Ultra-processed foods and health : are we correctly interpreting the available evidence?

European Journal of Clinical Nutrition

Visioli, Francesco; Del Rio, Daniele; Fogliano, Vincenzo; Marangoni, Franca; Ricci, Cristian et al

https://doi.org/10.1038/s41430-024-01515-8

European Journal of Clinical Nutrition www.nature.com/ejcn

PERSPECTIVE

Ultra-processed foods and health: are we correctly interpreting the available evidence?

Francesco Visioli[1]✉, Daniele Del Rio[2], Vincenzo Fogliano[3], Franca Marangoni[4], Cristian Ricci[5] and Andrea Poli[4]

Several studies have linked adverse health effects to the consumption of ultra-processed foods (UPF) according to the NOVA classification. However, whether the consumption of UPF is the actual causal factor for such health outcomes is still unknown. Indeed, different groups of UPF examined in the same epidemiologic study often show markedly different associations with the occurrence of the health endpoints. In this Comment, we discuss some such studies and point out that the available evidence on how different UPFs have been associated with health, as well as the results of studies examining specific food additives, call into question the possibility that ultra-processing per se is the real culprit. It is possible that other unaccounted for confounding factors play an important role. Future, urgently needed studies will clarify this issue.

European Journal of Clinical Nutrition; https://doi.org/10.1038/s41430-024-01515-8

In recent years, several studies have associated adverse health outcomes with the intake of ultra-processed foods (UPF) defined according to the NOVA classification [1]. The epidemiological basis of most of these studies ensures a rigorous approach. However, critics challenge these studies, pinpointing that methodological limits of the observational approach narrow the causal strength often suggested by the authors of these studies [2–4].

The main question of whether UPF intake is the actual causal factor of such health outcomes is unresolved. A contribution to the discussion and the understanding of this issue may derive from some recent developments in the literature. In our opinion, such evidence has not been sufficiently valorized.

First and foremost, different groups of UPF evaluated within the same epidemiological study often show markedly different associations with the incidence of the health endpoints. Although subgroup analysis is not frequently reported in published papers on UPF and health, some evidence in this direction is accumulating [5].

For example, a recent EPIC cohort study reported an overall association between high intake of UPF and the risk of multimorbidity for cancer, cardiovascular disease (CVD) and type-2 diabetes (T2D) (HR 1.09; 1.05–1.12) [6]. Yet, a separate analysis of the contribution of the different categories of UPF revealed that such unfavorable association only pertains to some food groups [6]. For example, high intakes of ultra-processed bread and cereals showed a borderline protective association with respect to the outcome (HR 0.97; 0.94–1.00).

In another study based on the Dutch EPIC cohort, a significant all-cause mortality risk excess (HR 1.17; 1.08–1.28) was associated with the highest consumption of UPF [7]. Again, a more detailed analysis of the data showed that this association was entirely dependent on the consumption of certain drinks classified as ultra-processed, whereas the consumption of solid UPF did not significantly correlate with risk (HR 1.06; 0.97–1.15).

In the US cohorts of Nurses and Health Professionals [8], the risk of developing T2D increased linearly with the total intake of UPF. Here, the associations of the various subgroups of UPF with the outcome were extremely heterogeneous, with eight of these groups showing a significantly increased diabetes risk and eight UPF subgroups (among which cereals, dark and whole wheat bread, sweet and savory snacks and fruits, yogurt, and dairy-based desserts) showing significant protection with respect to the outcome.

Similar observations emerged from the NutriNet Santé study, where the overall consumption of UPF was significantly associated with an increased risk of T2D, overweight and obesity, some cancer and CVD (with significant HRs in the range 1.04–1.17) [9–12]. In these papers, the authors provided results about the association of the various categories of UPF to endpoint incidence, again showing great heterogeneity among different UPF groups. For instance, no association between the incidence of endpoints and the intake of UPF fruits or vegetables was observed in any of the four studies published. A similar pattern was observed for ultra-processed starchy foods or breakfast cereals (only one study out of four showed a significant association). In this cohort, the only significant association between UPF and cancer was with ultra-processed fats, such as margarine and sauces. In the case of breast cancer, such an association only concerns sugary products, but not sugary drinks. To the best of our knowledge, no results showing an increased risk of adverse health outcomes for all or most of the different UPF subgroups considered have been reported yet.

