Family Medicine and Community Health

Ultra-processed food consumption and risk of multiple chronic diseases among 8,819,894 adults from 51 prospective cohorts: a dose-response meta-analysis

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ABSTRACT

Objective The consumption of ultra-processed foods (UPFs) has increased globally. This study comprehensively investigated the impact of consuming UPFs on the risk of major chronic diseases in adults.

Setting A systematic search identified prospective cohort studies up to April 2026 on consumption of UPFs and major chronic outcomes. Consumption of UPFs was assessed by food frequency questionnaires (FFQs), 24-hour recalls, or dietary history.

Participants Adults (≥18 years) without restriction to specific clinical conditions at baseline.

Results Fifty-one prospective cohort studies involving 8 819 894 participants were included. Consumption of UPFs was associated with cardiovascular events (Hazard Ratio (HR) 1.24, 95% Confidence Interval (CI) 1.14 to 1.36), cancer (HR 1.12, 95% CI 1.04 to 1.21), obesity/overweight (HR 1.23, 95% CI 1.17 to 1.30), metabolic syndrome (MetS)/diabetes (HR 1.24, 95% CI 1.08 to 1.42), depression/anxiety (HR 1.27, 95% CI 1.15 to 1.40), digestive diseases (HR 1.31, 95% CI 1.16 to 1.48) and all-cause mortality (HR 1.18, 95% CI 1.10 to 1.26). Dose-response analyses showed each additional 100 g/day associated with higher risks of cardiovascular events (HR 1.14, 95% CI 1.06 to 1.22), cancer (HR 1.04, 95% CI 1.02 to 1.06), all-cause mortality (HR 1.03, 95% CI 1.02 to 1.05), and MetS/diabetes (HR 1.02, 95% CI 1.01 to 1.04).

Conclusions Consuming UPFs was associated with higher risks of multiple chronic diseases and all-cause mortality with low or moderate evidence. Reducing dietary intake of UPFs may therefore be relevant for chronic disease prevention.

PROSPERO registration number CRD42023421092.

INTRODUCTION

The consumption of ultra-processed foods (UPFs) has risen markedly, constituting a substantial portion of daily dietary intake.[1] Defined under the NOVA Classification, a widely used framework that categorises foods based on the degree of industrial

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Global consumption of UPFs has increased rapidly in recent years, and accumulating evidence links higher UPF consumption to elevated risks of major chronic conditions, such as hypertension, cardiovascular events, cancer, and metabolic disorders. These conditions often co-occur as multimorbidity in primary care settings, thereby increasing clinical complexity, healthcare utilisation, and long-term management burden.

WHAT THIS STUDY ADDS

⇒ We found that higher consumption of UPFs was associated with higher risks of multiple chronic disease outcomes, including cardiovascular events (24%), obesity/overweight (23%), metabolic syndrome (MetS)/diabetes (24%), depression/anxiety (27%), digestive diseases (31%), cancer (12%), and all-cause mortality (18%).

⇒ Dose-response analyses demonstrated each additional 100 g/day intake was associated with 11% higher hypertension risk, 14% higher cardiovascular events risk, 4% higher cancer risk, and 3% higher all-cause mortality; each 10% increase in weight/energy intake was associated with a 16% higher MetS/diabetes risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Future research should develop more standardised and refined methods to classify and quantify intake of UPFs, report dose-response results using comparable intake units, examine whether risk estimates differ by population, dietary pattern, and baseline disease risk, and inform evidence-based intake recommendations.

⇒ In primary care settings, healthcare professionals may incorporate advice on reducing intake of UPFs into their routine lifestyle counselling and multimorbidity management, with practical guidance tailored to achievable dietary substitutions, patients' dietary preferences, and their existing metabolic, comorbidity, and emotional well-being profiles.

processing,[2] UPFs are ready-to-eat or heat-and-serve products that undergo extensive industrial processing[3 4] and commonly include items such as candies and packaged snacks,[1 2] often containing multiple additives.[4] They are typically energy-dense and high in sugar and salt but low in dietary fibre, protein, vitamins, and minerals,[2] contributing to their convenience, palatability, and long shelf-life.[4] Consumption of UPFs has increased globally over recent decades. Among adults in the United States, UPFs accounted for 53.5% of total energy intake in 2001, rising to 57.0% in 2018 and remaining at 53.0% during 2021–2023, maintaining historically high levels.[5] Similar increases have been observed in other countries, with UPFs consumption rising from 11.0% to 31.7% in Spain, from 10% to 23% in Mexico and Brazil, and from 3.5% to 10.4% in China over three decades.[6]

