Author’s response to reviews

Title: Efficacy of Aerobic Exercise and a Prudent Diet for Improving Selected Lipids and Lipoproteins in Adults: A Meta-Analysis of Randomized Controlled Trials

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Author’s response to reviews: see over
Responses to Reviewer 1 Comments (Dr. Williams)

Thank you for taking the time to review and strengthen this manuscript. In order to make it easier for you to review, we’ve copied your comments below in boldface, with our responses after them without the boldface. Changes in the revised manuscript appear in red font.

**Major Compulsory Revisions**

* I am pleased to see these analyses, but in my opinion the manuscript is too long (maybe this doesn’t matter too much because it’s online only). It contains endless details about how the small number of studies differed from each other, but it never explains why any of this is important. This information may be better suited for supplementary information.

Response – While we agree that the manuscript is long, we felt it was acceptable to present this information given the online format of the journal, something you have appropriately noted. In addition, it is our experience with meta-analysis that the information we omit from the body of the manuscript is the very information that one or more reviewers would like us to include. For example, despite the detailed information provided, Reviewer 3 is requesting *more* detail. Furthermore, in meta-analysis, we believe that the inclusion of this level of detail is important so as to provide direction for future research. This is especially true given that this is a meta-analysis versus a traditional randomized controlled trial.

*There are in fact three separate interventions: prudent diet, physical activity, and weight loss by calorie restriction. There is much work on exercise as an independent intervention, dietary fat reduction as an independent intervention, and weight loss as an independent intervention. It would seem that the relevant question is to provide some quantitative assessment of the effect of combining these interventions over their separate effects. There is not much quantitative discussion of this.

Response - We agree that an examination of the independent effects of exercise, dietary fat reduction, and weight loss on lipids and lipoproteins is important. However, as described in the Introduction section of our manuscript, that was not our research question for this meta-analysis. Our research question and subsequent inclusion criteria were based on the general recommendations currently proposed for improving lipids and lipoproteins in adults. In addition, addressing these independent effects quantitatively would result in us having to change our research question and redo the entire meta-analysis, a 2-3 year effort. The former notwithstanding, we think your comment is important. Therefore, we include a short paragraph in the Discussion section suggesting this as a potential area for future meta-analytic research (please see paragraph 3 on page 24).

* The Stanford studies may be the only ones sufficiently long enough for exercise
to have an effect on HDL-cholesterol. HDL may not have increased because: 1) exercise studies in women have not been as successful in achieving HDL-C increases than in men; 2) the studies were not long enough. The heterogeneity in designs makes it difficult to conclude HDL does not increase, although it is reasonable that it didn’t given the percent fat decreased.

Response – Nice observations here. Based on your comments and while cognizant of the small sample size, we went back and pooled the results for the two Stanford studies and analyzed the data separately for men and women. Using a random-effects model that incorporates both within and between-study heterogeneity into the analysis, non-significant changes in HDL-C were found for both women and men (women: mean change = 0.5 mg/dl, 95% confidence interval = -4.2 to 5.2 mg/dl, p = 0.84; men: mean change = 4.0 mg/dl, 95% confidence interval = -2.6 to 10.7 mg/dl, p = 0.23). While there was a larger increase in HDL-C in men versus women, you can see that there were no statistically significant within or between-group differences. Please note that we’re not saying that a difference does not exist, but rather, that we didn’t find one in this meta-analysis. We provide this information here but have not added it to the revised manuscript.

* The analyses treat the study differences as a random effects model, yet these are not identically sampled studies, rather they differ from each other as fixed effects; i.e.: male vs. female, weight loss vs. non-weight loss, selection for low HDL-C. So then what is the purpose of the meta-analyses? What is gained? Are the authors claiming that these finding represent the expected effects regardless of the differences between studies?

Response – In meta-analysis, fixed-effects models assume that all studies share the same common treatment effect while random-effects models incorporate between-study heterogeneity into the model, yielding a mean of a distribution of effects. Thus, when studies are gathered from the published literature, the random-effects model is the more plausible and currently recommended approach, allowing one the possibility to reach general conclusions regarding expected effects while controlling for within and between study heterogeneity. As examples, please see the applied discussion of this issue in Chapter 13, “Fixed-effect Versus Random-Effects Models” from the following: Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to Meta-Analysis. West Sussex: John Wiley & Sons, 2009. For a more technical discussion, please see Hunter JE, Schmidt FL. Fixed effects vs. random effects meta-analysis models: implications for cumulative research knowledge. Int J Sel Assess 2000;8:275-292.