To this end, it seems that the overall health risk associated with the highest intake of UPF is attributable to a relatively small

[1]Department of Molecular Medicine, University of Padova, Padova, Italy. [2]Department of Food and Drugs, Human Nutrition Unit, University of Parma, Parma, Italy. [3]Food Quality and Design Group, Wageningen University and Research, Wageningen, The Netherlands. [4]Nutrition Foundation of Italy, Milan, Italy. [5]Africa Unit for Transdisciplinary Health Research AUTHeR, North-West University, Potchefstroom, South Africa. ✉email: francesco.visioli@unipd.it

Received: 10 June 2024 Revised: 16 September 2024 Accepted: 19 September 2024
Published online: 26 September 2024

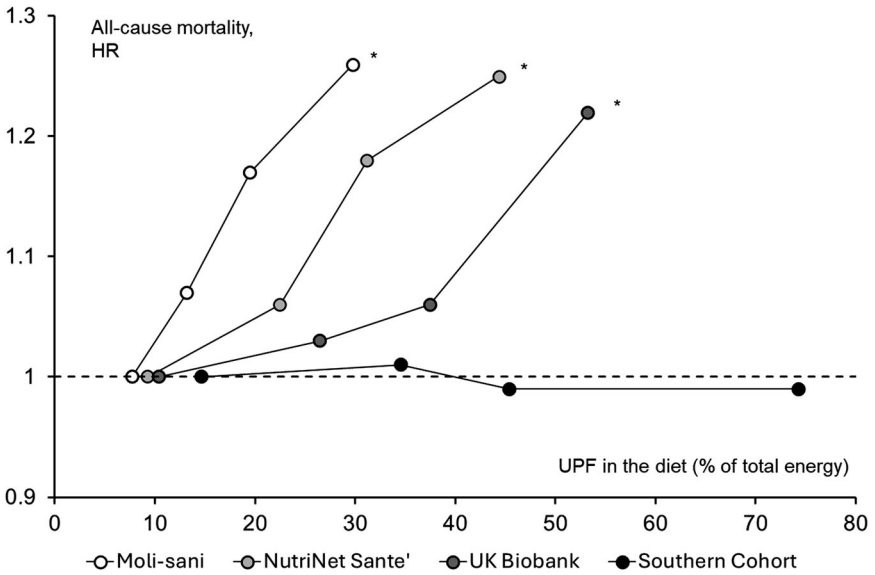

Fig. 1 Association between mortality risk and ultra-processed food intake. Representation of all-causes mortality Hazard ratio in relation to the percentage of ultra-processed food with respect to the total calories in the Moli-sani (Italy, $N = 22{,}475$; [16]), NutriNet sante' (France, $N = 44{,}551$; [23]), UK Biobank (United Kingdom, $N = 60{,}298$; [17]) and Southern Cohort (USA, $N = 77{,}060$; [18]). The asterisks represent statistically significant HRs.

number of such foods rather than to ultra-processing per se; those based on products of animal origin (information already well known before the launch of the NOVA classification) seem to play a leading role. Some readers (and we among them) interpret this evidence as due to an indirect mediator role of UPF on health, its use being a proxy of a non-optimal diet or lifestyle behavior. Alternatively, these data may support the view that some specific components of UPF preparation process (specific food additives, other ingredients, or technological procedures) may have a major role in determining the health risk observed. Moreover, as a further criticism of the evidence supporting the association between UPF and health we should consider that HRs are calculated ignoring variability in the terms taken for comparison. More precisely, statistical analyses are based on numerous assumptions such as the food intake is measured accurately and precisely, that food composition is known quantitatively, the methods of food storage, preparation and cooking have no effect on the values, etc. Those assumptions are potentially questionable, and so are the corresponding results. Thus, more studies investigating specific compounds or steps in food preparation should be performed to better integrate the current evidence about UPF and health [4].

Fortunately, examples of such analytical approaches are already available. The study of Sellem et al. investigating the role of emulsifiers in relation to the risk of cancer is paradigmatic [13]. In this study, the authors identified a significant association between some mono-diglycerides and some carrageenan with overall and site-specific cancer risk and suggested further investigation to address possible causality. The authors interpret these results very carefully, but we think that extending such evidence to the whole class of emulsifiers would be incorrect, since most of them were demonstrated not to be at all associated with cancer risk.

The same line of reasoning applies to a recent publication by Hang et al. [14] on the correlation between the consumption of ultra-processed foods after a diagnosis of colorectal cancer and total and cause-specific mortality during the follow-up. The increased CVD risk in the quintile of subjects with the highest consumption of ultra-processed foods is solely due to the likely higher consumption of fats, condiments, and ultra-processed sauces and the concomitant decrease of fiber intake. The other subgroups of ultra-processed foods do not appear to play a role in CVD. Similarly, the increase in colorectal cancer mortality (which does not correlate with either the ultra-processed foods consumption or all-cause mortality) is exclusively associated with the consumption of ultra-processed sherbets and ice cream. Biological plausibility is weak at best (these two desserts should contain potent carcinogens, which is rather unlikely).

