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LETTER TO THE EDITOR

Response to Boonpor et al: Types of diet, obesity, and incident type 2 diabetes: Findings from the UK Biobank prospective cohort study

The article by Boonpor et al,[1] recently published in *Diabetes Obesity and Metabolism*, highlights the interesting finding that, among participants enrolled in the UK Biobank, those with different diets have different total energy intake. The authors then proceed to use a counterfactual mediation analysis to show that the differences in energy intake inherent to these diets may affect body mass index (BMI), thus mediating any associations between diet and diabetes. Mediation analysis, especially of dietary exposures and BMI, requires special considerations that future investigators should take into account and that we believe deserve further discussion.

A number of previous studies have assessed a potential mediating role of BMI (or weight change, as the modelling implies that a change in diet would cause a change in weight) with regards to diet and disease using observational data.[2-4] It is well known that adjustment for total energy intake in these analyses implies an isocaloric comparison between diets, that is, the average relative causal effect of the exposure.[5] Studies can also consider the effect of increasing intake of some foods or macronutrients on top of the usual diet, that is, the total causal effect.

In this work, Boonpor et al hypothesize that weight change may mediate associations between different types of diet and diabetes partly due to the differences in energy intake resulting from each diet. To estimate this effect, they (correctly) did not adjust for total energy intake, as is commonly done in nutritional epidemiology to adjust for confounding, using total energy intake as a proxy. In effect, this means that the effect estimated in their main model is the effect of energy from this diet, plus any independent effect from the dietary composition itself (ie, potential harmful effects on diabetes from nitrites in processed meat).

On the other hand, some previous studies have assessed the mediating role of weight change using total energy intake-adjusted estimates for foods or dietary variables (for example[2-4]). As the energy-adjusted estimate implies an isocaloric comparison of foods or diet compositions at that time point, it is unclear how changes in weight would be achieved under this model. Randomized controlled trials have largely shown that dietary composition does not strongly affect weight loss when interventions of similar caloric restriction are used.[6,7] In these situations, it is possible that if weight change is a mediator in the causal pathway, this is due to other mechanisms affecting future energy expenditure or intake and that are also related to diet, that is, later changes in physical activity or lifestyle. These potential mechanisms should be specified. For example, a small trial by Hall et al[8] found that a large isocaloric change in carbohydrate foods to fat-based foods was accompanied by a marginal increase in energy expenditure (but small enough that it was deemed unlikely to strongly affect weight loss).

Another problem when considering unclear mediation pathways is that it becomes more difficult to identify confounders and makes it harder to rule out unmeasured confounding that can bias the estimate. Unmeasured confounders may make it seem as if mediation is occurring despite no plausible explanation. For example, prior habitual physical activity levels or dieting habits could have an effect on both food choices and weight change. The use of graphical models, such as directed-acyclic graphs, is recommended in this setting[9] as they allow specification of the mechanism being assessed and the set of factors that could confound any causal relationship. Figure 1 shows some possible scenarios that consider, for simplicity, intake of some foods of interest and future disease risk, including mediation from weight change via total energy intake (Figure 1A), mediation from weight change via an energy intake-independent mediator such as physical activity (Figure 1B), and a case where energy-independent mediation may be mistakenly inferred from a common unmeasured confounder (Figure 1C).

Additionally, investigators should try to use relevant counterfactual values of exposure and mediator so that the reader can decide if this represents a realistic situation, and whether the mediation analysis was based on appropriate assumptions. Categorical values for diet (eg, meat eater vs. vegetarian) as used in this study may not represent a sufficiently well-defined exposure, and such a drastic change in diet (from meat eater to vegetarian) would involve multiple different food substitutions, each with potentially different relative causal effects. Similarly, depending on the mediator effect estimate being used, mediator values should be chosen based on reasonable assumptions. BMI categorized as obese/nonobese may not represent realistic mediator values as it is unclear if such changes in diet may or may not induce such weight change over this time period.

Finally, it is important to note that, for mediation to occur, the mediator must be temporally separated from the exposure. Since food frequency questionnaires aim to estimate the average intake of foods over the previous year, it can be argued that BMI and diet assessed at the same time point, such as in this study, is acceptable. It may

