nature medicine

Article

https://doi.org/10.1038/s41591-025-03775-8

Health effects associated with consumption of processed meat, sugar-sweetened beverages and trans fatty acids: a Burden of Proof study

Received: 1 November 2024

Accepted: 16 May 2025

Published online: 30 June 2025

Check for updates

Demewoz Haile[1] ✉, Kassandra L. Harding[1], Susan A. McLaughlin[1], Charlie Ashbaugh[1], Vanessa Garcia[1], Nora M. Gilbertson[1,2], Hewan Kifle[1], Marie C. Parent[1,2], Reed J. D. Sorensen[1], Simon I. Hay[1,2], Aleksandr Y. Aravkin[1,3], Peng Zheng[1,2], Jeffrey D. Stanaway[1,2], Christopher J. L. Murray[1,2] & Michael Brauer[1,4]

Previous research suggests detrimental health effects associated with consuming processed foods, including processed meats, sugar-sweetened beverages (SSBs) and trans fatty acids (TFAs). However, systematic characterization of the dose–response relationships between these foods and health outcomes is limited. Here, using Burden of Proof meta-regression methods, we evaluated the associations between processed meat, SSBs and TFAs and three chronic diseases: type 2 diabetes, ischemic heart disease (IHD) and colorectal cancer. We conservatively estimated that—relative to zero consumption—consuming processed meat (at 0.6–57 g d^{-1}) was associated with at least an 11% average increase in type 2 diabetes risk and a 7% (at 0.78–55 g d^{-1}) increase in colorectal cancer risk. SSB intake (at 1.5–390 g d^{-1}) was associated with at least an 8% average increase in type 2 diabetes risk and a 2% (at 0–365 g d^{-1}) increase in IHD risk. TFA consumption (at 0.25–2.56% of daily energy intake) was associated with at least a 3% average increase in IHD risk. These associations each received two-star ratings reflecting weak relationships or inconsistent input evidence, highlighting both the need for further research and—given the high burden of these chronic diseases—the merit of continuing to recommend limiting consumption of these foods.

Ultra-processed foods high in calories, sugars, unhealthy fats and salt have been linked to a variety of adverse health outcomes[1,2]. Processed meat, sugar-sweetened beverages (SSBs) and trans fatty acids (TFAs) are widely consumed ultra-processed foods that are consistently associated with increased chronic disease risk[3,4]. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 estimated that diets high in processed meat contributed to nearly 300,000 deaths globally in 2021 and over 10 million disability-adjusted life years (DALYs, which combine years of life lost and years lived with disability); diets high in SSBs and TFAs were estimated to contribute to approximately 3.6 million and 2.5 million DALYs, respectively[5].

Processed meats, preserved by smoking, curing, salting or the addition of chemical preservatives, can contain harmful compounds, such as N-nitroso compounds[6], polycyclic aromatic hydrocarbons (PAHs)[7] and heterocyclic amines[8]. High consumption of processed meats has been linked to chronic diseases such as heart disease, type

[1]Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA. [2]Department of Health Metrics Sciences, School of Medicine, University of Washington, Seattle, WA, USA. [3]Department of Applied Mathematics, University of Washington, Seattle, WA, USA. [4]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada. ✉e-mail: dhwolde@uw.edu

2 diabetes and colorectal cancer. It is hypothesized that this is due to an increased visceral fat index[9], inflammation[10–12] and the potential for factors such as N-nitroso compounds, PAHs and heterocyclic amines to induce tumors[13–16]. SSBs encompass a wide range of beverages including sodas, fruit drinks, sports drinks, energy drinks, and sweetened teas and coffees, and they compose the primary source of added sugars in many people's diets[17]. High consumption of added sugars, particularly in liquid form, is associated with weight gain and increased risk of obesity, type 2 diabetes and ischemic heart disease (IHD)[18]. SSB consumption has risen globally during the past three decades, with the steepest increases in low- and middle-income countries[19]. TFAs are a type of unsaturated fat occurring naturally in small amounts in some meat and dairy products, but are also produced artificially to convert vegetable oil from a liquid to a solid via hydrogenation. Artificial TFAs, inexpensive and shelf-stable fats used in many processed foods and baked goods[20], have been associated with increased risk of systemic inflammation[21] and cardiovascular diseases[22–24].

Because processed meat, SSBs and TFAs are widely available and their consumption is commonplace, it is important to rigorously characterize the dose–response relationships between intake of these foods and the risk of prevalent chronic diseases, and to systematically evaluate the strength and consistency of evidence supporting these associations. Here we performed updated systematic reviews and meta-analyses using Burden of Proof methods to characterize relationships for dietary risk factors—specifically processed foods—and related health outcomes. Our present analysis examines the associations between processed meat consumption and three health outcomes (type 2 diabetes, IHD and colorectal cancer), between SSB intake and two outcomes (type 2 diabetes and IHD) and between TFA consumption and one outcome (IHD). These risk–outcome pairs were selected based on their inclusion—initially predicated on World Cancer Research Fund grades of convincing or probable evidence—in GBD 2021[5]. To accurately and reliably capture disease risk across the full intake range observed in input studies, we used Burden of Proof meta-regression methods[25] designed to (1) flexibly model risk–outcome associations that may not be linearly related across the entire relative risk function and (2) conservatively estimate relationships, accounting for consistency and inconsistency across input study findings. Results and policy implications of this study are summarized in Table 1.

Table 1 | Policy summary

Background	Previous research has indicated adverse effects of processed meat, SSB and TFA consumption on chronic disease outcomes. However, confidence in these findings has been limited by heterogeneous findings across research studies. In this meta-regression, we examined the relationships between processed meat and risk of type 2 diabetes, IHD and colorectal cancer; between SSBs and type 2 diabetes and IHD; and between TFAs and IHD. Using Burden of Proof methods that flexibly model nonlinear relationships and quantify and incorporate between-study heterogeneity, we generated measures that capture the strength of the input evidence and provide conservative estimates of association to more accurately and reliably identify adverse risk–outcome relationships.
Main findings and limitations	On the basis of our conservative interpretation of available data, we found that consuming processed meat at levels between the 15th and 85th percentiles of exposure observed in the data analyzed was associated, on average, with at least an 11% increased risk (at consumption levels between 0.6 g d^{-1} and 57 g d^{-1}) of type 2 diabetes and 7% increased risk (0.78–55 g d^{-1}) of colorectal cancer. SSB consumption was associated with at least 8% (1.5–390 g d^{-1}) and 2% (0–365 g d^{-1}) average increases in risk of type 2 diabetes and IHD, respectively. TFA consumption at 0.25–2.56% of daily energy intake was associated with at least a 3% average increase in IHD risk. In the Burden of Proof framework, these associations are rated as relatively weak two-star relationships, reflecting small effect sizes and/or lack of consistent evidence. We found a weaker one-star association between processed meat and IHD that did not support calculating percentage change in IHD risk; this finding may change with the addition of new evidence. Importantly, we observed, for all risk–outcome pairs analyzed, a monotonic increase in risk of the specified disease outcomes at all levels of consumption, with the steepest increases in risk occurring at exposure levels approximately equivalent to one serving or less for each dietary risk factor. The primary limitations of our meta-analysis were based on observational studies, which are prone to residual confounding, and the fact that the dominant exposure assessment method—the FFQ—is susceptible to measurement errors.
Policy implications	This study found evidence—under a conservative interpretation of the available data—to justify robust efforts and policies to promote the reduced consumption of processed meat, SSBs and TFAs, particularly industrially produced TFAs, to reduce the risk of chronic diseases. Our finding supports the recent initiative of the WHO to ban industrially produced trans fats and their call to tax SSBs to reduce diet-related noncommunicable diseases. Our observation that the greatest increases in disease risk occurred at low intake levels suggests that even lower levels of habitual consumption of these dietary risk factors are not safe. Policies promoting access to and affordability of healthier food options could help mitigate the risks associated with the consumption of processed meats, SSBs and TFAs. Therefore, efforts must be intensified to increase public awareness and policy action to reduce the consumption of these dietary risk factors and promotion of healthier food options. Future meta-analysis studies should prioritize examining the relationship between processed meat consumption and IHD, as the existing evidence, when interpreted conservatively, is weak.

Results

Overview

In this study, we conducted systematic reviews and meta-analyses to evaluate the dose–response associations between processed meat consumption and three chronic disease outcomes (type 2 diabetes, IHD and colorectal cancer); between SSB consumption and type 2 diabetes and IHD; and between TFA consumption and IHD based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[26]. The PRISMA workflow diagrams for processed meat are described in Extended Data Figs. 1–3. The PRISMA flow diagrams for the SSB and TFA systematic reviews are described in Extended Data Figs. 4–6. Further details on our search strategy and inclusionary and exclusionary criteria are detailed in Methods, Supplementary Sections 1–3 and Supplementary Tables 1–4. The characteristics of the studies included in these systematic reviews are presented in Supplementary Table 5. The definitions of bias covariates (Supplementary Table 6) and the bias covariate scores of each study are reported in Supplementary Tables 7–9. Most of the studies adjusted their effect size for age, sex, body mass index (BMI) and energy intake (Supplementary Tables 8 and 9).

Processed meat consumption and type 2 diabetes

Our analysis of processed meat consumption and type 2 diabetes included 96 observations from 15 prospective cohort studies[27–41] and one nested case–control study[42], which included a total of 1,115,885 participants and 64,607 type 2 diabetes events. The follow-up period ranged from 4.6 years to 40 years. Most of the studies ($n = 12$)[28,30–35,37,38,40–42] used type 2 diabetes incidence as the endpoint to estimate effect sizes, while four studies[27,29,36,39] considered both diabetes incidence and mortality as endpoints. Six studies[29,35,37,38,41] determined outcomes using administrative medical records, disease registries or death certificates; five studies used self-reported incidence[30,34,38,41,42]; three cohort studies used biomarkers[28,29,32]; and two cohorts used physician diagnosis[37,40].

https://doi.org/10.1038/s41591-025-03775-8

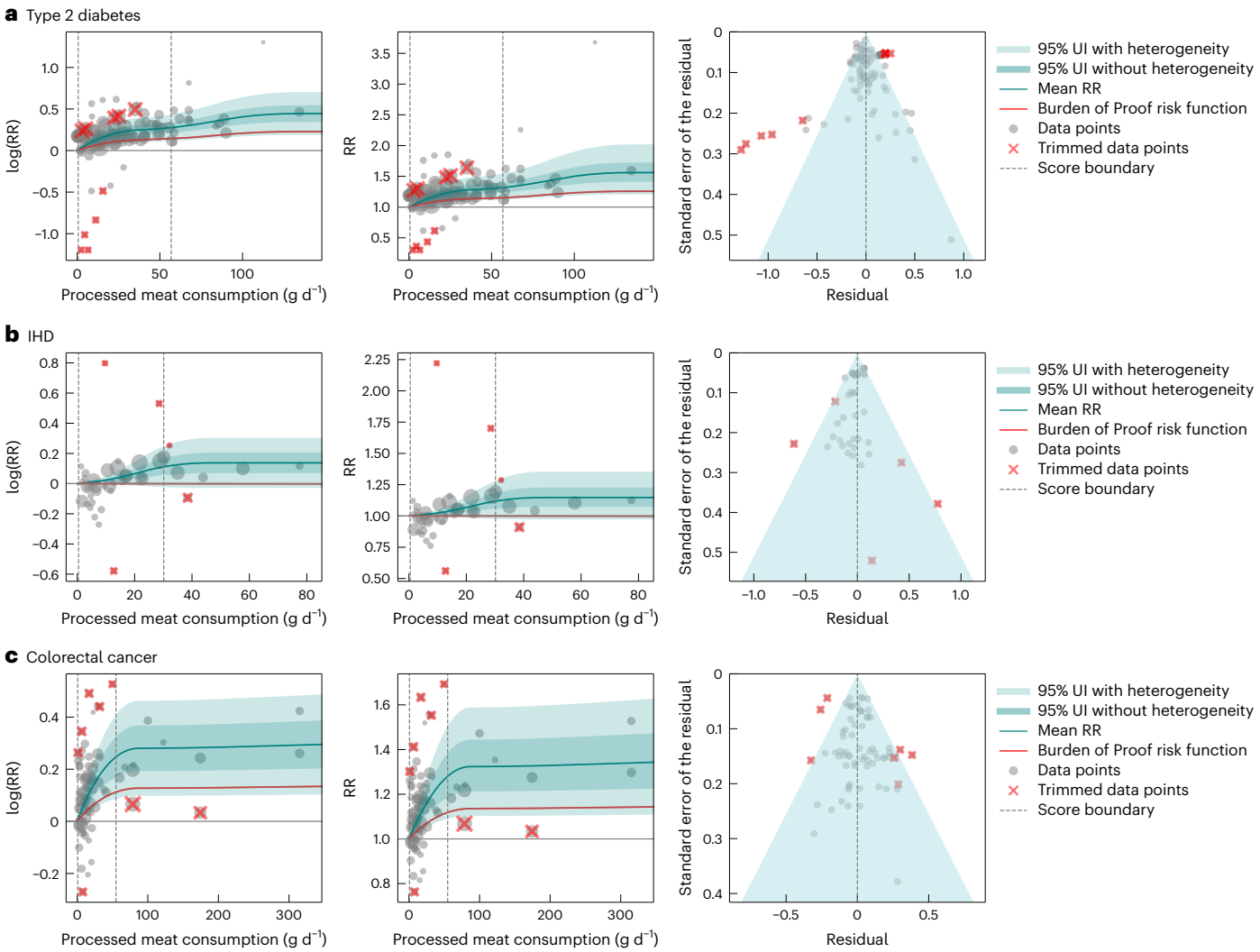


Fig. 1 | Relative risk of processed meat consumption on type 2 diabetes, IHD and colorectal cancer. a–c, The log(RR) function, the RR function and a modified funnel plot showing the residuals (relative to 0) on the *x* axis and the estimated standard error that includes the reported standard error and between-study heterogeneity on the *y* axis, for type 2 diabetes (**a**), IHD (**b**) and colorectal cancer (**c**). UI, uncertainty interval.

All studies adjusted their effect size measure for age and sex. All studies except one adjusted for smoking. Other common adjustment variables included energy intake ($n = 13$)[28,30–35,37,38,40–42], alcohol consumption ($n = 12$)[27–30,32,33,36–38,40–42] and BMI ($n = 14$)[27–30,32–36,38–42].

We observed a statistically significant, nonlinear, monotonic increase in type 2 diabetes risk associated with higher processed meat consumption; that is, disease risk increased with increased intake at all intake levels but, for a given unit increase in consumption risk, increased most steeply at lower intake levels (Fig. 1a). The mean relative risk (RR) of developing type 2 diabetes was 1.30 (1.12–1.52) at a daily intake of 50 g of processed meat compared with the theoretical minimum risk exposure level (TMREL; equal here to 0 g d^{-1} or no consumption).

As a complement to the main RR function, we generated a conservatively derived Burden of Proof risk function (BPRF), which, averaged across the central part of the exposure range, yielded an estimate of 1.11, indicating that consuming processed meat in the range of the 15th to 85th percentiles of exposure (0.6–57 g d^{-1}), compared with consuming no processed meat, was associated on average with at least an 11% higher risk of type 2 diabetes. This BPRF equated to a risk–outcome score (that is, the signed value of the average log(BPRF)) of 0.10, corresponding to a two-star rating within the Burden of Proof framework. We observed asymmetry in the funnel plot (Fig. 1a), and the result of Egger's regression suggested statistically significant evidence of publication or reporting bias (Egger's regression *P* value = 0.0001) (Table 2). We found that trimming had a substantial effect on the risk–outcome score: without trimming, the risk–outcome score increased to 0.14 suggesting that the conservatively estimated association between processed consumption and type 2 diabetes is relatively sensitive to outliers (Extended Data Fig. 7a and Supplementary Table 17).