Emerging evidence suggests that excessive intake of UPFs may adversely affect human health.[1] For example, a prospective UK Biobank study involving 60 298 participants reported that high consumption of UPFs was associated with higher risks of cardiovascular disease (CVD) and all-cause mortality over 10.9 years of follow-up.[7] Many health conditions associated with consuming UPFs—such as hypertension, obesity, diabetes, cardiovascular diseases, cancer, and depression—frequently co-exist in the same individuals, forming typical multimorbidity patterns seen in primary care.[8] Multimorbidity greatly increases healthcare burden, reduces quality of life, and complicates long-term disease management.[9 10] Direct medical costs have been estimated at around I$14,300 annually for hypertension with diabetes and up to I$85,820 for cancer with mental health conditions in the first year after diagnosis.[11] Therefore, understanding the shared upstream determinants of multiple chronic conditions, including dietary exposures such as UPFs, is essential for informing prevention strategies within primary care. Uncertainty remains regarding the overall health implications of adult consumption of UPFs, particularly concerning safe consumption levels and potential adverse thresholds. To address these gaps, we evaluated the associations between consuming UPFs and multiple health outcomes and quantified exposure-effect relationships to inform public health and primary care policy.

METHOD

Protocol registration and search strategy

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42023421092) and reported the results following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (online supplemental table S1).

We conducted a comprehensive literature search in PubMed, Embase, and the Cochrane Library from their inception to 28 April 2026. The search strategy incorporated both Medical Subject Headings (MeSH) terms and free-text keywords, including but not limited to 'ultra-processed food', 'cardiovascular disease', 'hypertension', 'diabetes', 'depression', 'anxiety', 'mortality', 'obesity', and 'digestive disease'. No filters or restrictions were applied during the initial search. Our search strategy was informed by a previously published and validated strategy,[12] with complete detailed search strategies for each database provided in online supplemental table S2. References from published reviews and meta-analyses were reviewed by a manual retrieval of relevant articles, and Google Scholar was searched for additional literature.

Selection criteria and study selection

Studies were selected according to the PECOS (Population, Exposure, Comparison, Outcome, and Study Design) criteria: (1) Participants: adults (≥18 years) without restriction to specific clinical conditions at baseline; (2) Exposure and comparator: comparison between the highest vs lowest categories of intake of UPFs. UPFs were defined according to the NOVA Classification; given its application across different dietary assessment instruments, some variation in the classification of certain foods across studies is possible; (3) Outcomes: all health outcomes such as hypertension, cardiovascular events, cancer events, MetS/diabetes, digestive diseases, and all-cause mortality, while excluding subclinical disease, such as arteriosclerosis, and hyperlipidemia; Cardiovascular events were defined as cardiovascular and cerebrovascular and/or cardiovascular death. We used a broad definition of cardiovascular and cerebrovascular, including myocardial infarction, stroke, transient ischaemic attack, ischaemic heart events, coronary artery disease, cardiovascular death, and major cardiovascular events, either individual or combined. Cancer events were defined as any cancer events and/or cancer mortality. (4) Study design: prospective cohort studies. Studies were excluded if they met any of the following criteria: (1) Protocols, reviews, animal studies, case-control, retrospective cohort, and cross-sectional studies; (2) Studies that lack a clear definition for UPFs (according to the NOVA Classification) or include only subcategories of UPFs; (3) Studies with unavailable data or relevant data cannot be obtained completely; (4) Studies conducted exclusively in specific clinical or high-risk populations (eg, pregnant women, critically ill patients, or individuals with liver, kidney, or cancer conditions) and those reporting only fatal outcomes (unless both fatal and non-fatal events were available) were excluded to maintain consistency and generalisability across the included data. In cases of multiple publications from the same cohort, the study with the most comprehensive data or the largest sample size was prioritised to avoid participant duplication. For each outcome, cohorts were grouped according to the specific health endpoints reported in the original studies; when a study reported multiple distinct outcomes of interest, all relevant outcomes were extracted. EndNote X9 software (Thomson Reuters, New York, NY, USA) was used to manage all records. After duplicate removal, titles and abstracts were screened, followed by full-text assessment.

