A Report on "Ultra-processed Food Exposure and Adverse Health Outcomes: Umbrella Review of Epidemiological Meta-analyses" by Lane et al. (2024)

Reviewer 2

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> I am wiser than this person; for it is likely that neither of us knows anything fine and good, but he thinks he knows something when he does not know it, whereas I, just as I do not know, do not think I know, either. I seem, then, to be wiser than him in this small way, at least: that what I do not know, I do not think I know, either.
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> Plato, *The Apology of Socrates*, 21d

> To err is human. All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty. That to err is human means not only that we must constantly struggle against error, but also that, even when we have taken the greatest care, we cannot be completely certain that we have not made a mistake.
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> Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

Citation: Lane, M. M., Gamage, E., Du, S., Ashtree, D. N., McGuinness, A. J., Gauci, S., Baker, P., Lawrence, M., Rebholz, C. M., Srour, B., Touvier, M., Jacka, F. N., O'Neil, A., Segasby, T., and Marx, W. (2024). Ultra-processed Food Exposure and Adverse Health Outcomes: Umbrella Review of Epidemiological Meta-analyses. *BMJ*. Vol. 384, e077310.

Abstract Summary: This umbrella review evaluated existing meta-analytic evidence of associations between ultra-processed food exposure, as defined by the Nova food classification system, and adverse health outcomes. The review found consistent evidence of a higher risk of adverse health outcomes, particularly cardiometabolic, common mental disorder, and mortality outcomes, associated with greater ultra-processed food exposure.

Key Methodology: Systematic umbrella review of existing meta-analyses of observational epidemiological studies (cohort, case-control, and/or cross-sectional designs). Evidence credibility was assessed using pre-specified classification criteria (Class *I*-*V*), and quality was assessed using the GRADE framework.

Research Question: To evaluate the existing meta-analytic evidence of associations between exposure to ultra-processed foods, as defined by the Nova food classification system, and adverse health outcomes.

Summary

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This umbrella review represents a massive synthesis of epidemiological data, aggregating 45 pooled analyses involving nearly 10 million participants to evaluate the health risks of ultra-processed foods (UPFs). The authors conclude that there is consistent evidence linking greater UPF exposure to 32 adverse health outcomes, including mortality, cancer, and mental health disorders. Most notably, the article applies a custom evidence classification system to label the associations for cardiovascular disease-related mortality, type 2 diabetes, and common mental disorders as supported by "convincing" (Class I) evidence (p. 1). While the scope and systematic rigor of the review are impressive, the strength of these headline claims relies heavily on how one interprets "convincing" evidence in the context of observational research.

A critical tension exists between the article's custom classification system and the established GRADE framework used alongside it. The authors' "Class I" rating is largely driven by statistical significance ($p < 10^{-6}$), sample size (> 1000 cases), and strict heterogeneity criteria ($I^2 < 50\%$) (p. 26). However, the GRADE assessments—which prioritize study design and penalize the lack of randomization inherent in nutritional epidemiology—frequently rate the quality of this same evidence as "low" or "very low." For example, while the association between UPF exposure and cardiovascular disease-related mortality is labeled "convincing" (Class I), the GRADE certainty for this outcome is "very low" for the non-dose-response analysis and "low" for the dose-response analysis (p. 1; Supplementary Table D, p. 28).

Similarly, the "convincing" evidence for anxiety and common mental disorders is based on cross-sectional study designs (p. 8), which are inherently unable to establish temporal order. This creates a risk of reverse causation; it is equally plausi-

ble that individuals with anxiety or depression alter their diets toward convenient, hyper-palatable foods, rather than the diet causing the disorder. It is important to note that the authors did find "highly suggestive" (Class II) evidence for depressive outcomes based on prospective cohort studies (p. 8), which are less prone to this specific bias. However, by prioritizing the "convincing" label in the abstract and conclusion—which applies to the cross-sectional anxiety and common mental disorder findings—the article may signal a level of causal certainty to policymakers that the underlying data does not fully support.

Furthermore, the credibility of the causal inference is limited by the handling of confounding factors. The authors acknowledge that they did not systematically review how the primary studies adjusted for key confounders such as socioeconomic status, smoking, or physical activity, noting that such analyses were "beyond the scope of our review" (p. 11). UPF consumption is often a marker for a broader lifestyle package associated with health disparities. While the authors cite a recent meta-analysis suggesting that adjusting for diet quality does not negate these associations (p. 11), the absence of a systematic evaluation of residual confounding in this specific dataset leaves open the possibility that UPF consumption is a proxy for other adverse health behaviors rather than the sole driver of disease.

Despite these limitations, the consistency of the signal across 71 percent of the analyzed health outcomes is striking. The review provides a comprehensive catalog of associations that supports the precautionary principle, even if it does not definitively prove causation. The authors' comparison of their findings to the evidence on sugar-sweetened beverages—noting that a previous review found no Class I evidence for sugar, whereas this review found Class I evidence for UPFs (p. 12)—is a bold policy stance. While the observational signal is indeed strong and consistent, the leap to "urgent" public health measures is based on data that remains, by the authors' own GRADE assessment, predominantly of low quality.

The Bottom Line

This article provides a high-quality synthesis of the available epidemiological evidence, demonstrating a robust and consistent statistical association between ultra-processed food consumption and poor health outcomes. However, the label "convincing evidence" should be interpreted with caution, as it reflects statistical significance in large datasets rather than high-certainty proof of causation. Readers should be aware that the underlying data are observational and subject to reverse causation—particularly regarding anxiety and common mental disorders—and residual confounding, meaning UPFs may be a major contributor to poor health but are likely not the sole culprit.