Assessing causality by means of observational epidemiologic studies is nearly impossible, and more experimental studies are needed to investigate and possibly disentangle the association between UPF and health from a causal and mechanistic viewpoint, though experiments on humans are difficult to plan for various reasons [15]. Fortunately, other approaches can help investigate the extent to which the observed associations between the overall UPF intake and adverse health events could be due to unidentified confounders.

First, the overall intake of UPF is very heterogeneous among the studies investigating UPF intake in relation to health. In countries with a low UPF intake, such as Italy, the risk of all-cause mortality is already significantly increased for a UPF intake of around 24% of the total energy intake. On the contrary, in countries consuming high quantities of UPF, figures are different (Fig. 1). In the French cohort of the NutriNet Santé, an average of 29% of energy from UPF was reported by authors, and a significant all-cause mortality risk was observed only for UPF intakes that exceed 30% of total weight. In Great Britain, where UPF intake is higher and can reach 50% of total energy, a significant all-cause mortality risk was observed for UPF intakes above 40% of energy intake. Furthermore, no significant mortality risk in relation to UPF was observed in the Southern Community Cohort Study (SCCS), a prospective cohort of low-income Americans with one of the highest percentages of energy intake from UPF ever recorded [16–18].

Furthermore, since it is unlikely that Italian UPFs (ultra-processed foods) are more harmful than those sold in other countries, these results suggest that the association between UPF consumption and negative health outcomes is probably not causal, but rather indicative of an unhealthy lifestyle prevalent among those who consume the most UPFs. This view is supported by an exploratory dose-response analysis of the data from the four studies mentioned above, which shows no significant trend (Fig. 2).

Nevertheless, the possibility cannot be entirely dismissed that the composition and consumption patterns of UPF differ between

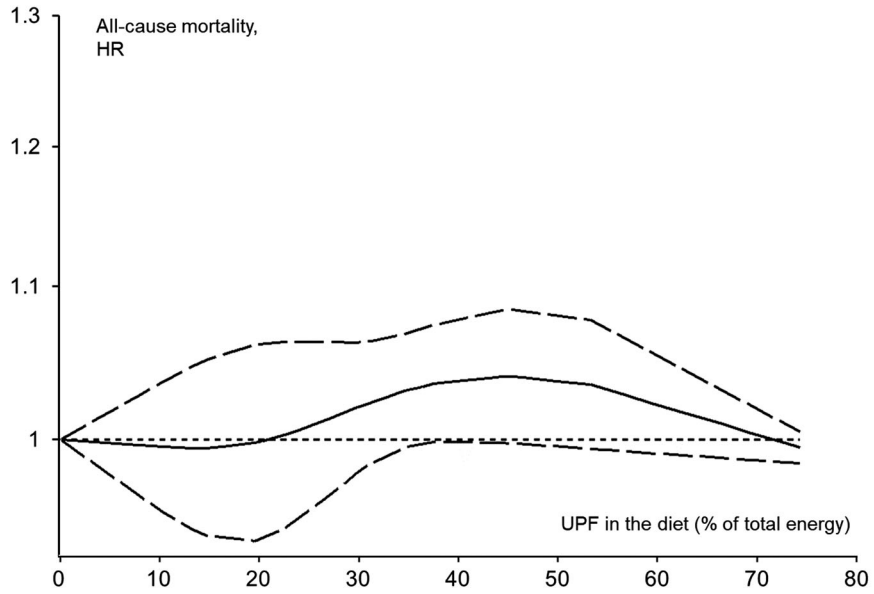

Fig. 2 Dose-response restricted cubic splines meta-regression analysis of the all-causes mortality Hazard ratio in relation to the percentage of ultra-processed food with respect to the total calories. Spline knots were placed at 5th, 35th, 65th and 95th percentiles. This analysis represents how the results from the different studies can be merged to determine the relation between UPF intake and all-cause mortality risk. The solid line represents the meta-analytical estimate, the dotted lines represent the 95% confidence limits. Analysis performed according to Greenland and Longnecker [24].

countries or cohorts, possibly contributing to the differences in health endpoints observed between different nations or cultures. For example, it is theoretically possible (though unlikely) that a higher proportion of 'nutritionally beneficial' UPF rich in whole grains is consumed in the UK, to take just one example, than in Italy. The emerging concept of 'nutritionally beneficial UPFs' is intriguing and remains to be discussed in depth. More detailed data on the composition of UPFs in different countries and surveys would be very valuable in this context.

