondi, 2005	Incomplete macronutrient data
Ditscheid, 2005	Incomplete macronutrient data
Binkoski, 2005	No S.D. for macronutrient data
Farnier, 2005	Incomplete macronutrient data
de Vries, 2005	Incomplete macronutrient data
Lau, 2005	Incomplete macronutrient data
Carrero, 2005	Incomplete macronutrient data
Charest, 2005	Incomplete macronutrient data

Study (By Year)	Reason for Exclusion
Cruz-Fernandez, 2005	Incomplete macronutrient data
Goedecke, 2005	Incomplete macronutrient data
Brohet, 2005	Incomplete macronutrient data
Daubioul, 2005	Incomplete macronutrient data
Feinglos, 2005	Incomplete macronutrient data
West, 2005	No S.D. reported for macronutrient data
Berne, 2005	Incomplete macronutrient data
Van Gaal, 2005	Incomplete macronutrient data
Suter, 2005	Incomplete macronutrient data
Teede, 2005	Incomplete macronutrient data
Swinburn, 2005	Incomplete macronutrient data
Rahbar, 2005	Incomplete macronutrient data
Koh-Banerjee, 2005	Incomplete macronutrient data
Gaullier, 2005	Incomplete macronutrient data
Engler, 2005	Incomplete macronutrient data
Charman, 2005	Incomplete macronutrient data
Grundy, 2005	Incomplete macronutrient data
Minhane, 2005	Incomplete macronutrient data
Tan, 2005	Incomplete macronutrient data
Whitney, 2005	Incomplete macronutrient data
Derosa, 2005	Incomplete macronutrient data
Fujioka, 2005	Incomplete macronutrient data
Seierstad, 2005	Data reported as medians, and not means
Most, 2005	Incomplete macronutrient data
Castano, 2005	Drug study that did not have an unaffected diet group
Bunea, 2004	Incomplete macronutrient data
Engler, 2004	Incomplete macronutrient data
Tricon, 2004	Incomplete macronutrient data
Schernthaner, 2004	Incomplete macronutrient data
Santos, 2004	Incomplete macronutrient data
Drouin, 2004	Incomplete macronutrient data
Derosa, 2004	Incomplete macronutrient data
Katz, 2004	Incomplete macronutrient data
Moloney, 2004	Incomplete macronutrient data
Lin, 2004	Incomplete macronutrient data
Halson, 2004	Incomplete lipid profile
Yli-Jokipii, 2004	Incomplete macronutrient data
Whigham, 2004	Incomplete macronutrient data
Fard, 2004	Incomplete macronutrient data
Braatvedt, 2004	Incomplete macronutrient data
Weinbrenner, 2004	Incomplete macronutrient data

Study (By Year)	Reason for Exclusion
O'Neill, 2004	Incomplete macronutrient data
Kosoglou, 2004	Drug study that did not have an unaffected diet group; AUC
Derosa, 2004	Incomplete macronutrient data
Guy-Grand, 2004	Incomplete macronutrient data
Yajima, 2004	Incomplete macronutrient data
Riserus, 2004	Incomplete macronutrient data
Singer, 2004	Incomplete macronutrient data
Esposito, 2004	Incomplete macronutrient data
Park, 2004	Incomplete macronutrient data
Baba, 2004	Incomplete macronutrient data
Bemelmans, 2004	Incomplete macronutrient data
Derosa, 2004	Incomplete macronutrient data
Tan, 2004	Drug study that did not have an unaffected diet group
Richelle, 2004	Incomplete macronutrient data
Park, 2004	Incomplete macronutrient data
Kosoglou, 2004	Drug study that did not have an unaffected diet group
Mattan, 2004	Incomplete macronutrient data
Insull, 2004	Drug study that did not have an unaffected diet group
Gaullier, 2004	Incomplete macronutrient data
Brady, 2004	Incomplete macronutrient data
Lovegrove, 2004	Incomplete macronutrient data
Erdmann, 2004	Incomplete macronutrient data
Stone, 2004	Drug study that did not have an unaffected diet group
Brady, 2004	Incomplete macronutrient data
Scholtz, 2004	Incomplete macronutrient data
Preuss, 2004	Incomplete macronutrient data
Marett, 2004	Incomplete macronutrient data
Tholstrup, 2004	Incomplete macronutrient data
Gradek, 2004	Incomplete macronutrient data
Hunninghake, 2004	Incomplete macronutrient data
Vanky, 2004	Incomplete macronutrient data
Charest, 2004	Incomplete macronutrient data
Koustari, 2004	No S.D. for macronutrient data
Robinson, 2004	Incomplete macronutrient data
Koebnick, 2004	Baseline diet data not reported
Bricarello, 2004	Incomplete lipid profile reported
Sagara, 2004	Incomplete macronutrient data
Kerenyi, 2004	Incomplete macronutrient data
Ludvik, 2004	Incomplete macronutrient data
Gambineri, 2004	Incomplete macronutrient data
Binkoski, 2004	No S.D. for macronutrient data

Study (By Year)	Reason for Exclusion
Rachmani, 2004	Incomplete macronutrient data
Wachtel-Galor, 2004	Incomplete macronutrient data
Tamura, 2003	Duration <1d; test meal
Davidson, 2003	Drug study that did not have an unaffected diet group
Perry, 2003	Incomplete macronutrient data
Manuel-Y-Keenoy, 2003	Incomplete macronutrient data
Lichtenstein, 2003	Incomplete macronutrient data
Stein, 2003	Drug study that did not have an unaffected diet group
Petridou, 2003	Incomplete macronutrient data
Davies, 2003	Incomplete macronutrient data
Quilez, 2003	Incomplete macronutrient data
Lovejoy, 2003	Incomplete macronutrient data
Schuster, 2003	Incomplete macronutrient data
Ciubotaru, 2003	Incomplete macronutrient data
Yil-Jokipii, 2003	Incomplete macronutrient data
Breithaupt, 2003	Incomplete macronutrient data
Jones. 2003	Incomplete macronutrient data
Engler, 2003	Incomplete macronutrient data
Howes, 2003	Incomplete macronutrient data
Pahl, 2003	Incomplete macronutrient data
Costa, 2003	Drug study that did not have an unaffected diet group
Garber, 2003	Drug study that did not have an unaffected diet group
Knopp, 2003	Incomplete macronutrient data
Cuevas, 2003	Incomplete macronutrient data
Nordoy, 2003	Incomplete macronutrient data; test meal
Ludvik, 2003	Incomplete macronutrient data
Tosi, 2003	Incomplete macronutrient data
Carroll, 2003	Incomplete macronutrient data
Nielsen, 2003	Incomplete macronutrient data
Laaksonen, 2003	Incomplete macronutrient data
Maron, 2003	Total kcals provided in kcal/kg, but weight not reported
Kamphuis, 2003	Incomplete macronutrient data
Derosa, 2003	Incomplete macronutrient data
Bourque, 2003	Incomplete macronutrient data
Lottenberg, 2003	Incomplete macronutrient data
Bokura, 2003	Incomplete macronutrient data
Lottenberg, 2003	Incomplete macronutrient data
Bokura, 2003	Incomplete macronutrient data
Pedersen, 2003	Incomplete macronutrient data
Hendriks, 2003	Incomplete macronutrient data
Plotnick, 2003	Test meal

Study (By Year)	Reason for Exclusion
Spilburg, 2003	Incomplete macronutrient data
Kamphuis, 2003	Incomplete macronutrient data
Krempf, 2003	Incomplete lipid profile
Ettinger, 2003	Incomplete macronutrient data
Feinle, 2003	Incomplete macronutrient data
Halpern, 2003	Incomplete macronutrient data
Pavo, 2003	Incomplete macronutrient data
Bookstaff, 2003	Incomplete macronutrient data
Portal, 2003	Incomplete macronutrient data
Johnson, 2003	Incomplete lipid profile
Ghazeeri, 2003	Incomplete macronutrient data
Park, 2003	Incomplete macronutrient data
Watts, 2003	Incomplete macronutrient data
Letexier, 2003	Incomplete macronutrient data
Capell, 2003	Incomplete macronutrient data
Gardner-Thorpe, 2003	No S.D. reported for lipid profile
Fischer, 2003	Incomplete macronutrient data
Castano, 2003	Incomplete macronutrient data
Andrews, 2003	Incomplete macronutrient data
Maki, 2003	No S.D. for TG
Schroeder, 2003	Incomplete macronutrient data
Cavallero, 2003	Incomplete macronutrient data
St-Onge, 2002	Incomplete macronutrient data
Castano, 2002	Drug study that did not have an unaffected diet group
Kasai, 2002	Incomplete macronutrient data
Davis, 2002	Drug study that did not have an unaffected diet group
Castano, 2002	Drug study that did not have an unaffected diet group
Fullert, 2002	Incomplete macronutrient data
Vanstone, 2002	Incomplete macronutrient data
Maki, 2002	Incomplete macronutrient data
Wallace, 2002	Incomplete macronutrient data
De Graaf, 2002	Incomplete macronutrient data
Dujovne, 2002	Incomplete macronutrient data
Tan, 2002	Incomplete macronutrient data
Jain, 2002	Incomplete macronutrient data
Raison, 2002	Incomplete macronutrient data
Bakris, 2002	Incomplete macronutrient data
Miller, 2002	Incomplete macronutrient data
Hanefeld, 2002	Incomplete macronutrient data
Woodman, 2002	Incomplete macronutrient data
Jain, 2002	Incomplete macronutrient data

Study (By Year)	Reason for Exclusion
Karvonen, 2002	Incomplete lipid profile
Simons, 2002	Incomplete macronutrient data
Wu, 2002	Drug study that did not have an unaffected diet group
Nosaka, 2002	Incomplete macronutrient data
Larsen, 2002	Incomplete macronutrient data
Koh, 2002	Incomplete macronutrient data
Jackson, 2002	Incomplete macronutrient data
Assawawitoontip, 2002	Drug study that did not have an unaffected diet group
Rosenbaum, 2002	Incomplete macronutrient data
Lepage, 2002	Incomplete macronutrient data
Takeuchi, 2002	Incomplete macronutrient data
Halpern, 2002	Incomplete macronutrient data
Anderson, 2002	Incomplete macronutrient data
Chevalier, 2002	Incomplete macronutrient data
Castano, 2002	Incomplete macronutrient data
Miles, 2002	Incomplete macronutrient data
Iwamoto, 2002	No S.D. for macronutrient data
Kabir, 2002	Incomplete macronutrient data
Young, 2002	Incomplete macronutrient data
Whitelaw, 2002	Incomplete macronutrient data
Ostlund, 2002	Incomplete macronutrient data
Gagne, 2002	Incomplete macronutrient data
Kelley, 2002	Incomplete macronutrient data
Nielsen, 2002	Incomplete macronutrient data
Raeini, 2002	Incomplete macronutrient data
Puska, 2002	Incomplete macronutrient data
Agrawal, 2002	Incomplete macronutrient data
Han, 2002	Incomplete macronutrient data
Pontrelli, 2002	Incomplete macronutrient data
Sebestjen, 2002	Incomplete macronutrient data
Saltissi, 2002	Incomplete macronutrient data
Davidson, 2002	Incomplete macronutrient data
Martin-Pena, 2002	Incomplete macronutrient data
Cotreau, 2002	Drug study that did not have an unaffected diet group
Jula, 2002	Incomplete macronutrient data
Davidson, 2002	Incomplete macronutrient data
Andersson, 2002	Incomplete macronutrient data
Bendixen, 2002	Incomplete macronutrient data
Lovejoy, 2002	Washout diet data not reported

APPENDIX F: INDUSTRY CONFLICT OF INTEREST TABLE FOR INCLUDED STUDIES

Study	Sample Size (Included in Meta-Analysis)	Funding Source	Focus of Intervention
Beavers, 2010	32	White-Wave Foods, Inc.	Soymilk and dairy milk
Chan, 2002	25	Pfizer	Statins and fish oil
Diaz, 2008	35	Nutrition 21	Chromium and CLA
Dodin, 2005	179	Flaxseed Council of Canada	Flaxseed supplement
Hjerkinn, 2005	244	Norwegian Retail Co.	n-3 supplements
Hollis, 2009	76	Welch	Concord Grape Juice
Kawashima, 2008	303	Kao Corporation	Di- and Triacylglycerol oils
Levin, 1990	28	Procter & Gamble	Psyllium and placebo capsules
Maki, 2005	57	Martek Biosciences	DHA supplement
Melanson, 2004	22	Pharmenex Inc.	Daily micronutrient supplements
Mensink, 2002	60	McNeil Consumer Healthcare	Plant stanol esters in yogurt
Pins, 2006	30	Davisco Foods International	Hydrolyzed whey protein
Polagruto, 2006	67	Masterfoods, USA	Flavanol-Enriched Snack bars with phytosterols
Tapsell, 2004	55	California Walnut Commission	Walnuts
Tonstad, 2002	101	NutriPharma	Soy protein and Casein
Wardlaw, 1991	31	Procter & Gamble	Canola oil and Safflower oil
Wood, 2006	29	Nutraquest	Soluble fiber and placebo

APPENDIX G: LIST OF NON-ENGLISH STUDIES EXCLUDED FROM THE SYSTEMATIC REVIEW

1. Gonzalez-Ortiz, M, Balcazar-Munoz, BR, Mora-Martinez, JM, Martinez-Abundis, E. [Effect of a high fat or high carbohydrate breakfast on postprandial lipid profile in healthy subjects with or without family history of type 2 diabetes mellitus]. *Arch Latinoam Nutr.* Sep 2004;54(3):274-279. PMID: 15807201
2. Hajdukovic, Z, Jovelic, A, Zivotic-Vanovic, M, Raden, S. [Influence of orlistat therapy on serum insulin level and morphological and functional parameters of peripheral arterial circulation in obese patients]. *Vojnosanit Pregl.* Nov 2005;62(11):803-810. PMID: 16375203
3. Kurokawa, M, Masuda, Y, Noda, M, Usuda, M, Takeda, S, Hasegawa, M, Homma, Y, Sugano, M. [Effects of dressing containing plant sterol on serum cholesterol concentration and the safety evaluation in borderline or mildly hypercholesterolemic Japanese subjects]. *J Oleo Sci.* 2008;57(1):35-45. PMID: 18075221
4. Pogozheva, AV, Derbeneva, SA. [Efficacy of the use of a sour milk product enriched with phytosterols in diet therapy of patients with cardiovascular diseases]. *Kardiologiia.* 2008;48(9):47-49. PMID: 18991820
5. Tedeschi-Reiner, E, Reiner, Z, Romic, Z, Ivankovic, D. [A randomized, double-blind, placebo-controlled study of the antilipemic efficacy and tolerability of food supplement policosanol in patients with moderate hypercholesterolemia]. *Lijec Vjesn.* Nov-Dec 2005;127(11-12):273-279. PMID: 16583932
6. Teplan, V, Schuck, O, Hanzal, V, Hajny, J, Horackova, M, Ryba, M, Stanek, I, Surel, S, Bret, M, Stollova, M, Sasakova, D. [Obesity and progression of chronic renal insufficiency: a Czech long term prospective double-blind randomised multicentre study]. *Vnitr Lek.* Jun 2006;52(6):571-576. PMID: 16871760
7. Zahorska-Markiewicz, B, Krotkiewski, M, Olszanecka-Glinianowicz, M, Zurakowski, A. [Effect of chitosan in complex management of obesity]. *Pol Merkur Lekarski.* Aug 2002;13(74):129-132. PMID: 12420344
8. Zhu, HJ, Pan, H, Gong, FY, Lu, XF, Peng, YD, Liu, ZM, Li, CJ, Yu, YR, Ji, QH, Xing, XP. [A comparison of the efficacy and safety of domestic orlistat and imported orlistat in Chinese overweight and obese patients]. *Zhonghua Nei Ke Za Zhi.* Oct 2009;48(10):825-829. PMID: 20079223

APPENDIX H: SUPPLEMENTAL FIGURES AND TABLES

Macronutrient Distribution & Change in TC (mg/dL)

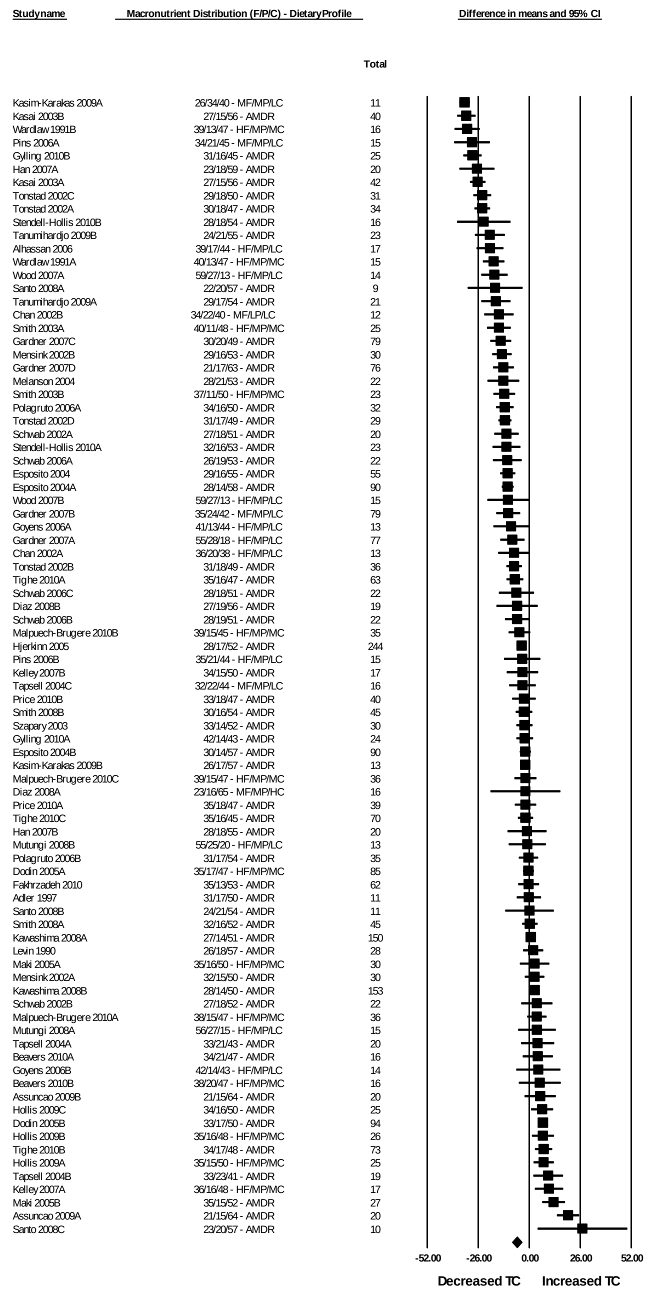

Figure S1. Forest Plot of Macronutrient Distribution and Change in Total Cholesterol [Random Effects Model, Raw Mean Difference (D)]. Macronutrient Distribution (% total energy): Fat/Protein/Carbohydrate.

Figure S2. Sensitivity Analysis: Funnel Plot and Assessment of Publication Bias of Macronutrient Distribution and Change in Total Cholesterol.

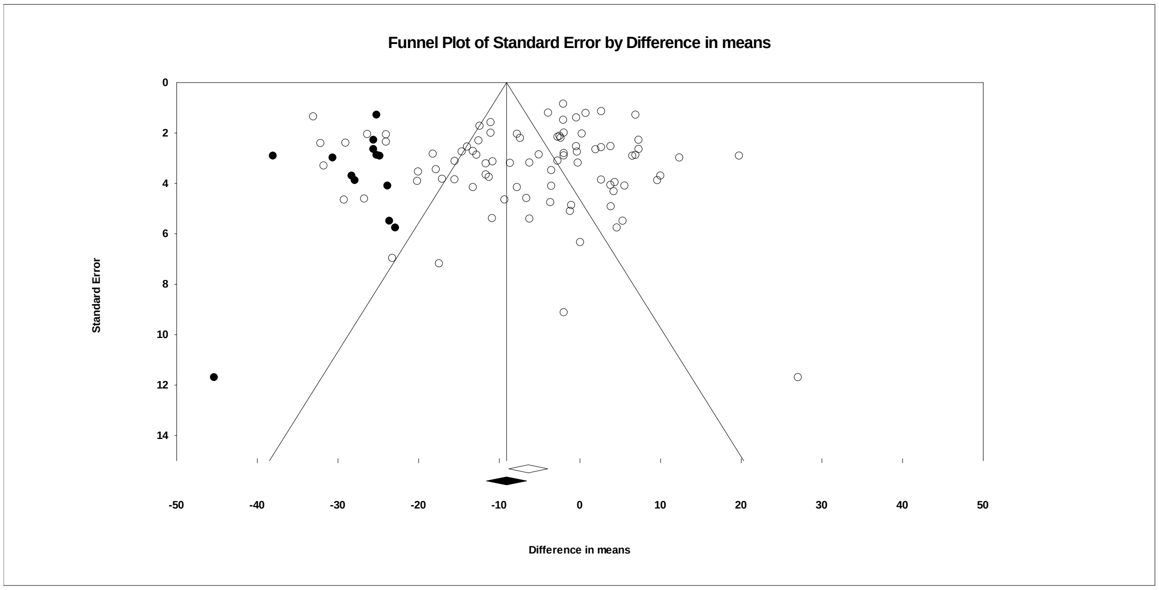

Table S1. Sensitivity Analyses: Trim-and-Fill, Egger's Test, and Classic Fail-Safe N for Macronutrient Distribution and Change in Total Cholesterol.

Duval and Tweedie's Trim-and-Fill (Random Effects Model)						
		Studies Trimmed	Summary Effect	Lower Limit	Upper Limit	Q-value
ΔTC	Observed Values		-6.40056	-8.81294	-3.98817	1716.57852
	Adjusted Values	13	-9.09817	-11.59355	-6.60278	2381.58853
Egger's Regression Intercept:			-0.80460; 95%CI: (-2.94814 to 1.33893) P: 0.457			

Rosenthal's Classic Fail-Safe N (For Observed Studies: Alpha = 0.05, 2-Tailed, Z for alpha = 1.96)				
	Z-value	P-value	Number of Studies	Number of Missing Studies That Would Bring P-value to > alpha
ΔTC	-21.40721	<0.001	86	174

Cumulative Meta-Analysis Macronutrient Distribution & Change in TC

Studyname	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
			Cumulative statistics				
Hjerkinn 2005	-3.870	1.218	1.483	-6.257	-1.483	-3.178	0.001
Kawashima 2008B	-0.569	3.290	10.824	-7.017	5.879	-0.173	0.863
Kawashima 2008A	-0.115	1.961	3.844	-3.958	3.727	-0.059	0.953
Dodin 2005B	1.633	2.194	4.813	-2.667	5.933	0.744	0.457
Esposito 2004A	-0.834	2.756	7.594	-6.235	4.567	-0.303	0.762
Esposito 2004B	-1.018	2.322	5.392	-5.570	3.533	-0.439	0.661
Dodin 2005A	-0.921	1.980	3.922	-4.803	2.960	-0.465	0.642
Gardner 2007C	-2.412	2.062	4.250	-6.452	1.629	-1.170	0.242
Gardner 2007B	-3.202	2.004	4.014	-7.129	0.725	-1.598	0.110
Gardner 2007A	-3.662	1.923	3.698	-7.431	0.107	-1.905	0.057
Gardner 2007D	-4.491	1.921	3.688	-8.255	-0.727	-2.339	0.019
Tighe 2010B	-3.542	1.873	3.509	-7.214	0.129	-1.891	0.059
Tighe 2010C	-3.399	1.746	3.048	-6.821	0.023	-1.947	0.052
Tighe 2010A	-3.674	1.677	2.814	-6.962	-0.387	-2.190	0.028
Fakhrzadeh 2010	-3.458	1.600	2.559	-6.593	-0.322	-2.161	0.031
Esposito 2004	-3.948	1.595	2.545	-7.075	-0.821	-2.475	0.013
Smith 2008B	-3.865	1.515	2.296	-6.835	-0.896	-2.551	0.011
Smith 2008A	-3.623	1.443	2.081	-6.451	-0.796	-2.512	0.012
Kasai 2003A	-4.904	1.771	3.137	-8.376	-1.433	-2.769	0.006
Kasai 2003B	-6.279	2.026	4.104	-10.250	-2.309	-3.100	0.002
Price 2010B	-6.117	1.961	3.846	-9.961	-2.274	-3.119	0.002
Price 2010A	-5.931	1.897	3.598	-9.649	-2.214	-3.127	0.002
Tonstad 2002B	-6.007	1.827	3.338	-9.588	-2.427	-3.288	0.001
Malpuech-Brugere 2010C	-5.844	1.773	3.144	-9.319	-2.368	-3.296	0.001
Malpuech-Brugere 2010A	-5.461	1.731	2.997	-8.855	-2.068	-3.155	0.002
Malpuech-Brugere 2010B	-5.444	1.683	2.833	-8.743	-2.145	-3.235	0.001
Polagruto 2006B	-5.259	1.635	2.673	-8.464	-2.054	-3.216	0.001
Tonstad 2002A	-5.944	1.722	2.966	-9.319	-2.568	-3.451	0.001
Polagruto 2006A	-6.169	1.688	2.850	-9.478	-2.860	-3.654	0.000
Tonstad 2002C	-6.764	1.729	2.989	-10.153	-3.376	-3.913	0.000
Mensink 2002B	-6.992	1.699	2.888	-10.323	-3.662	-4.115	0.000
Szapary 2003	-6.848	1.650	2.723	-10.082	-3.613	-4.149	0.000
Maki 2005A	-6.587	1.624	2.638	-9.770	-3.403	-4.056	0.000
Mensink 2002A	-6.317	1.594	2.542	-9.442	-3.192	-3.962	0.000
Tonstad 2002D	-6.495	1.561	2.438	-9.555	-3.435	-4.160	0.000
Levin 1990	-6.263	1.534	2.352	-9.269	-3.257	-4.084	0.000
Maki 2005B	-5.777	1.536	2.360	-8.789	-2.766	-3.761	0.000
Hollis 2009B	-5.452	1.521	2.314	-8.433	-2.471	-3.584	0.000
Gylling 2010B	-6.053	1.581	2.500	-9.153	-2.954	-3.828	0.000
Smith 2003A	-6.279	1.563	2.442	-9.342	-3.216	-4.018	0.000
Hollis 2009C	-5.974	1.547	2.393	-9.006	-2.942	-3.862	0.000
Hollis 2009A	-5.661	1.534	2.353	-8.667	-2.654	-3.690	0.000
Gylling 2010A	-5.582	1.500	2.251	-8.523	-2.642	-3.721	0.000
Tanumihardjo 2009B	-5.884	1.491	2.224	-8.807	-2.961	-3.945	0.000
Smith 2003B	-6.033	1.472	2.166	-8.917	-3.149	-4.100	0.000
Stendell-Hollis 2010A	-6.146	1.453	2.112	-8.994	-3.298	-4.229	0.000
Melanson 2004	-6.281	1.437	2.066	-9.098	-3.463	-4.369	0.000
Schwab 2006A	-6.376	1.420	2.016	-9.159	-3.593	-4.490	0.000
Schwab 2006C	-6.379	1.404	1.970	-9.130	-3.628	-4.545	0.000
Schwab 2006B	-6.375	1.383	1.912	-9.086	-3.665	-4.610	0.000
Schwab 2002B	-6.193	1.369	1.875	-8.876	-3.509	-4.523	0.000
Tanumihardjo 2009A	-6.386	1.359	1.846	-9.049	-3.722	-4.699	0.000
Han 2007A	-6.722	1.359	1.846	-9.385	-4.058	-4.947	0.000
Schwab 2002A	-6.809	1.343	1.803	-9.441	-4.177	-5.071	0.000
Han 2007B	-6.722	1.330	1.768	-9.329	-4.116	-5.055	0.000
Tapsell 2004A	-6.546	1.318	1.738	-9.130	-3.962	-4.965	0.000
Assuncao 2009B	-6.350	1.308	1.710	-8.914	-3.787	-4.855	0.000
Assuncao 2009A	-5.902	1.333	1.777	-8.515	-3.289	-4.427	0.000
Diaz 2008B	-5.906	1.321	1.746	-8.496	-3.317	-4.470	0.000
Tapsell 2004B	-5.663	1.315	1.728	-8.239	-3.086	-4.308	0.000
Alhassan 2006	-5.889	1.310	1.715	-8.456	-3.322	-4.496	0.000
Kelley 2007B	-5.853	1.296	1.680	-8.393	-3.313	-4.516	0.000
Kelley 2007A	-5.612	1.291	1.666	-8.142	-3.082	-4.348	0.000
Wardlaw 1991B	-6.012	1.311	1.719	-8.582	-3.443	-4.586	0.000
Stendell-Hollis 2010B	-6.207	1.306	1.705	-8.766	-3.649	-4.755	0.000
Tapsell 2004C	-6.167	1.291	1.667	-8.697	-3.636	-4.777	0.000
Diaz 2008A	-6.129	1.284	1.649	-8.645	-3.612	-4.773	0.000
Beavers 2010A	-5.982	1.274	1.623	-8.479	-3.484	-4.695	0.000
Beavers 2010B	-5.842	1.266	1.602	-8.323	-3.361	-4.616	0.000
Pins 2006A	-6.146	1.268	1.608	-8.631	-3.660	-4.846	0.000
Wardlaw 1991A	-6.319	1.263	1.595	-8.794	-3.844	-5.004	0.000
Wood 2007B	-6.373	1.254	1.571	-8.830	-3.916	-5.084	0.000
Pins 2006B	-6.338	1.243	1.545	-8.775	-3.902	-5.099	0.000
Mutungi 2008A	-6.214	1.235	1.524	-8.634	-3.795	-5.034	0.000
Wood 2007A	-6.368	1.228	1.508	-8.775	-3.960	-5.185	0.000
Goyens 2006B	-6.246	1.221	1.490	-8.639	-3.854	-5.117	0.000
Goyens 2006A	-6.282	1.211	1.467	-8.656	-3.908	-5.187	0.000
Chan 2002A	-6.300	1.201	1.442	-8.654	-3.946	-5.246	0.000
Kasim-Karakas 2009B	-6.238	1.145	1.311	-8.483	-3.994	-5.448	0.000
Mutungi 2008B	-6.180	1.137	1.292	-8.408	-3.952	-5.436	0.000
Chan 2002B	-6.291	1.130	1.277	-8.506	-4.076	-5.567	0.000
Kasim-Karakas 2009A	-6.646	1.256	1.579	-9.109	-4.184	-5.290	0.000
Adler 1997	-6.568	1.245	1.551	-9.009	-4.127	-5.274	0.000
Santo 2008B	-6.503	1.238	1.533	-8.930	-4.076	-5.252	0.000
Santo 2008C	-6.301	1.237	1.529	-8.725	-3.877	-5.095	0.000
Santo 2008A	-6.401	1.231	1.515	-8.813	-3.988	-5.200	0.000
	-6.401	1.231	1.515	-8.813	-3.988	-5.200	0.000

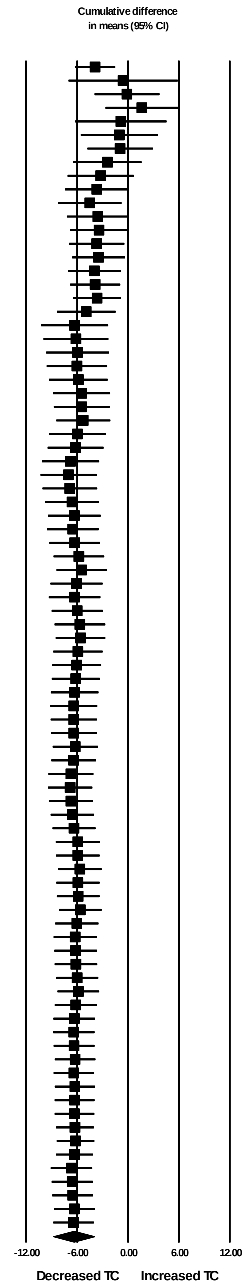

Figure S3. Cumulative Forest Plot of Macronutrient Distribution and Change in Total Cholesterol.
[Sorted by study precision to examine small study bias.]