Data collection and quality assessment

The following data were independently extracted by three authors (XL, S-WL, and Y-TZ): (1) first author, year, country/region; (2) study design and follow-up; (3) characteristics of the study population including data source, age/mean age, sample size and male %; (4) assessment and categories of consumption of UPFs; (5) outcomes; (6) OR or relative risk (RR) or HR with 95% CI from the most fully adjusted models. Two authors (XL and S-WL) independently screened titles and abstracts and subsequently performed full-text review. Any discrepancies in study selection, data extraction, and quality assessment were resolved through discussion with a third author (Y-TZ). Since MetS shares the pathogenesis of 'insulin resistance' with type 2 diabetes mellitus,[13] we combined these two outcomes. Potential risks of bias were assessed using the ROBINS-E (Risk of Bias in Non-randomised Studies of Exposures) tool.

Statistical analysis

For categorical analyses, the highest vs lowest consumption levels of UPFs were pooled using OR/RR/HR and 95% CI with DerSimonian-Laird models; inconsistent OR/RR estimates were standardised to HR. Dose-response relationships between consumption of UPFs and health outcomes were assessed using one-stage robust error meta-regression, with calculations of the amount of UPFs' consumed being based on our previous studies.[14–16] For exposure-effect analyses only, g/day was converted to servings using 50 g per serving.[17] Linear estimates were reported per 10% of total daily weight/energy intake, per 100 g/day, and per 10 servings/week.

Heterogeneity was assessed using tau² and Cochran's Q (p<0.10). And I^2 statistics were reported to describe inconsistency across studies. Publication bias was evaluated by funnel plots and Egger's test when >10 studies were available; otherwise, the risk of publication bias was considered insufficient according to the Cochrane Manual. Subgroup analysis (n ≥5 for included studies in each outcome) was performed by age, sex, sample size, publication years, and region. Leave-one-out sensitivity analyses assessed result stability. Evidence certainty was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). Analyses were performed using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration 2014; Nordic Cochrane Centre, Copenhagen, Denmark), and R version 4.6.0. p<0.05 was considered statistically significant.

RESULTS

Literature search

The database search process is summarised in online supplemental figure S1. A total of 10 699 articles (PubMed=7192; Embase=3262; Cochrane Library=245) were identified. After removing 1420 duplicates, 9279 articles remained for screening. Following a review of titles and abstracts, 9120 articles were excluded. The full texts of the remaining 159 articles were assessed for eligibility, resulting in the exclusion of 108 articles for the following reasons: (1) Meta-analysis or review articles (n=22); (2) No targeted population (n=4) or exposure (n=33); (3) Unrelated to the outcomes (n=19); (4) No relevant data (n=6); (5) Retrospective or cross-sectional design (n=20); (6) Duplicated population (n=4). Details of these exclusions are provided in online supplemental table S3. Ultimately, 51 articles were included.

Study characteristics and study quality

The baseline characteristics of the included studies are summarised in online supplemental table S4. There were 51 prospective cohort studies involving 8 819 894 participants. Follow-up ranged from 2 to 32 years, and mean participant ages varied from 23.9 to 77 years. Sample sizes ranged from 896 to 5 468 444, with 46.4% of participants being male. Geographically, 16 studies were conducted in the Americas, 25 in Europe, eight in Asia, and two in Oceania. Specifically, there were eight cohorts reported on hypertension, 12 on cardiovascular events, 11 on cancer events, four on obesity/overweight, eight on MetS/diabetes, four on depression/anxiety, six on digestive disease and nine on all-cause mortality. Consumption of UPFs was assessed using food frequency questionnaires, 24-hour dietary recalls, or dietary history. Age was the most commonly adjusted confounder, whereas adjustment for other confounders varied across studies. All studies had a low risk of bias except one with moderate risk of bias (online supplemental table S5).

