Author's response to reviews

Title: New insights into the health effects of dietary saturated and omega-6 and omega-3 polyunsaturated fatty acids

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Author's response to reviews: see over
Dear Claire Tree-Booker,

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Please find enclosed our revised manuscript as well as our answers to the reviewers (below). We do not have problems to answer as the comments were quite kind. Both reviewers were asking more discussion and details for the field in which they are specialists: myocardial preconditioning in one side and breast cancer on the other side. Of course it was not the aim of that (mini)review at fully discussing each issue. We tried however to satisfy the reviewers by either adding information and references, in particular about oleic acid (ref 44 to 49) and about two clinical trials (ref 33 and 34), or by attenuating certain of our sentences. We hope the revised manuscript satisfying for publication.

Best regards

Michel de Lorgeril

ANSWERS TO THE REVIEWERS

REVIEWER 1

1- “The authors reviewed animal and epidemiological data regarding the association between dietary saturated fatty acids (SFA), omega-6 polyunsaturated (PUFA) and omega-3 PUFA and health outcomes, particularly cardiovascular diseases and cancer risks. They concluded that the optimal dietary fat pattern recommended reducing the risk of both cardiovascular diseases and most cancers should contain a low intake of SFA and omega-6 PUFA along with a moderate intake of omega-3 PUFA, which is characteristic of the Mediterranean diet model but far to be consumed at present in many populations. This (mini)review is succinct, well-written, and well presented. The references are relevant and updated.”

Thank you very much for the excellent summary and kind comments.

2- “I have some major comments: regarding the association with (breast) cancer risk, the authors reviewed data mostly on omega-6 PUFA. I would suggest review also data on the association between saturated fatty acids, omega-3 fatty acids, monounsaturated fatty acids
(cis and trans) and cancer risk, fatty acids which are all mentioned in the “introduction” section.

This is a very important issue. However, when we have been invited to write that (mini)review about dietary fats and health, it was specified that we should focus that short text on recent and important findings. We were not asked to make a full or systematic review on any specific health aspects and the relations with dietary fats. We identified 3 really “new” research issues which could be considered (in our opinion) as potential major advances in medical research: myocardial protection (preconditioning) by specific fatty acid profile, the relations between (omega-6) polyunsaturated fatty acids and breast cancer and the effects of polyphenols on the endogenous synthesis of very long-chain omega-3 fatty acids. Importantly, we tried to discuss the three issues in relation with the concept of Mediterranean diet.

Having said that, we agree that it would be important to also discuss the possible roles of other fatty acids on cancers; but it would take 20 additional pages or more if we really want to fully discuss each issue. Systematic review or meta-analysis is not the appropriate approach, in our opinion, because of the huge medical heterogeneity of the various reports. However, to please the referee, we have added a short paragraph about oleic acid (a major dietary fatty acid in the Mediterranean diet) in the revised manuscript (see below). We also have added two references (and a short paragraph) regarding randomized trials testing in humans the effects of dietary fats, in particular omega-6. Both provide, in our opinion, critical information about the effects of dietary fats on cancers.

3- “In the “summary and prospects” section, the authors indicated that “regarding the intake of monounsaturated fatty acids…, it is critical to differentiate their food sources, since the health effects of oleic acid obtained from meat of from olive oil are obviously different. I would move (and develop) this sentence to the appropriate section (CVD and/or cancer) and add some references. Some recent studies reported an increased risk of cancer (including breast cancer) associated with increasing blood levels of oleic acid, a major fatty acid of the Mediterranean diet. The authors might add and comment these data in their review.”

This is again a very important issue.

As said above, we have added a paragraph about oleic acid, the main fatty acid of olive oil (which is the main oil traditionally used by the Mediterranean people) in the section “dietary fat and cancer”.

4- “Minor comments: - In the “dietary fat and cancer” section, the obesity status has been shown to affect the association between omega-3 long-chain PUFA and breast cancer risk, and not the association with omega-6 PUFA (reference 28).”

Thank you very much. The revised manuscript has been modified accordingly.

5- “- In the following sentence: “at the same time, omega-3 PUFA were shown to have chemopreventive properties against various cancers, including colon and breast cancer risk (references 33 and 34): for breast cancer, an association has been reported between omega-3 fatty acids and reduced risk of some breast cancer events after diagnosis and all cause mortality, and not with breast cancer risk.”

Thank you very much. The revised manuscript has been modified accordingly.
1- “Major Compulsory Revisions. 1. Whilst the two cited animal studies (ref 19,20) demonstrate the benefits of omega-3 PUFA over saturated fatty acids and omega-6 PUFA (and this has been demonstrated previously), they cannot be interpreted to advocate the reduction in either SFA or omega-6 PUFA but merely show the adverse effects of inadequate omega-3 PUFA intake. It is too bold to state (Page 3 end of para2): “These data should close the controversy regarding the optimal dietary fatty acid profile to reduce the complications of CVD.”

We agree that our sentence was too bold and had to be “attenuated”. In the revised manuscript, we now write: “These data should help identifying the optimal dietary fatty acid profile to reduce the risk and the complications of CVD”

We however disagree regarding the two other points raised by the referee: 1) the fact that the superiority “of omega-3 has been demonstrated in previous studies”; 2) the way of interpreting these two studies which, according to the referee, “merely show the adverse effects of inadequate omega-3 PUFA intake”. It would be too long in a (mini)review – aimed at raising new major findings in the field of dietary fats – to fully discuss the two issues. Actually, most previous studies were questionable in many aspects and we still say that ref 19 and 20 provide new major information which was not available in previous studies.

