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Ultra-processed foods linked to higher mortality

ORIGINAL RESEARCH Population based cohort study

Association of ultra-processed food consumption with all cause and cause specific mortality

Fang Z, Rossato SL, Hang D, et al

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Study question Is ultra-processed food consumption associated with higher mortality?

Methods This study used two large US prospective cohorts followed for up to 34 years: the Nurses' Health Study and the Health Professional Follow-up Study, including 74 563 women and 39 501 men with no history of cancer, cardiovascular diseases, or diabetes at baseline. The primary outcome was all cause mortality. Secondary outcomes were deaths from cancer, cardiovascular diseases, and other causes (including respiratory diseases and neurodegenerative diseases). Multivariable Cox proportional hazard models were used to examine the association of ultra-processed food intake measured by food frequency questionnaire every four years with all cause and cause specific mortality. Overall dietary quality was assessed with the Alternative Healthy Eating Index-2010 (AHEI) score.

Study answer and limitations Compared with those in the lowest quarter of ultra-processed food consumption (median 3.0 servings/day), participants in the highest quarter (median 7.4 servings/day) had 4% higher all cause mortality and 9% higher mortality from causes other than cancer or cardiovascular diseases. The all cause mortality rate among participants in the lowest and highest quarters was 1472 and 1536 per 100 000 person years, respectively. Meat, poultry, and seafood based ready-to-eat products (for example, processed meat) consistently showed strong associations with mortality outcomes (hazard ratios ranged from 1.06 to 1.43). Sugar sweetened and artificially sweetened beverages (1.09, 1.07 to 1.12), dairy based desserts (1.07, 1.04 to 1.10), and ultra-processed breakfast food (1.04, 1.02 to 1.07) were also associated with higher all cause mortality. No consistent associations between ultra-processed foods and mortality were observed within each quarter of dietary quality assessed by the AHEI-2010 score, whereas better dietary quality showed an inverse association with mortality within each quarter of ultra-processed foods. As this was an observational study, unmeasured and residual confounding cannot be ruled out. Also, the study population comprised health professionals and predominantly non-Hispanic white Americans, limiting

the generalisability of the findings. The dietary intakes collected may not capture the full spectrum of ultra-processed foods.

What this study adds A higher intake of ultra-processed foods was associated with slightly higher all cause mortality. Overall dietary quality was observed to have a more predominant influence on mortality than ultra-processed food consumption.

Funding, competing interests, and data sharing
This work was supported by US National Institutes of Health grants. Author NK received a consulting fee from the Pan American Health Organization for three months on the topic of nutrition disclosure initiatives and nutrient profiling models. Data can be shared through mechanisms detailed at https://www.nurseshealthstudy.org and https://www.hsph.harvard.edu/hpfs/.

Forest plot of multivariable hazard ratios comparing highest versus lowest quarter of UPF consumption for all cause mortality. CI=confidence interval; UPF=ultra-processed food

Multivariable hazard ratios and 95% confidence intervals for mortality according to quarters of subgroups of ultra-processed food consumption*

Total mortality	Energy adjusted ultra-processed food consumption† Quarter 1	Quarter 2	Quarter 3	Quarter 4	P for trend	Per difference in medians between quarters 4 and 1
Ultra-processed breads and breakfast foods	1	1.05 (1.02 to 1.07)	1.06 (1.03 to 1.09)	1.04 (1.02 to 1.07)	0.01	1.03 (1.01 to 1.06)
Fats, condiments, and sauces	1	1.01 (0.98 to 1.04)	1.03 (1.01 to 1.06)	1.00 (0.98 to 1.03)	0.86	1.00 (0.98 to 1.03)
Packaged sweet snacks and desserts	1	1.02 (0.99 to 1.05)	0.99 (0.97 to 1.02)	0.99 (0.97 to 1.02)	0.17	0.98 (0.96 to 1.01)
Sugar and artificially sweetened beverages	1	1.03 (1.01 to 1.06)	1.06 (1.03 to 1.08)	1.09 (1.07 to 1.12)	‹0.001	1.09 (1.06 to 1.12)
Ready-to-eat/heat mixed dishes	1	1.02 (1.00 to 1.05)	1.05 (1.03 to 1.08)	1.02 (0.99 to 1.05)	0.03	1.03 (1.00 to 1.06)
Meat/poultry/seafood based ready-to-eat products	1	1.06 (1.03 to 1.09)	1.10 (1.07 to 1.13)	1.13 (1.10 to 1.16)	‹0.001	1.13 (1.10 to 1.16)
Packaged savoury snacks	1	1.05 (1.02 to 1.08)	1.05 (1.02 to 1.08)	1.01 (0.99 to 1.04)	0.47	0.99 (0.97 to 1.02)
Dairy based desserts	1	1.06 (1.03 to 1.08)	1.06 (1.03 to 1.09)	1.07 (1.04 to 1.10)	‹0.001	1.06 (1.03 to 1.08)
Other	1	1.00 (0.98 to 1.03)	1.07 (1.05 to 1.10)	1.08 (1.05 to 1.11)	‹0.001	1.04 (1.03 to 1.06)