Processed meat consumption and IHD

In the processed meat consumption and IHD systematic review, we included 11 prospective cohort studies[36,43–52] representing a total of 1,173,821 participants and 31,549 IHD events. The median (range) follow-up period was 14 years (8–30 years). Most of the studies used incidence and mortality as the endpoints[36,43–46,48,49], based on administrative medical records, disease registries or death certificates[36,43–46,48–52]. All of the studies adjusted their effect size measure for age and sex. Most of the studies adjusted for physical activity ($n = 9$)[36,43,44,46–51], BMI ($n = 9$)[36,43–46,48–51], smoking ($n = 10$)[36,43,44,46–52] and energy intake ($n = 8$)[43,44,46–51].

We observed a weak, nonlinear, monotonic increase in IHD risk associated with processed meat consumption when accounting for between-study heterogeneity (Fig. 1b). We estimated the RR to be 1.15 (0.97–1.36) at 50 g d^{-1} consumption of processed meat compared with

Table 2 | Strength of the evidence for the relationship between processed meat, SSB and TFA consumption and health outcomes

Risk–outcome pair	85th percentile exposure level	Unit of exposure	RR (95% UI with γ)	RR (95% UI without γ)	BPRF	Risk–outcome score	Star rating	Publication bias	Number of studies
Processed meat–type 2 diabetes	56.81	g d^{-1}	1.32 (1.12, 1.55)	1.32 (1.24, 1.4)	11%	0.1	☆☆	Yes	16
Processed meat–colorectal cancer	54.88	g d^{-1}	1.28 (1.09, 1.5)	1.28 (1.19, 1.38)	7%	0.07	☆☆	No	18
Processed meat–IHD	30.16	g d^{-1}	1.12 (0.98, 1.28)	1.13 (1.06, 1.18)	NA	−0.001	☆	No	11
SSB–type 2 diabetes	390	g d^{-1}	1.24 (1.09, 1.41)	1.24 (1.19, 1.29)	8%	0.07	☆☆	No	19
SSB–IHD	365	g d^{-1}	1.12 (1.04, 1.2)	1.12 (1.08, 1.15)	2%	0.02	☆☆	No	8
Trans fat–IHD	2.56	Percentage of daily energy intake	1.24 (1.01, 1.52)	1.24 (1.15, 1.33)	3%	0.03	☆☆	No	6

The reported RR and its 95% UI reflect the risk an individual who has been exposed to the dietary risk factor of interest (that is, processed meat, SSB and TFA consumption) has of developing the outcome of interest relative to that of someone who has not been exposed. We report the 95% UI when not incorporating between-study heterogeneity (γ)—'95% UI without γ'—and when accounting for between-study heterogeneity—'95% UI with γ'. The BPRF is calculated for risk–outcome pairs that were found to have significant relationships at the 0.05 level of significance when not incorporating between-study heterogeneity (that is, the lower bound of the 95% UI without γ does not cross the null RR value of 1). The BPRF corresponds to the 5th quantile estimate of relative risk accounting for between-study heterogeneity closest to the null for each risk–outcome pair, and it reflects the most conservative estimate of excess risk associated with dietary risk factors of interest that is consistent with the available data. Negative risk–outcome scores indicate that the evidence of the association is very weak and inconsistent. For ease of interpretation, we have transformed the risk–outcome scores and BPRF into a star rating (0–5) with a higher rating representing a larger effect with stronger evidence. The selected bias covariates were chosen for inclusion in the model using an algorithm that systematically detects bias covariates that correspond to significant sources of bias in the observations included. If selected, the observations were adjusted to better reflect the gold standard values of the covariate. For more information about the definition of candidate bias covariates, see Supplementary Table 6, and for the bias covariates selected for each model, refer to Supplementary Table 12. NA, not available.

no consumption (Fig. 1b and Supplementary Table 14). Our conservative analysis yielded a risk–outcome score of −0.001, corresponding to a one-star rating, indicating a weak association after accounting for between-study heterogeneity. We did not find significant evidence of publication or reporting bias, and visual inspection of the funnel plot provided no evidence of substantial bias. The risk–outcome score calculated without trimming was consistent with the model using trimming (risk–outcome score = −0.01), which indicates that the model is insensitive to outliers (Extended Data Fig. 7b and Supplementary Table 17).

Processed meat consumption and colorectal cancer

In the meta-analysis that examined the association between processed meat consumption and colorectal cancer, we included 18 prospective cohort studies[53–70] with a total of 2,678,052 participants and 30,259 colorectal cancer events. The median (range) of follow-up was 9 years (5–27 years). Most of the studies (n = 15)[53–58,60–63,65,66,68–70] used incidence of colorectal cancer as an endpoint, and the remaining three studies used both incidence and mortality. Most of the studies (n = 14)[53,54,56–58,60–63,65–67,69,70] used administrative medical records or disease registries to determine the occurrence of colorectal cancer. All studies adjusted their effect size measures for age and sex. Most of the studies adjusted for BMI (n = 14)[53,55,56,58,59,61–66,68–70], smoking (n = 14)[53,55,56,58–62,64,66–70], education (n = 11)[53,55,56,58–60,63,65,66,69,70], energy intake (n = 15)[53–61,63–68], physical activity (n = 13)[53,55,59–62,64–70] and alcohol intake (n = 14)[53,55,58–64,66–70].

We observed a statistically significant nonlinear monotonic increase in colorectal cancer risk associated with higher processed meat consumption (Fig. 1c). The mean RR of developing colorectal cancer risk was 1.26 (1.08–1.47) at a daily intake of 50 g of processed meat compared with the TMREL (that is, no consumption). We estimated the exposure-averaged BPRF to be 1.07, indicating that consuming processed meat in the range of the 15th to 85th percentiles of exposure (0.78–55 g)—compared with consuming no processed meat—was associated with at least a 7% higher risk, on average, of colorectal cancer. The risk–outcome score (0.07) equates to a two-star rating, indicating a weak association between processed meat and colorectal cancer when accounting for between-study heterogeneity. We did not find significant evidence of publication bias. We found that using untrimmed data impacted between-study heterogeneity and notably influenced the risk–outcome score (0.02) but did not change the star rating of the strength of the evidence (Extended Data Fig. 7c and Supplementary Table 17).

SSB consumption and type 2 diabetes

Our analysis of SSB consumption and type 2 diabetes included 92 observations from 18 prospective cohort studies[71–88] and one nested case–control study[89], representing a total of 563,444 participants and 39,505 type 2 diabetes events. All studies used type 2 diabetes incidence as the endpoint to estimate effect sizes. A total of 14 studies used self-reported incidence[71,73–77,79–84,87,89]; 2 studies[72,78] used administrative medical records, disease registries or death certificates; and 1 study[88] used physician diagnosis to determine the outcome. All studies adjusted their effect size measure for age, sex, BMI and physical activity. All studies[71–87,89] except one adjusted for smoking. Other common adjustment variables included energy intake (n = 14)[71–76,78–80,84–87,89], alcohol consumption (n = 14)[71,73–75,77,79,80,82–87,89], education level (n = 14)[71–74,76,77,79–84,87,89] and hypertension (n = 8)[10,71,73–75,83–85].

We observed a statistically significant, nonlinear, monotonic increase in type 2 diabetes risk associated with higher SSB consumption (Fig. 2a). The mean RR of type 2 diabetes at a consumption level of 250 g d^{-1} (~8 oz) was 1.20 (1.07–1.34) compared with the TMREL (0 g d^{-1}) (Supplementary Table 15).

We estimated the exposure-averaged BPRF to be 1.08, indicating that consuming SSB in the range of the 15th to 85th percentiles of exposure (1.5–390 g d^{-1}) was associated, on average, with at least an 8% higher risk of type 2 diabetes. This BPRF equated to a risk–outcome score of 0.07, corresponding to a two-star rating (Table 2). We did not observe statistically significant evidence of publication or reporting bias (Egger's regression P value = 0.25) (Fig. 2a). We found that trimming had a minimal impact on the risk–outcome score, and without trimming, the risk–outcome score was 0.07 (Extended Data Fig. 8a and Supplementary Table 17).

SSB consumption and IHD

Our analysis of SSB consumption and IHD included 27 observations from 8 studies[90–97], representing a total of 961,176 participants and 24,542 IHD events. Three studies estimated effect size using IHD mortality[93,95,96] as the endpoint, and six studies evaluated both IHD

https://doi.org/10.1038/s41591-025-03775-8

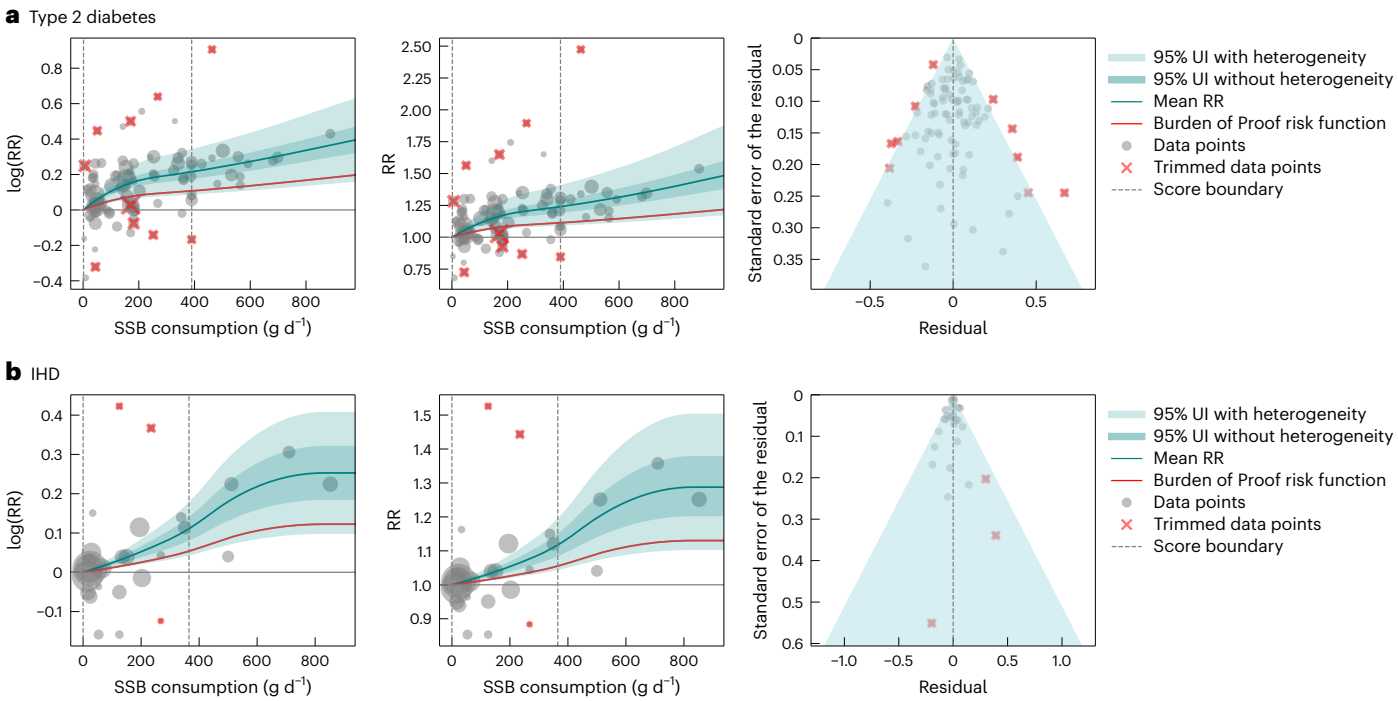


Fig. 2 | Relative risk of SSBs on type 2 diabetes and IHD. a,**b**, The log(RR) function, the RR function and a modified funnel plot showing the residuals (relative to 0) on the *x* axis and the estimated standard error that includes the reported standard error and between-study heterogeneity on the *y* axis, for type 2 diabetes (**a**) and IHD (**b**).

incidence and mortality as endpoints[90–92,94,96,97]. All studies determined outcomes using administrative medical records, disease registries or death certificates[90–97]. All studies adjusted their effect size measure for age, sex, smoking, physical activity, BMI and alcohol intake.

We observed a statistically significant, nonlinear, monotonic increase in IHD risk associated with higher SSB consumption (Fig. 2b). Compared with no consumption, the mean RR of IHD at a consumption level of 250 g d^{-1} (~8 oz) was 1.07 (1.03–1.12). We estimated the exposure-averaged BPRF to be 1.03, indicating that consuming SSB in the range of the 15th to 85th percentiles of exposure (0–365 g d^{-1}) was associated, on average, with at least a 2% higher risk of IHD. The BPRF equated to a risk–outcome score of 0.02, corresponding to a two-star rating. Egger's regression did not show statistically significant evidence of publication or reporting bias (Egger's regression *P* value = 0.36) (Table 2 and Fig. 2b). We found that trimming had no effect on the risk–outcome score (Extended Data Fig. 8b and Supplementary Table 17).

TFA consumption and IHD

We identified six prospective cohort studies to evaluate the relationship between TFA consumption[98–103] and IHD, representing 226,509 individuals and 12,548 IHD events. The median follow-up was 24 years (range, 6–30 years). All studies determined outcomes using administrative medical records or disease registries. In all studies, the effect size measures were adjusted for sex, BMI, energy intake and smoking. All studies adjusted the effect size for age except one[98,100–103]. Most of the studies adjusted their effect size for alcohol intake[99–103]. Four of the six studies adjusted their effect size for education[98,99,101,102] or hypertension[99,101–103]. Three studies adjusted their effect size measures for physical activity[99,101,102].

We observed a nonlinear, monotonic increase in risk of IHD with increasing consumption of TFAs (Fig. 3). The mean RR of IHD at 1% of daily energy intake from TFA compared with no TFA intake was 1.11 (1.00–1.24). Consumption of TFAs at higher levels (2% of daily energy intake) was associated with a 1.20 (1.00–1.44) increased risk of IHD. We observed considerable between-study heterogeneity (Fig. 3 and Supplementary Table 16).

When between-study heterogeneity was accounted for, our conservative interpretation of the evidence suggested that consuming TFA in the range of the 15th to 85th percentiles of exposure (0.25–2.56% of daily energy intake) increases the risk of IHD, on average, by at least 3%. This corresponded to a risk–outcome score of 0.03 (Table 2). This risk–outcome score equates to a two-star rating, indicating the association between TFA and IHD is weak but significant when accounting for between-study heterogeneity. There was no statistically significant evidence of publication or reporting bias (Egger's regression *P* value = 0.44). We found that trimming had a substantial effect on the risk–outcome score; without trimming, the risk–outcome score decreased to −0.12, which equates to a one-star rating, suggesting that the risk–outcome score for TFA consumption and IHD is sensitive to outliers (Extended Data Fig. 9).