Cumulative Display (Time-Lag Bias): Macronutrient Distribution & Change in TC

Studyname	Publication Year	Cumulative statistics: Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Levin 1990	1990	2.000	2.671	7.133	-3.235	7.235	0.749	0.454
Wardlaw 1991B	1991	-14.798	16.855	284.088	-47.833	18.237	-0.878	0.380
Wardlaw 1991A	1991	-15.887	9.761	95.270	-35.017	3.244	-1.628	0.104
Adler 1997	1997	-11.973	7.741	59.928	-27.146	3.200	-1.547	0.122
Tonstad 2002B	2002	-11.082	5.563	30.950	-21.986	-0.179	-1.992	0.046
Tonstad 2002A	2002	-13.276	5.133	26.345	-23.336	-3.216	-2.586	0.010
Tonstad 2002C	2002	-14.820	4.568	20.869	-23.774	-5.866	-3.244	0.001
Mensink 2002A	2002	-12.625	4.526	20.484	-21.495	-3.754	-2.789	0.005
Mensink 2002B	2002	-12.769	3.992	15.934	-20.593	-4.946	-3.199	0.001
Tonstad 2002D	2002	-12.727	3.400	11.563	-19.392	-6.062	-3.743	0.000
Schwab 2002B	2002	-11.325	3.326	11.059	-17.843	-4.807	-3.406	0.001
Schwab 2002A	2002	-11.353	3.089	9.544	-17.408	-5.298	-3.675	0.000
Chan 2002A	2002	-11.099	2.930	8.582	-16.840	-5.357	-3.789	0.000
Chan 2002B	2002	-11.398	2.775	7.702	-16.837	-5.958	-4.107	0.000
Kasai 2003A	2003	-12.423	2.782	7.739	-17.876	-6.971	-4.466	0.000
Kasai 2003B	2003	-13.665	2.863	8.195	-19.276	-8.054	-4.773	0.000
Szapary 2003	2003	-12.986	2.793	7.802	-18.460	-7.511	-4.649	0.000
Smith 2003A	2003	-13.125	2.659	7.071	-18.337	-7.913	-4.936	0.000
Smith 2003B	2003	-13.110	2.529	6.395	-18.066	-8.153	-5.184	0.000
Esposito 2004A	2004	-13.008	2.326	5.410	-17.567	-8.450	-5.593	0.000
Esposito 2004B	2004	-12.455	2.297	5.278	-16.958	-7.952	-5.421	0.000
Esposito 2004	2004	-12.390	2.170	4.711	-16.644	-8.136	-5.709	0.000
Melanson 2004	2004	-12.423	2.108	4.445	-16.556	-8.291	-5.892	0.000
Tapsell 2004A	2004	-11.791	2.089	4.364	-15.885	-7.696	-5.644	0.000
Tapsell 2004B	2004	-10.976	2.106	4.434	-15.103	-6.849	-5.212	0.000
Tapsell 2004C	2004	-10.698	2.056	4.227	-14.727	-6.669	-5.204	0.000
Hjerkinn 2005	2005	-10.436	1.954	3.820	-14.266	-6.605	-5.340	0.000
Dodin 2005B	2005	-9.759	2.099	4.407	-13.874	-5.645	-4.649	0.000
Dodin 2005A	2005	-9.422	2.021	4.083	-13.382	-5.462	-4.663	0.000
Maki 2005A	2005	-9.040	1.986	3.946	-12.933	-5.147	-4.551	0.000
Maki 2005B	2005	-8.350	1.997	3.989	-12.264	-4.435	-4.180	0.000
Polagruto 2006B	2006	-8.099	1.949	3.800	-11.920	-4.278	-4.155	0.000
Polagruto 2006A	2006	-8.237	1.896	3.596	-11.954	-4.520	-4.343	0.000
Schwab 2006A	2006	-8.321	1.859	3.458	-11.966	-4.677	-4.475	0.000
Schwab 2006B	2006	-8.262	1.818	3.307	-11.826	-4.698	-4.544	0.000
Schwab 2006C	2006	-8.221	1.788	3.197	-11.725	-4.716	-4.598	0.000
Alhassan 2006	2006	-8.528	1.768	3.125	-11.993	-5.064	-4.825	0.000
Pins 2006A	2006	-9.018	1.764	3.113	-12.476	-5.560	-5.111	0.000
Pins 2006B	2006	-8.894	1.738	3.021	-12.300	-5.487	-5.117	0.000
Goyens 2006B	2006	-8.611	1.720	2.958	-11.982	-5.240	-5.007	0.000
Goyens 2006A	2006	-8.627	1.694	2.870	-11.947	-5.306	-5.092	0.000
Gardner 2007B	2007	-8.678	1.662	2.762	-11.936	-5.421	-5.222	0.000
Gardner 2007C	2007	-8.819	1.633	2.666	-12.019	-5.619	-5.401	0.000
Gardner 2007A	2007	-8.815	1.603	2.568	-11.956	-5.674	-5.500	0.000
Gardner 2007D	2007	-8.916	1.573	2.475	-11.999	-5.832	-5.667	0.000
Han 2007A	2007	-9.266	1.568	2.458	-12.339	-6.193	-5.910	0.000
Han 2007B	2007	-9.115	1.550	2.403	-12.153	-6.077	-5.881	0.000
Kelley 2007A	2007	-8.726	1.548	2.396	-11.759	-5.692	-5.637	0.000
Kelley 2007B	2007	-8.625	1.527	2.332	-11.618	-5.632	-5.648	0.000
Wood 2007B	2007	-8.663	1.510	2.280	-11.622	-5.704	-5.737	0.000
Wood 2007A	2007	-8.841	1.494	2.232	-11.768	-5.913	-5.918	0.000
Kawashima 2008B	2008	-8.598	1.480	2.191	-11.499	-5.697	-5.809	0.000
Kawashima 2008A	2008	-8.406	1.443	2.081	-11.234	-5.579	-5.827	0.000
Smith 2008A	2008	-8.235	1.418	2.010	-11.014	-5.457	-5.809	0.000
Smith 2008B	2008	-8.129	1.390	1.933	-10.854	-5.404	-5.847	0.000
Diaz 2008B	2008	-8.100	1.377	1.895	-10.798	-5.402	-5.884	0.000
Diaz 2008A	2008	-8.035	1.368	1.871	-10.716	-5.354	-5.874	0.000
Mutungi 2008A	2008	-7.851	1.357	1.841	-10.511	-5.192	-5.787	0.000
Mutungi 2008B	2008	-7.747	1.344	1.805	-10.381	-5.114	-5.766	0.000
Santo 2008B	2008	-7.644	1.333	1.777	-10.257	-5.031	-5.734	0.000
Santo 2008C	2008	-7.378	1.332	1.775	-9.989	-4.767	-5.538	0.000
Santo 2008A	2008	-7.498	1.324	1.753	-10.093	-4.903	-5.663	0.000
Hollis 2009B	2009	-7.255	1.318	1.736	-9.838	-4.673	-5.507	0.000
Hollis 2009A	2009	-7.012	1.313	1.723	-9.584	-4.439	-5.342	0.000
Hollis 2009C	2009	-6.793	1.305	1.703	-9.350	-4.235	-5.205	0.000
Tanumihardjo 2009B	2009	-6.990	1.299	1.687	-9.536	-4.444	-5.381	0.000
Tanumihardjo 2009A	2009	-7.138	1.290	1.664	-9.666	-4.610	-5.534	0.000
Assuncao 2009A	2009	-6.717	1.315	1.730	-9.295	-4.138	-5.106	0.000
Assuncao 2009B	2009	-6.543	1.306	1.706	-9.103	-3.983	-5.010	0.000
Kasim-Karakas 2009B	2009	-6.482	1.238	1.532	-8.908	-4.056	-5.236	0.000
Kasim-Karakas 2009A	2009	-6.860	1.388	1.927	-9.581	-4.139	-4.941	0.000
Tighe 2010B	2010	-6.650	1.382	1.910	-9.358	-3.941	-4.812	0.000
Tighe 2010C	2010	-6.583	1.360	1.850	-9.249	-3.917	-4.840	0.000
Tighe 2010A	2010	-6.596	1.340	1.795	-9.222	-3.970	-4.922	0.000
Fakhrzadeh 2010	2010	-6.509	1.325	1.757	-9.107	-3.912	-4.911	0.000
Price 2010B	2010	-6.459	1.312	1.720	-9.030	-3.889	-4.925	0.000
Price 2010A	2010	-6.399	1.297	1.683	-8.942	-3.857	-4.933	0.000
Malpuech-Brugere 2010A	2010	-6.261	1.286	1.655	-8.783	-3.740	-4.867	0.000
Malpuech-Brugere 2010C	2010	-6.206	1.273	1.620	-8.701	-3.711	-4.875	0.000
Malpuech-Brugere 2010B	2010	-6.192	1.259	1.585	-8.659	-3.724	-4.918	0.000
Gylling 2010B	2010	-6.484	1.277	1.630	-8.986	-3.981	-5.078	0.000
Gylling 2010A	2010	-6.431	1.260	1.589	-8.902	-3.961	-5.103	0.000
Stendell-Hollis 2010A	2010	-6.494	1.250	1.563	-8.944	-4.043	-5.194	0.000
Beavers 2010A	2010	-6.368	1.242	1.543	-8.802	-3.933	-5.126	0.000
Beavers 2010B	2010	-6.246	1.236	1.527	-8.668	-3.825	-5.055	0.000
Stendell-Hollis 2010B	2010	-6.401	1.231	1.515	-8.813	-3.988	-5.200	0.000
		-6.401	1.231	1.515	-8.813	-3.988	-5.200	0.000

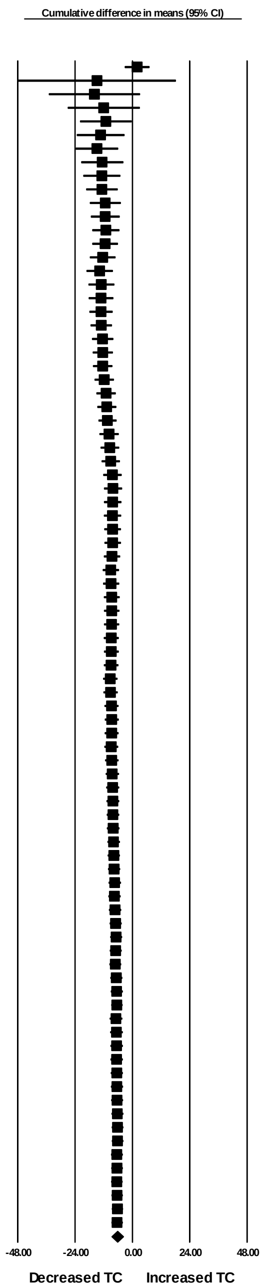

Figure S4. Cumulative Meta-Analysis for Time-Lag Bias: Macronutrient Distribution and Change in Total Cholesterol (mg/dL). Continuously Diminishing Effects Strongly Support Time-Lag Bias.

Direction of Effect (Inconsistency): Macronutrient Distribution & Change in TC

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hjerkinn 2005	-3.870	1.218	1.483	-6.257	-1.483	-3.178	0.001
Kawashima 2008B	2.710	1.156	1.337	0.444	4.976	2.344	0.019
Kawashima 2008A	0.780	1.230	1.512	-1.630	3.190	0.634	0.526
Dodin 2005B	6.960	1.299	1.688	4.414	9.506	5.357	0.000
Esposito 2004A	-11.000	1.597	2.550	-14.130	-7.870	-6.889	0.000
Esposito 2004B	-2.000	1.502	2.256	-4.944	0.944	-1.331	0.183
Dodin 2005A	-0.390	1.409	1.985	-3.152	2.372	-0.277	0.782
Gardner 2007B	-10.760	3.151	9.927	-16.935	-4.585	-3.415	0.001
Gardner 2007C	-14.580	2.760	7.616	-19.989	-9.171	-5.283	0.000
Gardner 2007A	-8.600	3.212	10.315	-14.895	-2.305	-2.678	0.007
Gardner 2007D	-13.200	2.738	7.494	-18.565	-7.835	-4.822	0.000
Tighe 2010B	7.340	2.295	5.269	2.841	11.839	3.198	0.001
Tighe 2010C	-1.930	2.011	4.044	-5.872	2.012	-0.960	0.337
Tighe 2010A	-7.350	2.222	4.935	-11.704	-2.996	-3.309	0.001
Fakhrzadeh 2010	-0.300	2.765	7.648	-5.720	5.120	-0.108	0.914
Esposito 2004	-11.000	2.015	4.059	-14.949	-7.051	-5.460	0.000
Smith 2008A	0.300	2.047	4.191	-3.712	4.312	0.147	0.883
Smith 2008B	-2.700	2.176	4.734	-6.964	1.564	-1.241	0.215
Kasai 2003A	-26.300	2.065	4.263	-30.347	-22.253	-12.738	0.000
Kasai 2003B	-32.100	2.424	5.877	-36.851	-27.349	-13.241	0.000
Price 2010B	-2.710	3.121	9.743	-8.828	3.408	-0.868	0.385
Price 2010A	-1.930	2.820	7.951	-7.457	3.597	-0.684	0.494
Tonstad 2002B	-7.730	2.058	4.234	-11.763	-3.697	-3.757	0.000
Malpuech-Brugere 2010A	3.870	2.546	6.484	-1.121	8.861	1.520	0.129
Malpuech-Brugere 2010C	-1.940	2.916	8.506	-7.656	3.776	-0.665	0.506
Polagruto 2006B	-0.400	2.550	6.500	-5.397	4.597	-0.157	0.875
Malpuech-Brugere 2010B	-5.030	2.875	8.263	-10.664	0.604	-1.750	0.080
Tonstad 2002A	-23.970	2.078	4.317	-28.042	-19.898	-11.536	0.000
Polagruto 2006A	-12.500	2.321	5.386	-17.049	-7.951	-5.386	0.000
Tonstad 2002C	-23.980	2.368	5.605	-28.620	-19.340	-10.129	0.000
Mensink 2002A	2.700	2.589	6.703	-2.374	7.774	1.043	0.297
Mensink 2002B	-13.930	2.564	6.574	-18.955	-8.905	-5.433	0.000
Szapary 2003	-2.450	2.138	4.572	-6.641	1.741	-1.146	0.252
Maki 2005A	2.700	3.875	15.016	-4.895	10.295	0.697	0.486
Tonstad 2002D	-12.370	1.739	3.023	-15.778	-8.962	-7.115	0.000
Levin 1990	2.000	2.671	7.133	-3.235	7.235	0.749	0.454
Maki 2005B	12.400	2.996	8.979	6.527	18.273	4.138	0.000
Hollis 2009B	6.960	2.892	8.366	1.291	12.629	2.406	0.016
Smith 2003A	-15.460	3.133	9.816	-21.601	-9.319	-4.935	0.000
Hollis 2009A	7.350	2.659	7.069	2.139	12.561	2.764	0.006
Hollis 2009C	6.570	2.927	8.567	0.833	12.307	2.245	0.025
Gylling 2010B	-29.000	2.410	5.808	-33.724	-24.276	-12.033	0.000
Gylling 2010A	-2.320	2.214	4.902	-6.659	2.019	-1.048	0.295
Smith 2003B	-12.760	2.886	8.328	-18.416	-7.104	-4.422	0.000
Tanumihardjo 2009B	-20.110	3.926	15.411	-27.804	-12.416	-5.123	0.000
Stendell-Hollis 2010A	-11.600	3.672	13.482	-18.797	-4.403	-3.159	0.002
Schwab 2002B	3.860	4.084	16.677	-4.144	11.864	0.945	0.345
Melanson 2004	-13.200	4.172	17.408	-21.378	-5.022	-3.164	0.002
Schwab 2006A	-11.220	3.768	14.197	-18.605	-3.835	-2.978	0.003
Schwab 2006B	-6.190	3.198	10.224	-12.457	0.077	-1.936	0.053
Schwab 2006C	-6.570	4.606	21.216	-15.598	2.458	-1.426	0.154
Tanumihardjo 2009A	-17.020	3.842	14.765	-24.551	-9.489	-4.429	0.000
Schwab 2002A	-11.600	3.231	10.438	-17.932	-5.268	-3.590	0.000
Tapsell 2004A	4.250	4.334	18.780	-4.244	12.744	0.981	0.327
Han 2007A	-26.680	4.626	21.397	-35.746	-17.614	-5.768	0.000
Han 2007B	-1.160	5.116	26.176	-11.188	8.868	-0.227	0.821
Assuncao 2009A	19.800	2.923	8.545	14.071	25.529	6.774	0.000
Assuncao 2009B	5.600	4.111	16.902	-2.458	13.658	1.362	0.173
Tapsell 2004B	9.660	3.895	15.168	2.027	17.293	2.480	0.013
Diaz 2008B	-6.190	5.421	29.391	-16.816	4.436	-1.142	0.254
Alhassan 2006	-20.000	3.553	12.622	-26.963	-13.037	-5.629	0.000
Kelley 2007A	10.050	3.715	13.804	2.768	17.332	2.705	0.007
Kelley 2007B	-3.480	4.120	16.975	-11.555	4.595	-0.845	0.398
Wardlaw 1991B	-31.710	3.315	10.991	-38.208	-25.212	-9.565	0.000
Tapsell 2004C	-3.480	3.498	12.237	-10.336	3.376	-0.995	0.320
Diaz 2008A	-1.930	9.136	83.465	-19.836	15.976	-0.211	0.833
Beavers 2010A	4.380	3.975	15.797	-3.410	12.170	1.102	0.270
Beavers 2010B	5.370	5.505	30.302	-5.419	16.159	0.976	0.329
Stendell-Hollis 2010B	-23.200	6.980	48.720	-36.880	-9.520	-3.324	0.001
Wardlaw 1991A	-18.170	2.846	8.098	-23.748	-12.592	-6.385	0.000
Pins 2006A	-29.200	4.665	21.765	-38.344	-20.056	-6.259	0.000
Pins 2006B	-3.600	4.768	22.731	-12.945	5.745	-0.755	0.450
Wood 2007B	-10.830	5.402	29.178	-21.417	-0.243	-2.005	0.045
Mutungi 2008A	3.900	4.933	24.334	-5.768	13.568	0.791	0.429
Goyens 2006B	4.640	5.773	33.328	-6.675	15.955	0.804	0.422
Wood 2007A	-17.790	3.464	12.002	-24.580	-11.000	-5.135	0.000
Chan 2002A	-7.740	4.172	17.408	-15.917	0.437	-1.855	0.064
Goyens 2006A	-9.280	4.663	21.741	-18.419	-0.141	-1.990	0.047
Mutungi 2008B	-1.000	4.881	23.821	-10.566	8.566	-0.205	0.838
Kasim-Karakas 2009B	-2.000	0.864	0.747	-3.694	-0.306	-2.314	0.021
Chan 2002B	-15.470	3.863	14.927	-23.042	-7.898	-4.004	0.000
Adler 1997	-0.200	3.200	10.240	-6.472	6.072	-0.062	0.950
Santo 2008B	0.100	6.351	40.339	-12.348	12.548	0.016	0.987
Kasim-Karakas 2009A	-33.000	1.368	1.872	-35.681	-30.319	-24.121	0.000
Santo 2008C	27.100	11.710	137.132	4.148	50.052	2.314	0.021
Santo 2008A	-17.400	7.195	51.768	-31.502	-3.298	-2.418	0.016
	-6.401	1.231	1.515	-8.813	-3.988	-5.200	0.000

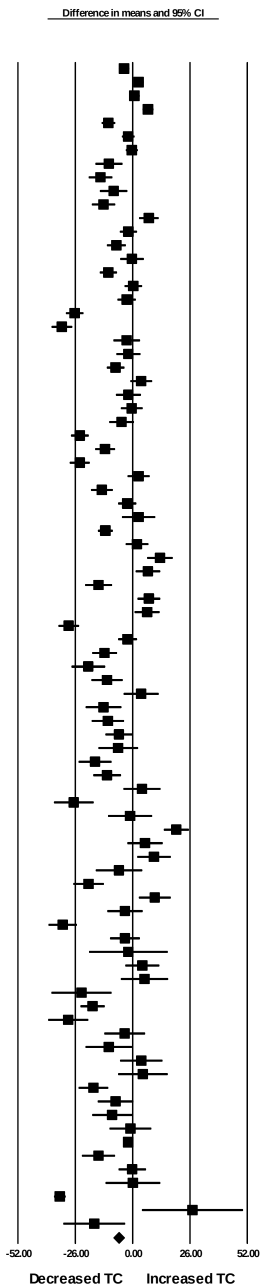

Figure S5. The Impact of Direction of Effect on Decisions Regarding Inconsistency: Macronutrient Distribution & Change in Total Cholesterol. (Studies Sorted by Precision)

Table S2. Sensitivity Analysis for Macronutrient Distribution and Change in Total Cholesterol: Random Effects Model versus Fixed Effect Model								
Table of Summary Effects (Random Effects versus Fixed Effect Model/Raw Mean Difference)								
Effect size and 95% confidence interval							Test of null (2-Tail)	
	N	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
ΔTC**	86	-6.40	1.23	1.52	-8.81	-3.99	-5.20	<0.001
ΔTC	86	-5.89	0.26	0.07	-6.41	-5.38	-22.28	<0.001

**From Random Effects Model.

Table S3. Sensitivity Analysis: Plausible Ranges for Pre- and Post-Treatment Correlations (Random Effects Model/Raw Mean Difference)								
Correlation		Effect size and 95% confidence interval					Test of null (2-Tail)	
	r	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
Δ TC	0.896*	-6.40	1.23	1.52	-8.81	-3.99	-5.20	<0.001
	0.5	-6.50	1.30	1.70	-9.06	-3.95	-4.99	<0.001
	0.75	-6.45	1.27	1.61	-8.93	-3.96	-5.08	<0.001
	0.99	-6.38	1.10	1.21	-8.53	-4.22	-5.79	<0.001

*Correlation calculated via the *CORREL* function in Microsoft Excel 2010 (Microsoft Corp., 2010), using the 86 comparisons ("studies") from the meta-analytic database. The correlation (r) between pre- and post-treatments was required for the calculation of the treatment effect variance (V_D): [$V_D = S^2_{diff}/n$; $S_{diff} = (\sqrt{S_{Pre}}^2 + S_{Post}^2 - 2 \times r \times S_{Pre} \times S_{Post})$].

Sensitivity Analysis (One Study Removed): Macronutrient Distribution & Change in TC

Studyname	Statistics with studyremoved						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hjerkinn 2005	-6.429	1.266	1.602	-8.910	-3.948	-5.079	0.000
Kawashima 2008B	-6.516	1.249	1.560	-8.964	-4.069	-5.218	0.000
Kawashima 2008A	-6.490	1.255	1.576	-8.951	-4.030	-5.170	0.000
Dodin 2005B	-6.575	1.227	1.505	-8.980	-4.170	-5.359	0.000
Esposito 2004A	-6.340	1.252	1.566	-8.793	-3.887	-5.065	0.000
Esposito 2004B	-6.454	1.255	1.575	-8.914	-3.995	-5.143	0.000
Dodin 2005A	-6.475	1.254	1.573	-8.934	-4.017	-5.162	0.000
Gardner 2007B	-6.347	1.242	1.542	-8.782	-3.913	-5.111	0.000
Gardner 2007C	-6.300	1.241	1.539	-8.732	-3.868	-5.078	0.000
Gardner 2007A	-6.373	1.242	1.543	-8.808	-3.939	-5.130	0.000
Gardner 2007D	-6.317	1.242	1.542	-8.750	-3.883	-5.087	0.000
Tighe 2010B	-6.573	1.235	1.525	-8.993	-4.153	-5.322	0.000
Tighe 2010C	-6.455	1.248	1.557	-8.901	-4.010	-5.174	0.000
Tighe 2010A	-6.387	1.247	1.555	-8.832	-3.943	-5.122	0.000
Fakhrzadeh 2010	-6.475	1.243	1.544	-8.910	-4.039	-5.210	0.000
Esposito 2004	-6.341	1.247	1.555	-8.785	-3.897	-5.086	0.000
Smith 2008A	-6.484	1.246	1.551	-8.925	-4.043	-5.206	0.000
Smith 2008B	-6.446	1.247	1.555	-8.889	-4.002	-5.169	0.000
Kasai 2003A	-6.153	1.214	1.473	-8.532	-3.775	-5.070	0.000
Kasai 2003B	-6.086	1.204	1.450	-8.446	-3.726	-5.054	0.000
Price 2010B	-6.444	1.242	1.544	-8.880	-4.009	-5.187	0.000
Price 2010A	-6.454	1.243	1.546	-8.891	-4.018	-5.192	0.000
Tonstad 2002B	-6.382	1.248	1.559	-8.829	-3.935	-5.112	0.000
Malpuech-Brugere 2010A	-6.527	1.240	1.538	-8.958	-4.097	-5.264	0.000
Malpuech-Brugere 2010C	-6.454	1.243	1.545	-8.890	-4.018	-5.193	0.000
Polagruto 2006B	-6.474	1.244	1.546	-8.911	-4.037	-5.206	0.000
Malpuech-Brugere 2010B	-6.416	1.244	1.547	-8.854	-3.979	-5.159	0.000
Tonstad 2002A	-6.182	1.221	1.492	-8.576	-3.788	-5.061	0.000
Polagruto 2006A	-6.324	1.244	1.547	-8.761	-3.886	-5.085	0.000
Tonstad 2002C	-6.183	1.226	1.502	-8.585	-3.781	-5.045	0.000
Mensink 2002A	-6.513	1.241	1.540	-8.945	-4.080	-5.248	0.000
Mensink 2002B	-6.307	1.242	1.542	-8.740	-3.873	-5.080	0.000
Szapary 2003	-6.449	1.247	1.555	-8.893	-4.005	-5.171	0.000
Maki 2005A	-6.506	1.239	1.536	-8.935	-4.077	-5.249	0.000
Tonstad 2002D	-6.323	1.248	1.557	-8.769	-3.878	-5.068	0.000
Levin 1990	-6.503	1.241	1.541	-8.937	-4.070	-5.238	0.000
Maki 2005B	-6.630	1.230	1.513	-9.041	-4.219	-5.390	0.000
Hollis 2009B	-6.564	1.237	1.529	-8.988	-4.140	-5.307	0.000
Smith 2003A	-6.291	1.240	1.536	-8.721	-3.862	-5.075	0.000
Hollis 2009A	-6.570	1.236	1.527	-8.993	-4.148	-5.316	0.000
Hollis 2009C	-6.559	1.237	1.530	-8.983	-4.134	-5.301	0.000
Gylling 2010B	-6.123	1.213	1.472	-8.501	-3.745	-5.047	0.000
Gylling 2010A	-6.450	1.246	1.554	-8.893	-4.008	-5.175	0.000
Smith 2003B	-6.322	1.242	1.542	-8.756	-3.889	-5.092	0.000
Tanumihardjo 2009B	-6.243	1.236	1.529	-8.666	-3.819	-5.049	0.000
Stendell-Hollis 2010A	-6.339	1.241	1.539	-8.771	-3.908	-5.110	0.000
Schwab 2002B	-6.518	1.239	1.534	-8.945	-4.090	-5.262	0.000
Melanson 2004	-6.323	1.239	1.536	-8.752	-3.894	-5.101	0.000
Schwab 2006A	-6.344	1.241	1.539	-8.775	-3.913	-5.114	0.000
Schwab 2006B	-6.402	1.243	1.544	-8.838	-3.967	-5.152	0.000
Schwab 2006C	-6.398	1.240	1.537	-8.828	-3.968	-5.160	0.000
Tanumihardjo 2009A	-6.277	1.238	1.533	-8.704	-3.851	-5.070	0.000
Schwab 2002A	-6.338	1.241	1.541	-8.771	-3.905	-5.105	0.000
Tapsell 2004A	-6.520	1.238	1.534	-8.947	-4.093	-5.265	0.000
Han 2007A	-6.178	1.233	1.520	-8.594	-3.761	-5.011	0.000
Han 2007B	-6.456	1.239	1.535	-8.885	-4.028	-5.211	0.000
Assuncao 2009A	-6.723	1.216	1.479	-9.107	-4.340	-5.528	0.000
Assuncao 2009B	-6.537	1.238	1.532	-8.964	-4.111	-5.281	0.000
Tapsell 2004B	-6.587	1.235	1.526	-9.008	-4.165	-5.331	0.000
Diaz 2008B	-6.402	1.239	1.535	-8.831	-3.974	-5.168	0.000
Alhassan 2006	-6.241	1.236	1.528	-8.663	-3.818	-5.048	0.000
Kelley 2007A	-6.593	1.235	1.525	-9.014	-4.173	-5.339	0.000
Kelley 2007B	-6.433	1.240	1.539	-8.865	-4.002	-5.186	0.000
Wardlaw 1991B	-6.101	1.221	1.491	-8.494	-3.708	-4.997	0.000
Tapsell 2004C	-6.435	1.242	1.542	-8.868	-4.001	-5.182	0.000
Diaz 2008A	-6.434	1.236	1.528	-8.857	-4.011	-5.205	0.000
Beavers 2010A	-6.524	1.239	1.534	-8.952	-4.097	-5.268	0.000
Beavers 2010B	-6.522	1.237	1.531	-8.948	-4.097	-5.271	0.000
Stendell-Hollis 2010B	-6.246	1.236	1.527	-8.668	-3.825	-5.055	0.000
Wardlaw 1991A	-6.257	1.237	1.531	-8.682	-3.832	-5.057	0.000
Pins 2006A	-6.151	1.231	1.516	-8.564	-3.738	-4.996	0.000
Pins 2006B	-6.431	1.240	1.537	-8.860	-4.001	-5.188	0.000
Wood 2007B	-6.354	1.239	1.534	-8.782	-3.926	-5.130	0.000
Mutungi 2008A	-6.512	1.238	1.533	-8.938	-4.085	-5.259	0.000
Goyens 2006B	-6.513	1.237	1.531	-8.938	-4.087	-5.263	0.000
Wood 2007A	-6.266	1.238	1.532	-8.692	-3.840	-5.062	0.000
Chan 2002A	-6.385	1.240	1.539	-8.816	-3.954	-5.147	0.000
Goyens 2006A	-6.369	1.240	1.537	-8.798	-3.939	-5.137	0.000
Mutungi 2008B	-6.459	1.239	1.536	-8.888	-4.030	-5.212	0.000
Kasim-Karakas 2009B	-6.450	1.285	1.651	-8.969	-3.931	-5.019	0.000
Chan 2002B	-6.295	1.239	1.535	-8.724	-3.867	-5.081	0.000
Adler 1997	-6.474	1.241	1.541	-8.908	-4.041	-5.215	0.000
Santo 2008B	-6.463	1.238	1.532	-8.890	-4.037	-5.222	0.000
Kasim-Karakas 2009A	-6.074	1.108	1.228	-8.245	-3.902	-5.482	0.000
Santo 2008C	-6.601	1.232	1.519	-9.017	-4.186	-5.356	0.000
Santo 2008A	-6.301	1.237	1.529	-8.725	-3.877	-5.095	0.000
	-6.401	1.231	1.515	-8.813	-3.988	-5.200	0.000

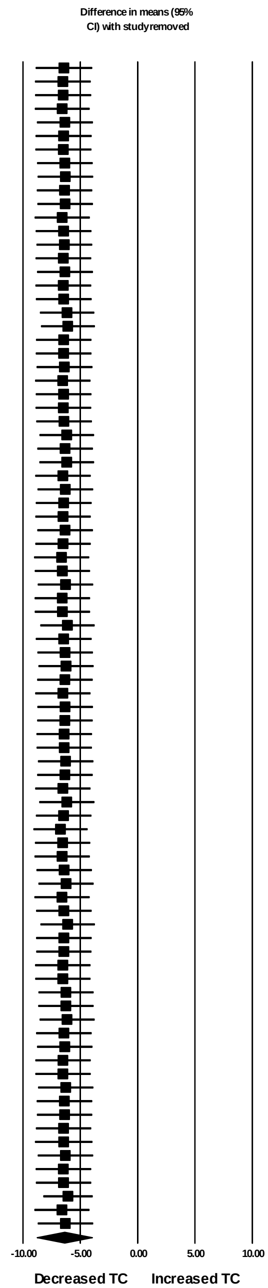

Figure S6. Sensitivity Analysis (One Study Removed): Macronutrient Distribution & Change in Total Cholesterol.