*Results from Cox proportional hazards model stratified by age (months), questionnaire cycle (two year interval), and cohort, and adjusted for total energy intake, race, marital status, physical activity, body mass index, smoking status and pack years, alcohol consumption, physical examination performed for screening purposes, and family history of diabetes mellitus, myocardial infarction, or cancer; for women, also menopausal status and hormone use.
†Quarter specific medians (servings/day) for each subgroup: ultra-processed breads and breakfast foods 0.1, 0.3, 0.6, 1.3; fats, condiments, and sauces 0.5, 1.0, 1.5, 2.5; packaged sweet snacks and desserts 0.4, 0,7, 1.1, 1.8; sugar sweetened and artificially sweetened beverages 0.09, 0.4, 0.8, 1.7; ready-to-eat/heat mixed dishes 0.07, 0.1, 0.2, 0.4; meat/poultry/seafood based ready-to-eat products 0.06, 0.2, 0.3, 0.5; packaged savoury snacks 0.04, 0.1, 0.3, 0.6; dairy based desserts, 0.06, 0.1, 0.3, 0.5; other 0.009, 0.01, 0.01, 0.4.

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COMMENTARY Debate about the "ultra-processed" concept must not delay food policies that improve health

As research into ultra-processed food gains momentum,[1] so too does the debate.[2-4] Foods that fall into the ultra-processed category according to the Nova classification are heterogeneous and include carbonated soft drinks, confectionery, extruded snack foods, distilled alcohol (spirits), and mass produced packaged wholegrain bread.[5] Ultra-processed foods are typically high in energy, added sugar, saturated fat, and salt, and a major criticism of previous studies is that they have not disentangled the effects of processing, per se, from the nutrient profile of food products. In their paper, Fang and colleagues address this concern and others in their evaluation of the relation between ultra-processed food consumption and mortality in two large US cohort studies.[6]

Fang and colleagues found a modest increase in the risk of total mortality with higher ultra-processed food consumption[6]; however, this association was no longer apparent after overall diet quality was taken into account. They also showed that the association between ultra-processed food consumption and mortality was somewhat stronger when distilled alcohol, which is a well established risk factor for premature mortality,[7] was included in the ultra-processed category, and somewhat weaker when packaged wholegrain products were included in the ultra-processed category.[6] Further adjustment for pack years of smoking (rather than current smoking status only) greatly attenuated the association between ultra-processed food consumption and respiratory mortality.[6] Thus, future studies must adjust more fully for lifetime smoking exposure or present results in non-smokers to reduce the impact of residual confounding.

The potential mechanisms put forward to explain observed associations between ultra-processed food and health outcomes are also heterogeneous and include over-consumption due to the energy density; fat, sugar, and salt content; potential deleterious effects of certain additives; and contaminants from packaging.[1] Combining heterogeneous foods into a single exposure variable does not help to progress our understanding of the potential harm, if any, of specific additives, processing, or packaging techniques, beyond any harmful effects of the poor nutrient profile of food products. Note that the Nova food processing categorisation system classifies foods on the basis of not only the level of processing and the presence of additives but also on the purpose of those additives.[5] From an aetiological perspective, the purpose of a food additive is irrelevant—either it is harmful for health or it is not.