Regarding the second point (and briefly), the intake of omega-3 was not low (not inadequate) in the SFA and omega-6 groups in the study by Zeghichi-Hamri (ref 20); and the intake of omega-6 and SFA was not low (not inadequate) in the omega-3 group. It can be concluded that the observed protection resulted from interactions between the different series of fatty acids and not solely from an adequate intake in omega-3. We – as any author of (mini)review – cannot detail each cited study. We here propose a simple synthesis of the available data; and we still say that ref 19 and 20 allow us to draw such a conclusion. However, readers will have the opportunity to react and to say their own opinion. The main aim of such a non exhaustive (mini)review is to raise new questions and provoke the reactions of the readers.

2- “Thus, maintaining high (or increasing) the intake of omega-6 – as still recently proposed [6,8,9] – in lieu of SFAs is definitely not the optimal strategy to prevent CVD complications”

Those references (6,8,9) do not advocate increasing omega-6 PUFA diets per se.

In fact, Mozaffarian writes in the Conclusions of his Abstract (ref 6): “These findings provide evidence that … a shift toward greater PUFA consumption in place of SFA would significantly reduce rates of CHD”. And in the conclusion of his article: “This suggests that current recommendations for an upper limit of PUFA consumption at 10% energy need to be revisited”. Thus, Mozaffarian clearly advocate increasing intake of omega-6.

3- Rather they provide evidence (far more than is presented here in the form of meta-analysis of randomized controlled trials and other large studies), that intakes of 5-10% energy as omega-6 PUFA are cardioprotective relative to lower intakes (also demonstrated in animal studies) and reducing omega-6 PUFA intake provides no advantage”

As discussed in our Introduction, the published controlled trials and meta-analyses present major bias and flaws which have been honestly discussed in ref 3 and 4. We thus maintain
that “the validity of meta-analyses of clinical trials showing that CVD can be prevented by replacing SFAs with polyunsaturated fatty acids (PUFAs) ... omitted relevant trials with unfavorable outcomes (publication bias) and included others that were poorly designed (no randomization).”

4- “Inadequate evidence is provided in this mini-review to reject omega-6 PUFA compared to saturated fat for CVD protection.”

We agree that our previous Introduction could be misinterpreted and we have done some changes in the revised manuscript. The end of our Introduction is now: “the interpretation of epidemiological data ... is very difficult and explains the ceaseless controversy about dietary fats and the risk of CVD. However, recent studies in experimental nutrition using the concept of myocardial preconditioning ...”

5- “The review should concentrate on the beneficial effects of correcting omega-3 PUFA deficiency in the diet (for which there is strong evidence) rather than advocating large reductions in omega-6 PUFA. (see point 3 below)”

We did not wish making a new review on omega-3 and we do not advocate large reductions in omega-6. We say that the only strong evidence to decrease the risk of CVD is to adopt a Mediterranean diet, and this dietary model is low in omega-6 and moderately high in plant and marine omega-3. We try to show that reasoning in terms of series of fatty acids is confusing and, as physicians and nutritionist aimed at protecting our patients, that it is much better to advocate the adoption a specific dietary pattern.

6- “The potential cancer associations of high omega-6 PUFA intakes is a stronger argument than adverse CVD effects and this is where the emphasis should be if advocating reduced omega-6 intake”

Thank you very much for that advice. The manuscript has been revised accordingly.

7- “Discretionary Revisions. 1. The authors introduce myocardial preconditioning, as a way of looking at the cardioprotective actions of omega-3 PUFA, highlighting “nutritional preconditioning” as first proposed in ref 19 being similar to the well established concept of “ischaemic preconditioning” (as first identified in ref 14). In this “mini-review” it would be helpful if some mechanism could be proposed or alluded to. For example, ischaemic preconditioning involves a paradoxical protection induced by imposition of small non-damaging ischaemia that prevents the expected damage caused by more severe ischaemia. Is there likely to be a similar paradoxical effect of omega-3 PUFA?”

Sorry, nutritional preconditioning was not proposed as first in ref 19, but already in 2004 in the JMCC (36:561-6) by Guiraud et al [Cardioprotective effect of chronic low dose ethanol drinking: insights into the concept of ethanol preconditioning]. Another form of chronic nutritional preconditioning (with polyphenols) was proposed by Toufekstian et al in 2008 (ref 18).

Sorry, we do not wish discussing “mechanisms” in that (mini)review. Rather, we wish introducing the critical idea that “although they were obtained in experimental conditions, data regarding chronic myocardial preconditioning as induced by lifestyle and nutrition are highly consistent with our general clinical knowledge regarding the effects of lifestyle and nutrition on CVD” as written at the end of first paragraph of the section on myocardial preconditioning.
8- “The “controversy” (with respect to CVD) is more about the relevance of omega-3: omega-6 PUFA dietary ratio, and the references cited (and others not cited) demonstrate that the benefits of omega-3 PUFA can only be achieved by increasing omega-3 intake and not by reducing the omega-6 intake. Maybe the authors could include some discussion of this controversy?

As discussed above and in our (revised) manuscript, the main aim of that (mini)review was to identify some major new items about dietary fats, not discussing again whether omega-3 are useful or not with respect to prevention of CVD.