Macronutrient Distribution & Change in LDL (mg/dL)

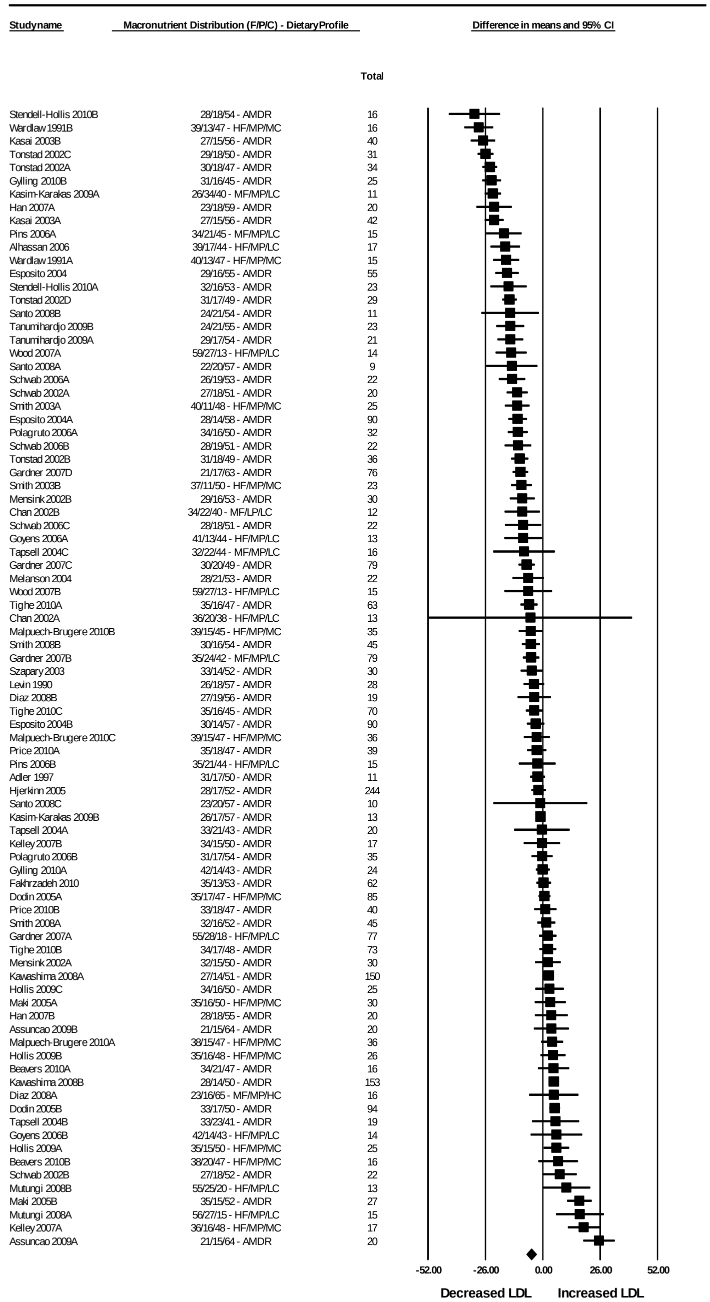

Figure S7. Forest Plot of Macronutrient Distribution and Change in LDL Cholesterol [Random Effects Model, Raw Mean Difference (D)]. Macronutrient Distribution (% total energy): Fat/Protein/Carbohydrate.

Figure S8. Sensitivity Analysis: Funnel Plot and Assessment of Publication Bias of Macronutrient Distribution and Change in LDL Cholesterol.

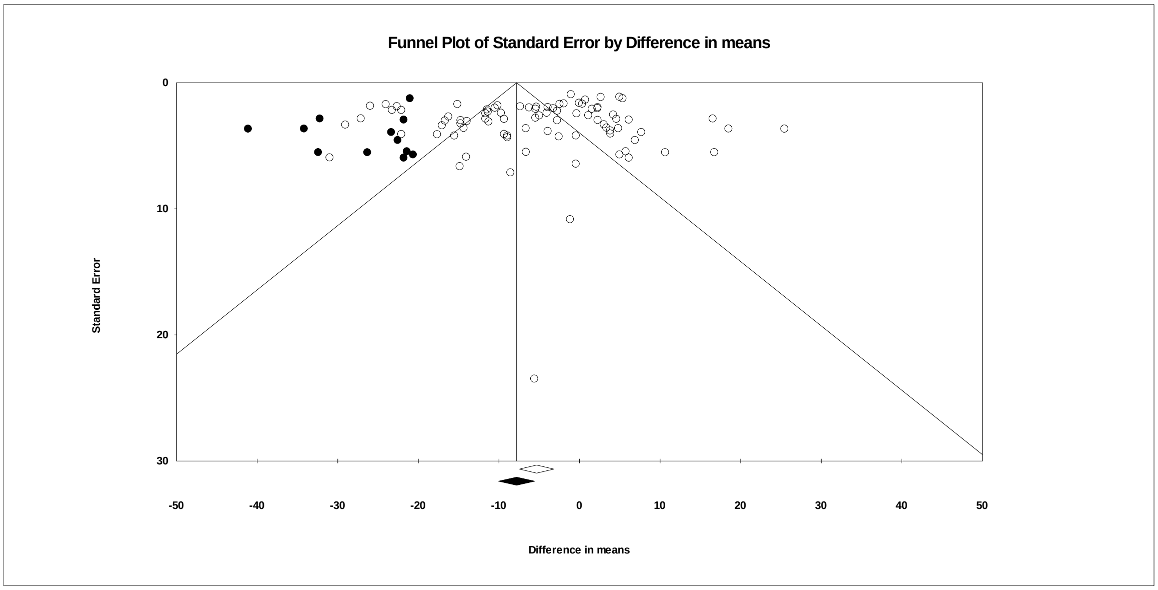

Table S4. Sensitivity Analyses: Trim-and-Fill, Egger's Test, and Classic Fail-Safe N for Macronutrient Distribution and Change in LDL Cholesterol.						
Duval and Tweedie's Trim-and-Fill (Random Effects Model)						
		Studies Trimmed	Summary Effect	Lower Limit	Upper Limit	Q-value
ΔLDL	Observed Values		-5.31734	-7.45998	-3.17469	1365.77878
	Adjusted Values	12	-7.80435	-10.05026	-5.55843	1873.71850
Egger's Regression Intercept:			-1.13964; 95%CI: (-3.13607 to 0.85679) P: 0.25953			
Rosenthal's Classic Fail-Safe N (For Observed Studies: Alpha = 0.05, 2-Tailed, Z for alpha = 1.96)						
	Z-value	P-value	Number of Studies	Number of Missing Studies That Would Bring P-value to > alpha		
ΔLDL	-18.08621	<0.001	86	7238		

Cumulative Meta-Analysis: Macronutrient Distribution & Change in LDL

Studyname	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Cumulative statistics						
Hjerkinn 2005	-1.890	1.693	2.867	-5.209	1.429	-1.116	0.264
Kawashima 2008B	1.674	3.453	11.925	-5.094	8.443	0.485	0.628
Kawashima 2008A	2.127	1.819	3.310	-1.439	5.693	1.169	0.242
Dodin 2005B	2.988	1.440	2.073	0.166	5.809	2.075	0.038
Esposito 2004A	0.230	2.403	5.773	-4.479	4.939	0.096	0.924
Esposito 2004B	-0.304	2.177	4.741	-4.572	3.963	-0.140	0.889
Dodin 2005A	-0.102	1.825	3.332	-3.679	3.476	-0.056	0.956
Gardner 2007C	-1.004	1.859	3.455	-4.647	2.639	-0.540	0.589
Gardner 2007B	-1.469	1.771	3.138	-4.940	2.003	-0.829	0.407
Gardner 2007A	-1.096	1.628	2.652	-4.287	2.096	-0.673	0.501
Gardner 2007D	-1.936	1.720	2.957	-5.307	1.434	-1.126	0.260
Tighe 2010B	-1.583	1.603	2.569	-4.725	1.558	-0.988	0.323
Tighe 2010C	-1.750	1.515	2.296	-4.720	1.220	-1.155	0.248
Tighe 2010A	-2.059	1.466	2.148	-4.932	0.813	-1.405	0.160
Fakhrzadeh 2010	-1.885	1.368	1.871	-4.565	0.796	-1.378	0.168
Esposito 2004	-2.705	1.452	2.108	-5.551	0.140	-1.863	0.062
Smith 2008B	-2.855	1.397	1.951	-5.593	-0.118	-2.044	0.041
Smith 2008A	-2.609	1.335	1.782	-5.225	0.008	-1.954	0.051
Kasai 2003A	-3.657	1.558	2.426	-6.710	-0.604	-2.348	0.019
Kasai 2003B	-4.774	1.705	2.907	-8.115	-1.432	-2.800	0.005
Price 2010B	-4.501	1.648	2.715	-7.730	-1.272	-2.732	0.006
Price 2010A	-4.416	1.585	2.511	-7.522	-1.310	-2.786	0.005
Tonstad 2002B	-4.679	1.557	2.423	-7.730	-1.628	-3.006	0.003
Malpuech-Brugere 2010C	-4.601	1.513	2.288	-7.565	-1.636	-3.042	0.002
Malpuech-Brugere 2010A	-4.260	1.478	2.185	-7.157	-1.363	-2.882	0.004
Malpuech-Brugere 2010B	-4.299	1.439	2.072	-7.120	-1.478	-2.987	0.003
Polagruto 2006B	-4.152	1.397	1.952	-6.891	-1.414	-2.972	0.003
Tonstad 2002A	-4.906	1.585	2.511	-8.011	-1.800	-3.096	0.002
Polagruto 2006A	-5.123	1.556	2.420	-8.172	-2.074	-3.293	0.001
Tonstad 2002C	-5.838	1.687	2.846	-9.144	-2.531	-3.461	0.001
Mensink 2002B	-5.944	1.652	2.728	-9.181	-2.707	-3.599	0.000
Szapary 2003	-5.912	1.611	2.597	-9.070	-2.753	-3.669	0.000
Mensink 2002A	-5.674	1.582	2.502	-8.774	-2.574	-3.587	0.000
Maki 2005A	-5.430	1.557	2.425	-8.482	-2.379	-3.488	0.000
Tonstad 2002D	-5.713	1.548	2.396	-8.747	-2.679	-3.691	0.000
Levin 1990	-5.666	1.511	2.285	-8.628	-2.703	-3.748	0.000
Maki 2005B	-5.086	1.533	2.349	-8.090	-2.083	-3.319	0.001
Hollis 2009B	-4.840	1.511	2.283	-7.801	-1.878	-3.203	0.001
Gylling 2010B	-5.311	1.542	2.379	-8.334	-2.288	-3.444	0.001
Smith 2003A	-5.463	1.519	2.307	-8.440	-2.486	-3.597	0.000
Hollis 2009C	-5.267	1.498	2.244	-8.203	-2.331	-3.516	0.000
Hollis 2009A	-5.004	1.482	2.196	-7.908	-2.100	-3.377	0.001
Gylling 2010A	-4.885	1.443	2.082	-7.713	-2.057	-3.385	0.001
Stendell-Hollis 2010A	-5.096	1.430	2.044	-7.898	-2.294	-3.565	0.000
Tanumihardjo 2009B	-5.299	1.415	2.003	-8.073	-2.525	-3.744	0.000
Smith 2003B	-5.393	1.392	1.938	-8.122	-2.665	-3.875	0.000
Schwab 2006A	-5.568	1.377	1.897	-8.267	-2.868	-4.042	0.000
Schwab 2006B	-5.680	1.360	1.849	-8.346	-3.015	-4.177	0.000
Schwab 2006C	-5.738	1.344	1.807	-8.373	-3.103	-4.269	0.000
Melanson 2004	-5.754	1.327	1.761	-8.355	-3.153	-4.336	0.000
Schwab 2002B	-5.515	1.317	1.735	-8.096	-2.933	-4.186	0.000
Tanumihardjo 2009A	-5.686	1.306	1.705	-8.245	-3.127	-4.355	0.000
Han 2007A	-5.963	1.303	1.697	-8.516	-3.410	-4.578	0.000
Schwab 2002A	-6.068	1.286	1.653	-8.588	-3.548	-4.719	0.000
Tapsell 2004A	-5.993	1.276	1.627	-8.493	-3.493	-4.698	0.000
Han 2007B	-5.831	1.264	1.598	-8.308	-3.353	-4.613	0.000
Assuncao 2009B	-5.676	1.253	1.570	-8.132	-3.220	-4.530	0.000
Assuncao 2009A	-5.170	1.278	1.634	-7.676	-2.665	-4.044	0.000
Diaz 2008B	-5.150	1.264	1.598	-7.628	-2.672	-4.074	0.000
Tapsell 2004B	-5.002	1.255	1.576	-7.463	-2.542	-3.985	0.000
Alhassan 2006	-5.191	1.248	1.558	-7.638	-2.745	-4.159	0.000
Kelley 2007B	-5.121	1.236	1.528	-7.544	-2.698	-4.142	0.000
Kelley 2007A	-4.763	1.244	1.548	-7.202	-2.324	-3.828	0.000
Stendell-Hollis 2010B	-5.083	1.245	1.551	-7.524	-2.642	-4.082	0.000
Wardlaw 1991B	-5.441	1.259	1.585	-7.908	-2.974	-4.322	0.000
Tapsell 2004C	-5.474	1.251	1.564	-7.925	-3.023	-4.377	0.000
Beavers 2010A	-5.325	1.241	1.540	-7.757	-2.893	-4.291	0.000
Diaz 2008A	-5.201	1.233	1.520	-7.618	-2.785	-4.219	0.000
Beavers 2010B	-5.043	1.225	1.501	-7.444	-2.642	-4.116	0.000
Pins 2006A	-5.210	1.219	1.485	-7.599	-2.822	-4.275	0.000
Wardlaw 1991A	-5.372	1.212	1.469	-7.747	-2.996	-4.432	0.000
Wood 2007B	-5.386	1.203	1.447	-7.744	-3.028	-4.477	0.000
Pins 2006B	-5.349	1.193	1.422	-7.687	-3.012	-4.485	0.000
Mutungi 2008A	-5.099	1.191	1.418	-7.433	-2.765	-4.282	0.000
Wood 2007A	-5.218	1.183	1.399	-7.536	-2.901	-4.413	0.000
Goyens 2006B	-5.097	1.176	1.383	-7.403	-2.792	-4.334	0.000
Goyens 2006A	-5.143	1.167	1.361	-7.430	-2.857	-4.408	0.000
Chan 2002A	-5.144	1.165	1.357	-7.428	-2.861	-4.416	0.000
Kasim-Karakas 2009B	-5.091	1.122	1.259	-7.290	-2.892	-4.538	0.000
Mutungi 2008B	-4.925	1.117	1.249	-7.115	-2.735	-4.407	0.000
Chan 2002B	-4.977	1.109	1.229	-7.150	-2.803	-4.488	0.000
Kasim-Karakas 2009A	-5.205	1.127	1.270	-7.414	-2.996	-4.618	0.000
Santo 2008B	-5.293	1.122	1.258	-7.492	-3.095	-4.719	0.000
Adler 1997	-5.257	1.103	1.216	-7.419	-3.096	-4.768	0.000
Santo 2008C	-5.233	1.099	1.208	-7.387	-3.080	-4.763	0.000
Santo 2008A	-5.317	1.093	1.195	-7.460	-3.175	-4.864	0.000
	-5.317	1.093	1.195	-7.460	-3.175	-4.864	0.000

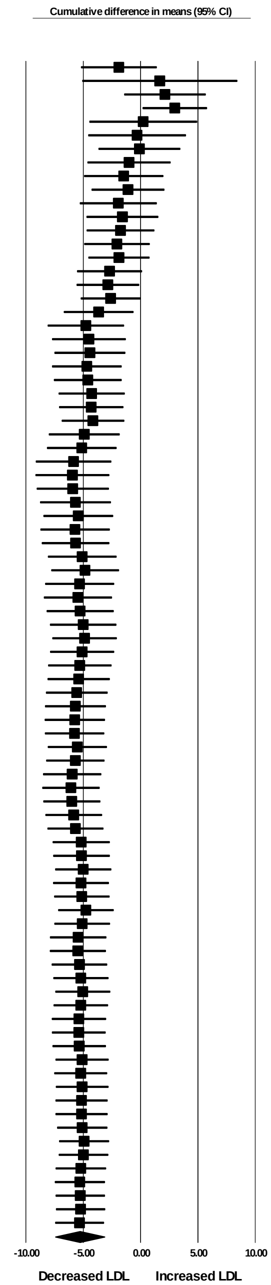

Figure S9. Cumulative Forest Plot of Macronutrient Distribution and Change in LDL Cholesterol.
[Sorted by study precision to examine small study bias.]

Cumulative Display (Time-Lag Bias): Macronutrient Distribution & Change in LDL

Studyname	Publication Year	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
		Cumulative statistics						
Levin 1990	1990	-4.000	2.435	5.931	-8.773	0.773	-1.642	0.101
Wardlaw 1991A	1991	-10.181	6.314	39.861	-22.556	2.193	-1.613	0.107
Wardlaw 1991B	1991	-16.401	7.318	53.546	-30.743	-2.059	-2.241	0.025
Adler 1997	1997	-12.754	5.664	32.081	-23.855	-1.653	-2.252	0.024
Chan 2002A	2002	-12.426	5.477	30.001	-23.161	-1.691	-2.269	0.023
Chan 2002B	2002	-11.856	4.613	21.279	-20.897	-2.815	-2.570	0.010
Mensink 2002A	2002	-9.554	4.155	17.260	-17.696	-1.411	-2.300	0.021
Mensink 2002B	2002	-9.502	3.552	12.613	-16.463	-2.541	-2.676	0.007
Schwab 2002A	2002	-9.753	3.083	9.505	-15.796	-3.710	-3.163	0.002
Schwab 2002B	2002	-7.979	3.080	9.485	-14.015	-1.943	-2.591	0.010
Tonstad 2002A	2002	-9.616	3.479	12.103	-16.434	-2.797	-2.764	0.006
Tonstad 2002B	2002	-9.712	3.064	9.386	-15.717	-3.708	-3.170	0.002
Tonstad 2002C	2002	-11.075	3.145	9.890	-17.239	-4.912	-3.522	0.000
Tonstad 2002D	2002	-11.418	2.809	7.889	-16.923	-5.913	-4.065	0.000
Kasai 2003A	2003	-12.191	2.673	7.147	-17.431	-6.951	-4.560	0.000
Kasai 2003B	2003	-13.158	2.623	6.879	-18.299	-8.017	-5.017	0.000
Smith 2003A	2003	-13.071	2.485	6.173	-17.940	-8.201	-5.261	0.000
Smith 2003B	2003	-12.878	2.351	5.526	-17.486	-8.271	-5.478	0.000
Szapary 2003	2003	-12.440	2.274	5.172	-16.897	-7.983	-5.470	0.000
Esposito 2004	2004	-12.643	2.168	4.699	-16.891	-8.394	-5.833	0.000
Esposito 2004A	2004	-12.588	2.048	4.194	-16.602	-8.574	-6.146	0.000
Esposito 2004B	2004	-12.127	2.012	4.049	-16.071	-8.184	-6.027	0.000
Melanson 2004	2004	-11.896	1.956	3.825	-15.729	-8.063	-6.082	0.000
Tapsell 2004A	2004	-11.538	1.927	3.715	-15.315	-7.760	-5.986	0.000
Tapsell 2004B	2004	-10.952	1.918	3.677	-14.710	-7.194	-5.711	0.000
Tapsell 2004C	2004	-10.887	1.885	3.551	-14.581	-7.194	-5.777	0.000
Dodin 2005A	2005	-10.368	1.945	3.785	-14.181	-6.555	-5.329	0.000
Dodin 2005B	2005	-9.699	2.087	4.356	-13.790	-5.608	-4.647	0.000
Hjerkinn 2005	2005	-9.411	2.009	4.037	-13.350	-5.473	-4.684	0.000
Maki 2005A	2005	-8.985	1.978	3.912	-12.861	-5.108	-4.542	0.000
Maki 2005B	2005	-8.112	2.038	4.154	-12.107	-4.118	-3.980	0.000
Alhassan 2006	2006	-8.394	1.999	3.998	-12.313	-4.475	-4.198	0.000
Goyens 2006A	2006	-8.410	1.960	3.841	-12.251	-4.569	-4.291	0.000
Goyens 2006B	2006	-8.044	1.937	3.751	-11.840	-4.248	-4.153	0.000
Pins 2006A	2006	-8.310	1.906	3.634	-12.047	-4.574	-4.360	0.000
Pins 2006B	2006	-8.156	1.873	3.507	-11.827	-4.486	-4.355	0.000
Polagruto 2006A	2006	-8.252	1.819	3.310	-11.818	-4.686	-4.536	0.000
Polagruto 2006B	2006	-8.032	1.782	3.174	-11.524	-4.541	-4.509	0.000
Schwab 2006A	2006	-8.190	1.747	3.052	-11.614	-4.766	-4.688	0.000
Schwab 2006B	2006	-8.271	1.711	2.927	-11.624	-4.918	-4.834	0.000
Schwab 2006C	2006	-8.287	1.682	2.831	-11.585	-4.990	-4.926	0.000
Gardner 2007A	2007	-8.015	1.659	2.753	-11.267	-4.763	-4.831	0.000
Gardner 2007B	2007	-7.952	1.609	2.589	-11.105	-4.798	-4.942	0.000
Gardner 2007C	2007	-7.941	1.560	2.432	-10.997	-4.884	-5.092	0.000
Gardner 2007D	2007	-7.998	1.513	2.289	-10.963	-5.033	-5.287	0.000
Han 2007A	2007	-8.289	1.503	2.259	-11.234	-5.343	-5.515	0.000
Han 2007B	2007	-8.036	1.489	2.217	-10.954	-5.118	-5.397	0.000
Kelley 2007A	2007	-7.481	1.514	2.292	-10.448	-4.514	-4.942	0.000
Kelley 2007B	2007	-7.344	1.495	2.236	-10.275	-4.413	-4.911	0.000
Wood 2007A	2007	-7.483	1.476	2.179	-10.376	-4.590	-5.070	0.000
Wood 2007B	2007	-7.469	1.460	2.131	-10.330	-4.608	-5.116	0.000
Diaz 2008A	2008	-7.265	1.448	2.098	-10.104	-4.426	-5.016	0.000
Diaz 2008B	2008	-7.204	1.429	2.042	-10.005	-4.403	-5.041	0.000
Kawashima 2008A	2008	-6.999	1.415	2.001	-9.771	-4.226	-4.947	0.000
Kawashima 2008B	2008	-6.752	1.416	2.006	-9.528	-3.976	-4.767	0.000
Mutungi 2008A	2008	-6.388	1.414	1.999	-9.159	-3.617	-4.518	0.000
Mutungi 2008B	2008	-6.128	1.406	1.977	-8.884	-3.372	-4.358	0.000
Santo 2008A	2008	-6.243	1.395	1.945	-8.976	-3.509	-4.476	0.000
Santo 2008B	2008	-6.357	1.384	1.917	-9.070	-3.644	-4.592	0.000
Santo 2008C	2008	-6.312	1.377	1.897	-9.011	-3.612	-4.583	0.000
Smith 2008A	2008	-6.171	1.357	1.841	-8.830	-3.512	-4.549	0.000
Smith 2008B	2008	-6.161	1.330	1.769	-8.768	-3.555	-4.633	0.000
Assuncao 2009A	2009	-5.645	1.357	1.842	-8.306	-2.985	-4.159	0.000
Assuncao 2009B	2009	-5.499	1.345	1.810	-8.136	-2.862	-4.087	0.000
Hollis 2009A	2009	-5.310	1.335	1.783	-7.927	-2.693	-3.976	0.000
Hollis 2009B	2009	-5.152	1.323	1.751	-7.745	-2.558	-3.893	0.000
Hollis 2009C	2009	-5.026	1.310	1.717	-7.594	-2.457	-3.835	0.000
Kasim-Karakas 2009A	2009	-5.302	1.330	1.770	-7.910	-2.694	-3.985	0.000
Kasim-Karakas 2009B	2009	-5.243	1.274	1.624	-7.741	-2.746	-4.114	0.000
Tanumihardjo 2009A	2009	-5.384	1.264	1.598	-7.862	-2.907	-4.259	0.000
Tanumihardjo 2009B	2009	-5.520	1.254	1.573	-7.978	-3.061	-4.401	0.000
Beavers 2010A	2010	-5.375	1.245	1.550	-7.815	-2.935	-4.318	0.000
Beavers 2010B	2010	-5.216	1.237	1.531	-7.641	-2.791	-4.216	0.000
Fakhrzadeh 2010	2010	-5.136	1.216	1.479	-7.519	-2.752	-4.223	0.000
Gylling 2010A	2010	-5.063	1.194	1.426	-7.404	-2.722	-4.239	0.000
Gylling 2010B	2010	-5.316	1.208	1.458	-7.683	-2.949	-4.402	0.000
Malpuech-Brugere 2010A	2010	-5.184	1.198	1.435	-7.532	-2.836	-4.328	0.000
Malpuech-Brugere 2010B	2010	-5.189	1.184	1.402	-7.509	-2.868	-4.382	0.000
Malpuech-Brugere 2010C	2010	-5.157	1.172	1.372	-7.453	-2.861	-4.402	0.000
Price 2010A	2010	-5.126	1.156	1.336	-7.392	-2.861	-4.436	0.000
Price 2010B	2010	-5.045	1.144	1.309	-7.288	-2.803	-4.410	0.000
Stendell-Hollis 2010A	2010	-5.167	1.138	1.294	-7.396	-2.937	-4.542	0.000
Stendell-Hollis 2010B	2010	-5.422	1.138	1.295	-7.653	-3.191	-4.764	0.000
Tighe 2010A	2010	-5.433	1.121	1.257	-7.631	-3.236	-4.846	0.000
Tighe 2010B	2010	-5.335	1.109	1.231	-7.509	-3.160	-4.808	0.000
Tighe 2010C	2010	-5.317	1.093	1.195	-7.460	-3.175	-4.864	0.000
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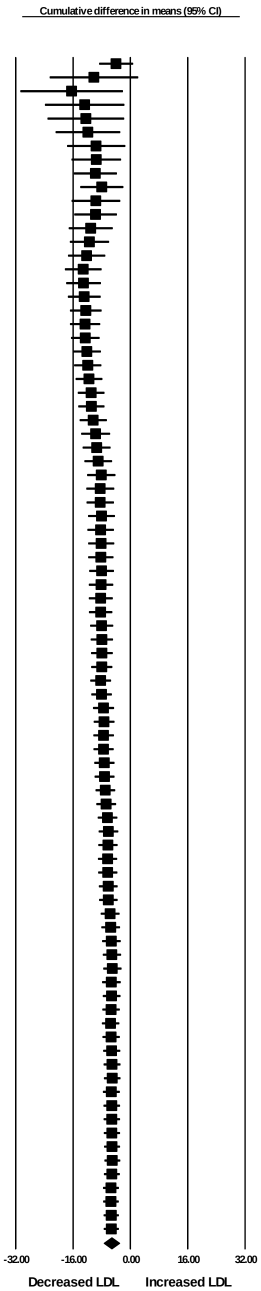


Figure S10. Cumulative Meta-Analysis for Time-Lag Bias: Macronutrient Distribution and Change in LDL Cholesterol (mg/dL). Continuously Diminishing Effects Strongly Support Time-Lag Bias.