If we approach the question of the differential effect of UPF in different countries from a different perspective, we could speculate that the alleged detrimental relationship between health and UPF intake may be more pronounced in countries with a low average consumption of UPF.

Indeed, we could speculate that the purported harmful association between health and UPF intake may be more prominent in countries with low average consumption of UPF. In these countries, people in the last quantile of the UPF intake distribution are likely quite dissimilar from the population average, and this difference may include an unaccounted-for unhealthier lifestyle, which would be responsible for the unfavorable health association observed. As the consumption of UPF in the population increases and becomes more homologized, the lifestyle differences between the last quantile of the population and the previous ones will be smaller, reducing the associated risk. This fact may explain the overall profile of the observed association between UPF intake and the risk of all-cause mortality shown in Fig. 1.

Finally, high intakes of UPF correlate with an extensive range of pathologic conditions in terms of morbidity or mortality, which is difficult to explain based on causal and mechanistic interpretation. The association between UPF consumption and higher CVD risk was among the first ones to be described and was subsequently integrated with evidence regarding some tumors, cardio-metabolic, respiratory, gastrointestinal diseases, anxiety, depression, as well as para-physiological conditions, such as insomnia [19]. In other studies, authors reported a statistically significant association between high UPF intake and mortality from other causes, excluding CVD and cancer. In these cases, the higher mortality risk associated with UPF use is largely attributable to deaths due to respiratory diseases and violence, which can hardly be causally related to higher UPF intake. In the SUN study, non-cancer, and non-CVD mortality accounts for 40% of the total mortality in the fourth quartile of UPF intake compared to 22% in the first quartile [20]. Again, it is difficult to find a biological plausibility explaining these results, and a potential role of unidentified confounding factors is difficult to rule out [21].

In summary, the available evidence regarding how different UPF were associated with health and the results of studies investigating specific food additives question the possibility that ultra-processing per se is the real culprit. Possibly, other unaccounted-for confounding factors play major roles. Consequently, the recommendation of limiting or avoiding foods carrying an unspecific "ultra-processed food" label based on the NOVA classification currently has poor scientific grounds and should be regarded as scientifically weak and in need of experimental confirmation. Furthermore, prompt public policy interventions on this topic, as advocated by some authors [22], are premature and should be thoroughly reconsidered before being released.

REFERENCES

1. Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN decade of nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutr. 2018;21:5–17. https://doi.org/10.1017/S1368980017000234.
2. Jones JM. Food processing: criteria for dietary guidance and public health? Proc Nutr Soc. 2019;78:4–18. https://doi.org/10.1017/S0029665118002513.
3. Gibney MJ, Forde CG, Mullally D, Gibney ER. Ultra-processed foods in human health: a critical appraisal. Am J Clin Nutr. 2017;106:717–24. https://doi.org/10.3945/ajcn.117.160440.
4. Bradbury KE, Mackay S. Ultra-processed foods linked to higher mortality. BMJ. 2024;385:q793 https://doi.org/10.1136/bmj.q793.
5. Vitale M, Costabile G, Testa R, D'Abbronzo G, Nettore IC, Macchia PE, et al. Ultra-processed foods and human health: a systematic review and meta-analysis of prospective cohort studies. Adv Nutr. 2024;15:100121 https://doi.org/10.1016/j.advnut.2023.09.009.
6. Cordova R, Viallon V, Fontvieille E, Peruchet-Noray L, Jansana A, Wagner KH, et al. Consumption of ultra-processed foods and risk of multimorbidity of cancer and cardiometabolic diseases: a multinational cohort study. Lancet Reg Health Eur. 2023;35:100771 https://doi.org/10.1016/j.lanepe.2023.100771.

