Dietary carbohydrate intake and mortality: reflections and reactions

In their Article in *The Lancet Public Health* (September 2018), Sara Seidelmann and colleagues[1] use data from a long-term prospective cohort study and do a meta-analysis of other related cohorts to assess the association between carbohydrate intake and mortality. Our main problem with this Article[1] was regarding the confounders that are related to an individual's consumption of carbohydrates and to that individual's associated mortality. Some of these confounders were included as control variables, but since it is impossible to account for all possible confounders, some confounders necessarily went unobserved. This problem is illustrated in the figure.

In any observational study, unobserved confounders prevent the identification of a causal relationship between carbohydrate intake and the risk of associated mortality. In this context, any statistical association between these two variables cannot be argued to be causal, no matter the level of statistical significance.

What could be an unobserved confounder? One example could be whether individuals tended to have highly variable bodyweight due to extreme diets (ie, diets that are too low or too high in carbohydrate intake), which was not observed in this study. Such variability in bodyweight is associated with an increased risk of diabetes and increased cardiometabolic risk factors.[3,4] Without a variable that measured whether a respondent dieted in this way (and there is no indication that Seidelmann and colleagues controlled for this confounder), the estimated association between carbohydrate consumption and related mortality could be biased. Hence, instead of concluding that diets that are either too low or too high in carbohydrates cause a higher risk of associated mortality, in fact, bodyweight variability due to extreme diets would be responsible.

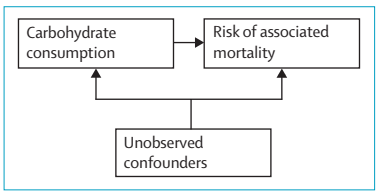

Figure: **A directed acyclic graph showing the identification problem**
Carbohydrate consumption is presumed to increase the risk of associated mortality and unobserved confounders are presumed to cause both.[2] That unobserved confounders are associated with both carbohydrate consumption and associated mortality is an example of the identification problem that almost always plagues empirical research done with non-experimental data: that correlation is not causation.

Some of our concerns could be easily assuaged with the inclusion of more information about the analysis, including the regression results for the Atherosclerosis Risk in Communities study itself instead of merely presenting only the adjusted odds ratios of interest and one figure. Additionally, robustness checks on the results could be presented, including falsification tests.[5]

With the increase in computing power, decreasing costs of data storage, and increased use of big data in the health sciences,[6] we would have expected additional analyses to support the findings.

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Dietary carbohydrate intake and mortality: reflections and reactions

I read Sara Seidelmann and colleagues study[1] with interest, and there are several shortcomings that deserve attention. Although, the authors appropriately acknowledge the limitations of data collection by questionnaire, in their study, participants were expected to recall their food intake over 25 years, in detail, over two sessions.

Another important issue is that participants in the lowest carbohydrate quintile consumed a daily mean of 1558 kcal, 37% of which was from carbohydrates. This grouping contrasts with the established energy intakes from carbohydrate of the classic ketogenic (in which carbohydrates comprise about 5% of calorie intake) and the modified Atkins diets (about 10%). The food items listed under the plant-based diet also included items that are usually highly restricted in modern low-carbohydrate diets (such as peanut butter, bread, chocolate, and soft drinks).

The authors state that low-carbohydrate diets with "increased animal protein and fat consumption have been hypothesised to stimulate inflammatory pathways, biological ageing, and oxidative stress". On the contrary, emerging evidence[2–4] shows that low-carbohydrate diets do exactly the opposite; these diets are shown to decrease inflammation, reduce oxidative stress, mitigate tumour signalling pathways, delay ageing, and slow down cancer growth and proliferation. Preclinical studies[5] of low glucose availability in cancer suggest that the lifespans of patients with cancer could increase when these people are given low-carbohydrate diets. In at least one study[6] in humans, a low-carbohydrate diet was well tolerated in patients with cancer.

Current low-carbohydrate diets were not correctly represented in the study by Seidelmann and colleagues. Further investigation should be encouraged before making broad claims about possible deleterious effects.

I declare no competing interests.

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Dietary carbohydrate intake and mortality: reflections and reactions

The Article by Sara Seidelmann and colleagues[1] presents the analysis from the Atherosclerosis Risk in Communities study of adults aged 45–64 years over a median duration of 25 years, at six timepoints. The mean caloric intake by each adult was 1558–1655 kcal per day. I have several issues with this study. First, this analysis seems to ignore the fact that, after 25 years, participants are aged 70–89 years, which is older than the 2016 estimate of life expectancy by the US Centers for Disease Control and Prevention: 78·6 years. Second, the study does not stratify carbohydrate consumption by sex and age; these data are only available for the whole study. Third, more than 40% of the test population died during the 25 years. However, this study defined all-cause mortality with the implication that low carbohydrate diets were the only factor to cause early death in older people. There were more smokers and physically inactive participants in the group who had less than 37% of their calories from carbohydrates, both of which are known contributors to a shorter lifespan.[2]

Importantly, in a diet containing 1558 kcal, 37% carbohydrates is equal to 144 g. The US recommended daily allowance for carbohydrates[3] is 130 g, which is lower than the low-carbohydrate diet defined in this research. 1655 kcal is considered to be a starvation diet,[4] which is not feasible for participants to have maintained over 25 years. Also, data collection from memory is riddled with errors[5] and cannot be used to establish causality.

Importantly, Seidelmann and colleagues did not update the carbohydrate exposures of participants that developed heart disease, diabetes, and stroke to reduce confounding from changes in diet that could arise from the diagnosis of metabolic diseases, which was the subject of the study. Removing the most important data for research invalidates the findings.