Direction of Effect (Inconsistency): Macronutrient Distribution & Change in LDL

Studyname	Statistics for each study						
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hjerkinn 2005	-1.890	1.693	2.867	-5.209	1.429	-1.116	0.264
Kawashima 2008B	5.020	1.164	1.355	2.739	7.301	4.313	0.000
Kawashima 2008A	2.700	1.181	1.396	0.384	5.016	2.285	0.022
Dodin 2005B	5.420	1.283	1.645	2.906	7.934	4.226	0.000
Esposito 2004A	-11.400	2.170	4.707	-15.652	-7.148	-5.255	0.000
Esposito 2004B	-3.200	2.080	4.326	-7.277	0.877	-1.538	0.124
Dodin 2005A	0.770	1.397	1.951	-1.968	3.508	0.551	0.581
Gardner 2007B	-5.300	1.952	3.812	-9.127	-1.473	-2.715	0.007
Gardner 2007C	-7.300	1.924	3.701	-11.071	-3.529	-3.795	0.000
Gardner 2007A	2.300	2.062	4.253	-1.742	6.342	1.115	0.265
Gardner 2007D	-10.100	1.844	3.401	-13.715	-6.485	-5.477	0.000
Tighe 2010B	2.320	1.991	3.966	-1.583	6.223	1.165	0.244
Tighe 2010C	-3.870	1.987	3.947	-7.764	0.024	-1.948	0.051
Tighe 2010A	-6.190	2.013	4.051	-10.135	-2.245	-3.075	0.002
Fakhrzadeh 2010	0.400	1.717	2.947	-2.964	3.764	0.233	0.816
Esposito 2004	-16.200	2.732	7.462	-21.554	-10.846	-5.931	0.000
Smith 2008A	1.600	2.121	4.499	-2.557	5.757	0.754	0.451
Smith 2008B	-5.400	2.117	4.483	-9.550	-1.250	-2.550	0.011
Kasai 2003A	-22.040	2.211	4.887	-26.373	-17.707	-9.969	0.000
Kasai 2003B	-27.070	2.878	8.282	-32.710	-21.430	-9.407	0.000
Price 2010B	1.160	2.630	6.919	-3.996	6.316	0.441	0.659
Price 2010A	-2.710	2.270	5.155	-7.160	1.740	-1.194	0.233
Tonstad 2002B	-10.440	2.032	4.130	-14.423	-6.457	-5.137	0.000
Malpuech-Brugere 2010A	4.250	2.574	6.625	-0.795	9.295	1.651	0.099
Malpuech-Brugere 2010C	-2.710	3.030	9.182	-8.649	3.229	-0.894	0.371
Polagruto 2006B	-0.300	2.476	6.133	-5.154	4.554	-0.121	0.904
Malpuech-Brugere 2010B	-5.410	2.826	7.988	-10.950	0.130	-1.914	0.056
Tonstad 2002A	-23.970	1.751	3.065	-27.402	-20.538	-13.691	0.000
Polagruto 2006A	-11.300	2.345	5.497	-15.895	-6.705	-4.820	0.000
Tonstad 2002C	-25.910	1.877	3.522	-29.588	-22.232	-13.806	0.000
Mensink 2002A	2.320	3.003	9.018	-3.566	8.206	0.773	0.440
Mensink 2002B	-9.290	2.918	8.512	-15.008	-3.572	-3.184	0.001
Szapary 2003	-4.930	2.645	6.994	-10.113	0.253	-1.864	0.062
Maki 2005A	3.400	3.611	13.041	-3.678	10.478	0.941	0.346
Tonstad 2002D	-15.080	1.739	3.026	-18.489	-11.671	-8.669	0.000
Levin 1990	-4.000	2.435	5.931	-8.773	0.773	-1.642	0.101
Maki 2005B	16.600	2.890	8.349	10.937	22.263	5.745	0.000
Hollis 2009B	4.640	2.912	8.481	-1.068	10.348	1.593	0.111
Smith 2003A	-11.600	2.903	8.427	-17.289	-5.911	-3.996	0.000
Hollis 2009A	6.190	2.977	8.864	0.355	12.025	2.079	0.038
Hollis 2009C	3.090	3.350	11.223	-3.476	9.656	0.922	0.356
Gylling 2010B	-23.200	2.206	4.868	-27.524	-18.876	-10.515	0.000
Gylling 2010A	0.000	1.646	2.710	-3.227	3.227	0.000	1.000
Smith 2003B	-9.670	2.435	5.929	-14.442	-4.898	-3.971	0.000
Tanumihardjo 2009B	-14.700	3.273	10.711	-21.114	-8.286	-4.492	0.000
Stendell-Hollis 2010A	-15.470	4.242	17.991	-23.783	-7.157	-3.647	0.000
Schwab 2002B	7.740	3.964	15.717	-0.030	15.510	1.952	0.051
Melanson 2004	-6.600	3.655	13.361	-13.764	0.564	-1.806	0.071
Schwab 2006A	-13.920	3.090	9.550	-19.977	-7.863	-4.504	0.000
Schwab 2006B	-11.220	3.128	9.783	-17.350	-5.090	-3.587	0.000
Schwab 2006C	-8.900	4.239	17.969	-17.208	-0.592	-2.100	0.036
Tanumihardjo 2009A	-14.690	3.019	9.116	-20.608	-8.772	-4.865	0.000
Schwab 2002A	-11.600	2.472	6.109	-16.444	-6.756	-4.693	0.000
Tapsell 2004A	-0.390	6.474	41.908	-13.078	12.298	-0.060	0.952
Han 2007A	-22.040	4.123	16.999	-30.121	-13.959	-5.346	0.000
Han 2007B	3.870	3.838	14.728	-3.652	11.392	1.008	0.313
Assuncao 2009A	25.500	3.694	13.646	18.260	32.740	6.903	0.000
Assuncao 2009B	3.900	4.084	16.677	-4.104	11.904	0.955	0.340
Tapsell 2004B	5.800	5.490	30.136	-4.959	16.559	1.057	0.291
Diaz 2008B	-3.870	3.879	15.046	-11.473	3.733	-0.998	0.318
Alhassan 2006	-17.000	3.427	11.745	-23.717	-10.283	-4.961	0.000
Kelley 2007A	18.560	3.686	13.590	11.335	25.785	5.035	0.000
Kelley 2007B	-0.380	4.236	17.945	-8.683	7.923	-0.090	0.929
Wardlaw 1991B	-29.000	3.376	11.397	-35.617	-22.383	-8.590	0.000
Tapsell 2004C	-8.500	7.160	51.273	-22.534	5.534	-1.187	0.235
Diaz 2008A	5.030	5.742	32.973	-6.224	16.284	0.876	0.381
Beavers 2010A	4.880	3.656	13.365	-2.285	12.045	1.335	0.182
Beavers 2010B	6.940	4.595	21.115	-2.066	15.946	1.510	0.131
Stendell-Hollis 2010B	-30.940	5.974	35.686	-42.648	-19.232	-5.179	0.000
Wardlaw 1991A	-16.630	3.051	9.311	-22.611	-10.649	-5.450	0.000
Pins 2006A	-17.600	4.139	17.132	-25.712	-9.488	-4.252	0.000
Pins 2006B	-2.500	4.305	18.532	-10.937	5.937	-0.581	0.561
Wood 2007B	-6.580	5.537	30.662	-17.433	4.273	-1.188	0.235
Mutungi 2008A	16.800	5.558	30.892	5.906	27.694	3.023	0.003
Goyens 2006B	6.190	5.995	35.940	-5.560	17.940	1.033	0.302
Wood 2007A	-14.310	3.638	13.235	-21.440	-7.180	-3.934	0.000
Chan 2002A	-5.540	23.518	553.075	-51.634	40.554	-0.236	0.814
Goyens 2006A	-8.890	4.380	19.184	-17.474	-0.306	-2.030	0.042
Mutungi 2008B	10.700	5.565	30.972	-0.208	21.608	1.923	0.055
Kasim-Karakas 2009B	-1.000	0.964	0.930	-2.890	0.890	-1.037	0.300
Chan 2002B	-9.290	4.118	16.958	-17.361	-1.219	-2.256	0.024
Adler 1997	-2.400	1.735	3.011	-5.801	1.001	-1.383	0.167
Santo 2008B	-14.800	6.667	44.454	-27.868	-1.732	-2.220	0.026
Kasim-Karakas 2009A	-22.600	1.917	3.674	-26.357	-18.843	-11.790	0.000
Santo 2008C	-1.100	10.876	118.282	-22.416	20.216	-0.101	0.919
Santo 2008A	-14.000	5.920	35.052	-25.604	-2.396	-2.365	0.018
	-5.317	1.093	1.195	-7.460	-3.175	-4.864	0.000

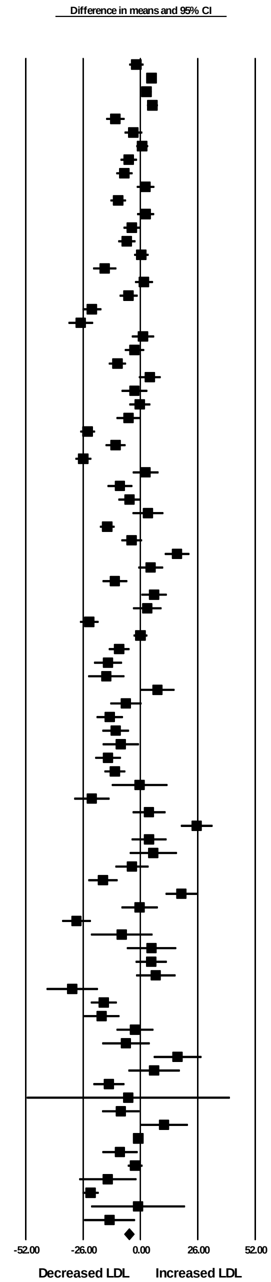


Figure S11. The Impact of Direction of Effect on Decisions Regarding Inconsistency: Macronutrient Distribution & Change in LDL Cholesterol. (Studies Sorted by Precision)

Table S5. Sensitivity Analysis for Macronutrient Distribution and Change in LDL Cholesterol: Random Effects Model versus Fixed Effect Model								
Table of Summary Effects (Random Effects versus Fixed Effect Model/Raw Mean Difference)								
Effect size and 95% confidence interval							Test of null (2-Tail)	
	N	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
ΔLDL**	86	-5.317	1.093	1.195	-7.460	-3.175	-4.864	<0.001
ΔLDL	86	-4.680	0.262	0.069	-5.194	-4.167	-17.868	<0.001

**From Random Effects Model.

Table S6. Sensitivity Analysis: Plausible Ranges for Pre- and Post-Treatment Correlations (Random Effects Model/Raw Mean Difference)								
Correlation		Effect size and 95% confidence interval					Test of null (2-Tail)	
	r	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
Δ LDL	0.880*	-5.317	1.093	1.195	-7.460	-3.175	-4.864	<0.001
	0.5	-5.438	1.151	1.325	-7.695	-3.182	-4.724	<0.001
	0.75	-5.375	1.121	1.257	-7.572	-3.178	-4.795	<0.001
	0.99	-5.241	1.046	1.094	-7.290	-3.191	-5.011	<0.001

*Correlation calculated via the *CORREL* function in Microsoft Excel 2010 (Microsoft Corp., 2010), using the 86 comparisons (“studies”) from the meta-analytic database. The correlation (r) between pre- and post-treatments was required for the calculation of the treatment effect variance (V_D): [$V_D = S^2_{diff}/n$; $S_{diff} = (\sqrt{S_{Pre}^2 + S_{Post}^2 - 2 \times r \times S_{Pre} \times S_{Post}})$].

Sensitivity Analysis (One Study Removed): Macronutrient Distribution & Change in LDL

Studyname	Statistics with studyremoved						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hjerkinn 2005	-5.360	1.112	1.236	-7.539	-3.181	-4.821	0.000
Kawashima 2008B	-5.455	1.097	1.204	-7.606	-3.304	-4.971	0.000
Kawashima 2008A	-5.422	1.110	1.231	-7.597	-3.247	-4.887	0.000
Dodin 2005B	-5.460	1.096	1.202	-7.609	-3.311	-4.980	0.000
Esposito 2004A	-5.239	1.104	1.219	-7.403	-3.075	-4.744	0.000
Esposito 2004B	-5.343	1.109	1.229	-7.516	-3.171	-4.820	0.000
Dodin 2005A	-5.395	1.113	1.238	-7.576	-3.215	-4.850	0.000
Gardner 2007B	-5.316	1.110	1.232	-7.491	-3.141	-4.790	0.000
Gardner 2007C	-5.290	1.109	1.231	-7.465	-3.116	-4.769	0.000
Gardner 2007A	-5.414	1.104	1.220	-7.579	-3.250	-4.903	0.000
Gardner 2007D	-5.254	1.108	1.227	-7.425	-3.083	-4.744	0.000
Tighe 2010B	-5.415	1.105	1.220	-7.580	-3.250	-4.902	0.000
Tighe 2010C	-5.335	1.109	1.231	-7.509	-3.160	-4.808	0.000
Tighe 2010A	-5.305	1.109	1.230	-7.478	-3.131	-4.783	0.000
Fakhrzadeh 2010	-5.390	1.109	1.230	-7.564	-3.216	-4.860	0.000
Esposito 2004	-5.183	1.098	1.206	-7.335	-3.030	-4.719	0.000
Smith 2008A	-5.405	1.105	1.221	-7.571	-3.239	-4.892	0.000
Smith 2008B	-5.315	1.108	1.228	-7.487	-3.143	-4.795	0.000
Kasai 2003A	-5.106	1.083	1.174	-7.230	-2.983	-4.714	0.000
Kasai 2003B	-5.052	1.081	1.168	-7.171	-2.934	-4.675	0.000
Price 2010B	-5.398	1.104	1.218	-7.561	-3.235	-4.891	0.000
Price 2010A	-5.349	1.107	1.226	-7.519	-3.180	-4.832	0.000
Tonstad 2002B	-5.251	1.106	1.223	-7.418	-3.083	-4.748	0.000
Malpuech-Brugere 2010A	-5.437	1.101	1.212	-7.595	-3.279	-4.938	0.000
Malpuech-Brugere 2010C	-5.348	1.104	1.219	-7.512	-3.185	-4.845	0.000
Polagruto 2006B	-5.380	1.105	1.221	-7.545	-3.214	-4.869	0.000
Malpuech-Brugere 2010B	-5.315	1.105	1.220	-7.481	-3.150	-4.812	0.000
Tonstad 2002A	-5.079	1.063	1.130	-7.163	-2.996	-4.779	0.000
Polagruto 2006A	-5.241	1.104	1.218	-7.404	-3.078	-4.748	0.000
Tonstad 2002C	-5.056	1.059	1.121	-7.131	-2.981	-4.775	0.000
Mensink 2002A	-5.410	1.102	1.214	-7.570	-3.250	-4.909	0.000
Mensink 2002B	-5.268	1.103	1.218	-7.431	-3.105	-4.774	0.000
Szapary 2003	-5.321	1.105	1.222	-7.488	-3.155	-4.814	0.000
Maki 2005A	-5.419	1.101	1.212	-7.577	-3.262	-4.923	0.000
Tonstad 2002D	-5.191	1.098	1.206	-7.343	-3.039	-4.727	0.000
Levin 1990	-5.333	1.106	1.224	-7.501	-3.165	-4.820	0.000
Maki 2005B	-5.590	1.083	1.173	-7.713	-3.467	-5.160	0.000
Hollis 2009B	-5.440	1.100	1.211	-7.596	-3.283	-4.943	0.000
Smith 2003A	-5.240	1.102	1.215	-7.400	-3.079	-4.754	0.000
Hollis 2009A	-5.458	1.099	1.208	-7.612	-3.304	-4.966	0.000
Hollis 2009C	-5.418	1.101	1.213	-7.576	-3.259	-4.920	0.000
Gylling 2010B	-5.092	1.080	1.166	-7.208	-2.976	-4.716	0.000
Gylling 2010A	-5.385	1.110	1.233	-7.561	-3.209	-4.850	0.000
Smith 2003B	-5.262	1.105	1.220	-7.427	-3.096	-4.763	0.000
Tanumihardjo 2009B	-5.205	1.100	1.210	-7.360	-3.049	-4.732	0.000
Stendell-Hollis 2010A	-5.204	1.099	1.208	-7.358	-3.049	-4.734	0.000
Schwab 2002B	-5.467	1.098	1.206	-7.619	-3.314	-4.978	0.000
Melanson 2004	-5.302	1.102	1.215	-7.463	-3.141	-4.809	0.000
Schwab 2006A	-5.213	1.100	1.211	-7.370	-3.056	-4.737	0.000
Schwab 2006B	-5.245	1.102	1.215	-7.405	-3.085	-4.760	0.000
Schwab 2006C	-5.277	1.101	1.213	-7.435	-3.119	-4.792	0.000
Tanumihardjo 2009A	-5.203	1.100	1.210	-7.359	-3.047	-4.731	0.000
Schwab 2002A	-5.238	1.103	1.217	-7.400	-3.076	-4.748	0.000
Tapsell 2004A	-5.362	1.099	1.208	-7.517	-3.208	-4.878	0.000
Han 2007A	-5.129	1.095	1.199	-7.275	-2.983	-4.685	0.000
Han 2007B	-5.423	1.100	1.211	-7.580	-3.267	-4.929	0.000
Assuncao 2009A	-5.680	1.076	1.159	-7.790	-3.570	-5.277	0.000
Assuncao 2009B	-5.422	1.100	1.210	-7.578	-3.265	-4.928	0.000
Tapsell 2004B	-5.429	1.099	1.207	-7.583	-3.275	-4.941	0.000
Diaz 2008B	-5.334	1.102	1.215	-7.494	-3.173	-4.839	0.000
Alhassan 2006	-5.179	1.098	1.206	-7.331	-3.027	-4.716	0.000
Kelley 2007A	-5.598	1.087	1.182	-7.728	-3.467	-5.149	0.000
Kelley 2007B	-5.372	1.101	1.213	-7.531	-3.214	-4.878	0.000
Wardlaw 1991B	-5.038	1.083	1.173	-7.160	-2.915	-4.652	0.000
Tapsell 2004C	-5.290	1.099	1.207	-7.444	-3.136	-4.814	0.000
Diaz 2008A	-5.419	1.099	1.208	-7.573	-3.265	-4.931	0.000
Beavers 2010A	-5.437	1.100	1.210	-7.592	-3.281	-4.943	0.000
Beavers 2010B	-5.451	1.099	1.207	-7.604	-3.297	-4.961	0.000
Stendell-Hollis 2010B	-5.073	1.092	1.193	-7.214	-2.932	-4.644	0.000
Wardlaw 1991A	-5.180	1.098	1.206	-7.332	-3.028	-4.717	0.000
Pins 2006A	-5.179	1.098	1.206	-7.331	-3.027	-4.717	0.000
Pins 2006B	-5.348	1.101	1.213	-7.507	-3.190	-4.856	0.000
Wood 2007B	-5.304	1.100	1.210	-7.461	-3.148	-4.822	0.000
Mutungi 2008A	-5.539	1.094	1.198	-7.683	-3.394	-5.061	0.000
Goyens 2006B	-5.428	1.099	1.207	-7.581	-3.275	-4.941	0.000
Wood 2007A	-5.212	1.100	1.210	-7.368	-3.056	-4.739	0.000
Chan 2002A	-5.317	1.095	1.198	-7.462	-3.171	-4.857	0.000
Goyens 2006A	-5.277	1.101	1.212	-7.436	-3.119	-4.793	0.000
Mutungi 2008B	-5.477	1.097	1.204	-7.628	-3.327	-4.992	0.000
Kasim-Karakas 2009B	-5.370	1.132	1.281	-7.588	-3.152	-4.745	0.000
Chan 2002B	-5.272	1.101	1.213	-7.431	-3.114	-4.787	0.000
Adler 1997	-5.353	1.112	1.236	-7.532	-3.175	-4.816	0.000
Santo 2008B	-5.232	1.098	1.206	-7.385	-3.079	-4.764	0.000
Kasim-Karakas 2009A	-5.097	1.075	1.156	-7.205	-2.990	-4.741	0.000
Santo 2008C	-5.342	1.097	1.203	-7.492	-3.192	-4.869	0.000
Santo 2008A	-5.233	1.099	1.208	-7.387	-3.080	-4.763	0.000
	-5.317	1.093	1.195	-7.460	-3.175	-4.864	0.000

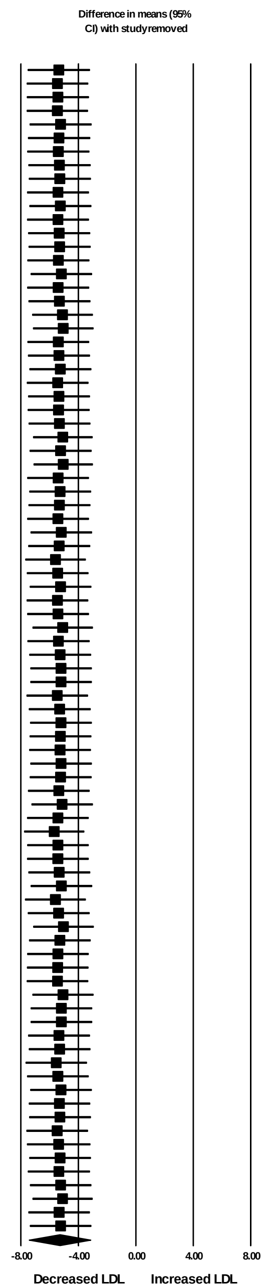


Figure S12. Sensitivity Analysis (One Study Removed): Macronutrient Distribution & Change in LDL Cholesterol.

Macronutrient Distribution & Change in HDL (mg/dL)

Study name	Macronutrient Distribution (F/P/C)	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Relative weight
		Statistics for each study								
Santo 2008C	23/20/57	27.300	3.722	13.853	20.005	34.595	7.335	0.000	0.60	
Santo 2008B	24/21/54	12.700	2.209	4.881	8.370	17.030	5.748	0.000	0.95	
Mutungi 2008A	56/27/15	9.500	2.107	4.439	5.371	13.629	4.509	0.000	0.98	
Esposito 2004	29/16/55	9.000	0.704	0.496	7.620	10.380	12.779	0.000	1.33	
Tapsell 2004B	33/23/41	8.900	1.109	1.229	6.727	11.073	8.028	0.000	1.25	
Stendell-Hollis 2010B	28/18/54	7.730	2.090	4.368	3.634	11.826	3.699	0.000	0.98	
Tapsell 2004C	32/22/44	7.730	4.191	17.567	-0.485	15.945	1.844	0.065	0.52	
Wood 2007B	59/27/13	5.800	1.844	3.400	2.186	9.414	3.145	0.002	1.05	
Tapsell 2004A	33/21/43	5.420	1.218	1.483	3.033	7.807	4.450	0.000	1.22	
Tonstad 2002C	29/18/50	4.640	1.310	1.716	2.072	7.208	3.542	0.000	1.20	
Hjerkinn 2005	28/17/52	4.450	0.541	0.293	3.390	5.510	8.227	0.000	1.36	
Tonstad 2002B	31/18/49	4.260	1.342	1.801	1.630	6.890	3.174	0.002	1.19	
Han 2007B	28/18/55	4.250	2.122	4.503	0.091	8.409	2.003	0.045	0.97	
Esposito 2004A	28/14/58	4.000	0.551	0.303	2.921	5.079	7.265	0.000	1.36	
Maki 2005B	35/15/52	3.900	0.675	0.456	2.577	5.223	5.778	0.000	1.34	
Stendell-Hollis 2010A	32/16/53	3.870	1.723	2.968	0.493	7.247	2.246	0.025	1.09	
Tonstad 2002D	31/17/49	3.860	1.387	1.925	1.141	6.579	2.782	0.005	1.18	
Wood 2007A	59/27/13	3.860	1.726	2.977	0.478	7.242	2.237	0.025	1.08	
Assuncao 2009B	21/15/64	3.200	1.163	1.353	0.920	5.480	2.751	0.006	1.24	
Kelley 2007A	36/16/48	3.090	1.415	2.001	0.317	5.863	2.184	0.029	1.17	
Levin 1990	26/18/57	3.000	1.082	1.172	0.878	5.122	2.771	0.006	1.25	
Schwab 2006C	28/18/51	2.710	1.081	1.169	0.591	4.829	2.507	0.012	1.26	
Tonstad 2002A	30/18/47	2.710	1.570	2.466	-0.368	5.788	1.726	0.084	1.13	
Schwab 2006B	28/19/51	2.700	1.511	2.283	-0.261	5.661	1.787	0.074	1.14	
Adler 1997	31/17/50	2.300	0.678	0.460	0.971	3.629	3.392	0.001	1.34	
Maki 2005A	35/16/50	2.200	0.675	0.455	0.878	3.522	3.262	0.001	1.34	
Hollis 2009A	35/15/50	1.940	1.263	1.594	-0.535	4.415	1.536	0.124	1.21	
Malpuech-Brugere 2010B	39/15/45	1.930	1.864	3.474	-1.723	5.583	1.036	0.300	1.05	
Polagruto 2006A	34/16/50	1.900	2.233	4.988	-2.477	6.277	0.851	0.395	0.94	
Goyens 2006B	42/14/43	1.540	2.485	6.175	-3.330	6.410	0.620	0.535	0.87	
Hollis 2009B	35/16/48	1.540	1.394	1.942	-1.191	4.271	1.105	0.269	1.18	
Tighe 2010B	34/17/48	1.540	0.969	0.940	-0.360	3.440	1.589	0.112	1.28	
Szapary 2003	33/14/52	1.430	1.662	2.763	-1.828	4.688	0.860	0.390	1.10	
Beavers 2010B	38/20/47	1.320	2.244	5.035	-3.078	5.718	0.588	0.556	0.94	
Pins 2006A	34/21/45	1.200	1.353	1.832	-1.453	3.853	0.887	0.375	1.19	
Dodin 2005B	33/17/50	1.160	0.831	0.690	-0.468	2.788	1.397	0.162	1.31	
Gylling 2010B	31/16/45	1.160	1.815	3.293	-2.397	4.717	0.639	0.523	1.06	
Kawashima 2008A	27/14/51	1.160	0.589	0.347	0.005	2.315	1.968	0.049	1.35	
Kawashima 2008B	28/14/50	1.160	0.533	0.284	0.115	2.205	2.177	0.030	1.36	
Kelley 2007B	34/15/50	1.160	0.797	0.635	-0.401	2.721	1.456	0.145	1.32	
Schwab 2006A	26/19/53	1.160	1.405	1.975	-1.595	3.915	0.825	0.409	1.17	
Pins 2006B	35/21/44	1.100	1.488	2.214	-1.816	4.016	0.739	0.460	1.15	
Alhassan 2006	39/17/44	1.000	1.625	2.641	-2.185	4.185	0.615	0.538	1.11	
Esposito 2004B	30/14/57	1.000	0.513	0.263	-0.005	2.005	1.951	0.051	1.36	
Smith 2008B	30/16/54	0.800	0.967	0.934	-1.095	2.695	0.828	0.408	1.28	
Tighe 2010C	35/16/45	0.770	1.024	1.048	-1.236	2.776	0.752	0.452	1.27	
Chan 2002B	34/22/40	0.390	1.297	1.681	-2.151	2.931	0.301	0.764	1.20	
Malpuech-Brugere 2010A	38/15/47	0.390	1.595	2.544	-2.736	3.516	0.245	0.807	1.12	
Price 2010A	35/18/47	0.390	1.193	1.423	-1.948	2.728	0.327	0.744	1.23	
Wardlaw 1991A	40/13/47	0.390	1.079	1.163	-1.724	2.504	0.362	0.718	1.26	
Mensink 2002A	32/15/50	0.380	1.220	1.489	-2.012	2.772	0.311	0.756	1.22	
Melanson 2004	28/21/53	0.300	1.298	1.686	-2.245	2.845	0.231	0.817	1.20	
Goyens 2006A	41/13/44	0.000	3.307	10.937	-6.482	6.482	0.000	1.000	0.68	
Hollis 2009C	34/16/50	0.000	1.421	2.020	-2.785	2.785	0.000	1.000	1.17	
Malpuech-Brugere 2010C	39/15/47	0.000	1.181	1.395	-2.315	2.315	0.000	1.000	1.23	
Schwab 2002A	27/18/51	0.000	1.435	2.058	-2.812	2.812	0.000	1.000	1.16	
Schwab 2002B	27/18/52	0.000	1.336	1.786	-2.619	2.619	0.000	1.000	1.19	
Polagruto 2006B	31/17/54	-0.300	1.574	2.478	-3.385	2.785	-0.191	0.849	1.13	
Beavers 2010A	34/21/47	-0.370	1.736	3.015	-3.773	3.033	-0.213	0.831	1.08	
Gylling 2010A	42/14/43	-0.380	2.229	4.969	-4.749	3.989	-0.170	0.865	0.94	
Gardner 2007A	55/28/18	-0.400	0.949	0.901	-2.261	1.461	-0.421	0.674	1.29	
Gardner 2007B	35/24/42	-0.500	0.722	0.521	-1.915	0.915	-0.692	0.489	1.33	
Mensink 2002B	29/16/53	-0.770	1.332	1.774	-3.380	1.840	-0.578	0.563	1.19	
Chan 2002A	36/20/38	-0.780	1.275	1.627	-3.280	1.720	-0.612	0.541	1.21	
Tighe 2010A	35/16/47	-0.780	1.132	1.282	-2.999	1.439	-0.689	0.491	1.24	
Kasim-Karakas 2009B	26/17/57	-1.000	0.349	0.122	-1.684	-0.316	-2.865	0.004	1.38	
Smith 2008A	32/16/52	-1.000	1.128	1.272	-3.210	1.210	-0.887	0.375	1.24	
Price 2010B	33/18/47	-1.160	1.057	1.117	-3.231	0.911	-1.098	0.272	1.26	
Wardlaw 1991B	39/13/47	-1.160	0.836	0.699	-2.799	0.479	-1.387	0.165	1.31	
Mutungi 2008B	55/25/20	-1.200	1.407	1.980	-3.958	1.558	-0.853	0.394	1.17	
Dodin 2005A	35/17/47	-1.540	0.775	0.600	-3.058	-0.022	-1.988	0.047	1.32	
Kasai 2003B	27/15/56	-1.550	1.027	1.055	-3.564	0.464	-1.509	0.131	1.27	
Diaz 2008A	23/16/65	-1.930	3.517	12.370	-8.823	4.963	-0.549	0.583	0.64	
Tanumihardjo 2009B	24/21/55	-1.930	1.468	2.155	-4.807	0.947	-1.315	0.189	1.16	
Diaz 2008B	27/19/56	-1.940	1.918	3.678	-5.699	1.819	-1.012	0.312	1.03	
Santo 2008A	22/20/57	-2.000	2.983	8.896	-7.846	3.846	-0.671	0.503	0.75	
Kasai 2003A	27/15/56	-2.320	1.257	1.581	-4.784	0.144	-1.845	0.065	1.21	
Tanumihardjo 2009A	29/17/54	-2.320	1.723	2.969	-5.697	1.057	-1.346	0.178	1.09	
Fakhrzadeh 2010	35/13/53	-2.500	0.667	0.445	-3.808	-1.192	-3.746	0.000	1.34	
Smith 2003A	40/11/48	-3.090	1.360	1.850	-5.756	-0.424	-2.272	0.023	1.18	
Smith 2003B	37/11/50	-3.480	1.386	1.920	-6.196	-0.764	-2.511	0.012	1.18	
Gardner 2007C	30/20/49	-3.800	0.738	0.545	-5.247	-2.353	-5.149	0.000	1.33	
Kasim-Karakas 2009A	26/34/40	-4.000	0.326	0.106	-4.639	-3.361	-12.275	0.000	1.38	
Gardner 2007D	21/17/63	-5.300	0.857	0.735	-6.980	-3.620	-6.183	0.000	1.30	
Assuncao 2009A	21/15/64	-6.500	1.336	1.786	-9.119	-3.881	-4.864	0.000	1.19	
Han 2007A	23/18/59	-8.890	1.308	1.712	-11.455	-6.325	-6.794	0.000	1.20	
		1.137	0.380	0.144	0.393	1.881	2.994	0.003		

Difference in means and 95% CI

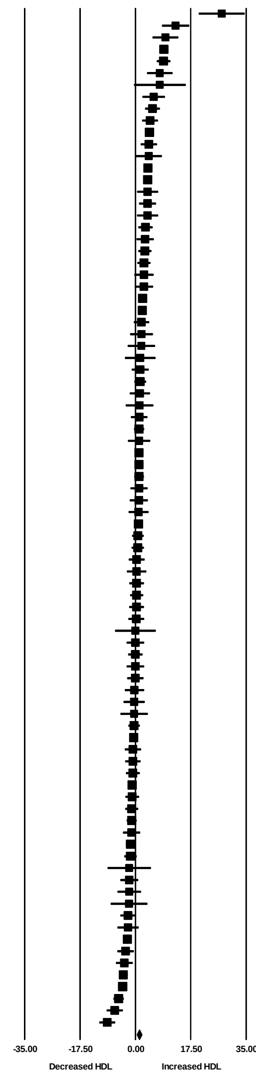


Figure S13. Forest plot of macronutrient distribution and change in HDL cholesterol [random-effects model, raw mean difference (D)]. Macronutrient distribution (% total energy): Fat/Protein/Carbohydrate.