Potential Issues

Inconsistent communication of evidence certainty: The article uses two different systems to grade evidence—the established GRADE framework and a custom five-tier classification (Class I–V)—which can lead to conflicting interpretations of the findings' certainty. For several outcomes, these systems produce sharply contrasting assessments. For instance, the abstract reports "convincing evidence (class I)" for an association between ultra-processed food (UPF) exposure and higher risks of cardiovascular disease-related mortality, while simultaneously noting the quality of this evidence under the GRADE framework is "very low" (p. 1). In the same sentence, however, the authors also report "convincing evidence (class I)" for type 2 diabetes, for which the GRADE quality is "moderate" (p. 1). The custom classification system relies heavily on statistical significance thresholds, sample sizes, and heterogeneity metrics ($I^2 < 50\%$), which do not inherently correct for the risk of bias in the underlying observational study designs (Supplementary Table C, p. 26). In contrast, the GRADE system is designed to start all observational evidence at a "low" quality rating precisely because of these potential biases. By prioritizing the semantically strong labels from their custom system ("convincing," "highly suggestive") in the abstract and summaries, the authors may overstate the strength of the causal inference to readers, even though both ratings are presented transparently side-by-side (pp. 1, 6–8).

High credibility rating for evidence prone to reverse causation: The review's strongest credibility ratings for mental health outcomes are assigned to findings from cross-sectional studies, a design that cannot establish temporal order and is highly susceptible to reverse causation. The abstract reports "convincing evidence (class I)" for associations with prevalent anxiety and combined common mental disorder outcomes (p. 1). Because these findings are derived from cross-sectional data, it is plausible that the health condition preceded the dietary pattern; for

instance, individuals with anxiety may alter their eating habits toward more convenient UPFs. The article's evidence classification criteria do not require longitudinal data to achieve the highest credibility rating, which is a significant limitation for outcomes where reverse causation is a plausible explanation (Supplementary Table C, p. 26). The review does report "highly suggestive (class II)" evidence for an association with depressive outcomes based on prospective cohort studies, which are less prone to this issue (p. 8). However, assigning the highest possible credibility rating (Class I) to the cross-sectional anxiety findings may be inappropriate given the study design.

Systematic assessment of confounding factors: The review does not systematically re-evaluate the extent to which the original primary studies controlled for critical non-dietary confounding variables. High UPF consumption often correlates with other risk factors like lower socioeconomic status, smoking, and lower physical activity, which could drive the observed associations. The authors state, "we did not consider specific confounder or mediator adjustments and sensitivity analyses as part of our review" (p. 11). They did assess whether the included meta-analyses accounted for risk of bias using the AMSTAR 2 tool and the GRADE framework (pp. 4, 9). However, without a new, systematic extraction and analysis of how specific key confounders were handled across the primary literature, it is difficult to determine the degree to which residual confounding may explain the results. The authors' discussion of confounding cites a separate meta-analysis to argue that adjusting for overall dietary quality does not alter the findings (p. 11), but this does not resolve the issue of other lifestyle and socioeconomic confounders. While the authors are transparent about this limitation, it remains a central challenge to interpreting the reported associations.

Strength of policy recommendations relative to evidence: The article's call for "urgent mechanistic research" and the development of public health measures (p. 1) may overstate what can be concluded from the available evidence. The review syn-

thesizes observational data that demonstrates associations but cannot, by design, establish causality, a point the authors acknowledge (p. 11). While public health decisions are often made based on consistent observational evidence, the evidence presented here is graded as predominantly "low" or "very low" quality by the GRADE framework and is subject to unresolved confounding. The authors argue in their policy implications section that the evidence for action on UPFs is stronger than that which prompted policy on sugar-sweetened beverages, as their review found Class I evidence where a similar review on sugar did not (p. 12). Nevertheless, whether the evidence base is sufficient to warrant a call for "urgent" action, as opposed to a primary call for higher-quality research to establish causality, is debatable.

Presentation issues: The placement of superscript citations in the main text may cause momentary confusion for the reader. On page 4, the text states that the total number of participants included across the pooled analyses was 9,888,373, "ranging from 1113[1]□ to 962593□□". The superscript citation numbers (17 and 48) are placed immediately after the participant counts without a space, which could be misread. The numbers themselves are correctly reported from the supplementary data (Supplementary Table G, pp. 47–51), so this is a minor formatting issue rather than a numerical error.

Future Research

Longitudinal designs for mental health: Future work must prioritize prospective cohort studies over cross-sectional designs to investigate the link between UPF consumption and mental health disorders. Establishing temporal order is essential to rule out reverse causation, where mental health struggles lead to dietary changes. Research should focus on baseline diet in healthy populations and track the subsequent incidence of anxiety and depression over time.

Mechanistic trials on biomarkers: To bridge the gap between observational associations and causality, researchers should conduct randomized controlled trials (RCTs) focused on intermediate biomarkers rather than hard disease endpoints, which are ethically and logistically difficult to test in long-term diet studies. These trials should isolate specific properties of UPFs—such as texture, additive content, or energy density—to determine which mechanisms (e.g., inflammation, microbiome alteration, satiety disruption) are driving the adverse outcomes identified in this review.

Systematic evaluation of confounding: Future meta-analyses should specifically stratify results based on the rigor of confounding adjustments in primary studies. By isolating studies that comprehensively control for socioeconomic status, smoking, and overall dietary pattern quality, researchers could better quantify the extent to which the UPF-health association is driven by the food itself versus the broader lifestyle factors often correlated with high UPF consumption.

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