Discussion

This meta-analysis evaluated the dose–response relationships between processed meat consumption and three chronic disease outcomes—type 2 diabetes, IHD and colorectal cancer; between SSB intake and type 2 diabetes and IHD; and between TFA consumption and IHD. For all six risk–outcome pairs assessed, even our intentionally conservative BPRF summary measures showed that a higher intake of the processed food under evaluation was associated with significantly increased risk of the specified health outcome. Higher consumption of processed meats was associated with increased risk of type 2 diabetes, colorectal cancer and IHD; a higher intake of SSBs was associated with increased type 2 diabetes and IHD risk; and increased consumption of TFAs was associated with increased IHD risk. Except for the association between processed meat consumption and IHD—which received a one-star rating suggesting a weaker association and/or less consistent evidence base—all of the risk–outcome relationships received two-star ratings, also defined as weak within the Burden of Proof framework. However, these low star ratings serve to indicate the need for further research to resolve inconsistencies across input study findings and clarify the level of health threat posed by increased consumption of the processed food in question. Moreover, the policy relevance of a risk factor must depend

https://doi.org/10.1038/s41591-025-03775-8

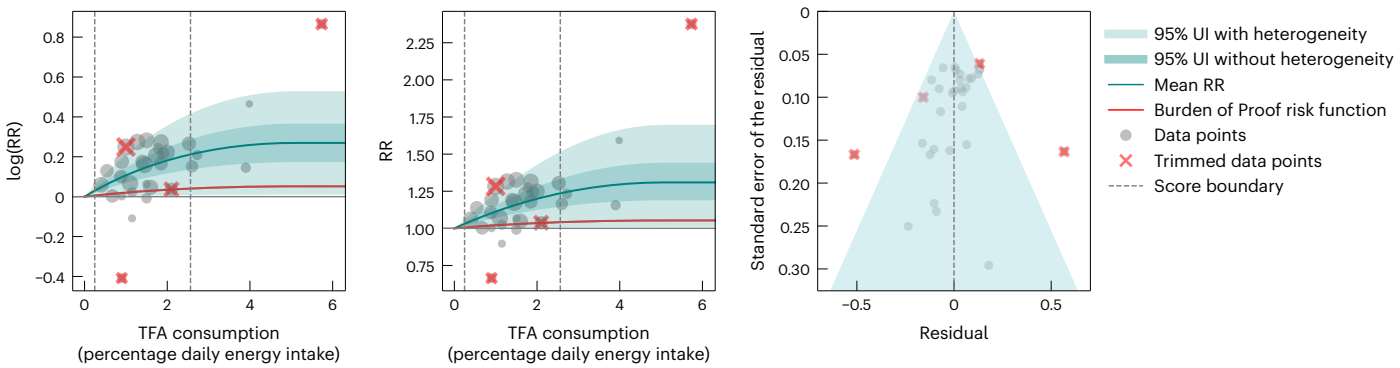


Fig. 3 | Relative risk of trans fat consumption and IHD. The log(RR) function, the RR function and a modified funnel plot showing the residuals (relative to 0) on the *x* axis and the estimated standard error that includes the reported standard error and between-study heterogeneity on the *y* axis.

both on the magnitude of the association and strength of underlying evidence along with the prevalence of the risk factor and associated disease outcomes.

Because Burden of Proof meta-regression methods allowed us to capture the shape of the risk–outcome association from the data rather than enforcing previous assumptions such as log-linearity, our findings more accurately reflect the dose–response relationship at specific levels of consumption than do results from traditional meta-analyses. For all six of the RR curves generated by our analysis, health risk increased monotonically; that is, across the full range of exposure, risk increased as consumption increased. Notably, however, the steepest slopes of the risk curves occurred at exposure levels approximately equivalent to one serving or less for each of the dietary risk factors. This indicates that the health risks associated with consuming processed meats, SSBs and TFAs increased the fastest at low levels of consumption, that is, one serving size a day. This information provides critical data for public health specialists and policymakers responsible for dietary guidelines and potential initiatives that aim to reduce the consumption of these processed foods.

With respect to specific risk–outcome pairs, our analyses yielded two-star ratings for the association of processed meat consumption with type 2 diabetes and with colorectal cancer, and—even based on our conservatively derived summary estimates—showed that consumption at commonly observed levels (compared with zero consumption) was associated with at least an 11% average increase in type 2 diabetes risk and 7% average increase in colorectal cancer risk. Our RR curves showed that regularly consuming 50 g d^{-1} of processed meat, roughly equivalent to eating a standard-sized hotdog, was associated with a 30% increase in type 2 diabetes risk and a 26% increase in colorectal cancer risk. The monotonic increases in health risk with increased consumption of processed meat suggest that there is not a 'safe' amount of processed meat consumption with respect to diabetes or colorectal cancer risk. Our findings are consistent with the World Health Organization (WHO) designation of processed meat as carcinogenic to humans[104] and designations by the World Cancer Research Fund and the American Institute for Cancer Research of processed meat consumption as a risk factor for colon cancer. The majority of the existing dietary guidelines provide qualitative recommendations to limit or avoid the consumption of processed meat without specifying intake levels, although a few do provide quantitative recommendations. On the basis of our findings, dietary guidelines should note the potential health risks of consuming even small amounts of processed meat.

Regarding the relationship between processed meat and IHD, our conservative interpretation indicates that the evidence for an association is weak, yielding a one-star rating owing to a negative risk–outcome score value. One-star ratings reflect risk–outcome relationships that are statistically significant using conventional analytic methods but do not achieve significance based on conservative BPRF methods incorporating between-study heterogeneity. For all of our analyses of processed meat consumption, we found considerable heterogeneity among input study findings, which contributed to low star ratings reflecting a combination of low effect size and/or inconsistent input evidence. This heterogeneity probably resulted from variations in input study characteristics that we were unable to fully account for with our covariate selection and adjustment methods, in addition to the impact of potential effect modifiers such as genetic factors[105] and confounders. Further research is needed to untangle confounding effects and ultimately coalesce on a more consistent body of evidence.

With respect to SSBs, they are an important source of added sugars in the diet, with consumption increasing globally[5,19]. Our conservative interpretation of the available evidence, based on BPRF metrics, showed that commonly observed SSB consumption levels were associated with at least an 8% average increase in type 2 diabetes risk and at least a 2% increase in IHD risk, equating to two-star ratings. As with processed meat consumption, the RR curves we derived showed monotonic increases in type 2 diabetes and IHD risk with increased SSB consumption; that is, across the entire intake range, any increase in SSB consumption was associated with increased disease risk, with the steepest increases in risk observed at intake levels below 250 g d^{-1}, roughly equivalent to 9 oz of soda or three-fourths of a typical soda drink. Our findings support the need for initiatives to avoid and reduce the consumption of SSBs[106,107]. The WHO recommends limiting the intake of added sugar, including SSBs, to 10% of total caloric intake and a further reduction below 5% total caloric intake for additional health benefits[108]. The Dietary Guidelines for Americans recommend limiting the intake of added sugar, including SSBs, to below 10% (ref. 109).

The relatively low two-star ratings for the disease outcomes tested in association with SSB intake were probably due in large part to high between-study heterogeneity, potentially resulting from variable health effects of particular SSBs depending on the amount of sugar content. Our SSB–type 2 diabetes model did test and include as a bias covariate whether input studies provided a clear definition of SSB (that is, whether sugar was explicitly mentioned as a sweetener). However, this covariate could not be used as a proxy measure for the sugar content of SSBs, meaning it could not fully account for the heterogeneity associated with variation in the sugar content of SSBs. It is also noteworthy that all the SSB studies included in our analysis adjusted their effect size measures for BMI and for physical activity, and the majority accounted for energy intake. These adjustments reduced the likelihood that our estimates of increased type 2 diabetes and IHD risk associated with SSB consumption were mediated through effects of SSBs on BMI, energy intake or physical activity.

On the basis of our meta-analysis examining the relationship between TFAs and IHD, our conservative BPRF estimate showed that commonly observed TFA consumption primarily from industrially

produced trans fat sources (0.24–2.5% of daily energy intake) was associated with at least a 3% average increased risk of IHD, equating to a two-star association. The RR curve indicated a monotonic increase in IHD risk associated with increased TFA consumption, with no safe level of exposure observed for industrially produced trans fats. The relatively low star rating is again due in large part to high between-study heterogeneity, probably resulting from residual confounding and measurement error. In the input studies included in our meta-analysis, only a single study adjusted its effect size measurement for saturated fat intake, and none adjusted for other potential diet-related confounders including sodium, SSB and processed meat intake. Our findings support the need for initiatives such as the best practice policies recommended by the WHO that aim to eliminate industrially produced TFAs from the food supply[110]. One policy is to establish mandatory national limits of 2 g of industrial trans fat per 100 g of total fat in all foods. The WHO additionally recommends instituting mandatory bans on the production and/or use of partially hydrogenated oil as an ingredient in all foods. The 'REPLACE' action package, developed by the WHO, supports the design and implementation of policies to eliminate industrially produced TFAs from the food supply.

All observational nutritional cohort analyses based on self-report and recall to quantify intake levels are subject to measurement error and residual confounding[111–113]. The present risk–outcome analyses are likewise susceptible to such errors; to the extent we were unable to account for them, they were likely primary contributors to the high between-study heterogeneity that resulted in the relatively low star ratings. To account for confounding, Burden of Proof methods systematically test and adjust for bias covariates that might influence the estimated risk–outcome relationship. An important bias covariate that we tested for was whether input studies adjusted their effect size for energy intake, a well-known approach in nutritional epidemiology studies[114,115]. Most of the studies included in our analyses made this adjustment, and it therefore was not identified by our algorithm as a significant bias covariate in our models. In addition to energy intake, we also accounted for whether studies adjusted for other dietary factors (for example, consumption of fruits and vegetables, unprocessed meat and alcohol) that could potentially confound the association between the dietary risk factors under investigation here and each outcome of interest. Relatively few input studies adjusted their effect size for these dietary factors, except for alcohol intake. Importantly, our bias covariate selection and adjustment methods were not able to eliminate all residual confounding and did not address the measurement error intrinsic in dietary assessment tools[111,112,116].

Although the primarily two-star (and one one-star) ratings we obtained for the risk–outcome associations evaluated in this study are considered relatively weak, this is in large part due to high between-study heterogeneity leading to wide uncertainty intervals, as estimated in the Burden of Proof framework, and the balance of evidence still points to adverse health outcomes associated with these foods. Policymakers should continue advocating for measures that reduce intake of processed meat, SSBs and TFAs as these food items are consumed widely and are associated with diseases that are highly prevalent[117]. In addition, nutritional epidemiology studies must incorporate advances in technology and new analytical techniques to address existing methodological challenges. For example, nutritional epidemiology studies can benefit considerably from recent developments in artificial intelligence and 'omics' technologies. Artificial intelligence-assisted dietary assessment has substantially reduced measurement error associated with dietary recall[118–120], a major challenge in nutritional epidemiology studies. The use of Mendelian randomization techniques, which use study participants' genetic profiles to predict their intake levels rather than relying on self-report and recall, show promise as a way to reduce the effects of residual confounding in analyses estimating associations between dietary intake factors and health outcomes[121,122].

The results of our meta-analysis are subject to a number of limitations. In our analysis, we investigated a small set of health outcomes for each dietary risk factor—limited to the relevant risk–outcome pairs included in GBD 2021—which did not encompass all possible health outcomes associated with these risk factors. Expanding the pool of potential health outcomes associated with these dietary risks could allow for a more complete accounting of the evidence and associated burden in the future. In addition, we focused on three dietary risk factors that are components of ultra-processed foods, but we did not investigate the health effects of other potentially harmful ultra-processed foods such as sweetened breakfast cereals and processed cheese products. We included prospective cohort and case–cohort studies, which inherently introduce residual confounding that our methods cannot completely eliminate. As noted previously, a considerable number of the studies included in this meta-analysis did not account for dietary confounding factors beyond energy intake. In addition, the primary exposure assessment tool in almost all studies included was the food frequency questionnaire (FFQ). The FFQ can introduce measurement errors arising primarily from difficulties experienced by respondents recalling long-term intake, along with instrument-specific limitations such as the finite inventory of foods listed and lack of detailed information about the foods. Several of the studies included assessed dietary exposure only at baseline, which might not accurately reflect future dietary habits. Furthermore, even though investigations of diet–gene interactions are becoming more common, we could not include genetic predisposition as a bias covariate in our analysis owing to the absence of genetic information in the studies included. When studies reported effect sizes for total TFA consumption without stratifying by TFA source (ruminant versus industrial), we elected to assume that the majority of the TFA was industrially produced. The risk model we use is based on effect sizes derived from incidence and/or mortality data, and we were unable to run separate models for incidence and mortality owing to data scarcity, except in the case of SSB–type 2 diabetes. Finally, although many of the studies included reported serving sizes in grams, some did not define serving size. In these cases, we applied a constant conversion factor to translate serving size into grams, which might not be consistent with the definition of and perception of serving size within the given study's context.

In conclusion, our conservative BPRF metrics support recommendations to avoid or limit the consumption of processed meat, SSBs and TFAs owing to their associations with prevalent chronic diseases. However, our analyses of the currently available evidence yielded associations with one- to two-star ratings, owing in large part to substantial heterogeneity between studies—probably attributable to differences in study-level characteristics, residual confounding and measurement error that we were unable to control for. To the extent these star ratings—particularly the one-star rating for the association between processed meat and IHD—reflect a lack of consistent data, they highlight the need for stronger, more diverse evidence beyond conventional observational epidemiological studies.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03775-8.

References

1. Monteiro, C. A. et al. Ultra-processed foods: what they are and how to identify them. *Public Health Nutr.* **22**, 936–941 (2019).
2. Lane, M. M. et al. Ultra-processed food exposure and adverse health outcomes: umbrella review of epidemiological meta-analyses. *Br. Med. J.* https://doi.org/10.1136/bmj-2023-077310 (2024).