Figure S14. Sensitivity analysis: funnel plot and assessment of publication bias of macronutrient distribution and change in HDL cholesterol.

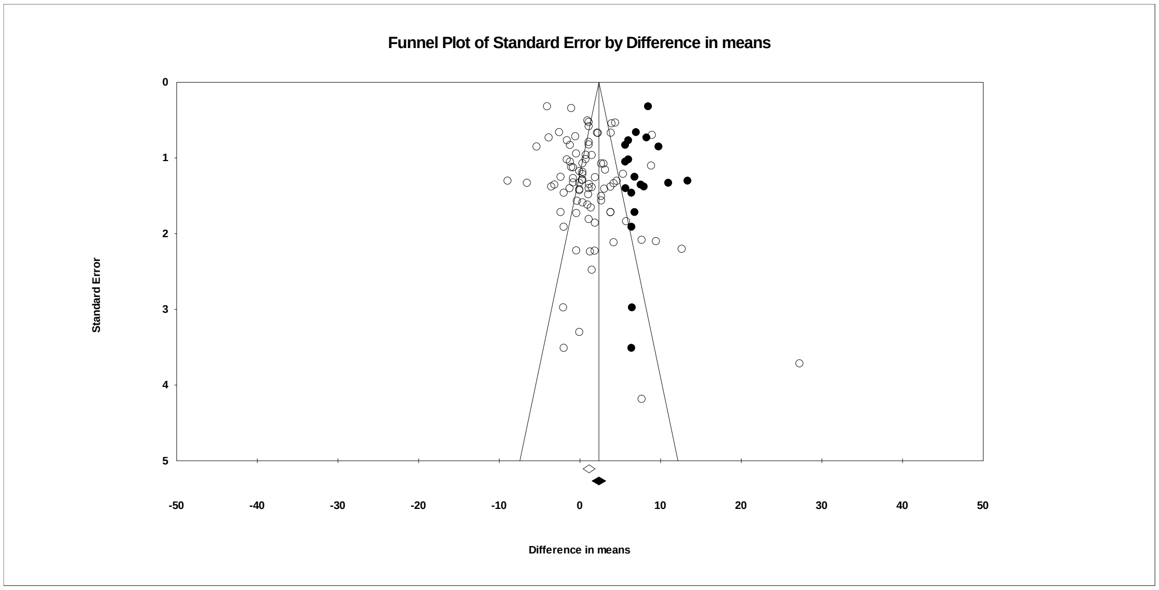


Table S7. Sensitivity analyses: trim-and-fill, Egger's test, and classic fail-safe N for macronutrient distribution and change in HDL cholesterol.						
Duval and Tweedie's Trim and Fill (Random Effects Model)						
		Studies Trimmed	Summary Effect	Lower Limit	Upper Limit	Q-value
ΔHDL	Observed Values		1.13656	0.39251	1.88060	987.35984
	Adjusted Values	19	2.35393	1.49721	3.21065	2099.63903
Egger's Regression Intercept:			+1.69154; 95%CI: (0.21745 to 3.16564) P: 0.02502			
Rosenthal's Classic Fail-Safe N (For Observed Studies: Alpha = 0.05, 2-Tailed, Z for alpha = 1.96)						
	Z-value	P-value	Number of Studies	Number of Missing Studies That Would Bring P-value to > alpha		
ΔHDL	+7.40645	<0.001	86	1143		

Cumulative Meta-Analysis Macronutrient Distribution & Change in HDL

Studyname	Subjects	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight	Relative weight
Hjerkinn 2005	244	4.450	0.541	0.293	3.390	5.510	8.227	0.000	244	1.36	
Kawashima 2008B	153	2.804	1.645	2.706	-0.420	6.028	1.704	0.088	397	2.72	
Kawashima 2008A	150	2.261	1.110	1.233	0.085	4.438	2.036	0.042	547	4.07	
Dodin 2005B	94	2.010	0.890	0.792	0.265	3.755	2.258	0.024	641	5.38	
Esposito 2004A	90	2.419	0.779	0.607	0.892	3.945	3.105	0.002	731	6.74	
Esposito 2004B	90	2.176	0.683	0.466	0.837	3.514	3.186	0.001	821	8.10	
Dodin 2005A	85	1.668	0.738	0.544	0.222	3.115	2.261	0.024	906	9.42	
Gardner 2007B	79	1.404	0.703	0.495	0.026	2.782	1.996	0.046	985	10.75	
Gardner 2007C	79	0.824	0.821	0.675	-0.786	2.434	1.003	0.316	1064	12.08	
Gardner 2007A	77	0.711	0.768	0.590	-0.795	2.217	0.925	0.355	1141	13.36	
Gardner 2007D	76	0.171	0.847	0.717	-1.489	1.831	0.202	0.840	1217	14.67	
Tighe 2010B	73	0.281	0.794	0.630	-1.274	1.837	0.355	0.723	1290	15.95	
Tighe 2010C	70	0.318	0.748	0.560	-1.149	1.785	0.425	0.671	1360	17.22	
Tighe 2010A	63	0.247	0.715	0.512	-1.155	1.649	0.346	0.730	1423	18.46	
Fakhrzadeh 2010	62	0.059	0.703	0.494	-1.319	1.437	0.084	0.933	1485	19.80	
Esposito 2004	55	0.613	0.839	0.703	-1.031	2.256	0.731	0.465	1540	21.13	
Smith 2008A	45	0.523	0.808	0.652	-1.059	2.106	0.648	0.517	1585	22.38	
Smith 2008B	45	0.539	0.772	0.596	-0.973	2.052	0.699	0.485	1630	23.66	
Kasai 2003A	42	0.400	0.752	0.566	-1.074	1.875	0.532	0.595	1672	24.87	
Kasai 2003B	40	0.306	0.729	0.531	-1.122	1.735	0.420	0.674	1712	26.14	
Price 2010B	40	0.240	0.706	0.498	-1.144	1.623	0.339	0.734	1752	27.40	
Price 2010A	39	0.247	0.683	0.467	-1.092	1.586	0.361	0.718	1791	28.63	
Malpuech-Brugere 2010A	36	0.253	0.666	0.444	-1.053	1.558	0.379	0.704	1827	29.75	
Malpuech-Brugere 2010C	36	0.243	0.646	0.418	-1.023	1.510	0.377	0.706	1863	30.98	
Tonstad 2002B	36	0.391	0.634	0.402	-0.853	1.634	0.616	0.538	1899	32.17	
Malpuech-Brugere 2010B	35	0.438	0.622	0.387	-0.780	1.657	0.705	0.481	1934	33.21	
Polagruto 2006B	35	0.415	0.608	0.370	-0.778	1.607	0.682	0.496	1969	34.34	
Tonstad 2002A	34	0.486	0.596	0.355	-0.681	1.654	0.816	0.414	2003	35.47	
Polagruto 2006A	32	0.522	0.586	0.344	-0.628	1.671	0.890	0.374	2035	36.41	
Tonstad 2002C	31	0.652	0.578	0.334	-0.481	1.785	1.128	0.260	2066	37.61	
Maki 2005A	30	0.705	0.556	0.309	-0.385	1.795	1.268	0.205	2096	38.94	
Mensink 2002A	30	0.695	0.543	0.295	-0.369	1.760	1.280	0.201	2126	40.17	
Mensink 2002B	30	0.654	0.533	0.284	-0.391	1.698	1.227	0.220	2156	41.36	
Szapary 2003	30	0.673	0.523	0.274	-0.353	1.699	1.286	0.198	2186	42.46	
Tonstad 2002D	29	0.758	0.516	0.266	-0.253	1.769	1.470	0.142	2215	43.64	
Levin 1990	28	0.820	0.505	0.255	-0.170	1.811	1.623	0.105	2243	44.89	
Maki 2005B	27	0.911	0.497	0.247	-0.063	1.885	1.833	0.067	2270	46.23	
Hollis 2009B	26	0.926	0.488	0.238	-0.030	1.883	1.899	0.058	2296	47.41	
Gylling 2010B	25	0.931	0.481	0.231	-0.011	1.874	1.937	0.053	2321	48.47	
Hollis 2009A	25	0.955	0.472	0.223	0.031	1.880	2.025	0.043	2346	49.68	
Hollis 2009C	25	0.934	0.464	0.216	0.024	1.844	2.011	0.044	2371	50.84	
Smith 2003A	25	0.844	0.461	0.213	-0.061	1.748	1.828	0.068	2396	52.03	
Gylling 2010A	24	0.823	0.457	0.208	-0.071	1.718	1.803	0.071	2420	52.97	
Smith 2003B	23	0.731	0.455	0.207	-0.160	1.622	1.608	0.108	2443	54.15	
Stendell-Hollis 2010A	23	0.791	0.450	0.202	-0.091	1.672	1.758	0.079	2466	55.24	
Tanumihardjo 2009B	23	0.736	0.445	0.198	-0.136	1.608	1.653	0.098	2489	56.39	
Melanson 2004	22	0.727	0.438	0.192	-0.131	1.585	1.660	0.097	2511	57.59	
Schwab 2002B	22	0.712	0.431	0.186	-0.133	1.558	1.652	0.099	2533	58.78	
Schwab 2006A	22	0.721	0.425	0.181	-0.112	1.554	1.697	0.090	2555	59.96	
Schwab 2006B	22	0.757	0.420	0.176	-0.065	1.580	1.805	0.071	2577	61.10	
Schwab 2006C	22	0.797	0.413	0.171	-0.012	1.606	1.930	0.054	2599	62.36	
Tanumihardjo 2009A	21	0.746	0.410	0.168	-0.057	1.549	1.820	0.069	2620	63.44	
Assuncao 2009A	20	0.613	0.417	0.174	-0.205	1.431	1.468	0.142	2640	64.63	
Assuncao 2009B	20	0.661	0.412	0.170	-0.146	1.469	1.605	0.108	2660	65.87	
Han 2007A	20	0.490	0.428	0.183	-0.350	1.329	1.144	0.253	2680	67.07	
Han 2007B	20	0.542	0.425	0.181	-0.291	1.375	1.274	0.203	2700	68.04	
Schwab 2002A	20	0.533	0.420	0.176	-0.290	1.356	1.269	0.204	2720	69.20	
Tapsell 2004A	20	0.617	0.418	0.175	-0.203	1.438	1.476	0.140	2740	70.42	
Diaz 2008B	19	0.582	0.415	0.172	-0.232	1.395	1.401	0.161	2759	71.45	
Tapsell 2004B	19	0.724	0.426	0.181	-0.111	1.558	1.700	0.089	2778	72.70	
Alhassan 2006	17	0.728	0.421	0.177	-0.097	1.553	1.729	0.084	2795	73.82	
Kelley 2007A	17	0.765	0.417	0.174	-0.052	1.581	1.836	0.066	2812	74.99	
Kelley 2007B	17	0.772	0.408	0.167	-0.028	1.572	1.892	0.059	2829	76.30	
Beavers 2010A	16	0.756	0.404	0.163	-0.036	1.549	1.871	0.061	2845	77.38	
Beavers 2010B	16	0.763	0.401	0.161	-0.023	1.549	1.903	0.057	2861	78.32	
Diaz 2008A	16	0.743	0.399	0.159	-0.040	1.525	1.861	0.063	2877	78.96	
Stendell-Hollis 2010B	16	0.826	0.399	0.159	0.044	1.608	2.071	0.038	2893	79.94	
Tapsell 2004C	16	0.868	0.398	0.158	0.087	1.648	2.180	0.029	2909	80.46	
Wardlaw 1991B	16	0.835	0.393	0.154	0.064	1.605	2.124	0.034	2925	81.77	
Mutungi 2008A	15	0.935	0.394	0.155	0.162	1.708	2.371	0.018	2940	82.74	
Pins 2006A	15	0.938	0.390	0.152	0.174	1.702	2.407	0.016	2955	83.93	
Pins 2006B	15	0.940	0.386	0.149	0.184	1.696	2.437	0.015	2970	85.08	
Wardlaw 1991A	15	0.932	0.381	0.145	0.186	1.678	2.448	0.014	2985	86.33	
Wood 2007B	15	0.989	0.379	0.144	0.246	1.732	2.609	0.009	3000	87.39	
Goyens 2006B	14	0.994	0.377	0.142	0.256	1.733	2.640	0.008	3014	88.26	
Wood 2007A	14	1.029	0.374	0.140	0.295	1.762	2.750	0.006	3028	89.34	
Chan 2002A	13	1.004	0.370	0.137	0.278	1.730	2.711	0.007	3041	90.55	
Goyens 2006A	13	0.997	0.369	0.136	0.274	1.720	2.704	0.007	3054	91.23	
Kasim-Karakas 2009B	13	0.964	0.358	0.128	0.262	1.666	2.693	0.007	3067	92.61	
Mutungi 2008B	13	0.937	0.355	0.126	0.241	1.633	2.639	0.008	3080	93.78	
Chan 2002B	12	0.930	0.351	0.124	0.241	1.618	2.645	0.008	3092	94.98	
Adler 1997	11	0.948	0.346	0.119	0.271	1.626	2.744	0.006	3103	96.32	
Kasim-Karakas 2009A	11	0.884	0.370	0.137	0.160	1.609	2.392	0.017	3114	97.71	
Santo 2008B	11	0.998	0.373	0.139	0.267	1.730	2.675	0.007	3125	98.65	
Santo 2008C	10	1.160	0.381	0.145	0.413	1.908	3.043	0.002	3135	99.25	
Santo 2008A	9	1.137	0.380	0.144	0.393	1.881	2.994	0.003	3144	100.00	
		1.137	0.380	0.144	0.393	1.881	2.994	0.003			

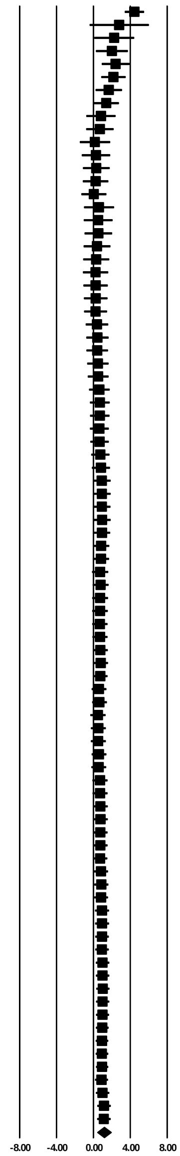


Figure S15. Cumulative forest plot of macronutrient distribution and change in HDL cholesterol. [Sorted by study design to examine small study bias.]

Recursive Cumulative Meta-Analysis Macronutrients & Change in HDL

Studyname	Year Published	Cumulative statistics						
		Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Levin 1990	1990	3.000	1.082	1.172	0.878	5.122	2.771	0.006
Wardlaw 1991A	1991	1.693	1.305	1.703	-0.864	4.251	1.298	0.194
Wardlaw 1991B	1991	0.676	1.235	1.526	-1.746	3.097	0.547	0.584
Adler 1997	1997	1.120	0.968	0.937	-0.777	3.017	1.157	0.247
Chan 2002A	2002	0.797	0.856	0.733	-0.881	2.474	0.931	0.352
Chan 2002B	2002	0.746	0.736	0.541	-0.696	2.188	1.014	0.311
Mensink 2002A	2002	0.707	0.641	0.411	-0.550	1.964	1.103	0.270
Mensink 2002B	2002	0.557	0.596	0.355	-0.611	1.724	0.934	0.350
Schwab 2002A	2002	0.517	0.545	0.297	-0.552	1.586	0.948	0.343
Schwab 2002B	2002	0.483	0.500	0.250	-0.498	1.463	0.965	0.335
Tonstad 2002A	2002	0.624	0.485	0.236	-0.327	1.575	1.286	0.198
Tonstad 2002B	2002	0.884	0.516	0.266	-0.127	1.895	1.715	0.086
Tonstad 2002C	2002	1.154	0.541	0.293	0.093	2.215	2.131	0.033
Tonstad 2002D	2002	1.329	0.533	0.284	0.284	2.374	2.493	0.013
Kasai 2003A	2003	1.094	0.547	0.299	0.023	2.166	2.001	0.045
Kasai 2003B	2003	0.914	0.539	0.291	-0.143	1.970	1.694	0.090
Smith 2003A	2003	0.697	0.549	0.302	-0.380	1.773	1.268	0.205
Smith 2003B	2003	0.481	0.559	0.312	-0.614	1.577	0.861	0.389
Szapary 2003	2003	0.522	0.538	0.289	-0.532	1.577	0.971	0.332
Esposito 2004	2004	0.990	0.817	0.667	-0.611	2.590	1.212	0.226
Esposito 2004A	2004	1.151	0.760	0.577	-0.338	2.640	1.516	0.130
Esposito 2004B	2004	1.151	0.689	0.475	-0.200	2.502	1.670	0.095
Melanson 2004	2004	1.116	0.667	0.444	-0.190	2.423	1.674	0.094
Tapsell 2004A	2004	1.294	0.654	0.428	0.012	2.577	1.978	0.048
Tapsell 2004B	2004	1.598	0.680	0.462	0.266	2.930	2.352	0.019
Tapsell 2004C	2004	1.699	0.674	0.454	0.378	3.020	2.520	0.012
Dodin 2005A	2005	1.568	0.664	0.442	0.265	2.870	2.359	0.018
Dodin 2005B	2005	1.551	0.635	0.404	0.306	2.796	2.441	0.015
Hjerkinn 2005	2005	1.663	0.611	0.373	0.466	2.860	2.723	0.006
Maki 2005A	2005	1.683	0.580	0.337	0.546	2.820	2.900	0.004
Maki 2005B	2005	1.763	0.558	0.311	0.669	2.857	3.158	0.002
Alhassan 2006	2006	1.742	0.547	0.299	0.669	2.814	3.182	0.001
Goyens 2006A	2006	1.715	0.542	0.294	0.653	2.777	3.164	0.002
Goyens 2006B	2006	1.711	0.535	0.286	0.664	2.759	3.202	0.001
Pins 2006A	2006	1.697	0.523	0.274	0.672	2.723	3.245	0.001
Pins 2006B	2006	1.682	0.513	0.263	0.677	2.687	3.279	0.001
Polagruto 2006A	2006	1.687	0.506	0.256	0.695	2.678	3.335	0.001
Polagruto 2006B	2006	1.638	0.498	0.248	0.662	2.614	3.288	0.001
Schwab 2006A	2006	1.626	0.489	0.239	0.669	2.584	3.328	0.001
Schwab 2006B	2006	1.652	0.480	0.230	0.712	2.593	3.444	0.001
Schwab 2006C	2006	1.681	0.468	0.219	0.763	2.599	3.589	0.000
Gardner 2007A	2007	1.626	0.461	0.212	0.723	2.530	3.528	0.000
Gardner 2007B	2007	1.569	0.453	0.206	0.680	2.458	3.460	0.001
Gardner 2007C	2007	1.428	0.474	0.225	0.499	2.358	3.011	0.003
Gardner 2007D	2007	1.264	0.497	0.247	0.290	2.238	2.544	0.011
Han 2007A	2007	1.045	0.519	0.269	0.027	2.062	2.013	0.044
Han 2007B	2007	1.100	0.514	0.264	0.094	2.107	2.142	0.032
Kelley 2007A	2007	1.141	0.506	0.256	0.149	2.133	2.255	0.024
Kelley 2007B	2007	1.141	0.493	0.243	0.175	2.106	2.316	0.021
Wood 2007A	2007	1.190	0.487	0.237	0.236	2.144	2.444	0.015
Wood 2007B	2007	1.270	0.483	0.234	0.323	2.217	2.627	0.009
Diaz 2008A	2008	1.237	0.480	0.231	0.295	2.179	2.574	0.010
Diaz 2008B	2008	1.184	0.476	0.227	0.251	2.118	2.487	0.013
Kawashima 2008A	2008	1.183	0.460	0.211	0.282	2.084	2.574	0.010
Kawashima 2008B	2008	1.182	0.442	0.195	0.315	2.048	2.673	0.008
Mutungi 2008A	2008	1.303	0.443	0.196	0.434	2.172	2.939	0.003
Mutungi 2008B	2008	1.259	0.439	0.192	0.399	2.119	2.871	0.004
Santo 2008A	2008	1.225	0.436	0.190	0.370	2.079	2.808	0.005
Santo 2008B	2008	1.381	0.441	0.195	0.516	2.246	3.130	0.002
Santo 2008C	2008	1.608	0.455	0.207	0.715	2.500	3.531	0.000
Smith 2008A	2008	1.561	0.450	0.202	0.679	2.443	3.469	0.001
Smith 2008B	2008	1.544	0.442	0.195	0.678	2.411	3.493	0.000
Assuncao 2009A	2009	1.420	0.448	0.200	0.543	2.297	3.173	0.002
Assuncao 2009B	2009	1.448	0.442	0.195	0.582	2.314	3.278	0.001
Hollis 2009A	2009	1.454	0.436	0.190	0.600	2.309	3.336	0.001
Hollis 2009B	2009	1.454	0.431	0.186	0.610	2.298	3.376	0.001
Hollis 2009C	2009	1.431	0.426	0.181	0.597	2.266	3.361	0.001
Kasim-Karakas 2009A	2009	1.364	0.460	0.212	0.462	2.266	2.963	0.003
Kasim-Karakas 2009B	2009	1.313	0.441	0.194	0.449	2.176	2.980	0.003
Tanumihardjo 2009A	2009	1.264	0.437	0.191	0.407	2.121	2.892	0.004
Tanumihardjo 2009B	2009	1.219	0.433	0.188	0.370	2.068	2.813	0.005
Beavers 2010A	2010	1.197	0.429	0.184	0.356	2.039	2.788	0.005
Beavers 2010B	2010	1.198	0.426	0.182	0.363	2.034	2.811	0.005
Fakhrzadeh 2010	2010	1.140	0.422	0.178	0.314	1.967	2.704	0.007
Gylling 2010A	2010	1.123	0.419	0.175	0.303	1.944	2.682	0.007
Gylling 2010B	2010	1.123	0.415	0.173	0.309	1.937	2.704	0.007
Malpuech-Brugere 2010A	2010	1.113	0.412	0.169	0.306	1.920	2.704	0.007
Malpuech-Brugere 2010B	2010	1.122	0.409	0.167	0.321	1.923	2.747	0.006
Malpuech-Brugere 2010C	2010	1.106	0.404	0.163	0.314	1.898	2.737	0.006
Price 2010A	2010	1.095	0.400	0.160	0.312	1.879	2.740	0.006
Price 2010B	2010	1.064	0.395	0.156	0.289	1.839	2.691	0.007
Stendell-Hollis 2010A	2010	1.096	0.393	0.154	0.326	1.866	2.789	0.005
Stendell-Hollis 2010B	2010	1.165	0.393	0.154	0.396	1.935	2.968	0.003
Tighe 2010A	2010	1.139	0.389	0.151	0.378	1.901	2.932	0.003
Tighe 2010B	2010	1.143	0.384	0.147	0.390	1.896	2.976	0.003
Tighe 2010C	2010	1.137	0.380	0.144	0.393	1.881	2.994	0.003
		1.137	0.380	0.144	0.393	1.881	2.994	0.003

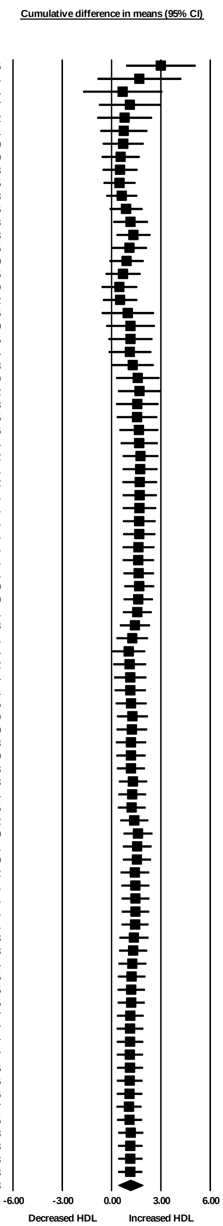


Figure S16. Cumulative meta-analysis for time-lag bias: macronutrient distribution and change in HDL cholesterol (mg/dL). Continuously diminishing effects strongly support time-lag bias.

