FERNANDA MORALES BERSTEIN, CAROLINA BORGES AND DEBORAH LAWLOR, MEDICAL RESEARCH COUNCIL (MRC) INTEGRATIVE EPIDEMIOLOGY UNIT AT UNIVERSITY OF BRISTOL - WRITTEN EVIDENCE (FDO0017)

Written Evidence submitted by Fernanda Morales Berstein, Carolina Borges and Deborah Lawlor from the Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol

About the Institution:

The MRC Integrative Epidemiology Unit (IEU) at the University of Bristol conducts some of the UK's most advanced population health science research. It uses genetics, population data and experimental interventions to look for the underlying causes of chronic disease. The unit exploits the latest advances in genetic and epigenetic technologies. It develops new analytic methods to improve our understanding of how our family background behaviours and genes interact to influence health outcomes.

Call for evidence addressed in this submission:

This submission addresses the call for evidence on the cost and availability of a) **UPF** and b) HFSS foods **and their impact on health outcomes.**

Summary:

- Although there are good reasons to believe ultra-processed food (UPF) consumption is detrimental to human health, it is important to acknowledge the limitations of the current evidence.
- Higher consumption of UPFs has been associated with higher risk of death and certain diseases, but the evidence could, at least in part, be explained by bias.
- Negative controls can be useful tools for the detection of bias in the associations between UPF consumption and the risk of adverse health outcomes.
- Findings of a positive association between UPF consumption and accidental death (a cause of death that we would not expect to be affected by UPF consumption other than via bias) alert us to the fact that the associations between UPF consumption and risk of adverse health outcomes may be biased.

Recommendations:

- Recommendation 1: The associations between UPF consumption and adverse health outcomes reported by numerous studies could be influenced, at least in part, by biases that cannot be fully accounted for in studies that solely rely on conventional multivariable regression analyses. Hence, findings should be interpreted with caution when attempting to infer cause and effect from these studies.
- Recommendation 2: More research is required to inform policy on the implementation of UPF regulation strategies in the UK. Comparing results from different research approaches with distinct key sources of bias such as conventional multivariable regression analyses, target trial emulation and instrumental variable analyses is essential. Furthermore, a greater use of negative control analyses across these could be particularly useful.

Response:

This submission draws on findings from the recently published study "Ultra-processed foods, adiposity and risk of head and neck cancer and oesophageal adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition study: a mediation analysis"[1] (sample size = 450,111 participants).

Current evidence for higher consumption of ultra-processed foods associated with higher risk of death and certain diseases

1. In our recent publication[1], we reaffirmed that a higher consumption of UPFs is associated with a higher risk of both head and neck cancer and oesophageal adenocarcinoma in the European Prospective Investigation into Cancer (EPIC) study. We also found that a higher consumption of UPFs is associated with higher measures of body fatness (specifically, body mass index and waist-to-hip ratio)[1]. These findings are in line with previous EPIC publications on UPF consumption[2] [3] .

[1] F. Morales-Berstein et al., "Ultra-Processed Foods, Adiposity and Risk of Head and Neck Cancer and Oesophageal Adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition Study: A Mediation Analysis," *Eur J Nutr* 63, no. 2 (Mar 2024), https://dx.doi.org/10.1007/s00394-023-03270-1.
[2] Nathalie Kliemann et al., "Food Processing and Cancer Risk in Europe: Results from the Prospective Epic Cohort Study," *The Lancet Planetary Health* 7, no. 3 (2023), https://dx.doi.org/10.1016/s2542-5196(23)00021-9.
[3] R. Cordova et al., "Consumption of Ultra-Processed Foods Associated with Weight Gain and Obesity in Adults: A Multi-National Cohort Study," *Clin Nutr* 40, no. 9 (Sep 2021), https://dx.doi.org/10.1016/j.clnu.2021.08.009.

2. Accumulating evidence suggests that a higher consumption of UPFs is associated with an increased risk of type 2 diabetes, overweight and obesity, mental disorders, cancer, cardiovascular diseases and death[4].

Bias in observational research

3. However, it is important to note that all this evidence comes from conventional multivariable regression analyses in observational studies (i.e., cohort studies, case-control studies, cross sectional studies). Although such research is valuable for the study of long-term adverse health outcomes, it is more prone to biases than experimental research, so should not be interpreted as evidence of a causal effect on its own[5].

