NOTES on our Response to Reviewer 3.

We address the comments one by one further below. Overall there was nothing of substance and nothing new in the Reviewer 3 comments. Finally, the comments had no impact on the content of our manuscript.

We could recommend that the reviewer attempts a pair of manuscripts on the topic of low-carbohydrate diets. It would not be appropriate for the reviewer to simply advertise his opinion, for that is all that has been provided, on the back of our more sincere efforts to address the science behind GI and GL before delivering our own conclusions.

The reviewer may find some quotes on the topic helpful in readjusting their viewpoint:

“We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears to be slight.” — Bradford Hill 1965.

“In asking for very strong evidence I would, however, repeat emphatically that this does not imply crossing every 't', and swords with every critic, before we act." — Bradford Hill 1965.

“The committee adapted the Hill (7) criteria for causality to interpret the diverse nutritional literature, qualitatively judging whether the totality of evidence pointed to an association that was strong, showed a dose-response relation, was temporally correct, was consistently observed, was specific, and had biologic plausibility”. — Expert group of nutritional epidemiologists on the role of nutritional epidemiology in the development of dietary recommendations for the public (Byres at al, 1999)

Below:

Black script with clear background are the reviewer’s comments
Black script with black background (as though redacted) are the reviewer’s opinions and unsupported material.
Blue script with clear background are first author comments (no co-authors recommend that changes be made on account of the reviewer’s comments.
Red script: is our prior response to the reviewer round 1 comments

This MS addresses the role of dietary glycemic index and glycemic load (GI/GL) and the association with risk of T2D and the extent to which causality can be inferred. The approach is to interpret the authors’ recent meta-analyses and related work in the literature with respect to adherence to Bradford-Hill’s criteria. The conclusion is that “all nine of the Hill’s criteria were met for GI and GL
indicating that we can be confident of a role for GI and GL as causal factors contributing to incident T2D.

I have previously submitted some comments which the authors have answered in part. The MS is largely on opinion and conclusions [1. untrue], rather than real data. [1. Objection: We refer to meta-analyses, not just those in Part 1 but also those in the wider literature]. In addition, the major limitations of GI/GL are underplayed ignoring the effect of total carbohydrate effect [3. This is because the concern is for lower GI and GL diets not low carbohydrate diets. It may be of interest that several of the current co-authors attended a debate on low carbohydrate diets use in diabetes therapy at DNSG 2019 - only approx.15% vote were in favour of low carbohydrate diets]. which is the major alternative to GI/GL and of which GL is a subset. [4. We firmly disagree; it is possible to elevate GL by choosing high GI carbohydrate and lower GL by choosing lower GI carbohydrate; GL is therefore not a subset of low carbohydrate and was never intended to be.] As suggested previously, the issues should receive the open discussion they deserve. [5. This is another subject and merits independent attention. The reviewer, however, may find in due course that low-carbohydrate diets haven’t yet made the breakthrough imaginable following the Diabetes Care paper from ADA and may not do so unless low GI and GL, eventually becomes understood and applied therein. Thus restriction of high GI carbohydrate is important, not simply the restriction of all carbohydrate. Low GI carbohydrate sources contributes important nutrients other than carbohydrate] [6. ‘Nutrients’ has already handled the issue of low carbohydrate diets in last few months to a year- nothing new has emerged from the reviewer in our correspondences.

My objections

Hill’s Major criterion is violated.

Hill was very clear that his criteria did not represent cut-and-dried rules but rather followed from common sense and experience. Hill’s first criterion was the magnitude of the association and this is seen in the context of the data. I reiterated in my previous comments the oft-quoted values of an RR of 20 for smoking and lung cancer or 30 for heavy smoking and the general idea that an RR of 2 was a kind of default value assuming reasonable error in the independent variable. In response to my original comment, the authors answers were:

7. Thank you for placing your point of view. The point was not ignored in our prior comments in pointing out the significant literature already in the manuscript (3 papers). We add here that there is
ample literature to show that this reviewer’s perspective is not accepted in nutritional epidemiology or among participants on dietary guideline committees. It would have been useful for the reviewer to not have selectively reported form the literature as noted further below***.

The question is why not? Many researchers cannot understand how the multitude of nutritional epidemiology papers can be published with HR in the range of 1.3 to 1.5 or even as low as 1.12, especially given that most, have, in fact, universally accepted high error in food consumed based on FFQ. The authors provide 2 references by Byers. An excerpt from one of these:

***-The Committee on Diet and Health of the National Research… adapted the Hill (7) criteria for causality to interpret the diverse nutritional literature, qualitatively judging whether the totality of evidence pointed to an association that was strong, showed a dose-response relation,… [missing text?] Even the committee recognized, however, that these criteria are of limited use in nutritional epidemiology. Not all meaningful associations are expected to be strong (hence a set of studies will not necessarily show either a dose-response relation or consistency), nutritional factors are not specific because they may affect several diseases similarly, and biologic plausibility is a product of the state of knowledge at any given time and subjective imagination.


8. We regret the reviewers selective reporting of the content of Byres 1999 AJCN 69(suppl) 1304S-8S (a reference we supplied). This reference stated: “The committee adapted the Hill (7) criteria for causality to interpret the diverse nutritional literature, qualitatively judging whether the totality of evidence pointed to an association that was strong, showed a dose-response relation, was temporally correct, was consistently observed, was specific, and had biologic plausibility”. The reviewer was simply misleading by select text that was meant to placate anyone with the reviewers point of view and was not provided simply to agree with anyone with the reviewers point of view.

There is adherence to Hill’s criteria or not? The conclusion is that nutritional epidemiology can ignore Hill’s criteria without suggesting alternatives. Clearly Hill’s criteria are not ignored by us or by Byres et al. rather Hill’s criteria are built upon to place the ideas of Hill into use in the nutrition context, both by us and by Byes on behalf of a group of expert epidemiologist.

A wide range of nutrients, foods and diets (33) have relative risks that all with the range 0.62 to 1.32. [1] [our prior response]
GL/GI is not reliable