3. Mendoza, K. et al. Ultra-processed foods and cardiovascular disease: analysis of three large US prospective cohorts and a systematic review and meta-analysis of prospective cohort studies. *Lancet Reg. Health Am.* **37**, 100859 (2024).
4. Srour, B. et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). *Br. Med. J.* https://doi.org/10.1136/bmj.l1451 (2019).
5. Brauer, M. et al. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* **403**, 2162–2203 (2024).
6. Deveci, G. & Tek, N. A. N-Nitrosamines: a potential hazard in processed meat products. *J. Sci. Food Agric.* **104**, 2551–2560 (2024).
7. Lee, J.-G. et al. Effects of grilling procedures on levels of polycyclic aromatic hydrocarbons in grilled meats. *Food Chem.* **199**, 632–638 (2016).
8. Zheng, W. & Lee, S.-A. Well-done meat intake, heterocyclic amine exposure, and cancer risk. *Nutr. Cancer* **61**, 437–446 (2009).
9. López-Hernández, L. et al. Identifying predictors of the visceral fat index in the obese and overweight population to manage obesity: a randomized intervention study. *Obes. Facts* **13**, 403–414 (2020).
10. Huang, Y. et al. Associations of visceral adipose tissue, circulating protein biomarkers, and risk of cardiovascular diseases: a Mendelian randomization analysis. *Front. Cell Dev. Biol.* **10**, 840866 (2022).
11. Marques, M. D. et al. Relation between visceral fat and coronary artery disease evaluated by multidetector computed tomography. *Atherosclerosis* **209**, 481–486 (2010).
12. Oostindjer, M. et al. The role of red and processed meat in colorectal cancer development: a perspective. *Meat Sci.* **97**, 583–596 (2014).
13. Bellamri, M., Walmsley, S. J. & Turesky, R. J. Metabolism and biomarkers of heterocyclic aromatic amines in humans. *Genes Environ.* **43**, 29 (2021).
14. Lala, P. K. & Chakraborty, C. Role of nitric oxide in carcinogenesis and tumour progression. *Lancet Oncol.* **2**, 149–156 (2001).
15. Moorthy, B., Chu, C. & Carlin, D. J. Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. *Toxicol. Sci.* **145**, 5–15 (2015).
16. Rao, C. V. Nitric oxide signaling in colon cancer chemoprevention. *Mutat. Res.* **555**, 107–119 (2004).
17. Sánchez-Pimienta, T. G., Batis, C., Lutter, C. K. & Rivera, J. A. Sugar-sweetened beverages are the main sources of added sugar intake in the Mexican population. *J. Nutr.* **146**, 1888S–1896S (2016).
18. Vartanian, L. R., Schwartz, M. B. & Brownell, K. D. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am. J. Public Health* **97**, 667–675 (2007).
19. Lara-Castor, L. et al. Sugar-sweetened beverage intakes among adults between 1990 and 2018 in 185 countries. *Nat. Commun.* **14**, 5957 (2023).
20. Stender, S., Astrup, A. & Dyerberg, J. Ruminant and industrially produced trans fatty acids: health aspects. *Food Nutr. Res.* **52**, 1651 (2008).
21. Mozaffarian, D. et al. Dietary intake of trans fatty acids and systemic inflammation in women. *Am. J. Clin. Nutr.* **79**, 606–612 (2004).
22. Bendsen, N. T., Christensen, R., Bartels, E. M. & Astrup, A. Consumption of industrial and ruminant trans fatty acids and risk of coronary heart disease: a systematic review and meta-analysis of cohort studies. *Eur. J. Clin. Nutr.* **65**, 773–783 (2011).
23. Mozaffarian, D., Katan, M. B., Ascherio, A., Stampfer, M. J. & Willett, W. C. Trans fatty acids and cardiovascular disease. *N. Engl. J. Med.* **354**, 1601–1613 (2006).
24. Naghavi, M. et al. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* **403**, 2100–2132 (2024).
25. Zheng, P. et al. The Burden of Proof studies: assessing the evidence of risk. *Nat. Med.* **28**, 2038–2044 (2022).
26. Page, M. J. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br. Med. J.* https://doi.org/10.1136/bmj.n71 (2021).
27. Ericson, U. et al. Food sources of fat may clarify the inconsistent role of dietary fat intake for incidence of type 2 diabetes. *Am. J. Clin. Nutr.* **101**, 1065–1080 (2015).
28. Fretts, A. M. et al. Associations of processed meat and unprocessed red meat intake with incident diabetes: the Strong Heart Family Study. *Am. J. Clin. Nutr.* **95**, 752–758 (2012).
29. Gu, X. et al. Red meat intake and risk of type 2 diabetes in a prospective cohort study of United States females and males. *Am. J. Clin. Nutr.* **118**, 1153–1163 (2023).
30. Kurotani, K. et al. Red meat consumption is associated with the risk of type 2 diabetes in men but not in women: a Japan Public Health Center-based Prospective Study. *Br. J. Nutr.* **110**, 1910–1918 (2013).
31. Lajous, M. et al. Processed and unprocessed red meat consumption and incident type 2 diabetes among French women. *Diabetes Care* **35**, 128–130 (2012).
32. Liu, M. et al. Quantity and variety of food groups consumption and the risk of diabetes in adults: a prospective cohort study. *Clin. Nutr.* **40**, 5710–5717 (2021).
33. Männistö, S., Kontto, J., Kataja-Tuomola, M., Albanes, D. & Virtamo, J. High processed meat consumption is a risk factor of type 2 diabetes in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study. *Br. J. Nutr.* **103**, 1817–1822 (2010).
34. Mari-Sanchis, A. et al. Meat consumption and risk of developing type 2 diabetes in the SUN project: a highly educated middle-class population. *PLoS ONE* **11**, e0157990 (2016).
35. Montonen, J. et al. Food consumption and the incidence of type II diabetes mellitus. *Eur. J. Clin. Nutr.* **59**, 441–448 (2005).
36. Papier, K. et al. Meat consumption and risk of 25 common conditions: outcome-wide analyses in 475,000 men and women in the UK Biobank study. *BMC Med.* **19**, 53 (2021).
37. Son, J., Lee, Y. & Park, K. Effects of processed red meat consumption on the risk of type 2 diabetes and cardiovascular diseases among Korean adults: the Korean Genome and Epidemiology Study. *Eur. J. Nutr.* **58**, 2477–2484 (2019).
38. Song, Y., Manson, J. E., Buring, J. E. & Liu, S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women. *Diabetes Care* **27**, 2108–2115 (2004).
39. Steinbrecher, A., Erber, E., Grandinetti, A., Kolonel, L. & Maskarinec, G. Meat consumption and risk of type 2 diabetes: the Multiethnic Cohort. *Public Health Nutr.* **14**, 568–574 (2011).
40. Van Woudenbergh, G. J. et al. Meat consumption and its association with C-reactive protein and incident type 2 diabetes. *Diabetes Care* **35**, 1499–1505 (2012).
41. Villegas, R. et al. The association of meat intake and the risk of type 2 diabetes may be modified by body weight. *Int. J. Med. Sci.* https://doi.org/10.7150/ijms.3.152 (2006).
42. The InterAct Consortium. Association between dietary meat consumption and incident type 2 diabetes: the EPIC-InterAct study. *Diabetologia* **56**, 47–59 (2013).
43. Al-Shaar, L. et al. Red meat intake and risk of coronary heart disease among US men: prospective cohort study. *BMJ* https://doi.org/10.1136/bmj.m4141 (2020).

44. Bernstein, A. M. et al. Major dietary protein sources and risk of coronary heart disease in women. *Circulation* **122**, 876–883 (2010).
45. Burke, V. et al. Health-related behaviours as predictors of mortality and morbidity in Australian Aborigines. *Prev. Med.* **44**, 135–142 (2007).
46. Haring, B. et al. Dietary protein intake and coronary heart disease in a large community based cohort: results from the Atherosclerosis Risk in Communities (ARIC) study. *PLoS ONE* **9**, e109552 (2014).
47. Iqbal, R. et al. Associations of unprocessed and processed meat intake with mortality and cardiovascular disease in 21 countries [Prospective Urban Rural Epidemiology (PURE) Study]: a prospective cohort study. *Am. J. Clin. Nutr.* **114**, 1049–1058 (2021).
48. Key, T. J. et al. Consumption of meat, fish, dairy products, and eggs and risk of ischemic heart disease: a prospective study of 7198 incident cases among 409 885 participants in the Pan-European EPIC Cohort. *Circulation* **139**, 2835–2845 (2019).
49. Møller, S. P., Mejborn, H., Christensen, A. I., Biltoft-Jensen, A. & Thygesen, L. C. Meat consumption, stratified by dietary quality, and risk of heart disease. *Br. J. Nutr.* **126**, 1881–1887 (2021).
50. Nagao, M. et al. Meat consumption in relation to mortality from cardiovascular disease among Japanese men and women. *Eur. J. Clin. Nutr.* **66**, 687–693 (2012).
51. Saito, E. et al. Association between meat intake and mortality due to all-cause and major causes of death in a Japanese population. *PLoS ONE* **15**, e0244007 (2020).
52. Whiteman, D., Muir, J., Jones, L., Murphy, M. & Key, T. Dietary questions as determinants of mortality: the OXCHECK experience. *Public Health Nutr.* **2**, 477–487 (1999).
53. Bernstein, A. M. et al. Processed and unprocessed red meat and risk of colorectal cancer: analysis by tumor location and modification by time. *PLoS ONE* **10**, e0135959 (2015).
54. Bostick, R. M. et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control* **5**, 38–52 (1994).
55. Chao, A. Meat consumption and risk of colorectal cancer. *JAMA* **293**, 172 (2005).
56. Cross, A. J. et al. A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. *Cancer Res.* **70**, 2406–2414 (2010).
57. English, D. R. et al. Red meat, chicken, and fish consumption and risk of colorectal cancer. *Cancer Epidemiol. Biomarkers Prev.* **13**, 1509–1514 (2004).
58. Etemadi, A. et al. Anatomical subsite can modify the association between meat and meat compounds and risk of colorectal adenocarcinoma: findings from three large US cohorts. *Int. J. Cancer* **143**, 2261–2270 (2018).
59. Flood, A. Meat, fat, and their subtypes as risk factors for colorectal cancer in a prospective cohort of women. *Am. J. Epidemiol.* **158**, 59–68 (2003).
60. Gilsing, A. M. J. et al. Vegetarianism, low meat consumption and the risk of colorectal cancer in a population based cohort study. *Sci. Rep.* **5**, 13484 (2015).
61. Islam, Z. et al. Meat subtypes and colorectal cancer risk: a pooled analysis of 6 cohort studies in Japan. *Cancer Sci.* **110**, 3603–3614 (2019).
62. Knuppel, A. et al. Meat intake and cancer risk: prospective analyses in UK Biobank. *Int. J. Epidemiol.* **49**, 1540–1552 (2020).
63. Larsson, S. C., Rafter, J., Holmberg, L., Bergkvist, L. & Wolk, A. Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. *Int. J. Cancer* **113**, 829–834 (2005).
64. Lin, J. Dietary fat and fatty acids and risk of colorectal cancer in women. *Am. J. Epidemiol.* **160**, 1011–1022 (2004).
65. Mehta, S. S. et al. A prospective analysis of red and processed meat consumption and risk of colorectal cancer in women. *Cancer Epidemiol. Biomarkers Prev.* **29**, 141–150 (2020).
66. Mejborn, H., Møller, S. P., Thygesen, L. C. & Biltoft-Jensen, A. Dietary intake of red meat, processed meat, and poultry and risk of colorectal cancer and all-cause mortality in the context of dietary guideline compliance. *Nutrients* **13**, 32 (2020).
67. Norat, T. et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J. Natl Cancer Inst.* **97**, 906–916 (2005).
68. Ollberding, N. J., Wilkens, L. R., Henderson, B. E., Kolonel, L. N. & Le Marchand, L. Meat consumption, heterocyclic amines and colorectal cancer risk: the Multiethnic Cohort Study. *Int. J. Cancer* **131**, E1125–E1133 (2012).
69. O'Sullivan, D. E. et al. Combinations of modifiable lifestyle behaviours in relation to colorectal cancer risk in Alberta's Tomorrow Project. *Sci. Rep.* **10**, 20561 (2020).
70. Pietinen, P. et al. Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* **10**, 387–396 (1999).
71. Bhupathiraju, S. N. et al. Caffeinated and caffeine-free beverages and risk of type 2 diabetes. *Am. J. Clin. Nutr.* **97**, 155–166 (2013).
72. Dhingra, R. et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation* **116**, 480–488 (2007).
73. Eshak, E. S. et al. Soft drink, 100% fruit juice, and vegetable juice intakes and risk of diabetes mellitus. *Clin. Nutr.* **32**, 300–308 (2013).
74. Fagherazzi, G. et al. Consumption of artificially and sugar-sweetened beverages and incident type 2 diabetes in the Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale-European Prospective Investigation into Cancer and Nutrition cohort. *Am. J. Clin. Nutr.* **97**, 517–523 (2013).
75. Gardener, H., Moon, Y. P., Rundek, T., Elkind, M. S. V. & Sacco, R. L. Diet soda and sugar-sweetened soda consumption in relation to incident diabetes in the Northern Manhattan Study. *Curr. Dev. Nutr.* **2**, nzy008 (2018).
76. Hirahatake, K. M. et al. Cumulative intake of artificially sweetened and sugar-sweetened beverages and risk of incident type 2 diabetes in young adults: the Coronary Artery Risk Development In Young Adults (CARDIA) Study. *Am. J. Clin. Nutr.* **110**, 733–741 (2019).
77. Huang, M. et al. Artificially sweetened beverages, sugar-sweetened beverages, plain water, and incident diabetes mellitus in postmenopausal women: the prospective Women's Health Initiative observational study. *Am. J. Clin. Nutr.* **106**, 614–622 (2017).
78. Montonen, J., Järvinen, R., Knekt, P., Heliövaara, M. & Reunanen, A. Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. *J. Nutr.* **137**, 1447–1454 (2007).
79. O'Connor, L. et al. Prospective associations and population impact of sweet beverage intake and type 2 diabetes, and effects of substitutions with alternative beverages. *Diabetologia* **58**, 1474–1483 (2015).
80. Odegaard, A. O., Koh, W.-P., Arakawa, K., Yu, M. C. & Pereira, M. A. Soft drink and juice consumption and risk of physician-diagnosed incident type 2 diabetes: the Singapore Chinese Health Study. *Am. J. Epidemiol.* **171**, 701–708 (2010).
81. Palmer, J. R. et al. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. *Arch. Intern. Med.* **168**, 1487–1492 (2008).

82. Pan, A. et al. Plain-water intake and risk of type 2 diabetes in young and middle-aged women. *Am. J. Clin. Nutr.* **95**, 1454–1460 (2012).
83. Papier, K. et al. Consumption of sugar-sweetened beverages and type 2 diabetes incidence in Thai adults: results from an 8-year prospective study. *Nutr. Diabetes* **7**, e283 (2017).
84. Paynter, N. P. et al. Coffee and sweetened beverage consumption and the risk of type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Am. J. Epidemiol.* **164**, 1075–1084 (2006).
85. Sakurai, M. et al. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men. *Eur. J. Nutr.* **53**, 251–258 (2014).
86. Siqueira, J. H. et al. Consumption of sugar-sweetened soft drinks and risk of metabolic syndrome and its components: results of the ELSA-Brasil study (2008–2010 and 2012–2014). *J. Endocrinol. Invest.* **46**, 159–171 (2022).
87. Torres-Ibarra, L. et al. Regular consumption of soft drinks is associated with type 2 diabetes incidence in Mexican adults: findings from a prospective cohort study. *Nutr. J.* **19**, 126 (2020).
88. Viana Dias, J. P. et al. Consumption of sweetened beverages is associated with the incidence of type 2 diabetes in Brazilian adults (CUME project). *Nutr. Metab. Cardiovasc. Dis.* **33**, 789–796 (2023).
89. The InterAct consortium. Consumption of sweet beverages and type 2 diabetes incidence in European adults: results from EPIC-InterAct. *Diabetologia* **56**, 1520–1530 (2013).
90. Eshak, E. S. et al. Soft drink intake in relation to incident ischemic heart disease, stroke, and stroke subtypes in Japanese men and women: the Japan Public Health Centre-based study cohort I. *Am. J. Clin. Nutr.* **96**, 1390–1397 (2012).
91. Warfa, K., Drake, I., Wallström, P., Engström, G. & Sonestedt, E. Association between sucrose intake and acute coronary event risk and effect modification by lifestyle factors: Malmö Diet and Cancer Cohort Study. *Br. J. Nutr.* **116**, 1611–1620 (2016).
92. Pacheco, L. S. et al. Sugar-sweetened beverage intake and cardiovascular disease risk in the California Teachers Study. *J. Am. Heart Assoc.* **9**, e014883 (2020).
93. Collin, L. J., Judd, S., Safford, M., Vaccarino, V. & Welsh, J. A. Association of sugary beverage consumption with mortality risk in US adults: a secondary analysis of data from the REGARDS Study. *JAMA Netw. Open* **2**, e193121 (2019).
94. Yang, B. et al. Added sugar, sugar-sweetened beverages, and artificially sweetened beverages and risk of cardiovascular disease: findings from the Women's Health Initiative and a network meta-analysis of prospective studies. *Nutrients* **14**, 4226 (2022).
95. Mullee, A. et al. Association between soft drink consumption and mortality in 10 European countries. *JAMA Intern. Med.* **179**, 1479–1490 (2019).
96. Keller, A. et al. Substitution of sugar-sweetened beverages for other beverages and the risk of developing coronary heart disease: results from the Harvard Pooling Project of Diet and Coronary Disease. *Prev. Med.* **131**, 105970 (2020).
97. Pacheco, L. S. et al. Sugar- or artificially-sweetened beverage consumption, physical activity, and risk of cardiovascular disease in US adults. Preprint at *medRxiv* https://doi.org/10.1101/2023.04.17.23288711 (2023).
98. Laake, I. et al. A prospective study of intake of *trans*-fatty acids from ruminant fat, partially hydrogenated vegetable oils, and marine oils and mortality from CVD. *Br. J. Nutr.* **108**, 743–754 (2012).
99. Li, Y. et al. Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease. *J. Am. Coll. Cardiol.* **66**, 1538–1548 (2015).
100. Oomen, C. M. et al. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. *Lancet* **357**, 746–751 (2001).
101. Pietinen, P. et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am. J. Epidemiol.* **145**, 876–887 (1997).
102. Virtanen, J. K., Mursu, J., Tuomainen, T.-P. & Voutilainen, S. Dietary fatty acids and risk of coronary heart disease in men: the Kuopio Ischemic Heart Disease Risk Factor Study. *Arterioscler. Thromb. Vasc. Biol.* **34**, 2679–2687 (2014).
103. Xu, J. et al. Dietary fat intake and risk of coronary heart disease: the Strong Heart Study. *Am. J. Clin. Nutr.* **84**, 894–902 (2006).
104. Bouvard, V. et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol.* **16**, 1599–1600 (2015).
105. Stern, M. C. et al. Genome-wide gene–environment interaction analyses to understand the relationship between red meat and processed meat intake and colorectal cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **33**, 400–410 (2024).
106. *WHO Manual on Sugar-Sweetened Beverage Taxation Policies to Promote Healthy Diets* (World Health Organization, 2022).
107. Andreyeva, T., Marple, K., Marinello, S., Moore, T. E. & Powell, L. M. Outcomes following taxation of sugar-sweetened beverages: a systematic review and meta-analysis. *JAMA Netw. Open* **5**, e2215276 (2022).
108. World Health Organization Guideline: Sugars intake for adults and children (WHO Department of Nutrition for Health and Development (NHD), 2015).
109. *Dietary Guidelines for Americans, 2020–2025* 9th edn (US Department of Agriculture and US Department of Health and Human Services, 2020).
110. *Countdown to 2023: WHO 5-Year Milestone Report on Global Trans Fat Elimination 2023* (World Health Organization, 2024).
111. Freedman, L. S., Schatzkin, A., Midthune, D. & Kipnis, V. Dealing with dietary measurement error in nutritional cohort studies. *J. Natl Cancer Inst.* **103**, 1086–1092 (2011).
112. Kipnis, V. et al. Effect of measurement error on energy-adjustment models in nutritional epidemiology. *Am. J. Epidemiol.* **146**, 842–855 (1997).
113. Dahm, C. C. Correcting measurement error in dietary exposure assessments: no piece of cake. *Am. J. Clin. Nutr.* **112**, 11–12 (2020).
114. McCullough, L. E. & Byrd, D. A. Total energy intake: implications for epidemiologic analyses. *Am. J. Epidemiol.* **192**, 1801–1805 (2023).
115. Willett, W. C., Howe, G. R. & Kushi, L. H. Adjustment for total energy intake in epidemiologic studies. *Am. J. Clin. Nutr.* **65**, 1220S–1228S (1997).
116. Day, N. E. et al. Correlated measurement error—implications for nutritional epidemiology. *Int. J. Epidemiol.* **33**, 1373–1381 (2004).
117. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* **403**, 2133–2161 (2024).
118. Kassem, H. et al. Investigation and assessment of AI's role in nutrition—an updated narrative review of the evidence. *Nutrients* **17**, 190 (2025).
119. Zheng, J., Wang, J., Shen, J. & An, R. Artificial intelligence applications to measure food and nutrient intakes: scoping review. *J. Med. Internet Res.* **26**, e54557 (2024).
120. Lo, F. P.-W. et al. AI-enabled wearable cameras for assisting dietary assessment in African populations. *npj Digit. Med.* **7**, 356 (2024).