Directness of Effect Macronutrient Distribution & Change in HDL

Studyname	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight	Relative weight
Hjerkinn 2005	4.450	0.541	0.293	3.390	5.510	8.227	0.000	244	1.36	
Kawashima 2008B	1.160	0.533	0.284	0.115	2.205	2.177	0.030	153	1.36	
Kawashima 2008A	1.160	0.589	0.347	0.005	2.315	1.968	0.049	150	1.35	
Dodin 2005B	1.160	0.831	0.690	-0.468	2.788	1.397	0.162	94	1.31	
Esposito 2004A	4.000	0.551	0.303	2.921	5.079	7.265	0.000	90	1.36	
Esposito 2004B	1.000	0.513	0.263	-0.005	2.005	1.951	0.051	90	1.36	
Dodin 2005A	-1.540	0.775	0.600	-3.058	-0.022	-1.988	0.047	85	1.32	
Gardner 2007B	-0.500	0.722	0.521	-1.915	0.915	-0.692	0.489	79	1.33	
Gardner 2007C	-3.800	0.738	0.545	-5.247	-2.353	-5.149	0.000	79	1.33	
Gardner 2007A	-0.400	0.949	0.901	-2.261	1.461	-0.421	0.674	77	1.29	
Gardner 2007D	-5.300	0.857	0.735	-6.980	-3.620	-6.183	0.000	76	1.30	
Tighe 2010B	1.540	0.969	0.940	-0.360	3.440	1.589	0.112	73	1.28	
Tighe 2010C	0.770	1.024	1.048	-1.236	2.776	0.752	0.452	70	1.27	
Tighe 2010A	-0.780	1.132	1.282	-2.999	1.439	-0.689	0.491	63	1.24	
Fakhrzadeh 2010	-2.500	0.667	0.445	-3.808	-1.192	-3.746	0.000	62	1.34	
Esposito 2004	9.000	0.704	0.496	7.620	10.380	12.779	0.000	55	1.33	
Smith 2008A	-1.000	1.128	1.272	-3.210	1.210	-0.887	0.375	45	1.24	
Smith 2008B	0.800	0.967	0.934	-1.095	2.695	0.828	0.408	45	1.28	
Kasai 2003A	-2.320	1.257	1.581	-4.784	0.144	-1.845	0.065	42	1.21	
Kasai 2003B	-1.550	1.027	1.055	-3.564	0.464	-1.509	0.131	40	1.27	
Price 2010B	-1.160	1.057	1.117	-3.231	0.911	-1.098	0.272	40	1.26	
Price 2010A	0.390	1.193	1.423	-1.948	2.728	0.327	0.744	39	1.23	
Malpuech-Brugere 2010A	0.390	1.595	2.544	-2.736	3.516	0.245	0.807	36	1.12	
Malpuech-Brugere 2010C	0.000	1.181	1.395	-2.315	2.315	0.000	1.000	36	1.23	
Tonstad 2002B	4.260	1.342	1.801	1.630	6.890	3.174	0.002	36	1.19	
Malpuech-Brugere 2010B	1.930	1.864	3.474	-1.723	5.583	1.036	0.300	35	1.05	
Polagruto 2006B	-0.300	1.574	2.478	-3.385	2.785	-0.191	0.849	35	1.13	
Tonstad 2002A	2.710	1.570	2.466	-0.368	5.788	1.726	0.084	34	1.13	
Polagruto 2006A	1.900	2.233	4.988	-2.477	6.277	0.851	0.395	32	0.94	
Tonstad 2002C	4.640	1.310	1.716	2.072	7.208	3.542	0.000	31	1.20	
Maki 2005A	2.200	0.675	0.455	0.878	3.522	3.262	0.001	30	1.34	
Mensink 2002A	0.380	1.220	1.489	-2.012	2.772	0.311	0.756	30	1.22	
Mensink 2002B	-0.770	1.332	1.774	-3.380	1.840	-0.578	0.563	30	1.19	
Szapary 2003	1.430	1.662	2.763	-1.828	4.688	0.860	0.390	30	1.10	
Tonstad 2002D	3.860	1.387	1.925	1.141	6.579	2.782	0.005	29	1.18	
Levin 1990	3.000	1.082	1.172	0.878	5.122	2.771	0.006	28	1.25	
Maki 2005B	3.900	0.675	0.456	2.577	5.223	5.778	0.000	27	1.34	
Hollis 2009B	1.540	1.394	1.942	-1.191	4.271	1.105	0.269	26	1.18	
Gylling 2010B	1.160	1.815	3.293	-2.397	4.717	0.639	0.523	25	1.06	
Hollis 2009A	1.940	1.263	1.594	-0.535	4.415	1.536	0.124	25	1.21	
Hollis 2009C	0.000	1.421	2.020	-2.785	2.785	0.000	1.000	25	1.17	
Smith 2003A	-3.090	1.360	1.850	-5.756	-0.424	-2.272	0.023	25	1.18	
Gylling 2010A	-0.380	2.229	4.969	-4.749	3.989	-0.170	0.865	24	0.94	
Smith 2003B	-3.480	1.386	1.920	-6.196	-0.764	-2.511	0.012	23	1.18	
Stendell-Hollis 2010A	3.870	1.723	2.968	0.493	7.247	2.246	0.025	23	1.09	
Tanumihardjo 2009B	-1.930	1.468	2.155	-4.807	0.947	-1.315	0.189	23	1.16	
Melanson 2004	0.300	1.298	1.686	-2.245	2.845	0.231	0.817	22	1.20	
Schwab 2002B	0.000	1.336	1.786	-2.619	2.619	0.000	1.000	22	1.19	
Schwab 2006A	1.160	1.405	1.975	-1.595	3.915	0.825	0.409	22	1.17	
Schwab 2006B	2.700	1.511	2.283	-0.261	5.661	1.787	0.074	22	1.14	
Schwab 2006C	2.710	1.081	1.169	0.591	4.829	2.507	0.012	22	1.26	
Tanumihardjo 2009A	-2.320	1.723	2.969	-5.697	1.057	-1.346	0.178	21	1.09	
Assuncao 2009A	-6.500	1.336	1.786	-9.119	-3.881	-4.864	0.000	20	1.19	
Assuncao 2009B	3.200	1.163	1.353	0.920	5.480	2.751	0.006	20	1.24	
Han 2007A	-8.890	1.308	1.712	-11.455	-6.325	-6.794	0.000	20	1.20	
Han 2007B	4.250	2.122	4.503	0.091	8.409	2.003	0.045	20	0.97	
Schwab 2002A	0.000	1.435	2.058	-2.812	2.812	0.000	1.000	20	1.16	
Tapsell 2004A	5.420	1.218	1.483	3.033	7.807	4.450	0.000	20	1.22	
Diaz 2008B	-1.940	1.918	3.678	-5.699	1.819	-1.012	0.312	19	1.03	
Tapsell 2004B	8.900	1.109	1.229	6.727	11.073	8.028	0.000	19	1.25	
Alhassan 2006	1.000	1.625	2.641	-2.185	4.185	0.615	0.538	17	1.11	
Kelley 2007A	3.090	1.415	2.001	0.317	5.863	2.184	0.029	17	1.17	
Kelley 2007B	1.160	0.797	0.635	-0.401	2.721	1.456	0.145	17	1.32	
Beavers 2010A	-0.370	1.736	3.015	-3.773	3.033	-0.213	0.831	16	1.08	
Beavers 2010B	1.320	2.244	5.035	-3.078	5.718	0.588	0.556	16	0.94	
Diaz 2008A	-1.930	3.517	12.370	-8.823	4.963	-0.549	0.583	16	0.64	
Stendell-Hollis 2010B	7.730	2.090	4.368	3.634	11.826	3.699	0.000	16	0.98	
Tapsell 2004C	7.730	4.191	17.567	-0.485	15.945	1.844	0.065	16	0.52	
Wardlaw 1991B	-1.160	0.836	0.699	-2.799	0.479	-1.387	0.165	16	1.31	
Mutungi 2008A	9.500	2.107	4.439	5.371	13.629	4.509	0.000	15	0.98	
Pins 2006A	1.200	1.353	1.832	-1.453	3.853	0.887	0.375	15	1.19	
Pins 2006B	1.100	1.488	2.214	-1.816	4.016	0.739	0.460	15	1.15	
Wardlaw 1991A	0.390	1.079	1.163	-1.724	2.504	0.362	0.718	15	1.26	
Wood 2007B	5.800	1.844	3.400	2.186	9.414	3.145	0.002	15	1.05	
Goyens 2006B	1.540	2.485	6.175	-3.330	6.410	0.620	0.535	14	0.87	
Wood 2007A	3.860	1.726	2.977	0.478	7.242	2.237	0.025	14	1.08	
Chan 2002A	-0.780	1.275	1.627	-3.280	1.720	-0.612	0.541	13	1.21	
Goyens 2006A	0.000	3.307	10.937	-6.482	6.482	0.000	1.000	13	0.68	
Kasim-Karakas 2009B	-1.000	0.349	0.122	-1.684	-0.316	-2.865	0.004	13	1.38	
Mutungi 2008B	-1.200	1.407	1.980	-3.958	1.558	-0.853	0.394	13	1.17	
Chan 2002B	0.390	1.297	1.681	-2.151	2.931	0.301	0.764	12	1.20	
Adler 1997	2.300	0.678	0.460	0.971	3.629	3.392	0.001	11	1.34	
Kasim-Karakas 2009A	-4.000	0.326	0.106	-4.639	-3.361	-12.275	0.000	11	1.38	
Santo 2008B	12.700	2.209	4.881	8.370	17.030	5.748	0.000	11	0.95	
Santo 2008C	27.300	3.722	13.853	20.005	34.595	7.335	0.000	10	0.60	
Santo 2008A	-2.000	2.983	8.896	-7.846	3.846	-0.671	0.503	9	0.75	
	1.137	0.380	0.144	0.393	1.881	2.994	0.003			

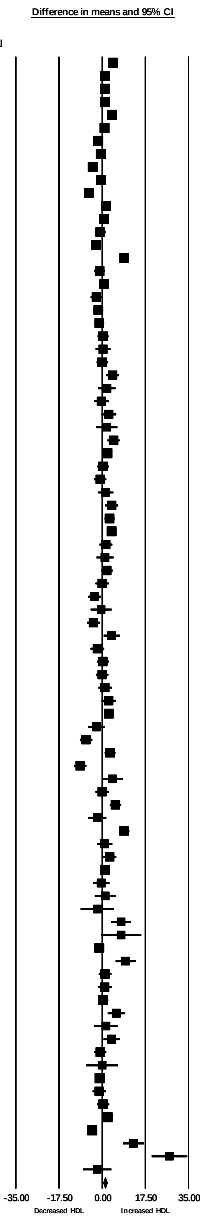


Figure S17. The impact of direction of effect on decisions regarding inconsistency: macronutrient distribution and change in HDL cholesterol. (Studies sorted by precision.)

Table S8. Sensitivity analysis for macronutrient distribution and change in HDL cholesterol: random-effects model versus fixed effect model.								
Effect size and 95% confidence interval							Test of null (2-Tail)	
	N	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
ΔHDL**	86	+1.137	0.380	0.144	0.393	1.881	2.994	0.003
ΔHDL	86	+0.448	0.105	0.011	0.242	0.654	4.265	<0.001

**From Random Effects Model.

Table S9. Sensitivity analysis: plausible ranges for pre- and post-treatment correlations (random-effects model/raw mean difference).								
Correlation		Effect size and 95% confidence interval					Test of null (2-Tail)	
	r	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
Δ HDL	0.854*	+1.137	0.380	0.144	0.393	1.881	2.994	0.003
	0.5	+0.984	0.396	0.157	0.208	1.760	2.487	0.013
	0.75	+1.078	0.385	0.149	0.323	1.833	2.797	0.005
	0.99	1.241	0.357	0.127	0.542	1.940	3.480	0.001

*Correlation calculated via the *CORREL* function in Microsoft Excel 2010 (Microsoft Corp., 2010), using the 86 comparisons ("studies") from the meta-analytic database. The correlation (r) between pre- and post-treatments was required for the calculation of the treatment effect variance (V_D): [$V_D = S^2{}_{diff}/n$; $S_{diff} = (\sqrt{S_{Pre}}^2 + S_{Post}{}^2 - 2 \times r \times S_{Pre} \times S_{Post})$].

Macronutrient Distribution & Change in HDL (One Study Removed)

Studyname	Macronutrient Distribution (F/P/C)	Statistics with studyremoved: Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hjerkinn 2005	28/17/52	1.088	0.378	0.143	0.346	1.829	2.875	0.004
Kawashima 2008B	28/14/50	1.141	0.389	0.151	0.379	1.903	2.936	0.003
Kawashima 2008A	27/14/51	1.140	0.388	0.150	0.381	1.900	2.942	0.003
Dodin 2005B	33/17/50	1.138	0.385	0.148	0.384	1.893	2.957	0.003
Esposito 2004A	28/14/58	1.096	0.381	0.145	0.350	1.842	2.879	0.004
Esposito 2004B	30/14/57	1.144	0.389	0.152	0.381	1.907	2.938	0.003
Dodin 2005A	35/17/47	1.174	0.384	0.148	0.421	1.927	3.055	0.002
Gardner 2007B	35/24/42	1.161	0.386	0.149	0.405	1.917	3.011	0.003
Gardner 2007C	30/20/49	1.201	0.380	0.144	0.457	1.945	3.164	0.002
Gardner 2007A	55/28/18	1.158	0.384	0.148	0.405	1.911	3.014	0.003
Gardner 2007D	21/17/63	1.217	0.377	0.142	0.479	1.955	3.233	0.001
Tighe 2010B	34/17/48	1.133	0.384	0.147	0.380	1.886	2.950	0.003
Tighe 2010C	35/16/45	1.143	0.384	0.147	0.390	1.896	2.976	0.003
Tighe 2010A	35/16/47	1.162	0.383	0.147	0.410	1.913	3.030	0.002
Fakhrzadeh 2010	35/13/53	1.187	0.383	0.147	0.436	1.937	3.098	0.002
Esposito 2004	29/16/55	1.008	0.358	0.128	0.307	1.709	2.819	0.005
Smith 2008B	30/16/54	1.143	0.384	0.148	0.389	1.896	2.973	0.003
Smith 2008A	32/16/52	1.165	0.383	0.147	0.413	1.916	3.038	0.002
Kasai 2003A	27/15/56	1.179	0.382	0.146	0.430	1.929	3.084	0.002
Price 2010B	33/18/47	1.167	0.384	0.147	0.415	1.919	3.043	0.002
Kasai 2003B	27/15/56	1.172	0.383	0.147	0.421	1.923	3.057	0.002
Price 2010A	35/18/47	1.147	0.383	0.147	0.395	1.899	2.991	0.003
Tonstad 2002B	31/18/49	1.099	0.382	0.146	0.351	1.847	2.879	0.004
Malpuech-Brugere 2010A	38/15/47	1.146	0.383	0.146	0.396	1.896	2.994	0.003
Malpuech-Brugere 2010C	39/15/47	1.152	0.384	0.147	0.400	1.904	3.004	0.003
Malpuech-Brugere 2010B	39/15/45	1.129	0.382	0.146	0.379	1.878	2.953	0.003
Polagruto 2006B	31/17/54	1.154	0.383	0.146	0.404	1.904	3.015	0.003
Tonstad 2002A	30/18/47	1.119	0.382	0.146	0.370	1.868	2.927	0.003
Polagruto 2006A	34/16/50	1.130	0.382	0.146	0.381	1.878	2.958	0.003
Tonstad 2002C	29/18/50	1.094	0.381	0.145	0.346	1.841	2.868	0.004
Maki 2005A	35/16/50	1.125	0.385	0.148	0.369	1.880	2.919	0.004
Szapary 2003	33/14/52	1.134	0.383	0.146	0.384	1.884	2.964	0.003
Mensink 2002A	32/15/50	1.147	0.383	0.147	0.396	1.899	2.992	0.003
Mensink 2002B	29/16/53	1.160	0.383	0.147	0.410	1.911	3.030	0.002
Tonstad 2002D	31/17/49	1.104	0.382	0.146	0.356	1.853	2.891	0.004
Levin 1990	26/18/57	1.114	0.383	0.147	0.363	1.864	2.909	0.004
Maki 2005B	35/15/52	1.099	0.382	0.146	0.351	1.847	2.879	0.004
Hollis 2009B	35/16/48	1.133	0.383	0.147	0.382	1.883	2.958	0.003
Hollis 2009A	35/15/50	1.128	0.383	0.147	0.377	1.878	2.944	0.003
Gylling 2010B	31/16/45	1.137	0.382	0.146	0.387	1.886	2.973	0.003
Hollis 2009C	34/16/50	1.151	0.383	0.147	0.400	1.901	3.005	0.003
Smith 2003A	40/11/48	1.187	0.382	0.146	0.439	1.936	3.109	0.002
Gylling 2010A	42/14/43	1.151	0.382	0.146	0.403	1.900	3.015	0.003
Stendell-Hollis 2010A	32/16/53	1.107	0.382	0.146	0.358	1.855	2.899	0.004
Tanumihardjo 2009B	24/21/55	1.173	0.382	0.146	0.423	1.922	3.067	0.002
Smith 2003B	37/11/50	1.191	0.382	0.146	0.443	1.939	3.122	0.002
Schwab 2006C	28/18/51	1.117	0.383	0.147	0.367	1.868	2.917	0.004
Schwab 2006B	28/19/51	1.119	0.382	0.146	0.369	1.868	2.926	0.003
Schwab 2006A	26/19/53	1.137	0.383	0.147	0.387	1.888	2.969	0.003
Melanson 2004	28/21/53	1.148	0.383	0.147	0.397	1.899	2.995	0.003
Schwab 2002B	27/18/52	1.151	0.383	0.147	0.400	1.902	3.005	0.003
Tanumihardjo 2009A	29/17/54	1.175	0.382	0.146	0.426	1.924	3.075	0.002
Tapsell 2004A	33/21/43	1.082	0.380	0.145	0.337	1.828	2.845	0.004
Han 2007B	28/18/55	1.106	0.381	0.146	0.358	1.854	2.899	0.004
Assuncao 2009B	21/15/64	1.111	0.383	0.146	0.361	1.861	2.905	0.004
Schwab 2002A	27/18/51	1.151	0.383	0.147	0.400	1.901	3.005	0.003
Assuncao 2009A	21/15/64	1.226	0.378	0.143	0.484	1.967	3.241	0.001
Han 2007A	23/18/59	1.252	0.374	0.140	0.519	1.984	3.349	0.001
Tapsell 2004B	33/23/41	1.031	0.373	0.139	0.300	1.762	2.764	0.006
Diaz 2008B	27/19/56	1.169	0.382	0.146	0.420	1.918	3.060	0.002
Kelley 2007A	36/16/48	1.114	0.382	0.146	0.364	1.863	2.913	0.004
Kelley 2007B	34/15/50	1.139	0.385	0.148	0.384	1.894	2.956	0.003
Alhassan 2006	39/17/44	1.139	0.383	0.146	0.389	1.889	2.976	0.003
Stendell-Hollis 2010B	28/18/54	1.070	0.380	0.144	0.325	1.815	2.817	0.005
Tapsell 2004C	32/22/44	1.102	0.380	0.145	0.357	1.848	2.898	0.004
Beavers 2010B	38/20/47	1.135	0.382	0.146	0.387	1.884	2.972	0.003
Beavers 2010A	34/21/47	1.154	0.382	0.146	0.404	1.903	3.016	0.003
Wardlaw 1991B	39/13/47	1.169	0.384	0.148	0.415	1.922	3.041	0.002
Diaz 2008A	23/16/65	1.156	0.381	0.145	0.409	1.903	3.034	0.002
Mutungi 2008A	56/27/15	1.052	0.379	0.143	0.310	1.794	2.778	0.005
Wood 2007B	59/27/13	1.086	0.381	0.145	0.340	1.833	2.853	0.004
Pins 2006A	34/21/45	1.137	0.383	0.147	0.386	1.887	2.967	0.003
Pins 2006B	35/21/44	1.138	0.383	0.147	0.387	1.888	2.972	0.003
Wardlaw 1991A	40/13/47	1.147	0.384	0.147	0.395	1.900	2.989	0.003
Wood 2007A	59/27/13	1.107	0.382	0.146	0.358	1.855	2.899	0.004
Goyens 2006B	42/14/43	1.133	0.382	0.146	0.385	1.882	2.969	0.003
Goyens 2006A	41/13/44	1.145	0.381	0.145	0.397	1.892	3.002	0.003
Chan 2002A	36/20/38	1.161	0.383	0.147	0.410	1.912	3.030	0.002
Kasim-Karakas 2009B	26/17/57	1.175	0.394	0.155	0.403	1.948	2.982	0.003
Mutungi 2008B	55/25/20	1.165	0.383	0.147	0.415	1.915	3.044	0.002
Chan 2002B	34/22/40	1.147	0.383	0.147	0.396	1.898	2.992	0.003
Santo 2008B	24/21/54	1.022	0.376	0.142	0.285	1.760	2.716	0.007
Adler 1997	31/17/50	1.123	0.385	0.148	0.368	1.878	2.916	0.004
Kasim-Karakas 2009A	26/34/40	1.190	0.358	0.128	0.489	1.892	3.325	0.001
Santo 2008C	23/20/57	0.976	0.372	0.138	0.248	1.704	2.627	0.009
Santo 2008A	22/20/57	1.160	0.381	0.145	0.413	1.908	3.043	0.002
		1.137	0.380	0.144	0.393	1.881	2.994	0.003

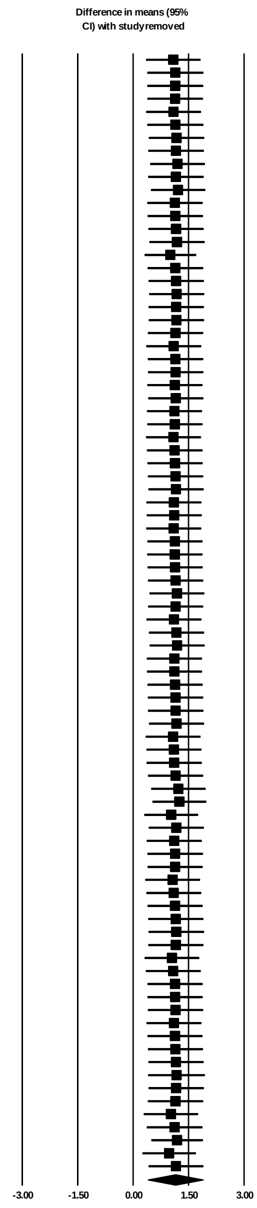


Figure S18. Sensitivity analysis (one study removed): macronutrient distribution and change in HDL cholesterol.

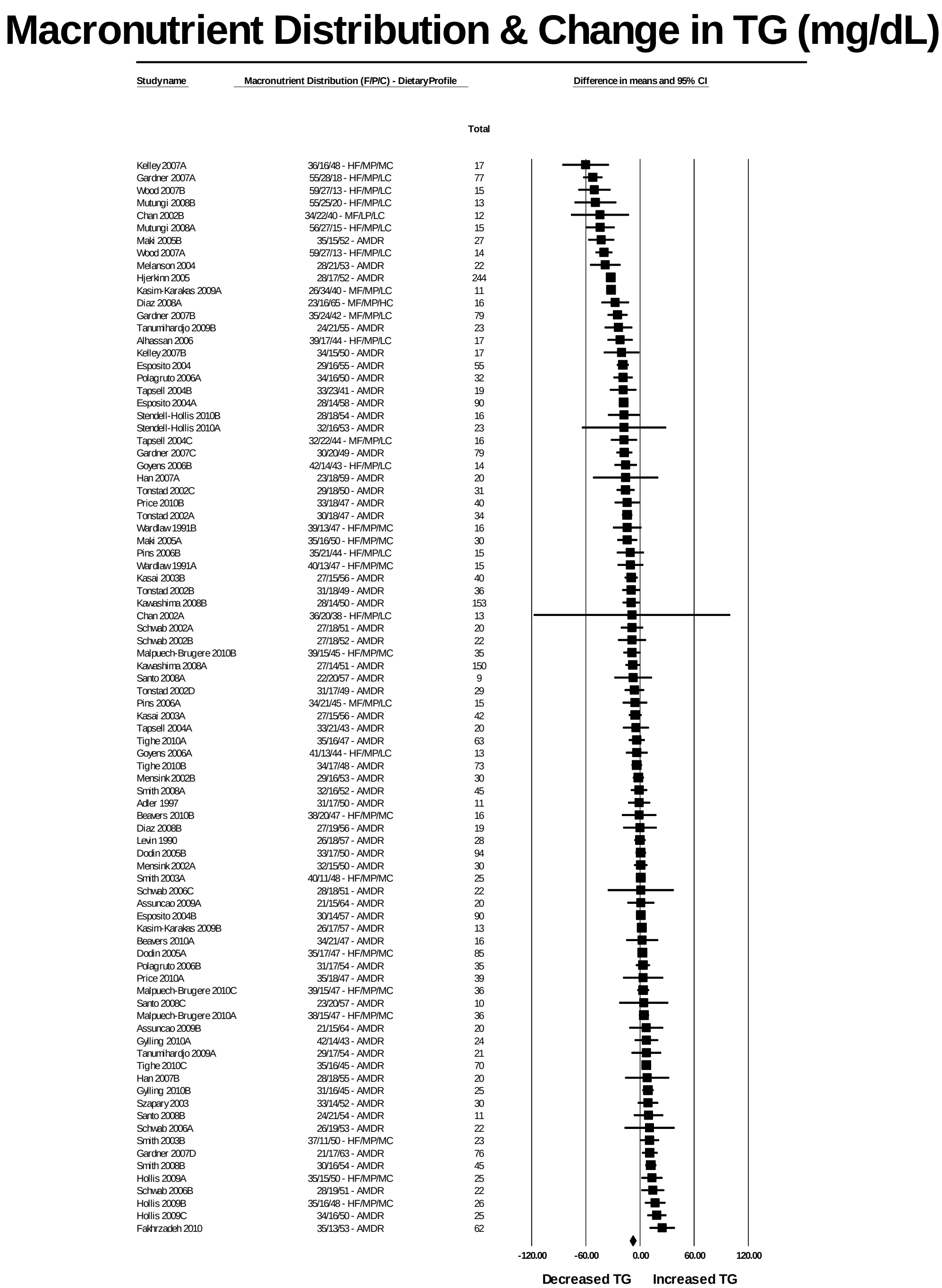


Figure S19. Forest Plot of Macronutrient Distribution and Change in Triglycerides [Random Effects Model, Raw Mean Difference (D)]. Macronutrient Distribution (%Total Energy): Fat/Protein/Carbohydrate.

Figure S20. Sensitivity Analysis: Funnel Plot and Assessment of Publication Bias of Macronutrient Distribution and Change in Triglycerides.

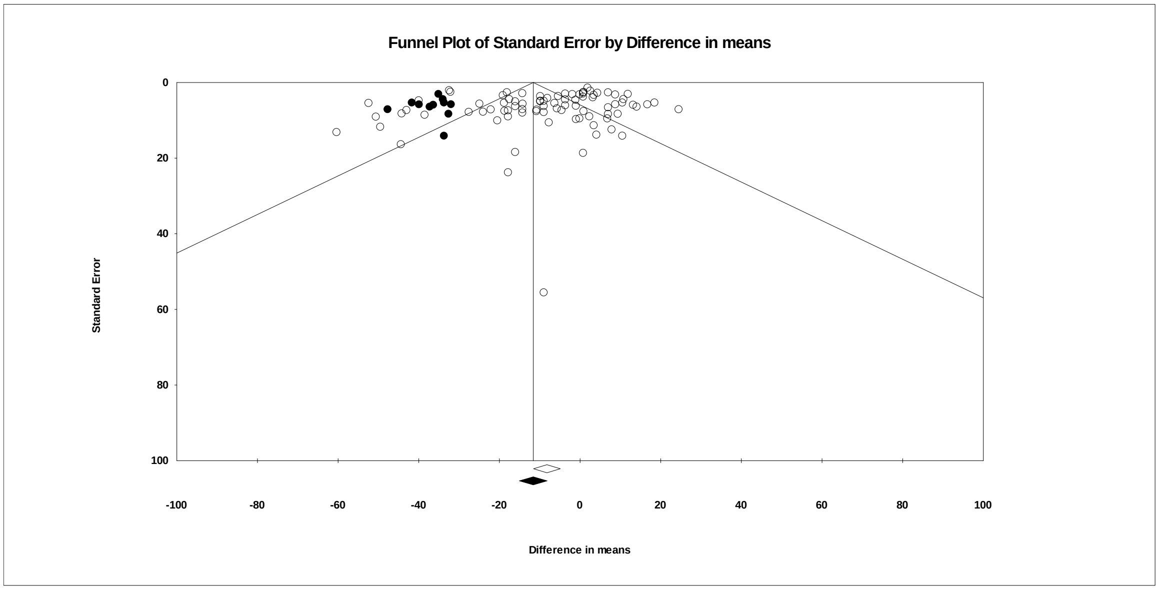


Table S10. Sensitivity analyses: Trim-and-Fill, Egger's Test, and Classic Fail-Safe N for Macronutrient Distribution and Change in Triglycerides.

Duval and Tweedie's Trim-and-Fill (Random Effects Model)						
		Studies Trimmed	Summary Effect	Lower Limit	Upper Limit	Q-value
ΔTG	Observed Values		-8.21877	-11.54982	-4.88772	863.28413
	Adjusted Values	11	-11.61281	15.06690	-8.15871	1168.90813
Egger's Regression Intercept:			-0.91902; 95%CI: (-2.29589 to 0.45786) P: 0.18800			
Rosenthal's Classic Fail-Safe N (For Observed Studies: Alpha = 0.05, 2-Tailed, Z for alpha = 1.96)						
	Z-value	P-value	Number of Studies	Number of Missing Studies That Would Bring P-value to > alpha		
ΔTG	-12.70738	<0.001	86	3530		

Cumulative Meta-Analysis:Macronutrient Distribution & Change in TG

Studyname	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Cumulative statistics						
Hjerkinn 2005	-32.330	2.226	4.956	-36.693	-27.967	-14.523	0.000
Kawashima 2008B	-21.477	11.286	127.381	-43.598	0.644	-1.903	0.057
Kawashima 2008A	-17.022	9.173	84.146	-35.001	0.957	-1.856	0.064
Dodin 2005B	-12.418	9.164	83.983	-30.379	5.544	-1.355	0.175
Esposito 2004A	-13.612	6.684	44.675	-26.713	-0.512	-2.037	0.042
Esposito 2004B	-11.116	6.336	40.146	-23.535	1.302	-1.754	0.079
Dodin 2005A	-9.103	5.846	34.180	-20.562	2.356	-1.557	0.119
Gardner 2007B	-10.916	5.454	29.747	-21.606	-0.226	-2.001	0.045
Gardner 2007C	-11.610	4.999	24.994	-21.408	-1.811	-2.322	0.020
Gardner 2007A	-15.491	5.284	27.916	-25.846	-5.135	-2.932	0.003
Gardner 2007D	-13.139	5.150	26.524	-23.233	-3.045	-2.551	0.011
Tighe 2010B	-12.301	4.713	22.211	-21.538	-3.064	-2.610	0.009
Tighe 2010C	-10.770	4.551	20.714	-19.690	-1.849	-2.366	0.018
Tighe 2010A	-10.256	4.303	18.514	-18.689	-1.822	-2.384	0.017
Fakhrzadeh 2010	-8.204	4.273	18.260	-16.579	0.172	-1.920	0.055
Esposito 2004	-8.892	4.053	16.431	-16.837	-0.947	-2.194	0.028
Smith 2008A	-8.437	3.878	15.041	-16.038	-0.836	-2.175	0.030
Smith 2008B	-7.269	3.841	14.750	-14.797	0.258	-1.893	0.058
Kasai 2003A	-7.166	3.646	13.294	-14.312	-0.019	-1.965	0.049
Kasai 2003B	-7.296	3.473	12.062	-14.103	-0.489	-2.101	0.036
Price 2010B	-7.583	3.379	11.417	-14.205	-0.960	-2.244	0.025
Price 2010A	-7.235	3.317	11.005	-13.737	-0.733	-2.181	0.029
Tonstad 2002B	-7.343	3.206	10.281	-13.628	-1.059	-2.290	0.022
Malpuech-Brugere 2010A	-6.825	3.093	9.569	-12.888	-0.762	-2.206	0.027
Malpuech-Brugere 2010C	-6.394	2.991	8.943	-12.255	-0.533	-2.138	0.033
Polagruto 2006B	-6.014	2.903	8.426	-11.704	-0.325	-2.072	0.038
Malpuech-Brugere 2010B	-6.118	2.820	7.950	-11.644	-0.592	-2.170	0.030
Tonstad 2002A	-6.423	2.716	7.378	-11.747	-1.099	-2.365	0.018
Polagruto 2006A	-6.827	2.664	7.095	-12.047	-1.606	-2.563	0.010
Tonstad 2002C	-7.122	2.605	6.786	-12.228	-2.017	-2.734	0.006
Mensink 2002A	-6.857	2.534	6.421	-11.823	-1.890	-2.706	0.007
Mensink 2002B	-6.689	2.448	5.991	-11.486	-1.891	-2.733	0.006
Szapary 2003	-6.250	2.414	5.828	-10.981	-1.518	-2.589	0.010
Maki 2005A	-6.467	2.369	5.611	-11.109	-1.824	-2.730	0.006
Tonstad 2002D	-6.459	2.319	5.379	-11.005	-1.914	-2.785	0.005
Levin 1990	-6.269	2.253	5.075	-10.684	-1.854	-2.783	0.005
Maki 2005B	-7.112	2.276	5.181	-11.573	-2.651	-3.124	0.002
Hollis 2009B	-6.524	2.269	5.149	-10.971	-2.077	-2.875	0.004
Smith 2003A	-6.315	2.199	4.836	-10.626	-2.005	-2.872	0.004
Hollis 2009A	-5.861	2.182	4.762	-10.139	-1.584	-2.686	0.007
Hollis 2009C	-5.289	2.183	4.764	-9.567	-1.011	-2.423	0.015
Gylling 2010B	-4.932	2.156	4.650	-9.159	-0.706	-2.287	0.022
Gylling 2010A	-4.682	2.130	4.538	-8.857	-0.506	-2.198	0.028
Smith 2003B	-4.346	2.109	4.446	-8.479	-0.213	-2.061	0.039
Tanumihardjo 2009B	-4.709	2.093	4.380	-8.811	-0.607	-2.250	0.024
Stendell-Hollis 2010A	-4.784	2.085	4.347	-8.871	-0.698	-2.295	0.022
Schwab 2002B	-4.857	2.060	4.242	-8.894	-0.820	-2.358	0.018
Melanson 2004	-5.427	2.063	4.256	-9.470	-1.383	-2.631	0.009
Schwab 2006A	-5.248	2.050	4.203	-9.267	-1.230	-2.560	0.010
Schwab 2006B	-4.883	2.036	4.146	-8.874	-0.893	-2.398	0.016
Schwab 2006C	-4.838	2.026	4.104	-8.809	-0.868	-2.388	0.017
Tanumihardjo 2009A	-4.644	2.007	4.026	-8.577	-0.711	-2.315	0.021
Schwab 2002A	-4.721	1.980	3.920	-8.601	-0.840	-2.384	0.017
Tapsell 2004A	-4.715	1.956	3.828	-8.550	-0.880	-2.410	0.016
Han 2007A	-4.797	1.947	3.792	-8.614	-0.980	-2.463	0.014
Han 2007B	-4.652	1.935	3.742	-8.444	-0.861	-2.405	0.016
Assuncao 2009A	-4.562	1.914	3.662	-8.313	-0.811	-2.384	0.017
Assuncao 2009B	-4.406	1.898	3.604	-8.126	-0.685	-2.321	0.020
Tapsell 2004B	-4.626	1.883	3.544	-8.315	-0.936	-2.457	0.014
Diaz 2008B	-4.564	1.866	3.482	-8.221	-0.907	-2.446	0.014
Alhassan 2006	-4.833	1.854	3.436	-8.466	-1.200	-2.607	0.009
Kelley 2007A	-5.384	1.867	3.486	-9.044	-1.725	-2.884	0.004
Kelley 2007B	-5.569	1.855	3.441	-9.205	-1.933	-3.002	0.003
Wardlaw 1991B	-5.689	1.839	3.380	-9.293	-2.086	-3.094	0.002
Tapsell 2004C	-5.862	1.823	3.325	-9.436	-2.288	-3.215	0.001
Diaz 2008A	-6.164	1.817	3.300	-9.724	-2.603	-3.393	0.001
Beavers 2010A	-6.054	1.802	3.246	-9.585	-2.523	-3.360	0.001
Beavers 2010B	-5.991	1.787	3.195	-9.494	-2.488	-3.352	0.001
Stendell-Hollis 2010B	-6.134	1.775	3.150	-9.613	-2.656	-3.457	0.001
Wardlaw 1991A	-6.194	1.758	3.089	-9.639	-2.749	-3.524	0.000
Pins 2006A	-6.183	1.739	3.026	-9.593	-2.774	-3.555	0.000
Pins 2006B	-6.240	1.724	2.971	-9.618	-2.862	-3.620	0.000
Wood 2007B	-6.766	1.741	3.030	-10.177	-3.355	-3.887	0.000
Mutungi 2008A	-7.234	1.752	3.070	-10.668	-3.800	-4.129	0.000
Goyens 2006B	-7.350	1.737	3.016	-10.754	-3.947	-4.233	0.000
Wood 2007A	-7.847	1.771	3.135	-11.317	-4.377	-4.432	0.000
Chan 2002A	-7.847	1.769	3.128	-11.314	-4.381	-4.437	0.000
Goyens 2006A	-7.786	1.750	3.062	-11.216	-4.356	-4.449	0.000
Mutungi 2008B	-8.175	1.754	3.077	-11.613	-4.737	-4.660	0.000
Kasim-Karakas 2009B	-7.982	1.688	2.849	-11.291	-4.674	-4.729	0.000
Chan 2002B	-8.213	1.687	2.845	-11.519	-4.907	-4.869	0.000
Adler 1997	-8.116	1.671	2.791	-11.390	-4.841	-4.858	0.000
Santo 2008B	-7.921	1.661	2.759	-11.177	-4.666	-4.769	0.000
Kasim-Karakas 2009A	-8.320	1.718	2.951	-11.687	-4.954	-4.844	0.000
Santo 2008C	-8.226	1.710	2.924	-11.578	-4.875	-4.811	0.000
Santo 2008A	-8.219	1.700	2.888	-11.550	-4.888	-4.836	0.000
	-8.219	1.700	2.888	-11.550	-4.888	-4.836	0.000