Finally, a time-variable sensitivity analysis was selected from visits 1 and 3, and the cumulative average of carbohydrate intake was used to derive the conclusions of the study. Predicting nutrition consumption over 25 years from two datapoints is not reliable.

I declare no competing interests.

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Dietary carbohydrate intake and mortality: reflections and reactions

There are several problematic issues in the Article by Seidelmann and colleagues.[1] First, the quality of the dietary data is weak, since they are based only on two samples. The food frequency questionnaire that they used appears not to have been independently validated, and it contained only 66 questions and excluded several popular items, such as pizza.[1] Food was clearly underreported, as evidenced by a reported average energy intake of roughly 1500 kcal per day.

Second, their results differ from many rigorous, randomised, controlled clinical trials that, taken together, concluded that carbohydrate restriction can reverse type 2 diabetes and improve most cardiovascular risk factors and that carbohydrate restriction is equal to or superior than any other diet for weight loss.[2–4] The authors need to explain a mechanism by which such improvements in health could ultimately shorten lifespan.

Third, the moderate-carbohydrate diet that Seidelmann and colleagues found to be optimal (at 50–55% of calorie intake) has, in fact, already been tested in clinical trials[5–7] on more than 50 000 people; results of these previous trials showed that this moderate-carbohydrate diet had no benefit in combatting diabetes, obesity, heart disease, or any kind of cancer. Such a moderate-carbohydrate diet was found to cause high-density lipoprotein-cholesterol to decrease and the blood concentration of triglycerides to increase, which are both signs of worsening cardiovascular risk.The authors need to address the disparity between the findings from their observational study and those from the more rigorous clinical trial evidence.

I report that I am the author of a book on this topic, The Big Fat Surprise.

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Dietary carbohydrate intake and mortality: reflections and reactions

Even if the Food Frequency Questionnaire had been robust and accurately reflective of what people had eaten during the whole 25-year study, a mean calorie intake of 1560–1660 kcal per day had been explained, and people had been allocated correctly to groups that reflected their actual carbohydrate consumption after a health diagnosis.

Even if carbohydrates did not mean many different things (from kale to cake), alcohol had been accounted for and adjusted for, and the study had adjusted for the whole diet of participants. Even if the study had managed to overcome the healthy person confounder and had analysed the groups fairly (as set out in the quintiles in the table of baseline characteristics). Even if the study had not benefitted from the small denominator advantage, the life expectancy had been calculated fairly without this substantial small denominator issue, and the reference group had been set at the most robust point of the Food Frequency Questionnaire quintiles (ie, at the extremes instead of the middle).

Even if the subject under examination—an entire macronutrient—were suitable for averaging across already limited Food Frequency Questionnaires, the strength of association had been double, and examination of the Bradford Hill criteria had established that causation might be likely. Even in the presence of all these factors, Seidelmann and colleagues[1] would then merely have had a hypothesis to test in a randomised controlled trial. The purpose of epidemiological studies is to establish associations that should then be tested in randomised controlled trials.

I report income from The Harcombe Diet Co and Columbus Publishing.

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Dietary carbohydrate intake and mortality: reflections and reactions

Authors' reply

We appreciate the interest in our work. We found that in long-term observational studies, low carbohydrate dietary intake (<40% of total energy from carbohydrates) was associated with higher mortality when animal-based fat and protein were substituted for carbohydrate.[1] However, when plant-based sources of fat and protein such as whole grains, legumes, and nuts are incorporated into low carbohydrate diets, they were associated with lower mortality. We fully acknowledge the limitations of observational studies, while recognising the difficulties associated with long-term randomised trials in the area. For example, the large Women's Health Initiative trial was largely uninformative because of poor adherence to the assigned diets as indicated by lack of difference in biomarkers sensitive to dietary fat.[2]

We agree that our findings should be considered within the context of previous work, including both observational data[3,4] and randomised trials,[5] and these strongly support better blood lipid patterns and lower risks of cardiometabolic disease and premature death with consumption of plant-based foods compared with animal-based foods. It is also essential to recognise that our study assessed long-term dietary patterns and outcomes in a predominantly healthy community population; we did not study prescribed diets to treat obesity or specific diseases. We also did not evaluate very-low carbohydrate diets (5–10% of energy) because so few participants in a general population consume such diets: the available evidence on these diets is limited to short-term studies, many of them without a control group.

We provided additional details on regression and quintile results in our Article's appendix.[1] As we noted, the food frequency questionnaire used in the Atherosclerosis Risk in Communities study was designed to capture eating patterns over the course of a year, and a similar questionnaire has been formally validated[6] by comparison with weighed and measured food intake. Although that questionnaire underestimated total energy intake, adjustment of specific nutrients for it provides values with good validity and that have predicted biomarkers of diet and disease risks in hundreds of published studies.

Recall of diet inevitably includes some error; however, bias with respect to the outcome was avoided by the prospective design. We observed no association between carbohydrate intake and change in bodyweight at 3-year and 6-year intervals, as noted in table 1 of our Article,[1] which is similar to the overall results of randomised trials. We adjusted for waist-to-hip ratio with no meaningful difference in the overall association, as did many of the studies included in our Article's meta-analysis. We did not exclude participants with heart disease, diabetes, and stroke from the primary analysis, but this exclusion was performed in the sensitivity analysis provided in the appendix. Finally, we acknowledge the problems of residual confounding, as with any observational data.

In conclusion, we reiterate that it is not enough to focus on carbohydrates alone, but to consider the types of food replacing them. This area is important for further research.

We declare no competing interests.

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