121. Burgess, S., Foley, C. N., Allara, E., Staley, J. R. & Howson, J. M. M. A robust and efficient method for Mendelian randomization with hundreds of genetic variants. *Nat. Commun.* **11**, 376 (2020).
122. Lai, W., Li, G., Peng, D., Li, N. & Wang, W. Mendelian randomization study reveals the relationship between dietary factors and respiratory diseases. *Sci. Rep.* **13**, 22601 (2023).

Methods

Overview

This study used the Burden of Proof methodology to examine the association between processed meat, SSB and TFA consumption and selected health outcomes. The Burden of Proof methodology comprises six main steps[25]: searching for and extracting data from published studies using a standardized approach, estimating the relationship between dietary exposure and relative risk of disease outcome, testing and adjusting for systematic bias arising from differences in known study design characteristics, quantifying remaining between-study heterogeneity, assessing the evidence for potential publication or reporting bias and ultimately estimating the BPRF, which is defined as the 5th percentile relative risk curve—inclusive of between-study heterogeneity—that is closest to the null for harmful risks. In the Burden of Proof methodology, we estimate both the mean risk of the outcome occurring at each level of exposure relative to the risk at the TMREL and the BPRF, which provides a conservative interpretation of the risk of a given disease outcome occurring that we summarize by calculating the average BPRF across the 15th to 85th percentiles of exposure observed in the data. Because they represent the data-dense part of the exposure range, the 15th to 85th percentiles are the exposure levels for which the risk curve is most relevant and avoids emphasis on extreme values for our conservatively estimated conservative BPRF metrics. In a Burden of Proof capstone paper[25], it was found that the correlation between risk–outcome score values derived from alternative ranges of exposure, such as the 10th and 90th percentiles and the 5th and 95th percentiles, and risk–outcome scores derived using the 15th and 85th percentiles across 180 risk–outcome pairs was very strong (~0.98). The Burden of Proof approach allows for a standardized methodology to be applied across multiple risk factors, which is relevant for policy or research prioritization. This approach was previously applied to evaluate the association between other dietary exposures, specifically vegetable and red meat consumption, and various health outcomes[123,124].

The Burden of Proof meta-regression methods developed previously[25] offer three main advantages over previous risk factor analyses to support policymakers, public health professionals and individuals interested in minimizing health risk by providing more precisely derived RR estimates, additional information about the shapes of the risk–outcome relationships and a framework to better capture the consistency of the underlying evidence and make comparisons across risk–outcome pairs. First, to improve rigor and accuracy of RR estimates, Burden of Proof methods systematically adjust for bias covariates representing known heterogeneity in input study design characteristics, correct for differences in exposure range across input studies and use a robust likelihood-based method to detect and trim data outliers. Second, the meta-regression uses a spline ensemble to flexibly model nonlinear relationships, allowing the data to determine the shape of the risk–outcome relationship. This avoids conventional assumptions of log-linearity that may amplify risk at higher exposure levels and obscure critical details at lower levels in the presence of a strong threshold effect. Information about the shape of the relationship can be used to inform cost–benefit analyses and policy determinations, including those targeting specific levels of exposure reduction or providing intake guidelines. Third—complementing RR estimates—Burden of Proof methods further formally quantify between-study heterogeneity that remains after adjusting for covariates representing known variation across input study characteristics, and incorporate this quantity directly into uncertainty estimates. These are used to derive the BPRF. The BPRF for a given risk–outcome pair is used to compute the risk–outcome score, which is defined as the signed value of the log(BPRF), averaged across the 15th to 85th percentiles of exposure (that is, the range of most likely exposure levels). The risk–outcome score is mapped onto a star-rating system comprising five levels of risk–outcome relationships, with more stars representing a stronger association and/or more consistent evidence. By providing a systematic method to capture the strength or consistency of the input evidence and generate a conservative measure of association, BPRF metrics highlight those risk–outcome relationships most likely to be accurate and reliable and allow for comparisons with other dietary (or non-dietary) risks to inform broader public health or research foci (for instance, low star ratings combining with high exposure or disease prevalence suggest a need for more research).

We estimated relative risks and BPRF and risk–outcome scores for each risk–outcome pair. Due to reporting inconsistencies across the input data, our pooled relative risk estimates are not location, sex or age specific. We evaluated the association between processed meat, SSB and TFA consumption and selected chronic diseases among adults. We excluded those studies that evaluated the health effects of these dietary risk factors on adolescents and children.

We followed the PRISMA guidelines through all stages of this study[26] (Supplementary Tables 1 and 2). This study complies with the Guidelines on Accurate and Transparent Health Estimates Reporting (GATHER) recommendations[125] (Supplementary Table 3). The study was approved by the University of Washington Institutional Review Board (study number 9060). The systematic review approach for processed meat was registered at PROSPERO (PROSPERO ID CRD42023457810), and the systematic review approach for SSBs and trans fat was also registered at PROSPERO (PROSPERO ID CRD42023495735).

Systematic review

We conducted systematic reviews to identify studies that present relative measures of association (for example, RRs, odds ratios (ORs) or hazard ratios) between the dietary exposure of interest and the selected health outcome. Our search strategy had two stages. The first stage was to identify the most recent existing meta-analysis or systematic review for each risk–outcome pair that met the inclusion criteria described below. The first reviewer screened the citations provided by the identified meta-analysis, and the second reviewer checked 100% of the studies excluded by the first reviewer. In the second stage, separate search strings were developed to identify sources in PubMed, EMBASE and Web of Science published after the period covered in the most recent PRISMA-compliant meta-analysis identified for each risk–outcome pair of interest. In both stages of the screening, two reviewers are required to exclude a study. Whenever there was a discrepancy, discussion and consultation were done with a senior personnel. The first reviewer extracted the data using the data extraction template. The second reviewer checked the correctness and completeness of the extracted data for all the studies. A detailed description of the search strings and search strategy is presented in Supplementary Information.

Our systematic review included prospective cohort, nested case–control and case–cohort studies that included participants aged 25 or older on average at the time of entry into the cohort. This restriction was applied because findings from this study will be used to calculate estimates of disease burden attributable to these risk factors for future iterations of GBD, which restricts dietary risk-attributable burden estimation to adults 25 or older. However, our search did not find any cohort studies conducted among younger adults (under 25 years). Prospective cohort studies entirely based on children, adolescents, pregnant women or adults younger than 25 on average at the time of entry into the cohort were therefore excluded. The method of assessing dietary intake was required to be either a quantitative 24-h recall, weight for record, food diary or FFQ. Cross-sectional studies, intervention studies and cohort studies that did not involve a quantitative assessment of dietary intake were excluded. The sample included in the final analysis had to be free of the outcomes of interest (IHD, type 2 diabetes, colorectal cancer) at the time of entry into the cohort.

Other inclusionary criteria were the use of suitable exposure and outcome definitions, and the reporting of some measure of uncertainty (for example, sample size, standard error or CIs) and RR (or related

measure) for which the exposed and unexposed groups were defined. Where multiple studies provided RR estimates derived from the same cohort, we included only the study that captured the largest sample or the longest follow-up time so as not to include duplicate data. For each study, one reviewer manually extracted data on study name, location, design, population (age, sex, race and sample size), duration of follow-up, exposure definition, exposure assessment method, exposure categories, outcome definition, outcome ascertainment method and covariates included in the statistical analysis of the study. A second reviewer inspected the extracted data and checked with the first reviewer whether there was a discrepancy between the extracted data and what was reported in the paper. All included studies published the data required by our inclusionary criteria, and no unpublished data were obtained for this analysis. For each exposure category, we also collected data on the range of exposure, number of participants, number of events, and the risk estimate and its corresponding uncertainty. The template for the data collection form is provided in Supplementary Table 4. The details of the systematic review for each risk–outcome pair are described below.

Processed meat. In the processed meat systematic review, we defined processed meat as any meat preserved by smoking, curing, salting or addition of chemical preservatives. This aligns with GBD 2021[5]. We defined our outcome as either incidence of, or mortality from, the specified health outcome, excluding studies that included other or nonspecific outcome definitions (for example, unspecified cardiovascular disease). As described above, we used search strings to identify the most recent PRISMA-compliant meta-analyses that examined associations between processed meat consumption and type 2 diabetes, IHD or colorectal cancer. For studies investigating the relationship between processed meat consumption and type 2 diabetes, we searched from 1 June 2022 (the last date of the identified meta-analysis) through 1 September 2023. For studies examining processed meat consumption and IHD, we searched from 5 June 2021 (the last date of the identified meta-analysis) through 15 August 2023. For studies examining processed meat and colorectal cancer, we searched from 1 February 2023 (the last date of the identified meta-analysis) through 1 September 2023. We also searched the Global Health Data Exchange (GHDx) databases. When studies reported effect sizes for colon cancer and rectum cancer separately, we included both effect sizes. However, if studies reported colorectal cancer in addition to effect sizes for colon cancer and rectum cancer, we chose the effect size reported for colorectal cancer.

We standardized the exposure unit to grams of consumption per day. For studies reporting the consumption in servings of processed meat with no other corresponding information about the serving size (13 of 44 studies), we assumed a serving size of 45 g d^{-1}.

This assumption was based on a previous study[126]. For studies that reported mean consumption rather than ranges of consumption, we used the midpoint between means as the cutoff for intake intervals. For undefined lower bounds, we assumed a consumption level of 0 g d^{-1}. For undefined upper bounds when the mean and standard deviation values were not available, we applied the range from the cohort's most adjacent quartile or tertile to estimate the upper bound of consumption specific to each study cohort. For studies that reported the frequency of consumption per day, week or month without specifying the serving size, we assumed that the frequency of consumption equated to the number of servings. When the units were presented as grams per kilocalorie, we used the mean energy intake to find absolute consumption (not relative to energy) in grams. If energy intake was not reported, we assumed 2,000 kcal as an average energy intake for conversion[127].

SSBs. In this systematic review, we defined SSB exposure as consumption of SSBs including carbonated beverages, sodas, energy drinks and fruit drinks, but excluding 100% fruit and vegetable juices. This aligns with the GBD 2021 (ref. 5). We examined the association of SSB consumption with type 2 diabetes and IHD. We used search strings to identify the most recent PRISMA-compliant meta-analyses that examined these associations. We also conducted an updated search of studies examining SSB consumption and type 2 diabetes by searching in PubMed, EMBASE and Web of Science from the last date of the identified meta-analysis (1 December 2022) to 20 December 2023. Similarly, for the updated search of SSB and IHD, we searched the three databases over the period from the last date of the identified meta-analysis (1 December 2022) to 20 December 2023. A detailed description of the search strings and search strategy is reported in Supplementary Information. For studies reporting the consumption in servings of SSBs without any other corresponding information about the serving size (8 of 27 studies), we assumed that a serving size is approximately equivalent to 12 oz (that is, the most commonly used serving size for SSB)[128], which is approximately 341 g. For studies that reported mean consumption rather than ranges of consumption, we used the midpoint between means as the cutoff for intake intervals. For undefined lower bounds, we assumed a consumption level of 0 g d^{-1}. For undefined upper bounds when the mean and standard deviation values were not available, we applied the range from the cohort's most adjacent quartile or tertile to estimate the upper bound of consumption, specific to each study cohort. For studies that reported the frequency of consumption per day, week or month without specifying the serving size, we assumed that the frequency of consumption equated to the number of servings. When the units were presented as grams per kilocalorie, we used the mean energy intake to find total consumption in grams. If energy was not reported, we assumed 2,000 kcal as an average energy intake for conversion.

Trans fat. TFA exposure is defined as consumption (percentage daily energy intake) of trans fats, primarily those that are industrially produced. The outcome of interest for this systematic review was IHD. The identified meta-analysis was a previous study[27]. The additional updated search covered the period from 1 December 2015 to 18 December 2023. We included only prospective cohort studies and nested case–control studies that examined the relationship of total TFA and industrially produced TFA consumption on IHD. For those studies examining total TFA consumption, we assumed the major contributor to be industrially produced TFAs. We excluded studies that examined the effect of TFAs from ruminant-only sources on IHD because our focus in this systematic review is industrially produced trans fats. In addition, we excluded studies when the outcome was not specifically IHD (that is, cardiovascular events). When studies reported measures of association for total IHD events, as well as for nonfatal and fatal IHD events, we used the effect measures based on total IHD events for our main analysis. Intake of TFAs was expressed as percentage per daily energy intake. For studies that did not report the percentage energy intake, we converted results into percentage per daily energy intake using reported intake of TFAs and energy intake. If energy intake was not reported, we assumed 2,000 kcal for calculating the percentage per daily energy intake.