UPFs and hypertension, cardiovascular events

Eight cohorts involving 118 946 participants showed consumption of UPFs was not significantly associated with a higher risk of hypertension (highest vs lowest HR 1.09, 95% CI 0.99 to 1.20, Q test p<0.00001, τ^2=0.01, I^2=81%; online supplemental table S6; online supplemental figure S2A), both when expressed as g/day (highest (median: 151.565 g/day) vs lowest (median: 13.89 g/day)) or total daily energy intake (highest (median: 55.4%/day) vs lowest (median: 10.0%/day)). Compared with the lowest in g/day, the pooled HR was 1.04 (95% CI 0.84 to 1.29, Q test p=0.005, τ^2=0.03, I^2=81%; online supplemental figure S2B). In dose-response analyses, each additional 100 g/day was positively linearly associated with hypertension risk (HR 1.11, 95% CI 1.02 to 1.21; p=0.041; figure 1A). However, no significant linear trend was observed when intake was expressed as % weight/energy, with each 10% increase associated with an HR of 1.02 (95% CI 0.98 to 1.05; p=0.375; online supplemental figure S3A).

Twelve cohorts involving 441 175 participants showed consumption of UPFs was significantly associated with cardiovascular events (highest vs lowest HR 1.24, 95% CI 1.14 to 1.36, Q test p<0.0001, τ^2=0.01, I^2=74%; online supplemental table S6; online supplemental figure S2D), both when expressed as servings/week (highest (median: 58.8 servings/wk) vs lowest (median: 9.8 servings/wk)) or total daily weight/energy intake (highest (median:

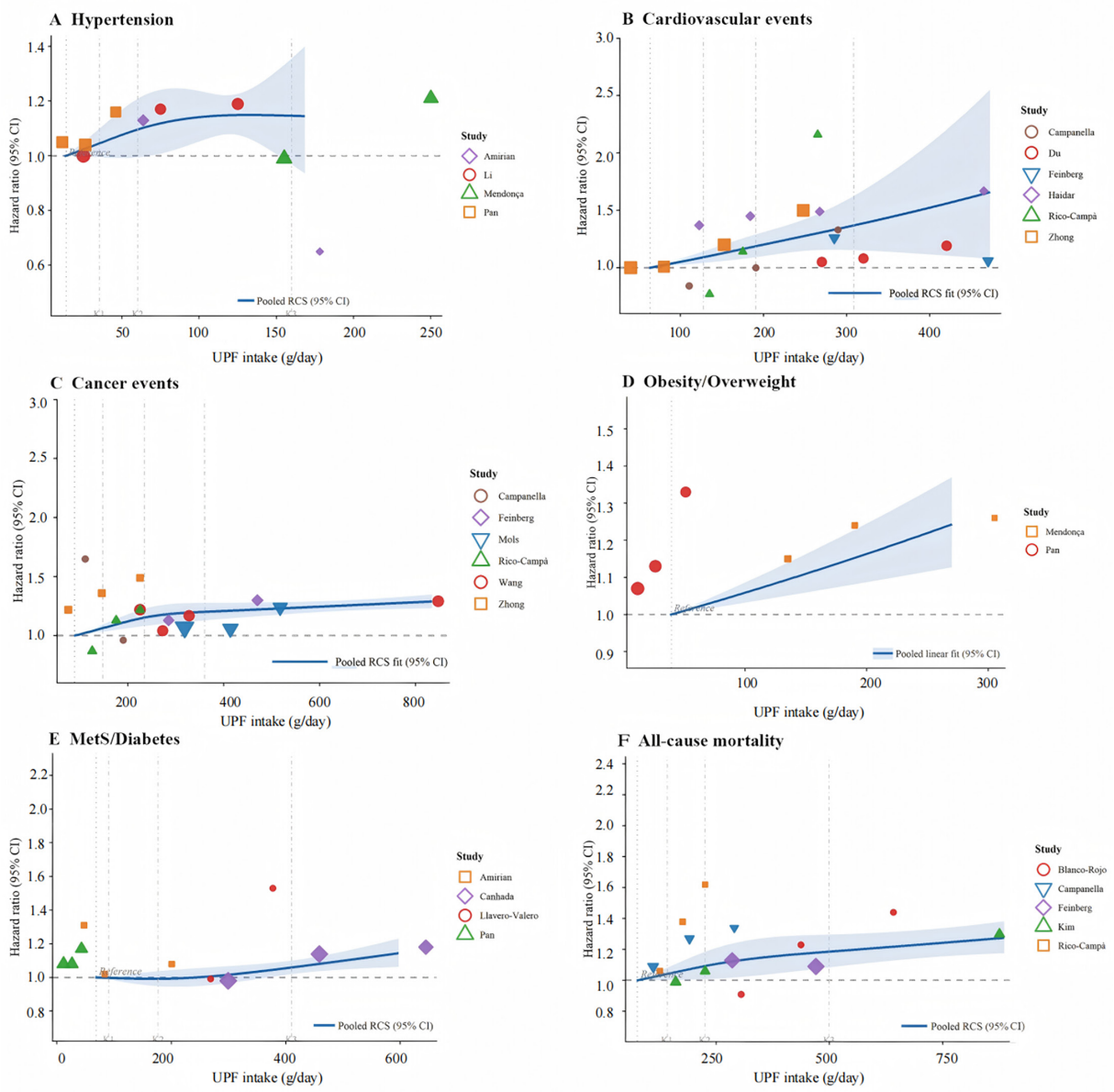

Figure 1 Non-linear exposure-effect analysis of ultra-processed foods and risk of hypertension, cardiovascular events, cancer events, obesity/overweight, metabolic syndrome/diabetes, and all-cause mortality. Hypertension in gram (A), Cardiovascular events in gram (B), Cancer events in gram (C), obesity/overweight in gram (D), metabolic syndrome/diabetes in gram (E), and all-cause mortality in gram (F). HR, hazard ratio.

31.75%/day) vs lowest (median: 5.4%/day)). Compared with the lowest in servings/wk, the pooled HR was 1.34 (95% CI 1.11 to 1.60, Q test p=0.002, τ^2=0.03, I^2=77%; online supplemental figure S2E). In dose-response analyses, positive linear associations were observed across all three exposure metrics: each additional 100 g/day (HR 1.14, 95% CI 1.06 to 1.22; p=0.002; figure 1B), each 10% increase in % weight/energy intake (HR 1.03, 95% CI 1.02 to 1.04; p<0.001; online supplemental figure S3B), and each additional 10 servings/week (HR 1.10, 95% CI 1.04 to 1.16; p=0.003; online supplemental figure S4A).

UPFs and cancer events

Eleven cohorts involving 1 246 153 participants showed consumption of UPFs was significantly associated with higher cancer events (highest vs lowest HR 1.12, 95% CI 1.04 to 1.21, Q test p<0.0001, τ^2=0.07, I^2=74%; online supplemental table S6; online supplemental figure S2G), both when expressed as servings/week (highest (median: 48.65 servings/wk) vs lowest (median: 12.5 servings/wk)) or total daily weight intake (highest (median: 32.5%/day) vs lowest (median: 5.0%/day)). Compared with the lowest in servings/wk, the pooled HR was 1.26 (95% CI 1.09 to 1.45, Q test p=0.62, τ^2=0.00, I^2=0%; online supplemental figure S2H). In dose-response analyses, positive associations were observed across all three exposure metrics: each additional 100 g/day (HR 1.04, 95% CI 1.02 to 1.06; p=0.002; figure 1C), each 10% increase in % weight/energy intake (HR 1.01, 95% CI 1.01 to 1.01;

p<0.001; online supplemental figure S3C), and each additional 10 servings/week (HR 1.02, 95% CI 1.01 to 1.03; p<0.001; online supplemental figure S4B). Evidence of non-linearity was observed for the 100 g/day exposure metric ($P_{non\text{-}linearity}$=0.012).

UPFs and obesity/overweight, MetS/diabetes

Four cohorts involving 135 685 participants showed consumption of UPFs was significantly associated with obesity/overweight (highest vs lowest HR 1.23, 95% CI 1.17 to 1.30, Q test p=0.50, τ^2=0.00, I^2=0%; online supplemental table S6; online supplemental figure S2J), when expressed as % of total daily weight/energy intake (highest (median: 32.4%/day) vs lowest (median: 7.5%/day)). Compared with the lowest in total daily weight/energy intake, the pooled HR was 1.20 (95% CI 1.13 to 1.28, Q test p=1.00, τ^2=0.00, I^2=0%; online supplemental figure S2K). In dose-response analyses, a significant non-linear association was observed for the % weight/energy intake exposure metric ($P_{non\text{-}linearity}$<0.001; online supplemental figure S3D). Overall, each 10% increase in the proportion of UPFs in total weight/energy intake was associated with a higher risk of obesity/overweight.