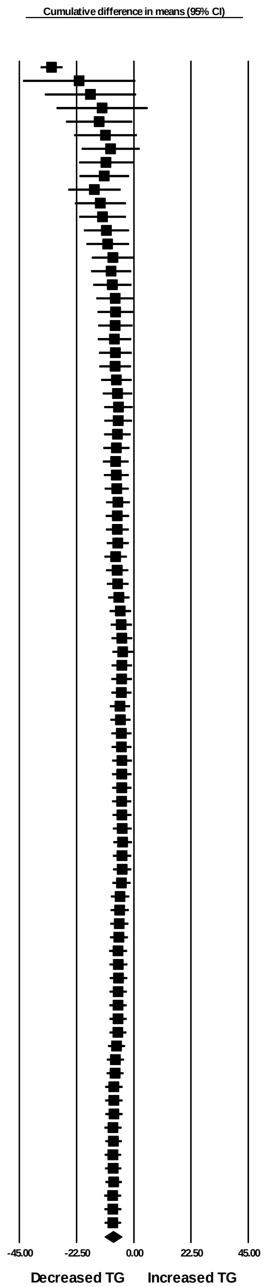


Figure S21. Cumulative Forest Plot of Macronutrient Distribution and Change in Triglycerides.
[Sorted by study design to examine small study bias.]

Cumulative Display (Time-Lag Bias):Macronutrient Distribution & Change in TG

Studyname	Publication Year	Cumulative statistics						
		Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Levin 1990	1990	0.000	3.301	10.898	-6.470	6.470	0.000	1.000
Wardlaw 1991A	1991	-3.299	4.918	24.184	-12.937	6.340	-0.671	0.502
Wardlaw 1991B	1991	-5.988	4.754	22.598	-15.305	3.330	-1.260	0.208
Adler 1997	1997	-3.868	3.240	10.496	-10.218	2.482	-1.194	0.233
Chan 2002A	2002	-2.901	2.575	6.632	-7.949	2.146	-1.127	0.260
Chan 2002B	2002	-7.789	4.635	21.487	-16.875	1.296	-1.680	0.093
Mensink 2002A	2002	-4.928	3.472	12.053	-11.733	1.876	-1.419	0.156
Mensink 2002B	2002	-3.522	2.581	6.660	-8.580	1.536	-1.365	0.172
Schwab 2002A	2002	-3.972	2.383	5.681	-8.643	0.700	-1.666	0.096
Schwab 2002B	2002	-4.145	2.221	4.934	-8.498	0.209	-1.866	0.062
Tonstad 2002A	2002	-6.540	2.581	6.662	-11.599	-1.481	-2.534	0.011
Tonstad 2002B	2002	-6.771	2.357	5.556	-11.390	-2.151	-2.873	0.004
Tonstad 2002C	2002	-7.647	2.306	5.319	-12.167	-3.126	-3.315	0.001
Tonstad 2002D	2002	-7.458	2.131	4.541	-11.635	-3.281	-3.500	0.000
Kasai 2003A	2003	-7.154	1.920	3.685	-10.916	-3.392	-3.727	0.000
Kasai 2003B	2003	-7.328	1.766	3.119	-10.790	-3.866	-4.149	0.000
Smith 2003A	2003	-6.599	1.760	3.098	-10.049	-3.149	-3.749	0.000
Smith 2003B	2003	-5.794	1.866	3.482	-9.451	-2.136	-3.105	0.002
Szapary 2003	2003	-5.117	1.886	3.558	-8.814	-1.420	-2.713	0.007
Esposito 2004	2004	-6.134	2.009	4.036	-10.072	-2.196	-3.053	0.002
Esposito 2004A	2004	-6.952	2.073	4.297	-11.014	-2.889	-3.354	0.001
Esposito 2004B	2004	-6.465	2.003	4.010	-10.390	-2.540	-3.228	0.001
Melanson 2004	2004	-7.473	2.090	4.370	-11.571	-3.376	-3.575	0.000
Tapsell 2004A	2004	-7.356	2.034	4.137	-11.343	-3.370	-3.617	0.000
Tapsell 2004B	2004	-7.718	2.003	4.013	-11.644	-3.792	-3.853	0.000
Tapsell 2004C	2004	-8.031	1.970	3.882	-11.893	-4.169	-4.076	0.000
Dodin 2005A	2005	-7.501	1.936	3.747	-11.295	-3.707	-3.875	0.000
Dodin 2005B	2005	-7.090	1.864	3.474	-10.743	-3.436	-3.803	0.000
Hjerkinn 2005	2005	-8.622	2.423	5.872	-13.371	-3.873	-3.558	0.000
Maki 2005A	2005	-8.798	2.364	5.587	-13.431	-4.165	-3.722	0.000
Maki 2005B	2005	-9.828	2.402	5.771	-14.537	-5.120	-4.091	0.000
Alhassan 2006	2006	-10.176	2.365	5.596	-14.813	-5.540	-4.302	0.000
Goyens 2006A	2006	-9.967	2.314	5.354	-14.502	-5.432	-4.307	0.000
Goyens 2006B	2006	-10.131	2.268	5.145	-14.576	-5.685	-4.467	0.000
Pins 2006A	2006	-10.001	2.224	4.946	-14.360	-5.642	-4.497	0.000
Pins 2006B	2006	-10.011	2.185	4.772	-14.293	-5.729	-4.583	0.000
Polagruto 2006A	2006	-10.250	2.145	4.602	-14.455	-6.046	-4.778	0.000
Polagruto 2006B	2006	-9.845	2.112	4.461	-13.985	-5.706	-4.662	0.000
Schwab 2006A	2006	-9.577	2.099	4.404	-13.690	-5.464	-4.564	0.000
Schwab 2006B	2006	-9.008	2.097	4.399	-13.119	-4.898	-4.295	0.000
Schwab 2006C	2006	-8.919	2.084	4.344	-13.004	-4.833	-4.279	0.000
Gardner 2007A	2007	-10.075	2.220	4.926	-14.425	-5.724	-4.539	0.000
Gardner 2007B	2007	-10.436	2.196	4.822	-14.739	-6.132	-4.752	0.000
Gardner 2007C	2007	-10.608	2.152	4.632	-14.826	-6.389	-4.929	0.000
Gardner 2007D	2007	-10.083	2.152	4.631	-14.301	-5.865	-4.686	0.000
Han 2007A	2007	-10.135	2.139	4.575	-14.327	-5.943	-4.738	0.000
Han 2007B	2007	-9.882	2.123	4.508	-14.044	-5.721	-4.654	0.000
Kelley 2007A	2007	-10.553	2.140	4.581	-14.748	-6.358	-4.931	0.000
Kelley 2007B	2007	-10.712	2.119	4.491	-14.866	-6.559	-5.055	0.000
Wood 2007A	2007	-11.402	2.163	4.680	-15.642	-7.162	-5.271	0.000
Wood 2007B	2007	-12.090	2.180	4.751	-16.362	-7.817	-5.546	0.000
Diaz 2008A	2008	-12.372	2.161	4.671	-16.608	-8.136	-5.724	0.000
Diaz 2008B	2008	-12.170	2.139	4.577	-16.363	-7.977	-5.688	0.000
Kawashima 2008A	2008	-12.068	2.094	4.383	-16.171	-7.965	-5.764	0.000
Kawashima 2008B	2008	-12.011	2.055	4.224	-16.039	-7.983	-5.844	0.000
Mutungi 2008A	2008	-12.555	2.063	4.257	-16.599	-8.511	-6.085	0.000
Mutungi 2008B	2008	-13.037	2.066	4.269	-17.086	-8.987	-6.310	0.000
Santo 2008A	2008	-12.959	2.047	4.190	-16.971	-8.947	-6.331	0.000
Santo 2008B	2008	-12.607	2.034	4.136	-16.593	-8.620	-6.199	0.000
Santo 2008C	2008	-12.427	2.021	4.085	-16.389	-8.466	-6.148	0.000
Smith 2008A	2008	-12.206	1.991	3.966	-16.109	-8.303	-6.129	0.000
Smith 2008B	2008	-11.760	2.015	4.060	-15.710	-7.811	-5.836	0.000
Assuncao 2009A	2009	-11.560	1.995	3.980	-15.470	-7.650	-5.795	0.000
Assuncao 2009B	2009	-11.311	1.981	3.923	-15.193	-7.428	-5.710	0.000
Hollis 2009A	2009	-10.911	1.975	3.901	-14.782	-7.040	-5.524	0.000
Hollis 2009B	2009	-10.468	1.977	3.907	-14.342	-6.595	-5.296	0.000
Hollis 2009C	2009	-10.005	1.984	3.938	-13.895	-6.116	-5.042	0.000
Kasim-Karakas 2009A	2009	-10.428	2.031	4.124	-14.408	-6.448	-5.135	0.000
Kasim-Karakas 2009B	2009	-10.184	1.965	3.860	-14.034	-6.333	-5.183	0.000
Tanumihardjo 2009A	2009	-9.953	1.950	3.804	-13.776	-6.131	-5.103	0.000
Tanumihardjo 2009B	2009	-10.143	1.937	3.751	-13.938	-6.347	-5.237	0.000
Beavers 2010A	2010	-9.984	1.922	3.693	-13.751	-6.218	-5.195	0.000
Beavers 2010B	2010	-9.876	1.907	3.638	-13.614	-6.137	-5.178	0.000
Fakhrzadeh 2010	2010	-9.416	1.911	3.652	-13.161	-5.670	-4.927	0.000
Gylling 2010A	2010	-9.189	1.896	3.597	-12.906	-5.471	-4.845	0.000
Gylling 2010B	2010	-8.909	1.885	3.552	-12.603	-5.215	-4.727	0.000
Malpuech-Brugere 2010A	2010	-8.697	1.858	3.453	-12.338	-5.055	-4.680	0.000
Malpuech-Brugere 2010B	2010	-8.694	1.835	3.367	-12.291	-5.097	-4.738	0.000
Malpuech-Brugere 2010C	2010	-8.507	1.811	3.280	-12.057	-4.957	-4.697	0.000
Price 2010A	2010	-8.391	1.801	3.242	-11.920	-4.862	-4.660	0.000
Price 2010B	2010	-8.460	1.786	3.188	-11.960	-4.960	-4.738	0.000
Stendell-Hollis 2010A	2010	-8.497	1.781	3.171	-11.988	-5.007	-4.771	0.000
Stendell-Hollis 2010B	2010	-8.596	1.769	3.130	-12.063	-5.128	-4.859	0.000
Tighe 2010A	2010	-8.522	1.747	3.053	-11.946	-5.097	-4.877	0.000
Tighe 2010B	2010	-8.440	1.715	2.941	-11.801	-5.079	-4.922	0.000
Tighe 2010C	2010	-8.219	1.700	2.888	-11.550	-4.888	-4.836	0.000
		-8.219	1.700	2.888	-11.550	-4.888	-4.836	0.000

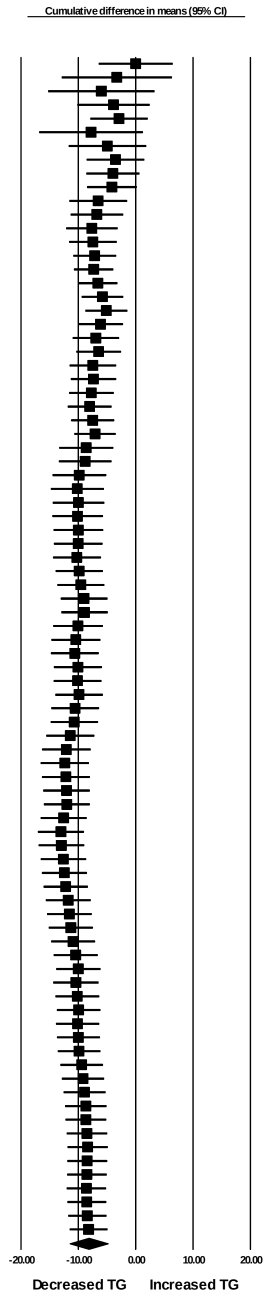


Figure S22. Cumulative Meta-Analysis for Time-Lag Bias: Macronutrient Distribution and Change in Triglycerides (mg/dL). Continuously Diminishing Effects Strongly Support Time-Lag Bias.

Direction of Effect (Inconsistency):Macronutrient Distribution & Change in TG

Studyname	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Statistics for each study						
Hjerkinn 2005	-32.330	2.226	4.956	-36.693	-27.967	-14.523	0.000
Kawashima 2008B	-9.740	4.993	24.935	-19.527	0.047	-1.951	0.051
Kawashima 2008A	-7.970	4.267	18.207	-16.333	0.393	-1.868	0.062
Dodin 2005B	0.880	3.084	9.511	-5.165	6.925	0.285	0.775
Esposito 2004A	-18.000	2.762	7.628	-23.413	-12.587	-6.517	0.000
Esposito 2004B	1.000	2.664	7.099	-4.222	6.222	0.375	0.707
Dodin 2005A	2.660	2.344	5.496	-1.935	7.255	1.135	0.257
Gardner 2007B	-24.800	5.757	33.138	-36.083	-13.517	-4.308	0.000
Gardner 2007C	-17.400	4.573	20.915	-26.364	-8.436	-3.805	0.000
Gardner 2007A	-52.300	5.578	31.112	-63.232	-41.368	-9.376	0.000
Gardner 2007D	10.900	4.563	20.822	1.956	19.844	2.389	0.017
Tighe 2010B	-3.540	3.092	9.562	-9.601	2.521	-1.145	0.252
Tighe 2010C	7.090	2.774	7.696	1.653	12.527	2.556	0.011
Tighe 2010A	-3.550	4.629	21.432	-12.624	5.524	-0.767	0.443
Fakhrzadeh 2010	24.600	7.243	52.458	10.404	38.796	3.396	0.001
Esposito 2004	-19.000	3.523	12.413	-25.905	-12.095	-5.393	0.000
Smith 2008A	-1.000	4.730	22.372	-10.270	8.270	-0.211	0.833
Smith 2008B	12.000	3.193	10.197	5.741	18.259	3.758	0.000
Kasai 2003A	-5.320	3.742	14.005	-12.655	2.015	-1.422	0.155
Kasai 2003B	-9.740	3.779	14.282	-17.147	-2.333	-2.577	0.010
Price 2010B	-14.170	7.211	52.001	-28.304	-0.036	-1.965	0.049
Price 2010A	3.540	11.474	131.651	-18.949	26.029	0.309	0.758
Tonstad 2002B	-9.740	5.148	26.503	-19.830	0.350	-1.892	0.058
Malpuech-Brugere 2010A	4.430	2.891	8.356	-1.236	10.096	1.533	0.125
Malpuech-Brugere 2010C	3.540	3.452	11.918	-3.226	10.306	1.025	0.305
Polagruto 2006B	3.300	4.086	16.696	-4.709	11.309	0.808	0.419
Malpuech-Brugere 2010B	-8.860	5.001	25.014	-18.663	0.943	-1.771	0.076
Tonstad 2002A	-14.170	2.997	8.983	-20.044	-8.296	-4.728	0.000
Polagruto 2006A	-18.700	5.540	30.689	-29.558	-7.842	-3.376	0.001
Tonstad 2002C	-15.940	5.152	26.546	-26.038	-5.842	-3.094	0.002
Mensink 2002A	0.880	3.907	15.262	-6.777	8.537	0.225	0.822
Mensink 2002B	-1.770	3.249	10.554	-8.137	4.597	-0.545	0.586
Szapary 2003	8.880	5.922	35.070	-2.727	20.487	1.499	0.134
Maki 2005A	-14.100	5.772	33.312	-25.412	-2.788	-2.443	0.015
Tonstad 2002D	-6.200	5.587	31.218	-17.151	4.751	-1.110	0.267
Levin 1990	0.000	3.301	10.898	-6.470	6.470	0.000	1.000
Maki 2005B	-42.900	7.451	55.520	-57.504	-28.296	-5.757	0.000
Hollis 2009B	16.830	5.939	35.269	5.190	28.470	2.834	0.005
Smith 2003A	0.880	2.764	7.639	-4.537	6.297	0.318	0.750
Hollis 2009A	13.290	6.063	36.761	1.407	25.173	2.192	0.028
Hollis 2009C	18.600	5.462	29.838	7.894	29.306	3.405	0.001
Gylling 2010B	8.860	3.345	11.192	2.303	15.417	2.648	0.008
Gylling 2010A	7.090	6.733	45.336	-6.107	20.287	1.053	0.292
Smith 2003B	10.630	5.462	29.837	-0.076	21.336	1.946	0.052
Tanumihardjo 2009B	-23.910	7.904	62.477	-39.402	-8.418	-3.025	0.002
Stendell-Hollis 2010A	-17.710	23.926	572.470	-64.605	29.185	-0.740	0.459
Schwab 2002B	-8.860	7.993	63.887	-24.526	6.806	-1.108	0.268
Melanson 2004	-38.400	8.699	75.674	-55.450	-21.350	-4.414	0.000
Schwab 2006A	10.620	14.248	202.999	-17.305	38.545	0.745	0.456
Schwab 2006B	14.170	6.562	43.055	1.310	27.030	2.160	0.031
Schwab 2006C	0.890	18.780	352.681	-35.918	37.698	0.047	0.962
Tanumihardjo 2009A	7.090	8.486	72.016	-9.543	23.723	0.835	0.403
Schwab 2002A	-8.860	6.375	40.644	-21.355	3.635	-1.390	0.165
Tapsell 2004A	-4.430	7.460	55.650	-19.051	10.191	-0.594	0.553
Han 2007A	-15.940	18.552	344.191	-52.302	20.422	-0.859	0.390
Han 2007B	7.970	12.583	158.339	-16.693	32.633	0.633	0.526
Assuncao 2009A	1.000	7.728	59.717	-14.146	16.146	0.129	0.897
Assuncao 2009B	6.900	9.673	93.570	-12.059	25.859	0.713	0.476
Tapsell 2004B	-18.600	7.644	58.438	-33.583	-3.617	-2.433	0.015
Diaz 2008B	0.000	9.649	93.103	-18.912	18.912	0.000	1.000
Alhassan 2006	-22.000	7.282	53.030	-36.273	-7.727	-3.021	0.003
Kelley 2007A	-60.230	13.284	176.459	-86.266	-34.194	-4.534	0.000
Kelley 2007B	-20.370	10.179	103.608	-40.320	-0.420	-2.001	0.045
Wardlaw 1991B	-14.170	8.130	66.093	-30.104	1.764	-1.743	0.081
Tapsell 2004C	-17.710	7.534	56.755	-32.476	-2.944	-2.351	0.019
Diaz 2008A	-27.460	7.946	63.136	-43.034	-11.886	-3.456	0.001
Beavers 2010A	2.440	9.119	83.155	-15.433	20.313	0.268	0.789
Beavers 2010B	-0.870	9.843	96.882	-20.162	18.422	-0.088	0.930
Stendell-Hollis 2010B	-17.720	9.143	83.603	-35.641	0.201	-1.938	0.053
Wardlaw 1991A	-10.630	7.332	53.762	-25.001	3.741	-1.450	0.147
Pins 2006A	-5.600	6.996	48.951	-19.313	8.113	-0.800	0.423
Pins 2006B	-10.700	7.737	59.864	-25.865	4.465	-1.383	0.167
Wood 2007B	-50.490	9.204	84.705	-68.529	-32.451	-5.486	0.000
Mutungi 2008A	-44.100	8.355	69.800	-60.475	-27.725	-5.279	0.000
Goyens 2006B	-15.940	6.434	41.392	-28.550	-3.330	-2.478	0.013
Wood 2007A	-39.860	4.893	23.942	-49.450	-30.270	-8.146	0.000
Chan 2002A	-8.860	55.672	3099.354	-117.975	100.255	-0.159	0.874
Goyens 2006A	-3.540	6.198	38.411	-15.687	8.607	-0.571	0.568
Mutungi 2008B	-49.400	11.882	141.188	-72.689	-26.111	-4.157	0.000
Kasim-Karakas 2009B	2.000	1.530	2.340	-0.998	4.998	1.307	0.191
Chan 2002B	-44.290	16.495	272.082	-76.619	-11.961	-2.685	0.007
Adler 1997	-0.900	6.328	40.045	-13.303	11.503	-0.142	0.887
Santo 2008B	9.500	8.435	71.145	-7.032	26.032	1.126	0.260
Kasim-Karakas 2009A	-32.000	2.642	6.978	-37.178	-26.822	-12.114	0.000
Santo 2008C	4.200	13.962	194.935	-23.165	31.565	0.301	0.764
Santo 2008A	-7.600	10.711	114.731	-28.594	13.394	-0.710	0.478
	-8.219	1.700	2.888	-11.550	-4.888	-4.836	0.000

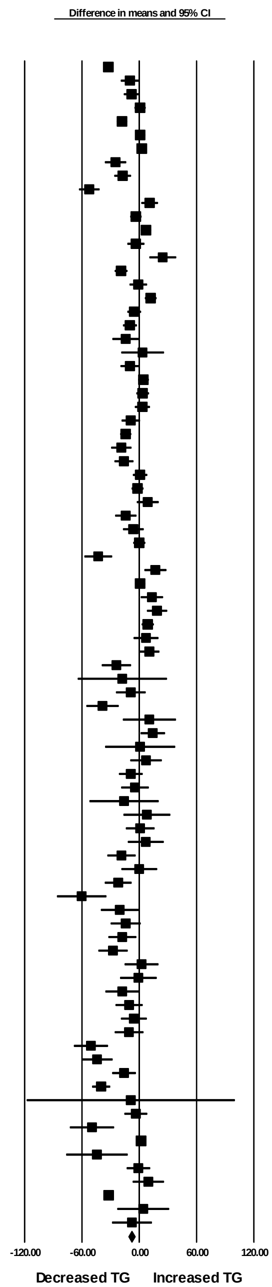


Figure S23. The Impact of Direction of Effect on Decisions Regarding Inconsistency: Macronutrient Distribution & Change in Triglycerides. (Study Sorted by Precision.)

Table S11. Sensitivity Analysis for Macronutrient Distribution and Change in Triglycerides: Random Effects Model versus Fixed Effect Model.								
Table of Summary Effects (Random Effects versus Fixed Effect Model/Raw Mean Difference)								
Effect size and 95% confidence interval							Test of null (2-Tail)	
	N	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
ΔTG**	86	-8.219	1.700	2.888	-11.55	-4.888	-4.836	<0.001
ΔTG	86	-6.053	0.495	0.245	-7.023	-5.082	-12.223	<0.001

**From Random Effects Model.

Table S12.Sensitivity Analysis: Plausible Ranges for Pre- and Post-Treatment Correlations (Random Effects Model/Raw Mean Difference)								
Correlation		Effect size and 95% confidence interval					Test of null (2-Tail)	
	r	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value
ΔTG	0.889*	-8.219	1.700	2.888	-11.55	-4.888	-4.836	<0.001
	0.5	-7.860	1.847	3.410	-11.48	-4.241	-4.257	<0.001
	0.75	-8.102	1.780	3.167	-11.59	-4.614	-4.533	<0.001
	0.99	-8.194	1.479	2.189	-11.09	-5.294	-5.538	<0.001

*Correlation calculated via the *CORREL* function in Microsoft Excel 2010 (Microsoft Corp., 2010), using the 86 comparisons ("studies") from the meta-analytic database. The correlation (r) between pre- and post-treatments was required for the calculation of the treatment effect variance (V_D): [$V_D = S^2{}_{diff}/n$; $S_{diff} = (\sqrt{S_{Pre}}^2 + S_{Post}{}^2 - 2 \times r \times S_{Pre} \times S_{Post})$].