The overall purpose of meta-analysis, applicable to this study, is to reach general conclusions regarding a body of research. As Gene Glass, the person who coined the term meta-analysis back in the 1970’s clearly pointed out: “The claim that only studies which are the same in all respects can be compared is self-contradictory; there is no need to compare them since they would obviously have the same findings within statistical error. The only studies which need to be synthesized or integrated are different studies” (from pages 22 and 23 of Glass GV, McGaw B, Smith ML. Meta-
Are the authors really arguing that the HDL and triglyceride response in men reported by Wood et al can be ignored? That pooling is in anyway superior that this individual result.

Response – While one might single out an individual study, the overall purpose of meta-analysis is to reach general conclusions based on the pooling of studies and not necessarily focus on one specific study unless it impacts the overall findings. As the seminal work of Sacks et al. pointed out some time ago, the specific purposes of meta-analysis are to “(1) increase statistical power for primary endpoints and for subgroups, (2) resolve uncertainty when studies disagree, (3) improve estimates of effect size, and (4) answer questions not posed at the start of individual trials” (see: Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analysis of randomized controlled trials. *N Engl J Med* 1987;316:450-455). One possible way to view meta-analysis is from a population health perspective. For example, and as you know, it is traditionally stated that aerobic exercise increases peak oxygen consumption in adults. However, as clearly illustrated in Figure G2.4 of the 2008 Physical Activity Guidelines Advisory Committee Report, this does not occur in every single person.

Some mention should be given to the fact that one of the studies specifically selected subjects with low HDL-cholesterol and persons with low HDL-C are known to respond less to exercise than those with high HDL-C.

Response – As suggested, we now include this information. However, as stated in our original manuscript, we also conducted influence analysis with each study and/or group deleted from the model once in order to see if it changed our overall findings. None did, including the deletion of the Stefanick et al. study. Regardless, we now include information specific to your comment on page 20, paragraph 1, lines 5-9.

To summarize, whereas most of the papers needs to be considerably shortened, the discussion needs to deal with the much harder question as to whether the basis of meta-analyses is justified for studies if such diverse samples and intervention, and what contribution does the meta-analyses make.

Response – Thank you for summarizing. We have previously addressed your comments above.

Minor Revisions

Page 16; “For in ml.kg-1.min-1, statistically significant…. I assume this is referring to VO2max, missing something

Response – Thank you for noticing this. You’re correct. This information was included in our original manuscript but was omitted when the document was converted from Word to pdf format. Regardless, it’s our responsibility for proofreading to make sure the pdf
copy is an exact match with our original Word document. We’ve double-checked and this information is now included in our pdf copy and hopefully everyone else’s also. Please see Tables 2 and 3 on pages 37 and 39 for these additions.
Responses to Reviewer 2 Comments (Dr. Mittendorfer)

Thank you for the taking the time to review and strengthen this manuscript as well as the positive feedback. In order to make it easier for you to review, we’ve copied your comments below in boldface, with our responses after them without the boldface. Changes in the revised manuscript appear in red font.

*This is a solid paper. A very strong study design and thorough data analysis and a clear message. It is amazing that there really are only 6 studies of the high quality required to be included in this report (the inclusion criteria are strict but no stricter than necessary). This alone is worth reporting.

Response - Thank you. Your positive comments are greatly appreciated.

* The authors could have increased the scope of the work by looking not only at exercise plus diet but also exercise alone as they say this needs to be done but I can see why they didn't do it. Along the same lines it seems that it may be important to consider exercise duration and intensity .... but with an n=6, obviously this is impossible.

Response – Thank you for realizing why we couldn’t increase the scope of our work, including an examination of duration and intensity of training.

* The authors may want to consider being a bit more specific right away regarding the "prudent" diet. I found it somewhat distracting to not find out until half-way into the manuscript what is meant by prudent diet. It is not a term usually used to describe the kind of dietary recommendations followed by the subjects under investigation.