Negative control analyses for the detection of bias in observational research

4. An important source of bias in conventional multivariable regression is confounding[6]. In the context of research on the health impacts of UPFs, confounders are factors that simultaneously influence the amount of UPFs consumed and the development of adverse health outcomes such as obesity and cancer (e.g., biological sex, age, socioeconomic position, smoking status, alcohol intake and physical activity). Confounders are often measured with imprecision and sometimes, are not measured at all. When confounders are not fully accounted for, the observed estimates do not reflect true causal estimates.
5. Negative control analyses are a useful sensitivity analysis to explore whether confounding may be affecting an observational study's results after confounder adjustments[7] [8] [9]. As their name suggests, negative control analyses are expected to produce null results. If they produce a similar (non-null) result to the main analysis, one could conclude that

---

[4] M. M. Lane et al., "Ultra-Processed Food Exposure and Adverse Health Outcomes: Umbrella Review of Epidemiological Meta-Analyses," *BMJ* 384 (Feb 28 2024), https://dx.doi.org/10.1136/bmj-2023-077310.
[5] A. Satija et al., "Understanding Nutritional Epidemiology and Its Role in Policy," *Adv Nutr* 6, no. 1 (Jan 2015), https://dx.doi.org/10.3945/an.114.007492.
[6] S. Greenland, and J. M. Robins, "Identifiability, Exchangeability, and Epidemiological Confounding," *Int J Epidemiol* 15, no. 3 (Sep 1986), https://dx.doi.org/10.1093/ije/15.3.413.
[7] M. Lipsitch, E. Tchetgen Tchetgen, and T. Cohen, "Negative Controls: A Tool for Detecting Confounding and Bias in Observational Studies," *Epidemiology* 21, no. 3 (May 2010), https://dx.doi.org/10.1097/EDE.0b013e3181d61eeb.
[8] Z. Fewell, G. Davey Smith, and J. A. Sterne, "The Impact of Residual and Unmeasured Confounding in Epidemiologic Studies: A Simulation Study," *Am J Epidemiol* 166, no. 6 (Sep 15 2007), https://dx.doi.org/10.1093/aje/kwm165.
[9] G. Davey Smith, and A. N. Phillips, "Correlation without a Cause: An Epidemiological Odyssey," *Int J Epidemiol* 49, no. 1 (Feb 1 2020), https://dx.doi.org/10.1093/ije/dyaa016.

confounding or other biases might at least partly explain the main result.

Applied example of a negative control analysis in the context of ultra-processed food consumption research

6. As the EPIC study has data on accidental death (e.g., transport accidents and falls), an adverse outcome that is implausibly related to UPF consumption, we conducted a negative control analysis using accidental death as a negative control outcome. We found that a higher consumption of UPFs is associated with a higher risk of accidental death[1]. This is unlikely to be causal and is rather likely due to confounders we could not account for in our analyses, either because they were not measured or were imprecisely measured in the study.
7. The association between UPF consumption and accidental death may be explained by confounding due to people from lower socioeconomic backgrounds being both more likely to eat UPFs[10] [11] and more likely to be killed in an accident [12] [13] [14] [15] [16] [17].
8. The same confounding by socioeconomic background could be biasing the associations observed between higher consumption of UPFs and risk of head and neck cancer and oesophageal adenocarcinoma in EPIC, at least to some extent. Hence, we should interpret these findings with caution.

---

[10] C. W. Leung et al., "Food Insecurity and Ultra-Processed Food Consumption: The Modifying Role of Participation in the Supplemental Nutrition Assistance Program (Snap)," *Am J Clin Nutr* 116, no. 1 (Jul 6 2022), https://dx.doi.org/10.1093/ajcn/nqac049.

[11] Y. Zhang, and E. L. Giovannucci, "Ultra-Processed Foods and Health: A Comprehensive Review," *Crit Rev Food Sci Nutr* 63, no. 31 (2023), https://dx.doi.org/10.1080/10408398.2022.2084359.

[12] R. Campbell et al., "Multiple Risk Behaviour in Adolescence Is Associated with Substantial Adverse Health and Social Outcomes in Early Adulthood: Findings from a Prospective Birth Cohort Study," *Prev Med* 138 (Sep 2020), https://dx.doi.org/10.1016/j.ypmed.2020.106157.

[13] R. R. Kipping et al., "Multiple Risk Behaviour in Adolescence and Socio-Economic Status: Findings from a Uk Birth Cohort," *Eur J Public Health* 25, no. 1 (Feb 2015), https://dx.doi.org/10.1093/eurpub/cku078.