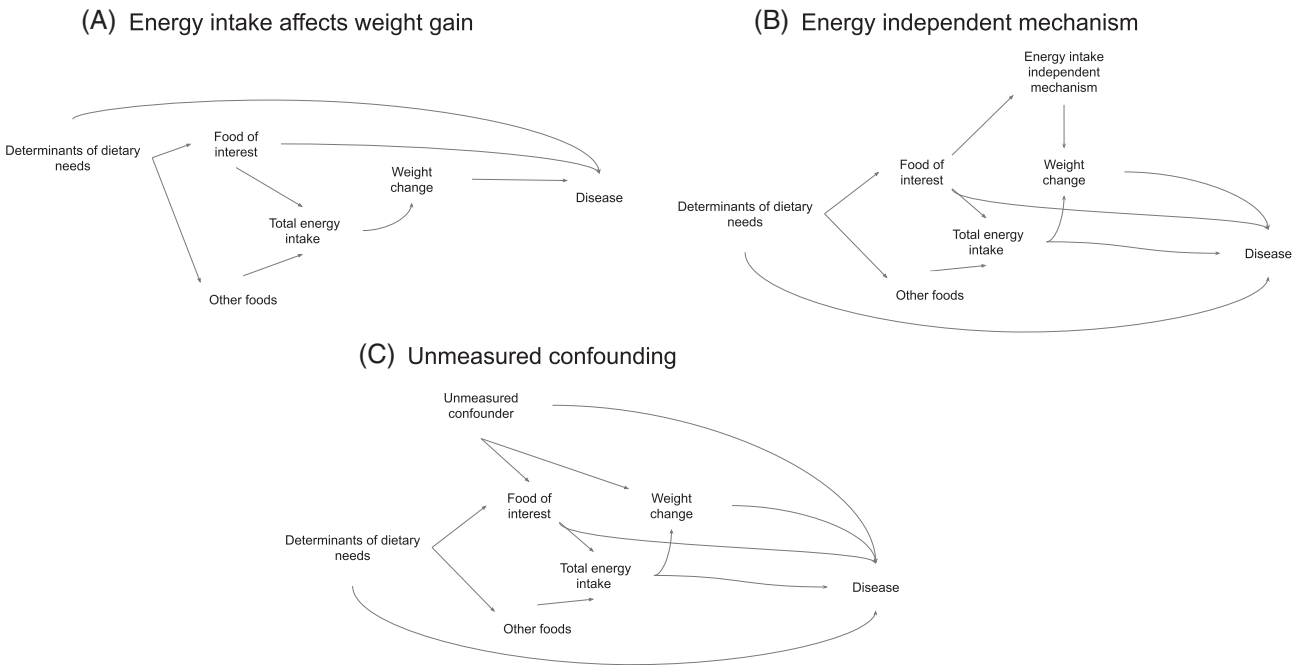

FIGURE 1 Directed acyclic graphs showing potential relationships among diet, weight change and disease. (A) A situation where caloric intake of some food of interest contributes to total energy intake. An increase in this food would potentially increase total energy intake, causing weight change. This weight change could be an intermediate step between the food of interest and disease. There is also hypothesized to be some energy-independent effect of this food on disease risk. (B) A situation where, in addition to an effect from total energy intake on weight change, there is another energy-independent mechanism by which the food affects weight. Since this mediator is independent from total energy intake, there is no arrow from total energy intake. Such a mechanism should be based on a specific hypothesis, such as increased energy expenditure from physical activity. (C) A situation where energy-independent mediation between the food of interest and weight change may be erroneously inferred due to bias from an unmeasured confounder. This unmeasured confounder (ie, previous physical activity) can introduce an association between the food of interest and weight change via a backdoor path that is not closed by controlling for energy intake. Being unable to control for this unmeasured confounder would cause us to believe there is some energy-independent mediation through weight change, even though there is no open path between weight change and the food of interest.

however be more reassuring in the mediation setting to assess BMI a year after dietary assessment if data permit. As Boonpor et al note, BMI is also commonly considered a confounder, being a major determinant of energy intake as well as a major determinant of chronic disease risk. Considering the temporality of the measurement can help clarify the role of BMI.

In conclusion, models used in nutritional epidemiology, especially if considering mediation, should be guided by the hypothesized and well-defined mechanisms. In particular, energy adjustment choices can significantly change the interpretation of the results. Consideration should be given to the temporality of measurements, and authors should be encouraged to state their assumptions and hypotheses using graphical models.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Not applicable.

Conor James MacDonald PhD[1,2]
Pauline Frenoy MSc[1]
Marie-Christine Boutron-Ruault PhD[1]

[1]*Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Gustave Roussy, Équipe "Exposome et Hérédité", CESP, Villejuif, France*
[2]*Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Solna, Sweden*

Correspondence
Conor James MacDonald, Unit of Epidemiology, Intitute of Environmental Medicine, Karolinska Institutet, Solna, Sweden
Email: conor.macdonald@ki.se

ORCID

Conor James MacDonald https://orcid.org/0000-0002-4989-803X

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