Eight cohorts involving 333 242 participants showed consumption of UPFs was significantly associated with a higher risk of MetS/diabetes (highest vs lowest HR 1.24, 95% CI 1.08 to 1.42, Q test p<0.00001, τ^2=0.03, I^2=94%; online supplemental table S6; online supplemental figure S5A), both when expressed as g/day (highest (median: 289.07 g/day) vs lowest (median: 68.31 g/day)) or total daily weight intake (highest (median: 45.725%/day) vs lowest (median: 15.425%/day)). Compared with the lowest in g/day, the pooled HR was 1.19 (95% CI 1.09 to 1.29, Q test p=0.54, τ^2=0.00, I^2=0%; online supplemental figure S5B). In dose-response analyses, each additional 100 g/day was also positively associated (HR 1.02, 95% CI 1.01 to 1.04; p=0.009; figure 1E). Each 10% increase in % weight/energy intake was positively linearly associated with MetS/diabetes risk (HR 1.16, 95% CI 1.09 to 1.23; p=0.004; online supplemental figure S3E).

UPFs and depression/anxiety

Four cohorts involving 228 597 participants showed consumption of UPFs was significantly associated with depression/anxiety (highest vs lowest HR 1.27, 95% CI 1.15 to 1.40, Q test p=0.13, τ^2=0.00, I^2=46%; online supplemental table S6; online supplemental figure S5E).

UPFs and digestive diseases

Six cohorts involving 6 073 960 participants showed consumption of UPFs was significantly associated with digestive diseases (highest vs lowest HR 1.31, 95% CI 1.16 to 1.48, Q test p=0.16, τ^2=0.01, I^2=37%; online supplemental table S6; online supplemental figure S5F). Consumption of UPFs was not significantly associated with ulcerative colitis (highest vs lowest HR 1.27, 95% CI 1.00 to 1.61, Q test p=0.17, τ^2=0.02, I^2=43%; online supplemental figure S5G). Consumption of UPFs was significantly associated with Crohn's disease (highest vs lowest HR 1.75, 95% CI 1.02 to 3.02, Q test p=0.03, τ^2=0.15, I^2=71%; online supplemental figure S5H).

UPFs and all-cause mortality

Nine cohorts involving 400 000 participants showed consumption of UPFs was significantly associated with all-cause mortality (highest vs lowest HR 1.18, 95% CI 1.10 to 1.26, Q test p=0.007, τ^2=0.01, I^2=62%; online supplemental table S6; online supplemental figure S5I), both when expressed as servings/week (highest (median: 65.8 servings/wk) vs lowest (median: 10.5 servings/wk)) or total daily weight/energy intake (highest (median: 41.35%/day) vs lowest (median: 5.9%/day)). Compared with the lowest in servings/wk, the pooled HR was 1.37 (95% CI 1.14 to 1.65, Q test p=0.29, τ^2=0.00, I^2=12%; online supplemental figure S5J). In dose-response analyses, positive associations were observed across all three exposure metrics: each additional 100 g/day (HR 1.03, 95% CI 1.02 to 1.05; p<0.001; figure 1F), each 10% increase in % weight/energy intake (HR 1.03, 95% CI 1.02 to 1.05; p<0.001; online supplemental figure S3F), and each additional 10 servings per week (HR 1.02, 95% CI 1.02 to 1.02; p<0.001; online supplemental figure S4C). Evidence of non-linearity was observed for the % weight/energy intake exposure metric ($P_{non\text{-}linearity}$=0.003).

Sensitivity analysis, subgroup analysis and meta-regression, and publication bias

Sensitivity analyses showed stable results (online supplemental figure S6). Publication bias was not assessed because fewer than 10 studies were included for each outcome. As most studies included mixed-gender populations, gender-specific subgroup analyses were not feasible. Other subgroup analyses and meta-regression by age, sample size, region, and publication year showed no significant sources of heterogeneity across outcomes (online supplemental table S7).

Quality of evidence

GRADE assessment showed low certainty for cardiovascular events, cancer events, MetS/diabetes, depression/anxiety, digestive diseases and all-cause mortality, moderate certainty for obesity/overweight and very low certainty for hypertension (online supplemental tables S8 and S9).