7. Vellinga RE, van den Boomgaard I, M A Boer J, van der Schouw YT, Harbers MC, Verschuren WMM, et al. Different levels of ultraprocessed food and beverage consumption and associations with environmental sustainability and all-cause mortality in EPIC-NL. Am J Clin Nutr. 2023;118:103–13. https://doi.org/10.1016/j.ajcnut.2023.05.021.
8. Chen Z, Khandpur N, Desjardins C, Wang L, Monteiro CA, Rossato SL, et al. Ultra-processed food consumption and risk of type 2 diabetes: three large prospective U.S. cohort studies. Diabetes Care. 2023;46:1335–44. https://doi.org/10.2337/dc22-1993.
9. Beslay M, Srour B, Mejean C, Alles B, Fiolet T, Debras C, et al. Ultra-processed food intake in association with BMI change and risk of overweight and obesity: a prospective analysis of the French NutriNet-Sante cohort. PLoS Med. 2020;17:e1003256. https://doi.org/10.1371/journal.pmed.1003256.
10. Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Alles B, Mejean C, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Sante prospective cohort. BMJ. 2018;360:k322. https://doi.org/10.1136/bmj.k322.
11. Srour B, Fezeu LK, Kesse-Guyot E, Alles B, Mejean C, Andrianasolo RM, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Sante). BMJ. 2019;365:l1451. https://doi.org/10.1136/bmj.l1451.
12. Srour B, Fezeu LK, Kesse-Guyot E, Alles B, Debras C, Druesne-Pecollo N, et al. Ultraprocessed food consumption and risk of type 2 diabetes among participants of the NutriNet-Sante prospective cohort. JAMA Intern Med. 2020;180:283–91. https://doi.org/10.1001/jamainternmed.2019.5942.
13. Sellem L, Srour B, Javaux G, Chazelas E, Chassaing B, Viennois E, et al. Food additive emulsifiers and cancer risk: results from the French prospective NutriNet-Sante cohort. PLoS Med. 2024;21:e1004338. https://doi.org/10.1371/journal.pmed.1004338.
14. Hang D, Du M, Wang L, Wang K, Fang Z, Khandpur N, et al. Ultra-processed food consumption and mortality among patients with stages I-III colorectal cancer: a prospective cohort study. EClinicalMedicine. 2024;71:102572. https://doi.org/10.1016/j.eclinm.2024.102572.
15. Visioli F, Marangoni F, Fogliano V, Del Rio D, Martinez JA, Kuhnle G, et al. The ultra-processed foods hypothesis: a product processed well beyond the basic ingredients in the package. Nutr Res Rev. 2023;36:340–50. https://doi.org/10.1017/S0954422422000117.
16. Bonaccio M, Di Castelnuovo A, Costanzo S, De Curtis A, Persichillo M, Sofi F, et al. Ultra-processed food consumption is associated with increased risk of all-cause and cardiovascular mortality in the Moli-sani Study. Am J Clin Nutr. 2021;113:446–55. https://doi.org/10.1093/ajcn/nqaa299.
17. Chen X, Chu J, Hu W, Sun N, He Q, Liu S, et al. Associations of ultra-processed food consumption with cardiovascular disease and all-cause mortality: UK Biobank. Eur J Public Health. 2022;32:779–85. https://doi.org/10.1093/eurpub/ckac104.
18. Wang L, Pan XF, Munro HM, Shrubsole MJ, Yu D. Consumption of ultra-processed foods and all-cause and cause-specific mortality in the Southern Community Cohort Study. Clin Nutr. 2023;42:1866–74. https://doi.org/10.1016/j.clnu.2023.08.012.
19. Lane MM, Gamage E, Du S, Ashtree DN, McGuinness AJ, Gauci S, et al. Ultra-processed food exposure and adverse health outcomes: umbrella review of epidemiological meta-analyses. BMJ. 2024;384:e077310. https://doi.org/10.1136/bmj-2023-077310.
20. Rico-Campa A, Martinez-Gonzalez MA, Alvarez-Alvarez I, Mendonca RD, de la Fuente-Arrillaga C, Gomez-Donoso C, et al. Association between consumption of ultra-processed foods and all cause mortality: SUN prospective cohort study. BMJ. 2019;365:l1949. https://doi.org/10.1136/bmj.l1949.
21. Valicente VM, Peng CH, Pacheco KN, Lin L, Kielb EI, Dawoodani E, et al. Ultra-processed foods and obesity risk: a critical review of reported mechanisms. Adv Nutr. 2023;14:718–38. https://doi.org/10.1016/j.advnut.2023.04.006.
22. Monteiro CA, Martinez-Steele E, Cannon G. Reasons to avoid ultra-processed foods. BMJ. 2024;384:q439. https://doi.org/10.1136/bmj.q439.
23. Schnabel L, Kesse-Guyot E, Alles B, Touvier M, Srour B, Hercberg S, et al. Association between ultraprocessed food consumption and risk of mortality among middle-aged adults in France. JAMA Intern Med. 2019;179:490–8. https://doi.org/10.1001/jamainternmed.2018.7289.
24. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135:1301–9. https://doi.org/10.1093/oxfordjournals.aje.a116237.

AUTHOR CONTRIBUTIONS

AP drafted the first version of the manuscript. FV, VF, FM, DDR, and CR contributed to the revision of the manuscript.

COMPETING INTERESTS

AP and FM are the Chairman and Scientific Director, respectively, of NFI—Nutrition Foundation of Italy, a non-profit organisation partially supported by Italian and non-Italian Food Companies. All other authors declare no conflict of interest associated with this publication.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Francesco Visioli.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.