Our global food system is dominated by packaged foods that often have a poor nutritional profile

Cautious deliberation needed

Expert bodies such as the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JEFCA) exist to evaluate individual food additives for safety and to determine the potential carcinogenicity of foods and their components. The International Agency for Research on Cancer (IARC) and the World Cancer Research Fund (WCRF) both concluded that alcohol and processed meat cause cancer in humans.[8-10] Both alcohol and processed meat, as defined by IARC, span both the "processed" (for example, beer and wine; salted, dried, and cured meat) and "ultra-processed" (for example, distilled alcohol; sausages and hot dogs) Nova categories.[5]

Fang and colleagues sensibly concluded that not all ultra-processed food needs to be universally restricted, and that careful deliberation is needed when considering whether to include recommendations about ultra-processed food in dietary guidelines.[6] Most dietary guidelines already implicitly emphasise the consumption of less processed foods.[11] In countries where affordable, mass produced packaged wholegrain products such as breads are a recommended dietary staple and a major source of fibre, adding a sweeping statement in dietary guidelines about avoiding ultra-processed foods is not helpful.

Recommendations to avoid ultra-processed food may also give the impression that foods that are not ultra-processed are healthy and can be freely consumed. This is problematic—for example, IARC and WCRF have concluded that red meat (categorised by the Nova system as "unprocessed or minimally processed") probably increases the risk of bowel cancer.[8 9] In addition to effects on health, beef and lamb come from ruminant animals, which produce methane—a greenhouse gas that has a particularly potent warming effect over the short term.[12]

Embracing best buys

Our global food system is dominated by packaged foods that often have a poor nutritional profile.[13] This system largely serves the goals of multinational food companies, which formulate food products from cheap raw materials into marketable, palatable, and shelf stable food products for profit.[13] We should not let the debate on the usefulness of the ultra-processed food concept delay the implementation of evidence based interventions such as WHO's "best buys" for health.[14]

Several countries have already implemented and demonstrated the effectiveness of best buys and other interventions to better serve population health. These include the restriction of marketing of unhealthy foods to children and the addition of warning labels on nutritionally poor food products,[15] taxes on sugar sweetened beverages,[16] and bans on partially hydrogenated oils that are a source of industrial trans fatty acids.[17] Our focus should be on advocating for greater global adoption of these and more ambitious interventions, and increasing safeguards to prevent policies from being influenced by multinational food companies with vested interests that do not align with public health or environmental goals.

Kathryn E Bradbury
k.bradbury@auckland.ac.nz
Sally Mackay
See bmj.com for author details

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Comparative effectiveness of second line oral antidiabetic treatments among people with type 2 diabetes mellitus

Bidulka P, Lugo-Palacios DG, Carroll O, et al

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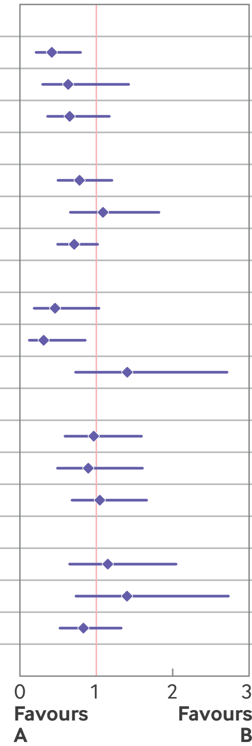
Study question What is the comparative effectiveness of three commonly prescribed oral antidiabetic drugs added to metformin as second line oral antidiabetic treatment for people with type 2 diabetes mellitus?

Methods The target trial emulation framework was combined with an instrumental variable analysis to reduce the risk of bias from confounding. Data were obtained from the Clinical Practice Research Datalink and included people with type 2 diabetes mellitus registered with a general practice in England who initiated second line oral antidiabetic treatment with either a sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, or sodium-glucose cotransporter-2 (SGLT-2) inhibitor added to metformin monotherapy between 2015 and 2020. The primary outcome was absolute change in glycated haemoglobin A_{1c} (HbA_{1c}) between baseline and one year follow-up. Secondary outcomes were change in body mass index (BMI), systolic blood pressure, and estimated glomerular filtration rate (eGFR) at one year and two years, change in HbA_{1c} at two years, and time to ≥40% decline in eGFR, major adverse kidney event, hospital admission for heart failure, major adverse cardiovascular event (MACE), and all cause mortality.