DISCUSSION

Major findings

The meta-analysis involving 51 prospective cohorts and 8 819 894 participants revealed higher consumption of UPFs was associated with higher risks of multiple chronic diseases and all-cause mortality, with dose-response evidence supporting positive exposure-risk relationships. Because these UPF-related conditions often form recognised multimorbidity clusters in primary care populations, these findings position intake of UPFs as

a potential shared upstream determinant of multimorbidity. In this context, reducing the relative contribution of UPFs within the overall diet may represent a practical and scalable strategy for mitigating the burden of multimorbidity at the population level. To our knowledge, this is the first meta-analysis on consumption of UPFs and health outcomes to incorporate both exposure-effect modelling and dose–response analysis.

Comparison with previous studies

Global consumption of UPFs has surged over the past two decades, largely driven by their cost-effectiveness, convenience, and shifting dietary patterns. Despite this trend, considerable debate persists regarding their health effects, and a safe consumption level remains undefined, partly due to inconsistent findings across studies. Our findings suggest that inconsistent results across studies may partly reflect differences in UPFs exposure quantification. Significant dose-response associations were observed for both absolute intake measures (g/day and servings/week) and proportional intake measures (% of total daily weight/energy intake), with gram-based intake showing relatively consistent linear associations across outcomes.

Sex distribution also requires consideration. Although sex may modify associations between intake of UPFs and health outcomes, in many included mixed-gender cohorts in our study, women accounted for the majority of participants, limiting our ability to conduct robust sex-specific subgroup analyses. Evidence from individual studies suggests that risks related to UPFs may differ by sex. A large US prospective cohort study found that high intake of UPFs was associated with colorectal cancer outcomes in men (HR 1.29, 95% CI, 1.08 to 1.53), but not in women (HR 1.04, 95% CI, 0.90 to 1.20) .[18] This discrepancy has been hypothesised to be related to a higher estrogen-to-testosterone ratio in women, which may confer a protective effect against colorectal cancer.[19]

Subgroup analyses provided additional insight into potential sources of heterogeneity. For MetS/diabetes, significant differences were observed by region (p=0.02) and sample size (p=0.008), with higher estimates in Europe (HR=1.53) and Asia (HR=1.16) than in the Americas (HR=1.14). These findings suggest possible regional differences, but whether they reflect true regional variation remains uncertain because several strata, particularly the Americas and Asia, were based on few studies. Consistent with our findings, a recent meta-analysis also reported stronger associations for cardiovascular events outside the United States (RR=1.28) compared with within the United States (RR=1.10).[20] Such differences may reflect variation in dietary habits, health policies, and food cultures across regions. Another recent study found that the types and quantities of UPFs and beverages are higher in high-income countries such as Europe and the United States.[21] Given the limited evidence available for several regions, these differences require further investigation.

Heterogeneity and exposure classification in UPFs-health associations

It is necessary to recognise that the NOVA Classification emphasises the degree and purpose of food processing rather than nutritional composition. As a result, foods with markedly different nutritional profiles and potential health effects may be grouped within the same UPF category. This may introduce exposure heterogeneity and misclassification of both UPFs and non-UPFs, particularly when information on food formulation and ingredient composition is limited.[22 23] And the broad category may include wholegrain breads, unsweetened yoghurt, nut-based products, chocolate, sugar-sweetened beverages, confectionery, and processed meats, which are unlikely to have equivalent biological effects. Evidence from individual studies supports this concern. The US Million Veteran Program (n=188 447) reported an inverse association between chocolate consumption and coronary heart disease risk (HR 0.89, 95% CI, 0.84 to 0.96),[24] high nut consumption was associated with lower coronary heart disease risk in an observational meta-analysis (RR 0.69, 95% CI 0.59 to 0.78).[25] A prospective study also found that each additional weekly intake of walnuts was associated with a 3% lower incidence of MetS (OR 0.97, 95% CI 0.93 to 0.99).[26] These examples illustrate that not all foods classified as UPFs are likely to have equivalent health effects. In other words, analysing heterogeneous foods with potentially neutral or beneficial components as a single exposure category may dilute or obscure the adverse effects of more harmful UPF subtypes.