Statistical analysis

The statistical analyses conducted in this study are described in detail below. We used the Burden of Proof analytical framework, which includes estimation of the shape of the relationships between the risk and the outcome, testing and adjusting for the bias covariates, quantifying between-study heterogeneities, evaluating publication bias and estimating the Burden of Proof function. No statistical method was used to predetermine the sample size. As all data used in this meta-analysis were from observational studies, no experiments were conducted, and no randomization or blinding took place.

Estimating the risk–outcome relationship

For each risk–outcome pair, we modeled relative risk of the disease outcome occurring as a function of exposure to the risk factor using

Burden of Proof methods, a suite of Bayesian meta-regression tools, which are detailed elsewhere[129]. Burden of Proof methods offer several valuable features for evaluating relative risk curves and assessing the robustness of evidence available to support the analyzed risk–outcome associations. These features include, among others, (1) the ability to model nonlinear relationships using splines, provided in the analysis framework with automated knot selection and shape constraints; (2) systematic incorporation of covariates related to differences among input study design characteristics, allowing for the mitigation of potential biases; (3) methods to quantify remaining between-study heterogeneity and incorporate it into uncertainty, creating the basis for a single measure that provides a conservative estimate of the magnitude of the risk–outcome association and the strength of the supporting evidence; (4) a mechanism to adjust the parameter for between-study variability to account for the effects of limited data; and (5) a means to evaluate the presence of publication or reporting bias.

In this study, we first modeled the association of each risk–outcome pair with no constraints to assess the nature of the association. Then we applied a constraint based on the shape of the risk curve derived from this initial model. For the analyses involving processed meat and SSBs, we applied a quadratic spline model with an increasing shape constraint (risk increasing with increasing exposure) for each of the outcomes. For the TFA analysis, we applied a cubic spline model with an increasing shape constraint.

Testing and adjusting for biases across input study designs and characteristics

For each study reporting an effect size for the association between consumption and the selected health outcomes, we extracted information about aspects of study design that could potentially bias the reported effect size and coded this information to generate study-level covariates. These study-level covariates included length of follow-up period (≤10 years and >10 years), precision of the exposure and outcome definitions, study design (that is, RCT or prospective cohort study), reported measure of association (RRs or ORs), outcome measures (incidence or mortality), number of exposure measurements (single or repeat), method by which outcomes were ascertained (administrative records, self-reports, biomarkers or physician diagnosis) and level of adjustment for relevant confounders (for example, age, sex, smoking, education, income, calorie intake, BMI, physical activity, alcohol intake, saturated fat intake and other dietary factors). We adjusted for these covariates in our meta-regression if they significantly biased our estimated RR function. See Supplementary Tables 7–9 for results from our assessment of study quality for all included studies.

Quantifying remaining between-study heterogeneity

After using the aforementioned study-level covariates to account for known differences in study design characteristics, we used a linear mixed-effects model to quantify the remaining unexplained between-study heterogeneity, as captured by gamma (γ). The remaining between-study heterogeneity captured by γ contributes to the overall assessment of effect size and evidence strength as reflected in the BPRF. The details of the methods for quantifying between-study heterogeneity are described elsewhere[25]. Uncertainty intervals for estimated relative risks are reported in two forms: (1) exclusive of γ, derived without fully accounting for between-study heterogeneity (thus aligned with conventional uncertainty estimates typically reported in traditional meta-analyses), and (2) inclusive of γ, which better reflects the degree of consistency across the underlying evidence. In this study, we present relative risk values with uncertainty intervals that include γ unless otherwise specified.

Evaluating the potential for publication and reporting bias

We examined the presence of publication and reporting bias using Egger's regression and by visually inspecting funnel plots. A significant relationship between effect size and standard error suggests bias or methodological differences across studies. Positive Egger's regression results signal potential publication and reporting bias. Although we tested for and reported our findings regarding publication and reporting bias, we followed standard guidelines and did not adjust our risk assessment based on these results.

Estimating the TMREL

The TMREL refers to the exposure level that, among all the theoretically possible values at the population level, minimizes the risk of all associated outcomes combined. For harmful exposures that can theoretically be eliminated, the TMREL is usually set at zero. In our analysis, we applied a TMREL of zero for processed meat, SSBs and TFAs.

Estimating the BPRF

We estimated the BPRF as the function that corresponds to the 5th percentile (for harmful risk factors) of the RR curve, inclusive of γ, that is closest to the null. The BPRF represents a conservative estimate of the risk–outcome association that is consistent with the available data after incorporating between-study heterogeneity. The further the BPRF is from the null, the stronger the estimated association is, both in terms of effect size and/or strength of supporting evidence. We then estimated the risk–outcome score as the mean value of the log(BPRF) averaged over the 15th and 85th percentiles of the distribution of exposure observed in the relevant input studies. The risk–outcome score provides a single summary metric of the BPRF that is comparable across both protective and harmful effects[25]. A higher positive risk–outcome score corresponds to a stronger association, supported by more consistent evidence. We translated the risk–outcome score for each risk–outcome pair into a star rating ranging from one to five stars to reflect our conservative estimate of association strength. Increasing stars—in the case of harmful risk factors—represent increasing evidence of health risk with increased levels of exposure to the risk factor (averaged across the evidence-dense range of exposure levels observed), relative to no exposure. Specifically, the Burden of Proof framework defines star rating categories as 0% increased risk for one star, 0–15% for two stars, >15–50% for three stars, >50–85% for four stars and over 85% increased risk for five stars.

Sensitivity analyses

For each risk–outcome pair, we conducted sensitivity analyses that compared the relative risk curves generated with and without trimming the 10% least coherent data points (Supplementary Results).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The findings of this study were based on data from public repositories and published literature, with systematic searches conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com) and Web of Science (https://www.webofscience.com) using the search strings provided in Supplementary Information. The estimates produced in this study are accessible via the Burden of Proof visualization tool (https://vizhub.healthdata.org/burden-of-proof/). The relevant studies were identified through a systematic literature review, and citations for all input studies are listed in the main text as references[27–103]. Study characteristics for all input data used in the analyses are also provided in Supplementary Table 5. The template for the data collection form is provided in Supplementary Table 4.

Code availability

This study was a secondary analysis of existing data obtained through systematic reviews using meta-analytic methods. The study did not involve primary data collection, randomization, blinding or

determination of sample size. Analyses were carried out using R version 4.0.5 and Python version 3.10.9. Code used for data processing (https://github.com/ihmeuw-msca/burden-of-proof/tree/main/risks/processed_foods) and for running the Burden of Proof models (https://github.com/ihmeuw-msca/bopforge) is publicly available online.

References

123. Lescinsky, H. et al. Health effects associated with consumption of unprocessed red meat: a Burden of Proof study. *Nat. Med.* **28**, 2075–2082 (2022).
124. Stanaway, J. D. et al. Health effects associated with vegetable consumption: a Burden of Proof study. *Nat. Med.* **28**, 2066–2074 (2022).
125. Stevens, G. A. et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *Lancet* **388**, e19–e23 (2016).
126. Pan, A. et al. Red meat consumption and mortality: results from 2 prospective cohort studies. *Arch. Intern. Med.* **172**, 555–563 (2012).
127. de Souza, R. J. et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *Br. Med. J.* **351**, h3978 (2015).
128. Zhang, Y.-B., Jiang, Y.-W., Chen, J.-X., Xia, P.-F. & Pan, A. Association of consumption of sugar-sweetened beverages or artificially sweetened beverages with mortality: a systematic review and dose–response meta-analysis of prospective cohort studies. *Adv. Nutr.* **12**, 374–383 (2021).
129. Zheng, P., Barber, R., Sorensen, R. J. D., Murray, C. J. L. & Aravkin, A. Y. Trimmed constrained mixed effects models: formulations and algorithms. *J. Comput. Graph. Stat.* **30**, 544–556 (2021).

Acknowledgements

Research reported in this publication was supported by the Gates Foundation (OPP1152504). The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the final report, or the decision to publish.

Author contributions

D.H., S.I.H., M.B., C.A. and J.D.S. managed the estimation or publications process. D.H., K.L.H. and C.J.L.M. wrote the first draft of the paper. D.H. had primary responsibility for applying analytical methods to produce estimates. D.H. and H.K. had primary responsibility for seeking, cataloging, extracting or cleaning data and designing or coding figures and tables. D.H., V.G., M.C.P, R.J.D.S., J.D.S. and C.J.L.M. provided data or critical feedback on data sources. D.H., R.J.D.S., P.Z., N.M.G. and A.Y.A. developed methods or computational machinery. D.H., K.L.H., V.G., A.Y.A., J.D.S., M.B. and S.I.H. provided critical feedback on methods or results. D.H., K.L.H., S.A.M. C.J.L.M. and M.B. drafted the work or revised it critically for important intellectual content. D.H., C.A. and S.I.H. managed the overall research enterprise.

Competing interests

The authors declare no competing interests.

Additional information

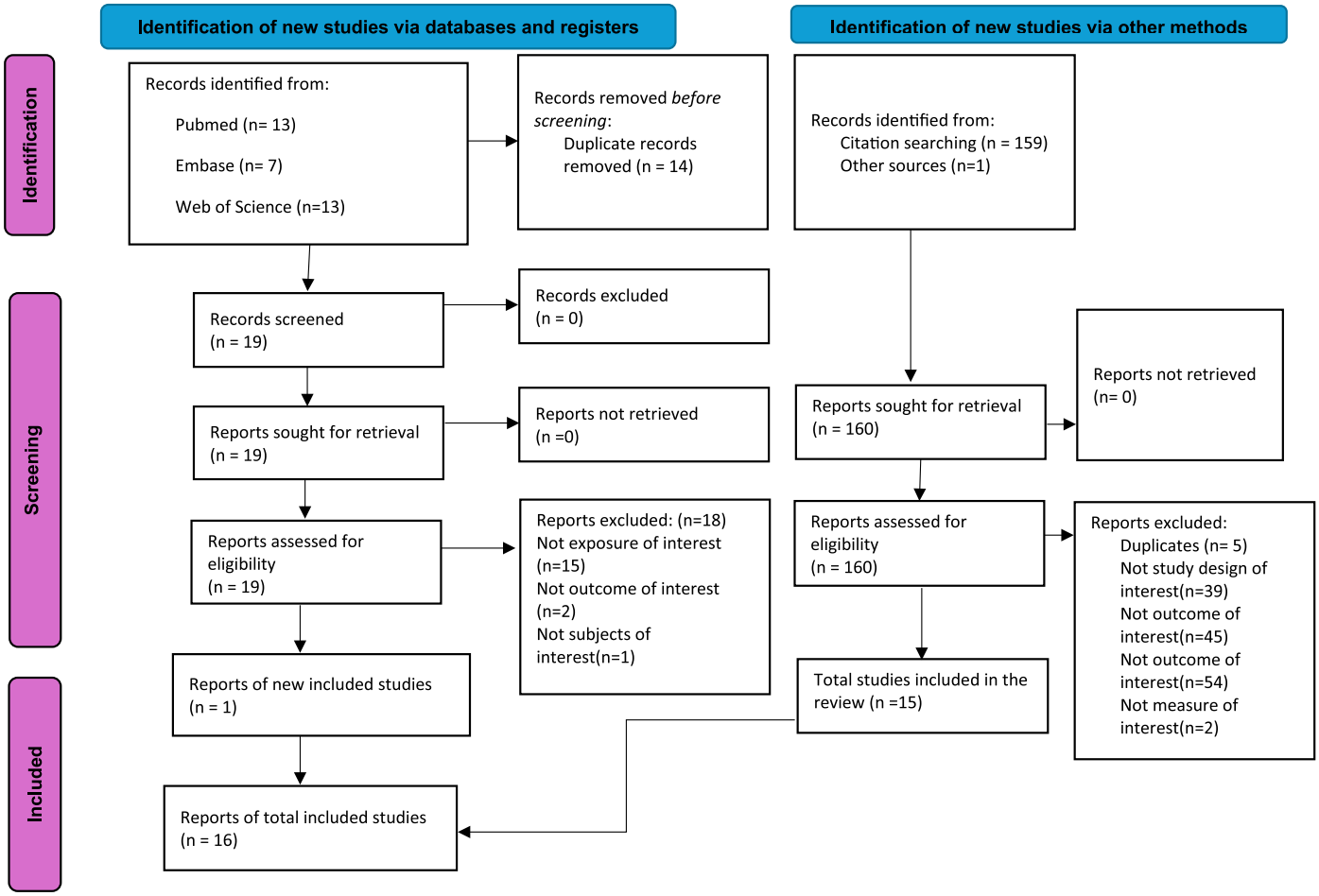
Extended data is available for this paper at https://doi.org/10.1038/s41591-025-03775-8.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-03775-8.

Correspondence and requests for materials should be addressed to Demewoz Haile.

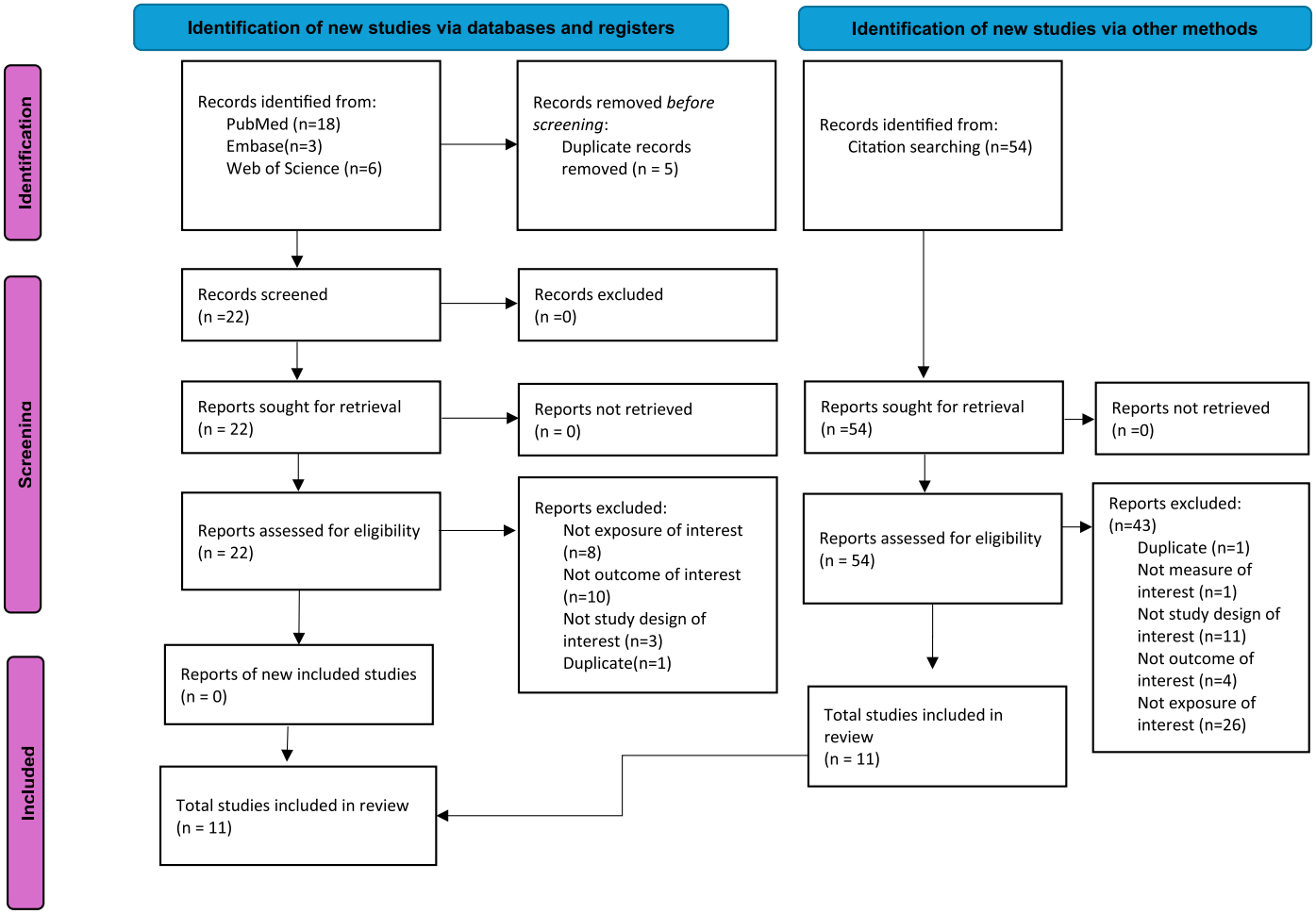
Peer review information *Nature Medicine* thanks Yan-Bo Zhang and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Ming Yang, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-025-03775-8