Response – Good suggestion. We now define this at first mention in the Introduction as well as some clarification of references 4-19. Please see page 4, paragraph 2, lines 1-7.

* Page 3. No data for non-HDL-C? I am a bit confused here because the authors do provide data on LDL-C and total C in addition to HDL-C.

Response – Good observation. We weren’t specific enough here. As you know, non-HDL-C can easily be calculated from TC and HDL-C. However, the issue was that we didn’t have the necessary variance data for non-HDL-C, something we need when conducting an aggregate data meta-analysis. While the corresponding author is currently working on a possible method for estimating variance statistics for non-HDL-C by pooling variance data from TC and HDL-C, he did not feel it was ready for release yet. Ideally, it would have been nice if the authors of the original studies had reported mean non-HDL-C levels, including their variance statistics. Based on your suggestion, we now provide a more specific reason for not including non-HDL-C. Please see the abstract on page 3, lines 3 and 4, as well as page 15, paragraph 2, lines 4 and 5 for this clarification.
* In the abstract and elsewhere, the authors should refer to lipid CONCENTRATIONS since this is what they looked at.

Response – Thank you for pointing this out. It appears that we were operating at the basal ganglia level on this one. We’ve now added the term “concentrations” 38 times throughout the abstract and manuscript.

* Page 4, last paragraph. If refs 4-19 were randomized controlled trials on this topic, why weren't all of them included in the analysis?

Response – Good question. While the 16 studies may have used some type of diet aimed at improving lipid and lipoprotein concentrations in adult humans, they did not meet our strict inclusion criteria. Based on your previous comment regarding clarifying a prudent diet earlier in the manuscript as well as this comment, we’ve revised the Introduction so that this is clearer. Please see page 4, paragraph 2, lines 1-7.

* Figure 1. Reasons for elimination after full-text review. Why would one reject a paper due to information in the abstract, when the full paper is available?

Response – What we mean here is that we were able to judge that the study would not meet our inclusion criteria based on the information provided in the title and abstract. For example, if it was clear from the title and abstract that it was an observational study and not a randomized controlled trial, then there would be no need to further inspect and retrieve the full study from a study inclusion perspective (waste of time and resources). If one cannot discern from the title and abstract whether or not a study meets one’s inclusion criteria, then the full article is retrieved for review. This is a common and recommended procedure when screening studies for potential inclusion in a systematic review with or without meta-analysis. Please see: Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65-W94; Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions (version 5.0.2). The Cochrane Collaboration 2009 available online at http://www.cochrane-handbook.org/
Thank you for taking the time to review the statistical aspects of this meta-analysis. In order to make it easier for you to review, we’ve copied your comments below in **boldface**, with our responses after them without the boldface. Changes in the revised manuscript appear in **red font**.