[14] E. C. Hair et al., "Risky Behaviors in Late Adolescence: Co-Occurrence, Predictors, and Consequences," *J Adolesc Health* 45, no. 3 (Sep 2009), https://dx.doi.org/10.1016/j.jadohealth.2009.02.009.

[15] N. Meader et al., "A Systematic Review on the Clustering and Co-Occurrence of Multiple Risk Behaviours," *BMC Public Health* 16 (Jul 29 2016), https://dx.doi.org/10.1186/s12889-016-3373-6.

[16] D. R. Hale, and R. M. Viner, "The Correlates and Course of Multiple Health Risk Behaviour in Adolescence," *BMC Public Health* 16 (May 31 2016), https://dx.doi.org/10.1186/s12889-016-3120-z.

[17] B. D. Reyes, D. S. Hargreaves, and H. Creese, "Early-Life Maternal Attachment and Risky Health Behaviours in Adolescence: Findings from the United Kingdom Millennium Cohort Study," *BMC Public Health* 21, no. 1 (Nov 8 2021), https://dx.doi.org/10.1186/s12889-021-12141-5.

9. To the best of our knowledge, negative control analyses have not been implemented in UPF consumption studies other than in ours[1].

Strengthening evidence base through triangulation

10. Triangulation is the practice of strengthening causal inference by comparing results obtained using multiple approaches with different sources of bias[18] (e.g., conventional multivariable regression [where the key source of bias could be confounding], instrumental variable analyses[19] [where the key source of bias could be that the instrument is not specific to the risk factor of interest] and target trial emulation[20] [21] [where the key source of bias could be selection bias]).
11. When the different approaches suggest similar findings (as in they all suggest no effect, a protective effect or a detrimental effect), it increases confidence that the effect is causal. It would be unusual for approaches with different biases to give the same answer[18].
12. Conversely, when the different approaches suggest contradictory answers, careful consideration of the biases of each approach (for the particular causal question) can be used to decide what further research is needed[18].
13. A greater use of negative control analyses across different approaches could be particularly useful for the detection of bias.

Conclusion

14. Although there are good reasons to hypothesise UPF consumption is detrimental to human health, we think it is important to acknowledge the limitations of the current evidence. In particular, the associations between UPF consumption and adverse health outcomes reported by numerous studies could be influenced, at least in part, by biases that cannot be easily (or ever) accounted for in conventional multivariable analyses. These findings should be interpreted with caution when attempting to infer cause and effect.

---

[18] D. A. Lawlor, K. Tilling, and G. Davey Smith, "Triangulation in Aetiological Epidemiology," *Int J Epidemiol* 45, no. 6 (Dec 1 2016), https://dx.doi.org/10.1093/ije/dyw314.

[19] M. A. Hernan, and J. M. Robins, "Instruments for Causal Inference: An Epidemiologist's Dream?," *Epidemiology* 17, no. 4 (Jul 2006), https://dx.doi.org/10.1097/01.ede.0000222409.00878.37.

[20] Y. H. Chiu et al., "Estimating the Effect of Nutritional Interventions Using Observational Data: The American Heart Association's 2020 Dietary Goals and Mortality," *Am J Clin Nutr* 114, no. 2 (Aug 2 2021), https://dx.doi.org/10.1093/ajcn/nqab100.

[21] M. A. Hernan, and J. M. Robins, "Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available," *Am J Epidemiol* 183, no. 8 (Apr 15 2016), https://dx.doi.org/10.1093/aje/kwv254.

About the submitting individuals:

Fernanda Morales Berstein is a final year PhD student in Molecular, Genetic and Lifecourse Epidemiology at the University of Bristol. The aim of her PhD is to investigate the associations between ultra-processed food (UPF) consumption, obesity and cancer (specifically, those of the mouth, throat and oesophagus). Fernanda has an MSc in Nutrition for Global Health from the London School of Hygiene and Tropical Medicine and a BSc in Nutrition and Dietetics from the Pontifical Catholic University of Chile.

Carolina Borges is an MRC IEU Programme Lead Track at the University of Bristol. Her research is focussed on improving evidence around mechanisms and treatments for chronic disease and pregnancy complications. Carolina has a BSc and MSc in Nutrition and Public Health (University of Sao Paulo, Brazil) and a PhD in Epidemiology (University of Pelotas, Brazil).

Deborah Lawlor is a Professor of Epidemiology with a clinical background. She is Deputy (currently acting) director of the MRC Integrative Epidemiology Unit. Her research focuses on applying novel causal methods to understanding the causes and consequences of ill-health, mainly in relation to fertility, pregnancy, perinatal and cardiovascular health.

28 March 2024