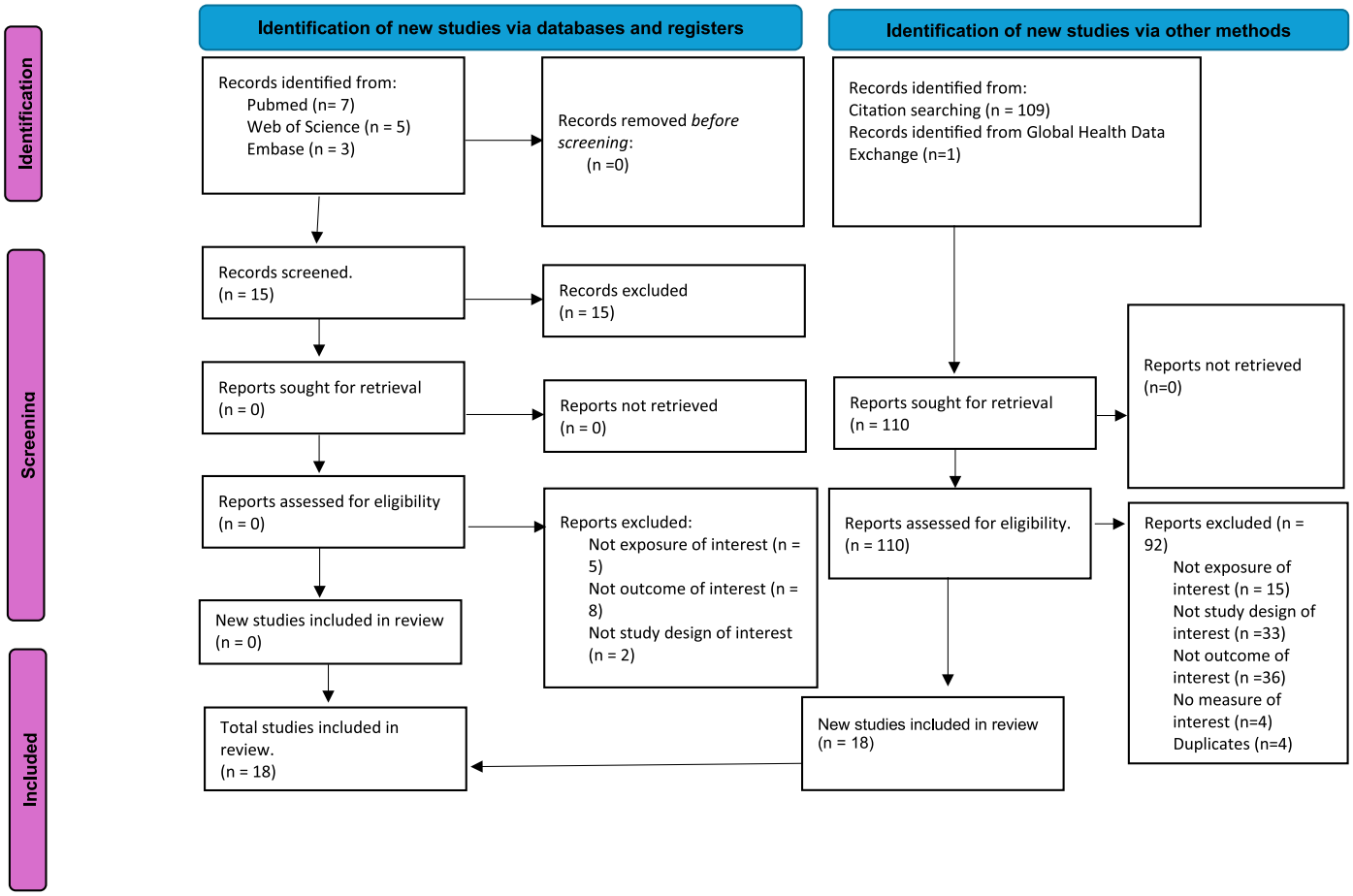
Extended Data Fig. 1 | PRISMA flow diagram of processed meat consumption and type 2 diabetes. Template is from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

https://doi.org/10.1038/s41591-025-03775-8



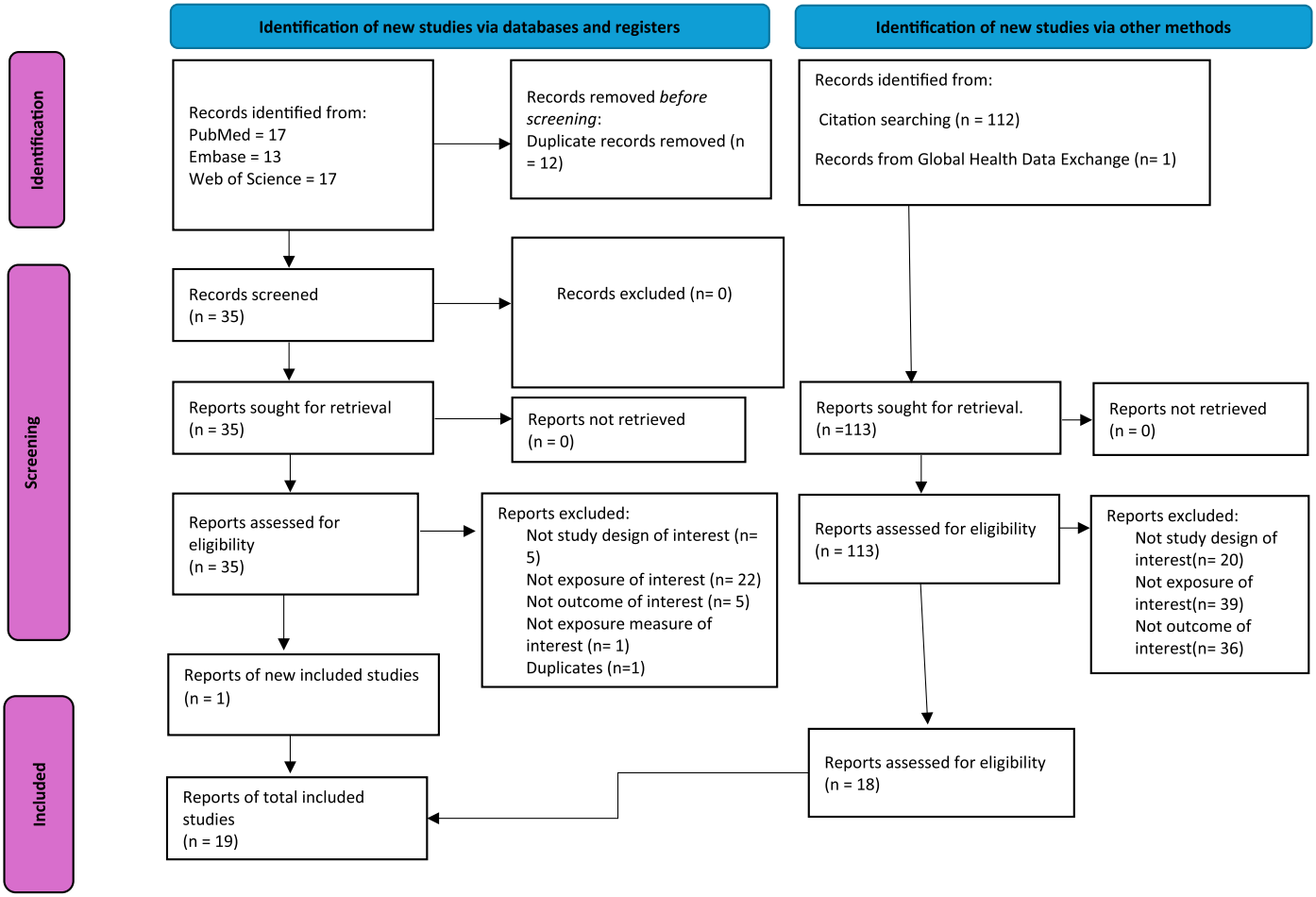
Extended Data Fig. 2 | PRISMA flow diagram of processed meat consumption and ischemic heart diseases. Template is from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

https://doi.org/10.1038/s41591-025-03775-8



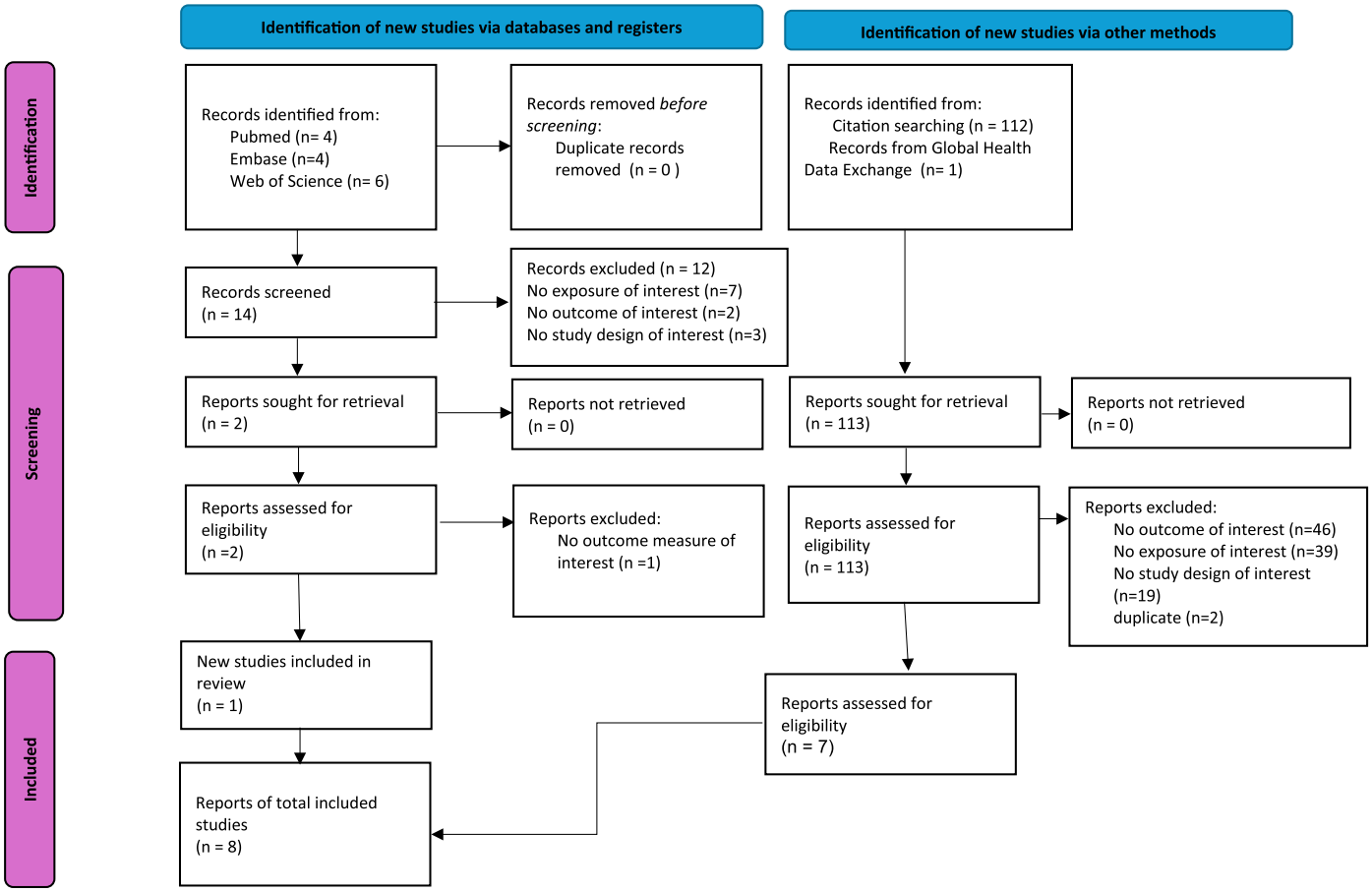
Extended Data Fig. 3 | PRISMA flow diagram of processed meat consumption and colorectal cancer. Template is from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

https://doi.org/10.1038/s41591-025-03775-8



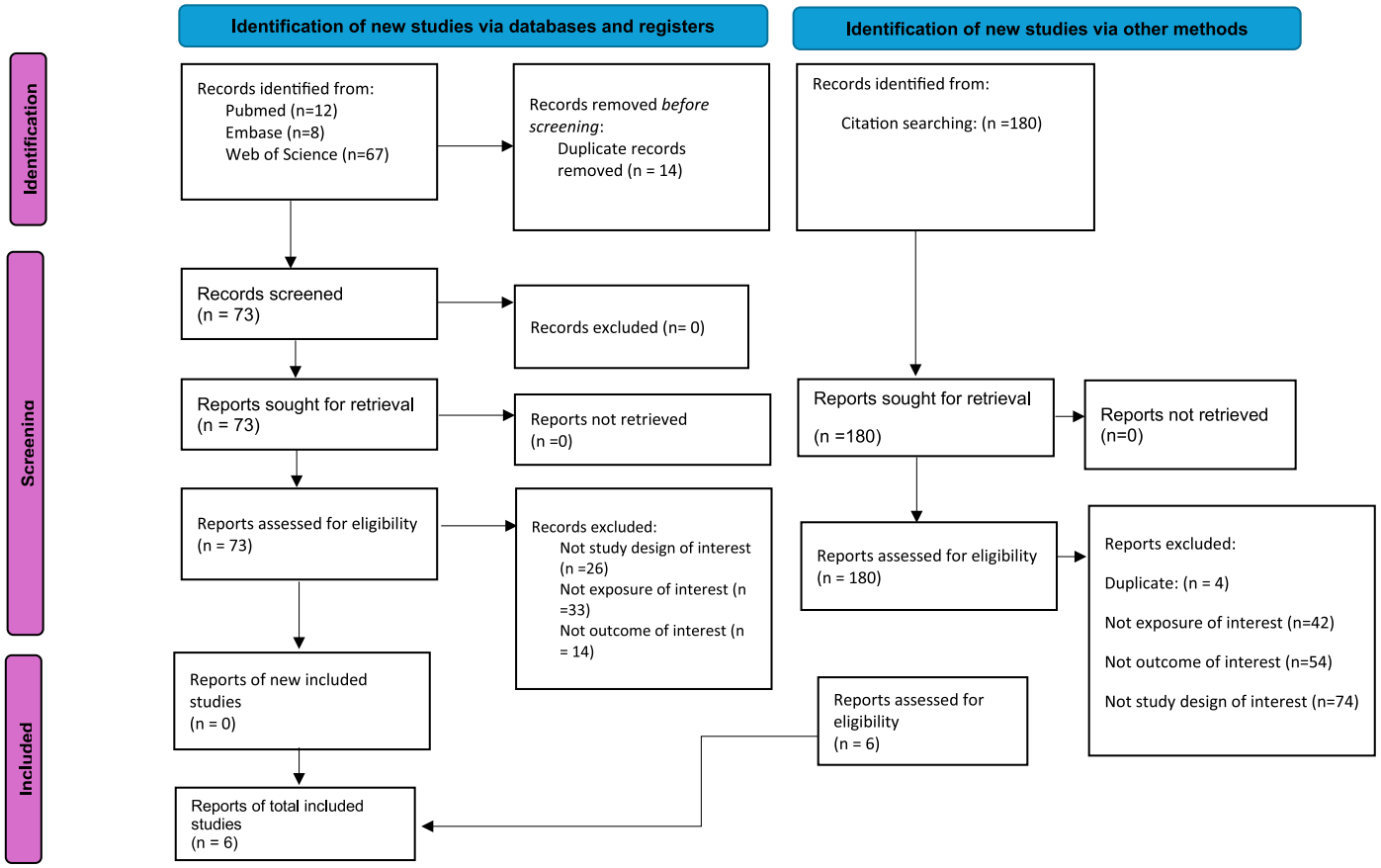
Extended Data Fig. 4 | PRISMA flow diagram of sugar sweetened beverages and type 2 diabetes. Template is from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