* My overall impression is that this work is a thorough traditional meta-analysis that uses 1. the DerSimonian and Laird [32] random effects model to combine study results. (see 2nd par, page 8) and 2. a 'simple, random effects meta-regression (method of moments approach)' to test for dependence of effects on covariates. see top of page 9). No reference is given to this 'simple' approach, although the authors later state that they carried out all meta-analytic analyses using Comprehensive Meta-Analysis, version 2.2 [41]. When I searched the WEB for details, I found a package and a picture of experts who created the package, but no scholarly references or description of the methods used. I therefore assume they are using the traditional weighted regression with inverse variance weights. Since it is a random effects meta-regression I presume they are also estimating a variance component. If the authors know more about the methodology used in this package I would like to see it. My concern is that these traditional meta-analytic methods have not really been subjected very much to rigorous statistical analysis or even simulations. The fact that they are widely used is no reason to believe that they are reliable. For example, see the Statistics in Medicine paper by Brockwell and Gordon (2001). They show that even for large sample sizes the DerSimonian and Laird methodology intervals do not achieve desired coverage for the odds-ratio. The reason is the use of estimated inverse variance weights which include estimates of the variance component. See also Hardy and Thompson (1996), Statistics in Medicine, for a critique of the traditional approach. Also, Mallow, Prendergast and Staudte about to appear in the Electronic Journal of Statistics, an Institute of Mathematical Statistics journal, that shows large bias when using the inverse variance weights approach in meta-regression. Thus I was hoping to compare the presumably traditional approach results of this paper with those obtained by more modern methods involving stable weights (Kulinskaya,Morgenthaler and Staudte, Wiley 2008), to see if there is much difference. However, while the authors supply the differences in means in their forest plots, they do not supply the pooled estimates of the assumed common variance in control and treatment groups. On the second half of page 7, the authors do calculate these basic statistics, but for some reason do not make them available. Thus if someone, even a reviewer like myself, wants to replicate their results, he has to start from scratch. Why not make it easier for the reader? I would like to see references to the literature where the methods of the package Comprehensive Meta-Analysis are described, since they do not seem to be described in the package or the WEBsite or this manuscript. The authors might also be interested in the Multivariate Meta-regression methodology of Lidia J. Arends and her coauthors. Sorry I cannot be more positive about the manuscript, which appears to have been a careful and substantial effort.
Response – It appears that your main concern is that we have used “traditional” meta-analytic methods that you believe have not been subjected to much rigorous analysis. Consequently, you suggest more “modern” methods might be superior. We address this issue in the information that follows. In the spirit of full-disclosure, we will let you know that we consulted with two other experts in meta-analysis, Dr. Michael Borenstein and Dr. Larry Hedges, regarding your comments.

The corresponding author of this manuscript, an NIH-R01 funded Principal Investigator with a specific focus on applied meta-analysis, is keenly aware of the peer-reviewed work of Brockwell and Gordon, both of which appear to be employed at your institution, Hardy and Thompson and Arends et al. We were not aware of the textbook that you co-authored (the corresponding author just ordered this on February 21, 2011) and obviously not the other co-authored article you state is “about to appear” in the Electronic Journal of Statistics. With respect to newly proposed models, we would also direct you to the varying coefficient model recently proposed by Bonett as well as the quality effects model of Doi et al.

As a point of information, the corresponding author is aware of 7 general models for pooling the results of an aggregate data meta-analysis: (1) fixed effects, (2) Dersimonian and Laird random-effects, (3) random-effects maximum likelihood, (4) random-effects restricted maximum likelihood, (5) random-effects profile likelihood, (6) random-effects permutation, (7) varying coefficient.

There are several reasons that we did not use one or more of the methods that you referred to as well as some of the others listed above. First, the approach we used is indeed widely accepted. Second, we believe it would be imprudent to over-react to newly proposed models. Third, it is our experience that many of the alternatives proposed as a means of dealing with specific problems in meta-analysis have turned out to have problems of their own, often with substantially worse impact than the problems they were intended to solve. Fourth, it is our experience that the usually minor differences in results from the use of different random-effects approaches for meta-analysis often have little effect on the “big picture”, something that we believe is practically relevant. For example, using the random-effects profile likelihood method for our total cholesterol (TC) data in Figure 3, the pooled treatment effect was -15.3 mg/dl (95% CI, -19.9 to -11.1 mg/dl) as opposed to our originally reported results of -15.5 mg/dl (95% CI, -20.3 to -10.7 mg/dl). From our perspective, these differences are trivial with respect to real world application. Furthermore, there is no guarantee that the results from the profile likelihood method, or any other method, are superior to those from the traditional random-effects approaches we used.

In addition to the issues you’ve alluded to, others have raised questions about almost every aspect of meta-analysis. In time, most of the “traditional” statistics used in meta-analysis are likely to be revised, but for now we believe the “traditional” ones that we’ve used for this project are the best available and as you know, are widely accepted as such.
Based on your suggestions, we now include a reference that describes all the methods used in the Comprehensive Meta-Analysis software package that we used, including the meta-regression analysis (please see reference 39, cited in the text on page 9, paragraph 2, line 4 as well as page 9, paragraph 3, line 3). In addition, we’ve included additional data for each outcome, from each group, from each study (See Supplement File 13). Furthermore, we briefly discuss our rationale for using the more traditional models we employed. Please see paragraph 2 on page 24.

References in Response to Reviewer 3 Comments