Study answer and limitations 75 739 people initiated second line oral antidiabetic treatment with sulfonylureas (n=25 693, 33.9%), DPP-4 inhibitors (n=34 464 ,45.5%), or SGLT-2 inhibitors (n=15 582, 20.6%). SGLT-2 inhibitors were more effective than DPP-4 inhibitors or sulfonylureas in reducing mean HbA_{1c} values at one year. After using an instrumental variable analysis to reduce the risk of confounding, the mean differences in HbA_{1c} change between baseline and one year were −2.5 mmol/mol (95% confidence interval (CI) −3.7 to −1.3) for SGLT-2 inhibitors versus sulfonylureas and −3.2 mmol/mol (−4.6 to −1.8) for SGLT-2 inhibitors versus DPP-4 inhibitors. SGLT-2 inhibitors were more effective than sulfonylureas or DPP-4 inhibitors in reducing BMI and systolic blood pressure. SGLT-2 inhibitors were associated with reduced hazards of hospital admission for heart failure compared with DPP-4 inhibitors (0.32, 0.12 to 0.90) and sulfonylureas (0.46, 0.19 to 1.05). The hazard ratio for a ≥40% decline in eGFR indicated a protective effect versus sulfonylureas (0.42, 0.22 to 0.82), with high uncertainty in the estimated hazard ratio versus DPP-4 inhibitors (0.64, 0.29 to 1.43). Glucagon-like peptide-1 receptor agonists were not compared as they are not currently recommended for second line antidiabetic treatment in England.

What this study adds This emulation study of a target trial found that SGLT-2 inhibitors were more effective than sulfonylureas or DPP-4 inhibitors in lowering mean HbA_{1c}, BMI, and systolic blood pressure and in reducing the hazards of hospital admission for heart failure (compared with DPP-4 inhibitors) and kidney disease progression (compared with sulfonylureas).

Comparison (drug A *v* drug B)	Hazard ratio (95% CI)
eGFR decline of ≥40%	
SGLT-2 inhibitor *v* sulfonylurea	0.42 (0.22 to 0.81)
SGLT-2 inhibitor *v* DPP-4 inhibitor	0.64 (0.29 to 1.43)
DPP-4 inhibitor *v* sulfonylurea	0.66 (0.37 to 1.17)
Major adverse kidney event	
SGLT-2 inhibitor *v* sulfonylurea	0.79 (0.51 to 1.23)
SGLT-2 inhibitor *v* DPP-4 inhibitor	1.11 (0.66 to 1.84)
DPP-4 inhibitor *v* sulfonylurea	0.72 (0.50 to 1.03)
Heart failure	
SGLT-2 inhibitor *v* sulfonylurea	0.46 (0.20 to 1.05)
SGLT-2 inhibitor *v* DPP-4 inhibitor	0.32 (0.12 to 0.85)
DPP-4 inhibitor *v* sulfonylurea	1.41 (0.73 to 2.71)
MACE	
SGLT-2 inhibitor *v* sulfonylurea	0.99 (0.61 to 1.62)
SGLT-2 inhibitor *v* DPP-4 inhibitor	0.91 (0.51 to 1.63)
DPP-4 inhibitor *v* sulfonylurea	1.09 (0.70 to 1.69)
All cause mortality	
SGLT-2 inhibitor *v* sulfonylurea	1.14 (0.64 to 2.03)
SGLT-2 inhibitor *v* DPP-4 inhibitor	1.39 (0.71 to 2.74)
DPP-4 inhibitor *v* sulfonylurea	0.82 (0.51 to 1.32)



Forest plot showing adjusted hazard ratios of cardiovascular disease and kidney outcomes comparing second line antidiabetic treatments and using an instrumental variable analysis to reduce the risk of confounding. The analysis used multiple imputation to account for missing data, using all available information and assuming data are missing at random. CI=confidence interval; MACE=major adverse cardiovascular event (composite for the earliest of myocardial infarction, stroke, or cardiovascular death); eGFR=estimated glomerular filtration rate; DPP-4=dipeptidyl peptidase-4; SGLT-2=sodium-glucose cotransporter 2

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