https://doi.org/10.1038/s41591-025-03775-8



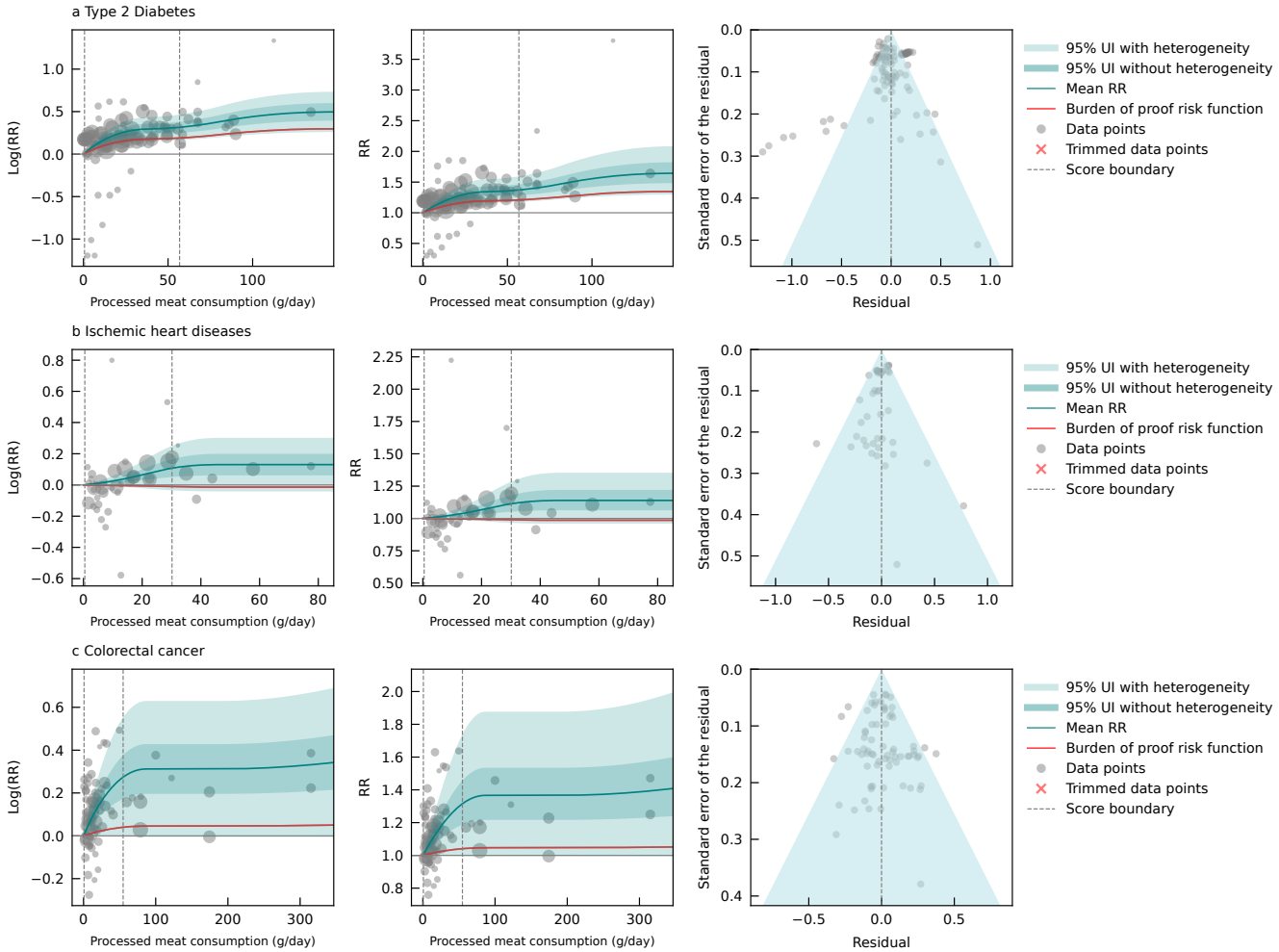
Extended Data Fig. 5 | PRISMA flow diagram of sugar sweetened beverages and ischemic heart diseases. Template is from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

https://doi.org/10.1038/s41591-025-03775-8



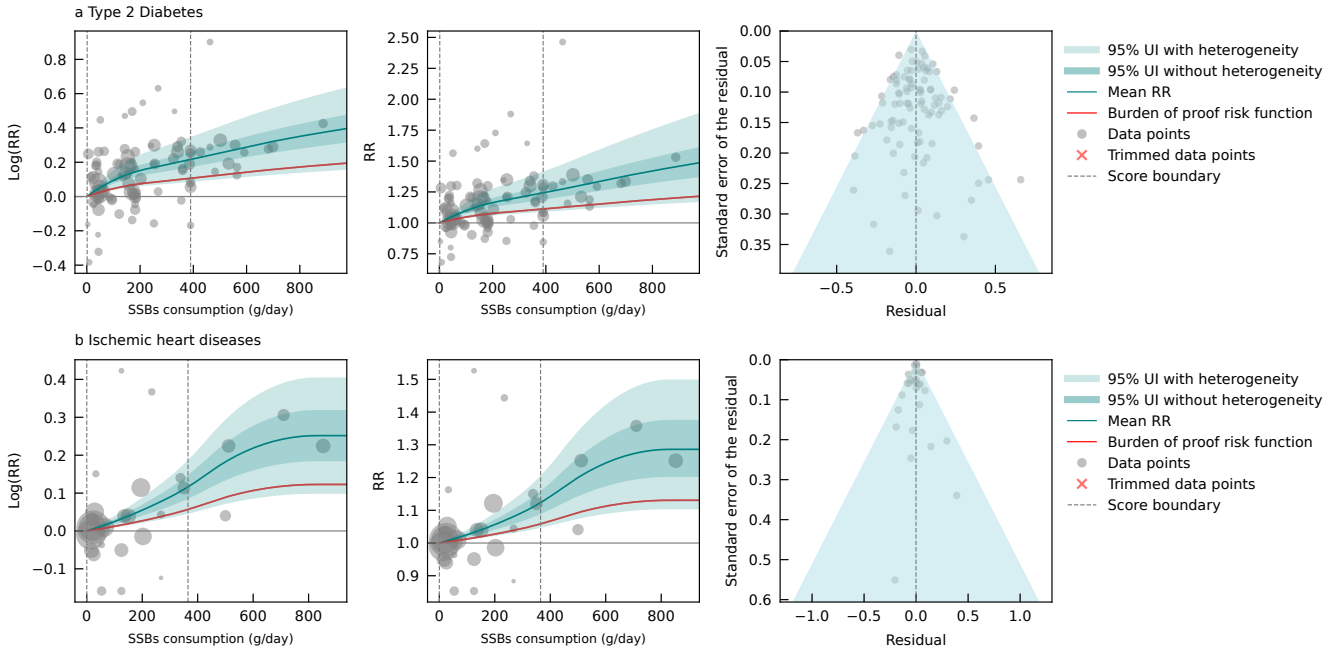
Extended Data Fig. 6 | PRISMA flow diagram of trans-fat consumption and ischemic heart diseases. Template is from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

https://doi.org/10.1038/s41591-025-03775-8



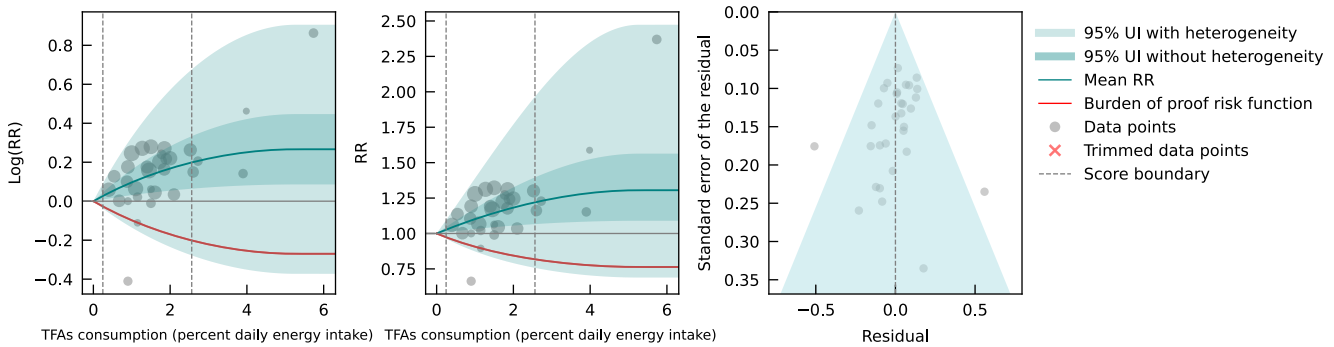
Extended Data Fig. 7 | Relative Risk of Processed Meat Consumption on type 2 diabetes (Panel a), ischemic heart diseases (Panel b), and colorectal cancer (Panel c): Non-trimmed data. The panels show the log(relative risk) function, the relative risk function, and a modified funnel plot showing the residuals (relative to 0) on the x-axis and the estimated standard error that includes the reported standard error and between-study heterogeneity on the y-axis. RR relative risk, UI uncertainty interval.

https://doi.org/10.1038/s41591-025-03775-8



Extended Data Fig. 8 | Relative risk of sugar-sweetened beverages on type 2 diabetes (Panel a) and ischemic heart diseases (Panel b): non-trimmed data. The panels show the log(relative risk) function, the relative risk function, and a modified funnel plot showing the residuals (relative to 0) on the x-axis and the estimated standard error that includes the reported standard error and between-study heterogeneity on the y-axis. RR relative risk, UI uncertainty.

https://doi.org/10.1038/s41591-025-03775-8



Extended Data Fig. 9 | Relative risk of trans-fat consumption and ischemic heart diseases: Non-trimmed data. The panels show the log(relative risk) function, the relative risk function, and a modified funnel plot showing the residuals (relative to 0) on the x-axis and the estimated standard error that includes the reported standard error and between-study heterogeneity on the y-axis. RR relative risk, UI uncertainty interval.

nature portfolio

Corresponding author(s): Demewoz Haile

Last updated by author(s): May 7, 2025

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No primary data was collected for this analysis. Secondary data was collected through systematic reviews. No software were used for collection of data
Data analysis	Analyses were carried out using R version 4.0.5 and Python versionn 3.10.9. All codes used for data processing (https://github.com/ihmeuw-msca/burden-of-proof/tree/main/risks/processed_foods) and to run the Burden of Proof model (https://github.com/ihmeuw-msca/bopforge) are publicly available online. This includes code for the meta-regression engine, the model specification interface, the data processing and cleaning, and risk-specific custom code, as appropriate.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The findings of this study were based on data from public repositories and published literature, with systematic searches conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com), and Web of Science (https://www.webofscience.com) using the search strings provided in the supplementary information. Study sources and citation for each risk-outcome pair are provided as reference in the current paper from 27-103. Study characteristics and extracted values for all the studies used in the analyses are also provided as supplementary information in supplementary Tables 5, 7-10. The estimates and risk curves produced in this study are accessible via the Burden of Proof visualization tool (https://preview.healthdata.org/burden-of-proof/).

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	No primary data collection was carried out for this analysis, so the study does not involve human research participants. Our estimates are based on data from prospective cohort and case-cohort studies. Our estimates are not specific to demographic populations, including by sex or gender, and we did not exclude studies that did not report sex- or gender-specific estimates. If a study only reported information on disaggregated effect sizes, that data would be used. However, due to heterogeneity in the way underlying studies collected and reported on sex or gender, we did not distinguish between the two concepts in our extractions and refer to them as sex-specific data.
Reporting on race, ethnicity, or other socially relevant groupings	No primary data collection was carried out for this analysis, so the study does not involve human research participants. We did not disaggregate the findings by race, ethnicity, or other socially relevant groupings.
Population characteristics	This study is a meta-analysis of estimates published in peer-reviewed literature. No primary data collection was carried out for this analysis, so the study does not involve human research participants. We did not disaggregate findings by race, ethnicity, or other socially relevant groupings. Included studies were not limited by geography, sex, or other demographic characteristics.
Recruitment	No primary data collection was carried out for this analysis, so we did not recruit participants.
Ethics oversight	This study was approved by the University of Washington IRB Committee (study #9060) as a component of the Global Burden of Disease, Injuries, and Risk Factors (GBD) study.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample size calculation was performed for this meta-analysis; all available datasets meeting the inclusion criteria are included. As reported in the main text results sections, the number of individuals included in each risk-outcome pair as follows: Processed meat and Type 2 diabetes: 1,115,885 participants ; Processed meat and Ischemic Heart diseases: 1,173,821 participants ; Processed meat and colorectal cancer: 2,678,052 participants; Sugar Sweetened Beverages and Type 2 diabetes: 563,444 participants; Sugar Sweetened Beverages and Ischemic Heart diseases: 961,176 participants; Trans fat and Ischemic Heart diseases: 226,509 participants.
Data exclusions	As described in the systematic review method section of the main paper and Supplementary Information Section 1.2, studies were excluded if they did not use a prospective cohort study design or case-cohort design, lacked a suitable exposure and outcome definition, failed to provide measures of uncertainty, or did not report a relative risk, hazard ratio, or odds ratio with clearly defined exposed and unexposed groups. When multiple studies were reported from the same cohorts, we included only the study that captured the largest sample size or follow-up time to avoid duplicate data.
Replication	This is a meta-analysis of existing observational studies. Therefore, traditional replication is not directly applicable. However, we have

Replication	provided all data sources, selection criteria, and open-source code for statistical analysis, allowing other researchers to reproduce our findings using the same methodology.
Randomization	This is a meta-analysis of existing observational studies. Thus, there were no experimental groups and no need for randomization.
Blinding	This study is a meta-analysis of existing longitudinal cohort studies; therefore, no blinding procedures were involved.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☐	☐ ChIP-seq
☐	☐ Flow cytometry
☐	☐ MRI-based neuroimaging

Plants

Seed stocks	We did not use any plant data.
Novel plant genotypes	We did not use any plant data.
Authentication	We did not use any plant data.

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	*For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.*
Files in database submission	*Provide a list of all files available in the database submission.*
Genome browser session (e.g. UCSC)	*Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.*

Methodology

Replicates	*Describe the experimental replicates, specifying number, type and replicate agreement.*
Sequencing depth	*Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.*
Antibodies	*Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.*
Peak calling parameters	*Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.*

Data quality	*Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.*
Software	*Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.*

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	*Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.*
Instrument	*Identify the instrument used for data collection, specifying make and model number.*
Software	*Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.*
Cell population abundance	*Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.*
Gating strategy	*Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.*

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	*Indicate task or resting state; event-related or block design.*
Design specifications	*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*
Behavioral performance measures	*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

Acquisition

Imaging type(s)	*Specify: functional, structural, diffusion, perfusion.*
Field strength	*Specify in Tesla*
Sequence & imaging parameters	*Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.*
Area of acquisition	*State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.*

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software	*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*
Normalization	*If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.