Sensitivity Analysis (One Study Removed):Macronutrient Distribution & Change in TG

Studyname	Statistics with studyremoved						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hjerkinn 2005	-7.789	1.606	2.579	-10.937	-4.642	-4.850	0.000
Kawashima 2008B	-8.204	1.719	2.953	-11.572	-4.835	-4.774	0.000
Kawashima 2008A	-8.229	1.722	2.965	-11.604	-4.854	-4.779	0.000
Dodin 2005B	-8.357	1.727	2.983	-11.742	-4.972	-4.839	0.000
Esposito 2004A	-8.083	1.719	2.954	-11.452	-4.715	-4.703	0.000
Esposito 2004B	-8.363	1.732	2.999	-11.757	-4.969	-4.829	0.000
Dodin 2005A	-8.388	1.732	3.001	-11.784	-4.993	-4.842	0.000
Gardner 2007B	-8.006	1.707	2.914	-11.351	-4.660	-4.690	0.000
Gardner 2007C	-8.098	1.715	2.941	-11.459	-4.737	-4.722	0.000
Gardner 2007A	-7.614	1.652	2.731	-10.853	-4.375	-4.608	0.000
Gardner 2007D	-8.474	1.708	2.917	-11.821	-5.127	-4.962	0.000
Tighe 2010B	-8.297	1.731	2.997	-11.690	-4.904	-4.793	0.000
Tighe 2010C	-8.440	1.715	2.941	-11.801	-5.079	-4.922	0.000
Tighe 2010A	-8.287	1.720	2.959	-11.658	-4.916	-4.818	0.000
Fakhrzadeh 2010	-8.596	1.697	2.881	-11.922	-5.269	-5.064	0.000
Esposito 2004	-8.070	1.714	2.939	-11.430	-4.710	-4.707	0.000
Smith 2008A	-8.320	1.719	2.955	-11.689	-4.951	-4.840	0.000
Smith 2008B	-8.498	1.700	2.890	-11.830	-5.166	-4.999	0.000
Kasai 2003A	-8.268	1.725	2.977	-11.649	-4.886	-4.792	0.000
Kasai 2003B	-8.206	1.724	2.973	-11.585	-4.826	-4.759	0.000
Price 2010B	-8.151	1.713	2.934	-11.508	-4.794	-4.759	0.000
Price 2010A	-8.324	1.709	2.920	-11.673	-4.975	-4.872	0.000
Tonstad 2002B	-8.203	1.718	2.952	-11.571	-4.836	-4.775	0.000
Malpuech-Brugere 2010A	-8.405	1.722	2.965	-11.780	-5.031	-4.881	0.000
Malpuech-Brugere 2010C	-8.389	1.720	2.960	-11.761	-5.017	-4.876	0.000
Polagruto 2006B	-8.381	1.718	2.952	-11.749	-5.013	-4.878	0.000
Malpuech-Brugere 2010B	-8.215	1.719	2.954	-11.584	-4.847	-4.780	0.000
Tonstad 2002A	-8.143	1.726	2.979	-11.526	-4.760	-4.718	0.000
Polagruto 2006A	-8.085	1.713	2.933	-11.442	-4.729	-4.721	0.000
Tonstad 2002C	-8.120	1.715	2.941	-11.482	-4.759	-4.735	0.000
Mensink 2002A	-8.350	1.721	2.963	-11.724	-4.977	-4.851	0.000
Mensink 2002B	-8.320	1.728	2.987	-11.707	-4.933	-4.814	0.000
Szapary 2003	-8.435	1.711	2.926	-11.787	-5.082	-4.931	0.000
Maki 2005A	-8.147	1.715	2.941	-11.508	-4.786	-4.751	0.000
Tonstad 2002D	-8.249	1.717	2.949	-11.615	-4.883	-4.804	0.000
Levin 1990	-8.343	1.726	2.979	-11.726	-4.960	-4.834	0.000
Maki 2005B	-7.806	1.691	2.859	-11.120	-4.492	-4.616	0.000
Hollis 2009B	-8.530	1.703	2.899	-11.867	-5.193	-5.010	0.000
Smith 2003A	-8.360	1.731	2.995	-11.752	-4.968	-4.831	0.000
Hollis 2009A	-8.486	1.707	2.913	-11.831	-5.141	-4.972	0.000
Hollis 2009C	-8.558	1.699	2.885	-11.887	-5.229	-5.038	0.000
Gylling 2010B	-8.458	1.710	2.924	-11.810	-5.107	-4.947	0.000
Gylling 2010A	-8.405	1.711	2.928	-11.758	-5.051	-4.911	0.000
Smith 2003B	-8.461	1.709	2.920	-11.811	-5.112	-4.951	0.000
Tanumihardjo 2009B	-8.041	1.708	2.918	-11.390	-4.693	-4.707	0.000
Stendell-Hollis 2010A	-8.184	1.704	2.903	-11.523	-4.844	-4.803	0.000
Schwab 2002B	-8.214	1.713	2.933	-11.571	-4.857	-4.796	0.000
Melanson 2004	-7.890	1.699	2.887	-11.220	-4.560	-4.643	0.000
Schwab 2006A	-8.356	1.706	2.911	-11.700	-5.012	-4.897	0.000
Schwab 2006B	-8.489	1.706	2.911	-11.834	-5.145	-4.975	0.000
Schwab 2006C	-8.268	1.705	2.908	-11.610	-4.925	-4.848	0.000
Tanumihardjo 2009A	-8.386	1.710	2.924	-11.737	-5.034	-4.904	0.000
Schwab 2002A	-8.214	1.715	2.942	-11.576	-4.852	-4.789	0.000
Tapsell 2004A	-8.265	1.714	2.936	-11.624	-4.907	-4.824	0.000
Han 2007A	-8.178	1.705	2.908	-11.520	-4.836	-4.796	0.000
Han 2007B	-8.352	1.707	2.915	-11.699	-5.006	-4.892	0.000
Assuncao 2009A	-8.326	1.712	2.932	-11.682	-4.970	-4.862	0.000
Assuncao 2009B	-8.371	1.709	2.922	-11.722	-5.021	-4.898	0.000
Tapsell 2004B	-8.101	1.711	2.927	-11.454	-4.748	-4.735	0.000
Diaz 2008B	-8.303	1.711	2.926	-11.656	-4.950	-4.854	0.000
Alhassan 2006	-8.058	1.709	2.922	-11.408	-4.707	-4.714	0.000
Kelley 2007A	-7.807	1.693	2.866	-11.125	-4.489	-4.612	0.000
Kelley 2007B	-8.101	1.709	2.919	-11.450	-4.752	-4.741	0.000
Wardlaw 1991B	-8.154	1.712	2.930	-11.509	-4.799	-4.764	0.000
Tapsell 2004C	-8.111	1.711	2.928	-11.465	-4.757	-4.740	0.000
Diaz 2008A	-8.001	1.706	2.911	-11.345	-4.657	-4.689	0.000
Beavers 2010A	-8.331	1.711	2.926	-11.684	-4.978	-4.870	0.000
Beavers 2010B	-8.293	1.711	2.926	-11.646	-4.941	-4.849	0.000
Stendell-Hollis 2010B	-8.121	1.710	2.924	-11.472	-4.769	-4.749	0.000
Wardlaw 1991A	-8.193	1.713	2.936	-11.551	-4.835	-4.782	0.000
Pins 2006A	-8.253	1.714	2.939	-11.613	-4.893	-4.814	0.000
Pins 2006B	-8.193	1.713	2.934	-11.550	-4.836	-4.783	0.000
Wood 2007B	-7.771	1.690	2.856	-11.083	-4.458	-4.598	0.000
Mutungi 2008A	-7.817	1.693	2.867	-11.135	-4.498	-4.617	0.000
Goyens 2006B	-8.126	1.713	2.935	-11.484	-4.768	-4.743	0.000
Wood 2007A	-7.775	1.675	2.804	-11.057	-4.493	-4.643	0.000
Chan 2002A	-8.219	1.701	2.894	-11.553	-4.884	-4.831	0.000
Goyens 2006A	-8.280	1.716	2.943	-11.643	-4.918	-4.826	0.000
Mutungi 2008B	-7.859	1.697	2.879	-11.185	-4.533	-4.631	0.000
Kasim-Karakas 2009B	-8.396	1.759	3.094	-11.843	-4.949	-4.773	0.000
Chan 2002B	-7.994	1.701	2.895	-11.328	-4.659	-4.698	0.000
Adler 1997	-8.312	1.715	2.941	-11.673	-4.951	-4.847	0.000
Santo 2008B	-8.412	1.709	2.921	-11.762	-5.062	-4.922	0.000
Kasim-Karakas 2009A	-7.827	1.643	2.700	-11.048	-4.607	-4.764	0.000
Santo 2008C	-8.312	1.707	2.914	-11.658	-4.966	-4.869	0.000
Santo 2008A	-8.226	1.710	2.924	-11.578	-4.875	-4.811	0.000
	-8.219	1.700	2.888	-11.550	-4.888	-4.836	0.000

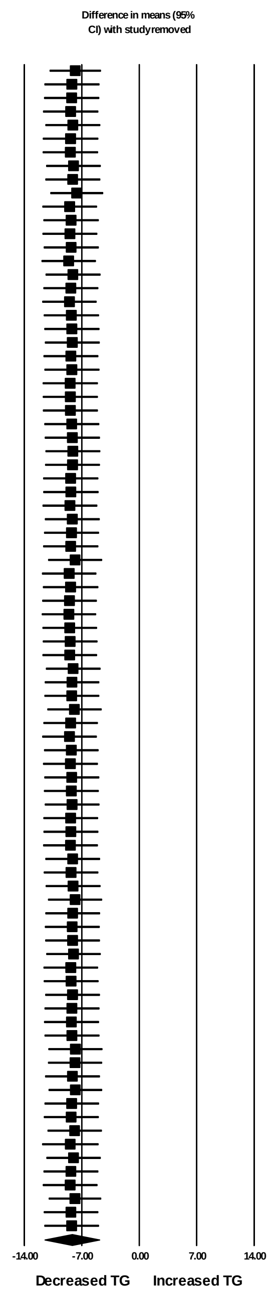


Figure S24. Sensitivity Analysis (One Study Removed): Macronutrient Distribution & Change in Triglycerides.

Table S13. Subgroup Comparisons for Macronutrient Distribution and Change in Total Cholesterol (mg/dL).

Summary Effects (Mixed Effects Analysis/Raw Mean Difference)						
Effect size and 95% confidence interval						
Subgroup	Comparisons	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit
Macronutrient Distribution (Full Set)	86	-6.401	1.231	1.515	-8.813	-3.988
∆ Total Fat:	Heterogeneity: p(Q = 5.259, df = 2) = 0.072					
Decreased Fat	9	-14.844	4.186	17.526	-23.049	-6.638
Fixed Fat	68	-5.657	1.256	1.577	-8.119	-3.196
Increased Fat	9	-3.671	2.739	7.504	-9.040	1.698
Overall Fat	86	-5.972	1.101	1.213	-8.131	-3.814
∆ Total Protein:	Heterogeneity: p(Q = 0.821, df = 1) = 0.072					
Fixed Protein	73	-5.745	1.182	1.397	-8.062	-3.429
Increased Protein	13	-9.790	4.306	18.538	-18.229	-1.352
Overall Protein	86	-6.029	1.140	1.299	-8.262	-3.795
∆ Total Carb:	Heterogeneity: p(Q = 3.565, df = 2) = 0.168					
Decreased Carb	11	-8.517	5.548	30.785	-19.391	2.358
Fixed Carb	65	-5.184	1.220	1.489	-7.576	-2.792
Increased Carb	10	-11.987	3.508	12.310	-18.863	-5.110
Overall Carb	86	-6.025	1.129	1.274	-8.237	-3.813
Distribution:	Heterogeneity: p(Q = 9.230, df = 5) = 0.100					
AMDR	57	-5.843	1.345	1.808	-8.478	-3.207
HF/MP/LC	10	-7.610	2.612	6.820	-12.728	-2.491
HF/MP/MC	13	-3.876	3.077	9.466	-9.906	2.154
*MF/LP/LC	1	-15.470	3.863	14.927	-23.042	-7.898
*MF/MP/HC	1	-1.930	9.136	83.465	-19.836	15.976
*MF/MP/LC	4	-19.147	7.964	63.425	-34.756	-3.538
Overall Distr.	86	-6.797	1.054	1.111	-8.863	-4.731

*Insufficient data to make a reliable comparison.

Definitions & Abbreviations:

Decreased: < -3.4%, Fixed -3.4% to 3.4%, Increased: >+3.4%

AMDR: Acceptable Macronutrient Distribution Ranges, HF: High-Fat, MP: Moderate-Protein, LC: Low-Carbohydrate, MF: Moderate-Fat, HC: High-Carbohydrate, LC: Low-Carbohydrate, HC: High-Carbohydrate, MC: Moderate-Carbohydrate.

Low < AMDR (Moderate) < High

Table S14. Quantifying the Difference Between Various Macronutrient Subgroups on Change in Total Cholesterol (mg/dL).				
	Comparing		The True Difference Between the Two Compared Subgroups Probably Falls Within This Range (95% Confidence Interval):	
	Subgroup A	Subgroup B	Lower Limit	Upper Limit
1	Decreased Fat	Fixed Fat	0.6204	17.754
2	Decreased Fat	Increased Fat	1.367	20.979
3	Fixed Fat	Increased Fat	-3.920	7.892
4	Fixed Protein	Increased Protein	-12.796	4.706
5	Decreased Carbohydrate	Fixed Carbohydrate	-7.802	14.468
6	Decreased Carbohydrate	Increased Carbohydrate	-16.337	9.397
7	Fixed Carbohydrate	Increased Carbohydrate	-14.084	0.478
8	AMDR	HF/MP/LC	-7.524	3.990
9	AMDR	HF/MP/MC	-4.614	8.548
10	HF/MP/LC	HF/MP/MC	-4.176	11.644

Table S15. Subgroups for Macronutrient Distribution and Change in LDL Cholesterol (mg/dL).						
Summary Effects (Mixed Effects Analysis/Raw Mean Difference)						
Effect size and 95% confidence interval						
Subgroup	Comparisons	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit
Macronutrient Distribution (Full Set)	86	-5.317	1.093	1.195	-7.460	-3.175
∆ Total Fat:	Heterogeneity: p(Q = 19.968 , df = 2) = <0.001					
Decreased Fat	9	-13.019	1.851	3.426	-16.646	-9.391
Fixed Fat	68	-5.065	1.218	1.483	-7.452	-2.678
Increased Fat	9	1.195	3.093	9.565	-4.866	7.257
Overall Fat	86	-6.622	0.966	0.934	-8.516	-4.728
∆ Total Protein:	Heterogeneity: p(Q = 0.033 , df = 1) = 0.856					
Fixed Protein	73	-5.388	1.168	1.363	-7.676	-3.099
Increased Protein	13	-4.759	3.261	10.633	-11.150	1.632
Overall Protein	86	-5.316	1.099	1.208	-7.471	-3.162
∆ Total Carb:	Heterogeneity: p(Q = 4.248, df = 2) = 0.120					
Decreased Carb	11	-2.413	4.684	21.943	-11.595	6.768
Fixed Carb	65	-4.886	1.187	1.409	-7.213	-2.559
Increased Carb	10	-10.652	2.731	7.456	-16.004	-5.301
Overall Carb	86	-5.629	1.060	1.125	-7.707	-3.550
Distribution:	Heterogeneity: p(Q = 8.693, df = 5) = 0.122					
AMDR	57	-5.969	1.312	1.720	-8.539	-3.398
HF/MP/LC	10	-2.067	3.531	12.465	-8.987	4.853
HF/MP/MC	13	-2.425	2.894	8.377	-8.098	3.247
*MF/LP/LC	1	-9.290	4.118	16.958	-17.361	-1.219
*MF/MP/HC	1	5.030	5.742	32.973	-6.224	16.284
*MF/MP/LC	4	-13.806	5.453	29.735	-24.494	-3.119
Overall Distr.	86	-5.294	1.052	1.106	-7.355	-3.232

*Insufficient data to make a reliable comparison.
Definitions & Abbreviations:
Decreased: < -3.4%, Fixed -3.4% to 3.4%, Increased: >+3.4%
AMDR: Acceptable Macronutrient Distribution Ranges, HF: High-Fat, MP: Moderate-Protein, LC: Low-Carbohydrate, MF: Moderate-Fat, HC: High-Carbohydrate, LC: Low-Carbohydrate, HC: High-Carbohydrate, MC: Moderate-Carbohydrate.
Low < AMDR (Moderate) < High

Table S16. Quantifying the Difference Between Various Macronutrient Subgroups on Change in LDL Cholesterol (mg/dL).				
	Comparing		The True Difference Between the Two Compared Subgroups Probably Falls Within This Range (95% Confidence Interval):	
	Subgroup A	Subgroup B	Lower Limit	Upper Limit
1	Decreased Fat	Fixed Fat	3.611372408	12.29662759
2	Decreased Fat	Increased Fat	7.149566151	21.27843385
3	Fixed Fat	Increased Fat	-0.254752244	12.77475224
4	Fixed Protein	Increased Protein	-6.159507465	7.417507465
5	Decreased Carbohydrate	Fixed Carbohydrate	-11.9444858	6.998485797
6	Decreased Carbohydrate	Increased Carbohydrate	-18.86628556	2.388285561
7	Fixed Carbohydrate	Increased Carbohydrate	-11.60173337	0.069733373
8	AMDR	HF/MP/LC	-3.479943917	11.28394392
9	AMDR	HF/MP/MC	-2.68405228	9.77205228
10	HF/MP/LC	HF/MP/MC	-9.305995709	8.589995709

Table S17. Subgroups for Macronutrient Distribution and Change in H DL Cholesterol (mg/dL).

Summary Effects (Mixed Effects Analysis/Raw Mean Difference)						
Effect size and 95% confidence interval						
Subgroup	# Comparison Groups	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit
Macronutrient Distribution (Full Set)	86	1.137	0.380	0.144	0.393	1.881
∆ Total Fat:	Heterogeneity: p(Q = 7.364, df = 2) = 0.025					
Decreased Fat	9	-0.841	1.076	1.158	-2.950	1.269
Fixed Fat	68	1.097	0.392	0.154	0.329	1.865
Increased Fat	9	3.651	1.258	1.582	1.186	6.116
Overall Fat	86	1.090	0.353	0.125	0.397	1.783
∆ Total Protein:	Heterogeneity: p(Q = 1.151, df = 1) = 0.283					
Fixed Protein	73	0.975	0.380	0.144	0.231	1.720
Increased Protein	13	2.345	1.219	1.486	-0.044	4.734
Overall Protein	86	1.097	0.363	0.132	0.386	1.808
∆ Total Carb:	Heterogeneity: p(Q = 6.120, df = 2) = 0.047					
Decreased Carb	11	0.920	1.184	1.401	-1.400	3.239
Fixed Carb	65	1.462	0.410	0.168	0.659	2.265
Increased Carb	10	-0.818	0.826	0.682	-2.438	0.801
Overall Carb	86	1.004	0.351	0.123	0.316	1.691
Distribution:	Heterogeneity: p(Q = 4.745, df = 5) = 0.448					
AMDR	57	1.350	0.465	0.217	0.438	2.262
HF/MP/LC	10	1.865	0.987	0.973	-0.069	3.798
HF/MP/MC	13	0.187	0.582	0.339	-0.955	1.328
*MF/LP/LC	1	0.390	1.297	1.681	-2.151	2.931
*MF/MP/HC	1	-1.930	3.517	12.370	-8.823	4.963
*MF/MP/LC	4	-0.317	1.638	2.684	-3.528	2.893
Overall Distr.	86	0.898	0.322	0.104	0.267	1.529

*Insufficient data to make a reliable comparison.

Definitions & Abbreviations:

Decreased: < -3.4%, Fixed -3.4% to 3.4%, Increased: >+3.4%

AMDR: Acceptable Macronutrient Distribution Ranges, HF: High-Fat, MP: Moderate-Protein, LC: Low-Carbohydrate, MF: Moderate-Fat, HC: High-Carbohydrate, LC: Low-Carbohydrate, HC: High-Carbohydrate, MC: Moderate-Carbohydrate.

Low < AMDR (Moderate) < High

Table S18. Quantifying the Difference Between Various Macronutrient Subgroups on Change in HDL Cholesterol (mg/dL).				
	Comparing		The True Difference Between the Two Compared Subgroups Probably Falls Within This Range (95% Confidence Interval):	
	Subgroup A	Subgroup B	Lower Limit	Upper Limit
1	Decreased Fat	Fixed Fat	-0.307034343	4.183034343
2	Decreased Fat	Increased Fat	1.24762271	7.73637729
3	Fixed Fat	Increased Fat	-0.028444114	5.136444114
4	Fixed Protein	Increased Protein	-1.132360486	3.872360486
5	Decreased Carbohydrate	Fixed Carbohydrate	-1.913090711	2.997090711
6	Decreased Carbohydrate	Increased Carbohydrate	-4.566789989	1.090789989
7	Fixed Carbohydrate	Increased Carbohydrate	-4.087030714	-0.472969286
8	AMDR	HF/MP/LC	-1.623107574	2.653107574
9	AMDR	HF/MP/MC	-2.624481988	0.298481988
10	HF/MP/LC	HF/MP/MC	-3.923034343	0.567034343

Table S19. Subgroups for Macronutrient Distribution and Change in Triglycerides (mg/dL).

Summary Effects (Mixed Effects Analysis/Raw Mean Difference)

Effect size and 95% confidence interval

Subgroup	Comparisons	Summary Effect	Standard Error	Variance	Lower Limit	Upper Limit
Macronutrient Distribution (Full Set)	86	-8.219	1.700	2.888	-11.550	-4.888
∆ Total Fat:	Heterogeneity: p(Q = 9.644, df = 2) = 0.008					
Decreased Fat	9	-7.315	8.137	66.212	-23.263	8.633
Fixed Fat	68	-5.579	1.603	2.571	-8.721	-2.436
Increased Fat	9	-28.602	7.241	52.430	-42.794	-14.410
Overall Fat	86	-6.678	1.537	2.363	-9.691	-3.665
∆ Total Protein:	Heterogeneity: p(Q = 28.346, df = 1) = <0.001					
Fixed Protein	73	-4.534	1.552	2.408	-7.576	-1.493
Increased Protein	13	-29.215	4.368	19.082	-37.777	-20.654
Overall Protein	86	-7.300	1.462	2.138	-10.166	-4.434
∆ Total Carb:	Heterogeneity: p(Q = 22.906, df = 2) = <0.001					
Decreased Carb	11	-30.504	5.225	27.300	-40.745	-20.263
Fixed Carb	65	-5.382	1.721	2.960	-8.754	-2.010
Increased Carb	10	-2.076	3.679	13.535	-9.287	5.134
Overall Carb	86	-6.890	1.494	2.231	-9.817	-3.963
Distribution:	Heterogeneity: p(Q = 38.293, df = 5) = <0.001					
AMDR	57	-4.495	1.826	3.334	-8.074	-0.917
HF/MP/LC	10	-31.234	6.359	40.440	-43.698	-18.770
HF/MP/MC	13	-1.033	2.805	7.867	-6.530	4.465
*MF/LP/LC	1	-44.290	16.495	272.082	-76.619	-11.961
*MF/MP/HC	1	-27.460	7.946	63.136	-43.034	-11.886
*MF/MP/LC	4	-21.154	5.966	35.598	-32.848	-9.460
Overall Distr.	86	-6.896	1.415	2.003	-9.670	-4.123

*Insufficient data to make a reliable comparison.

Definitions & Abbreviations:

Decreased: < -3.4%, Fixed -3.4% to 3.4%, Increased: >+3.4%

AMDR: Acceptable Macronutrient Distribution Ranges, HF: High-Fat, MP: Moderate-Protein, LC: Low-Carbohydrate, MF: Moderate-Fat, HC: High-Carbohydrate, LC: Low-Carbohydrate, HC: High-Carbohydrate, MC: Moderate-Carbohydrate.

Low < AMDR (Moderate) < High

Table S20. Quantifying the Difference Between Various Macronutrient Subgroups on Change in Triglycerides (mg/dL).				
	Comparing		The True Difference Between the Two Compared Subgroups Probably Falls Within This Range (95% Confidence Interval):	
	Subgroup A	Subgroup B	Lower Limit	Upper Limit
1	Decreased Fat	Fixed Fat	-14.51936136	17.99136136
2	Decreased Fat	Increased Fat	-42.63589007	0.06189007
3	Fixed Fat	Increased Fat	-37.55888118	-8.487118823
4	Fixed Protein	Increased Protein	-33.76703236	-15.59496764
5	Decreased Carbohydrate	Fixed Carbohydrate	14.34021833	35.90378167
6	Decreased Carbohydrate	Increased Carbohydrate	15.90315525	40.95284475
7	Fixed Carbohydrate	Increased Carbohydrate	-4.654351249	11.26635125
8	AMDR	HF/MP/LC	-39.70673683	-13.77126317
9	AMDR	HF/MP/MC	-3.097707433	10.02170743
10	HF/MP/LC	HF/MP/MC	16.57836548	43.82363452

Figure S25. Bubble Plot Macronutrient Distribution and Change in LDL, moderated by Pre-treatment levels of LDL (mg/dL). (Mixed Effects Regression/Method of Moments)

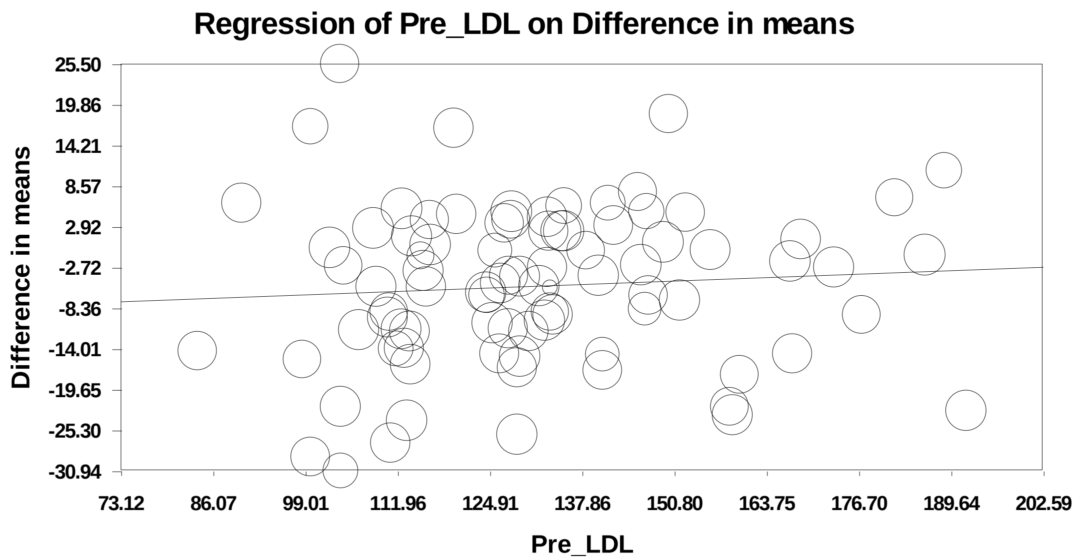


Figure S26. Bubble Plot Macronutrient Distribution and Change in HDL, Moderated by Study Duration. (Mixed Effects Regression/Method of Moments)

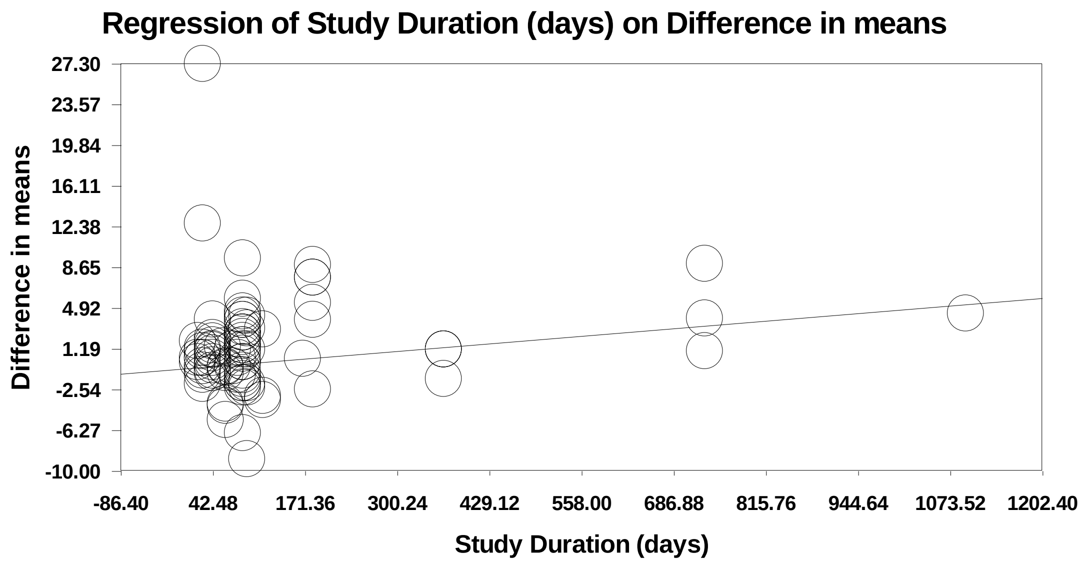


Figure S27. Bubble Plot for Macronutrient Distribution and Change in Triglycerides, Moderated by Pre-Treatment Triglycerides.

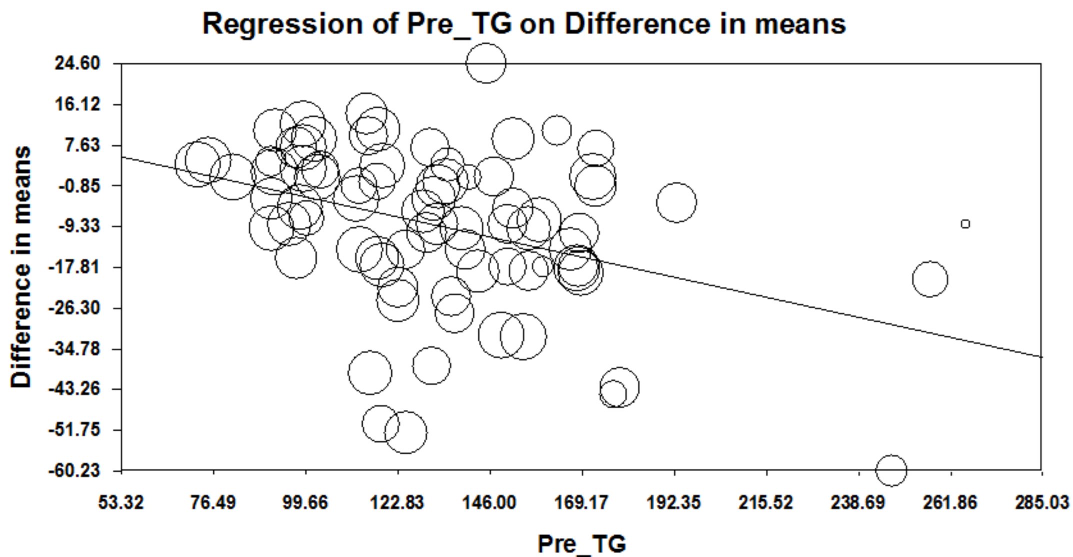
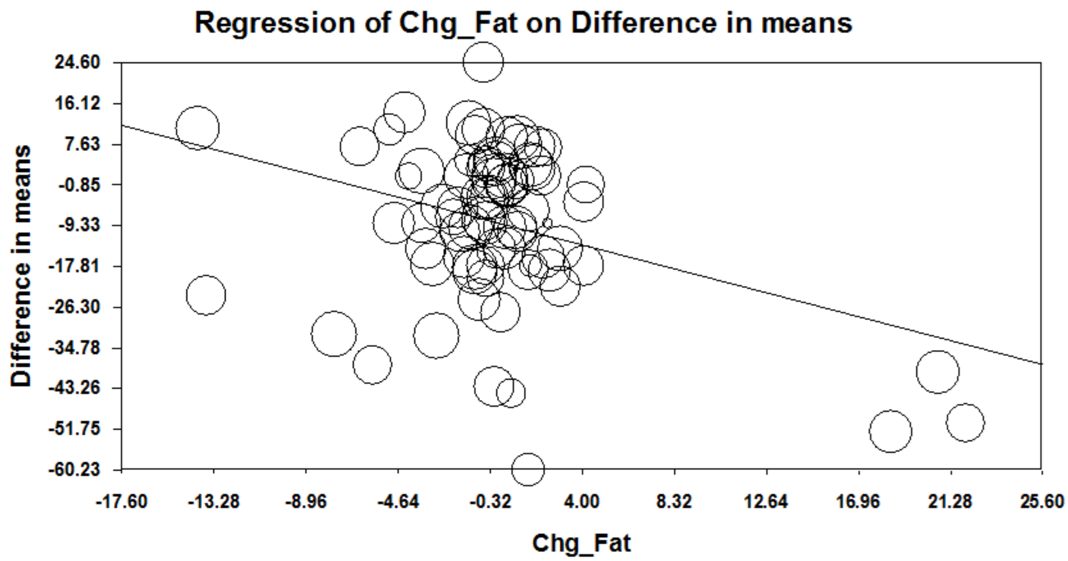


Figure S28. Bubble Plot Macronutrient Distribution and Change in Triglycerides, Moderated by the Percent Change in Total Fat. (Mixed Effects Regression/Method of Moments)



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