A further source of misclassification arises from dietary assessment methods. All included studies relied on self-reported instruments, such as food frequency questionnaires (FFQs), dietary records, or 24-hour recalls, which are prone to systematic bias and measurement error. Participants may over-report perceived 'healthy' foods (eg, fruits, vegetables, wholegrains) and under-report energy dense or socially undesirable items (eg, sugary beverages, fried foods, confectionery).[27 28] Validation studies using doubly labelled water show that under-reporting is common and varies across dietary assessment methods.[27] Such selective under-reporting may disproportionately affect UPFs, particularly sugar-sweetened beverages and processed snacks.[28] Measurement validity may also vary by participant characteristics: older adults showed lower validity coefficients than younger adults for intake of UPFs assessed by semi-quantitative FFQs (Spearman correlations 0.48 vs 0.67),[29] and individuals with higher body mass index (BMI) were more likely to under-report total energy intake and omit foods high in fat, sugar, and salt (OR 3.73, 95% CI 3.01 to 4.63).[30] In addition, commonly used dietary instruments may not adequately capture industrial processing characteristics and may combine homemade and UPFs within the same item, such as 'cake,' introducing further misclassification of UPF subtypes.[29] Overall, these sources of misclassification and measurement error are likely to bias associations towards the null rather than inflate risk

estimates, suggesting that the adverse effects of harmful UPF subtypes may be underestimated. As few included studies examined specific UPF subtypes, subtype-specific analyses were not feasible. Future studies should incorporate information on food formulation, ingredient composition, and key nutritional characteristics, such as added sugars, fibre content, sodium, and fat quality, to improve classification accuracy and distinguish harmful UPF subtypes from neutral or potentially beneficial products.

Beyond heterogeneity within the UPF category itself, the high I^2 values observed for cardiovascular events, hypertension, and MetS/diabetes do not necessarily invalidate the observed associations between UPFs and health outcomes; rather, they indicate that a single pooled HR may oversimplify a complex relationship. Exposure scaling may illustrate this: an individual consuming 100 g/day of UPFs within a 1500 g diet derives 6.7% of intake from UPFs, whereas the same 100 g/day within a 3000 g diet derives only 3.3%. These differences may increase between-study variability when absolute intake measures or heterogeneous categorical cut-offs are pooled. Accordingly, pooled HRs from highly heterogeneous studies should be interpreted as average associations across populations, exposure definitions, dietary contexts, and study methods, rather than as uniform effect sizes. Differences in dietary assessment tools, food classification, confounding adjustment, follow-up duration, baseline risk, and dietary patterns may also have contributed. Nevertheless, the consistent direction of associations suggests that heterogeneity mainly affects the precision and magnitude of pooled estimates, rather than the overall inference that higher consumption of UPFs is associated with higher chronic disease risk.

Potential mechanism

UPFs have lower nutritional value and high energy, which may increase eating rate and delay satiety signalling, leading to higher overall food intake and higher body weight.[31] Additionally, emerging evidence suggests that the combination of multiple additives, such as artificial sweeteners, may have a potential 'cocktail effect', potentially having a greater impact on human health than exposure to a single additive.[32] Laboratory research showed that the extensively altered physical composition of UPFs may have implications for cardiometabolic health by affecting key biological pathways such as gut microbiota composition, host-microbiota interactions, inflammation, oxidative stress, and insulin resistance.[33] Furthermore, several compounds may form during food processing, such as acrylamide—a contaminant formed in heat-treated processed foods through the Maillard reaction[34] and acrolein—a reactive aldehyde generated during fat heating[35] —have been associated with a higher incidence of CVD. And some endocrine-disrupting chemicals may be introduced into the food packaging. For example, food packaging materials like those labelled 'bisphenol A (BPA)' or 'bisphenol S (BPS)', widely used in plastic packaging, are associated with a higher risk of CVDs according to our and others' previous reports.

Implications for primary care

The observed associations between intake of UPFs and multiple chronic conditions that frequently cluster as multimorbidity underscore the need for integrated, risk factor-oriented management in primary care, which often serves as the first point of contact for managing coexisting conditions.[36] In this context, primary care practitioners may advise gradual reduction of UPFs intake towards approximately 10%–20% of total daily energy intake,[37] while considering which UPF subtypes are most strongly associated with adverse outcomes. Replacing UPFs with minimally processed alternatives, rather than restriction alone, may provide a more sustainable and patient-centred approach.[38] Given variability in consumption of UPFs and dose-response relationships, recommendations should be tailored to baseline intake, dietary preferences, cultural background, and socioeconomic status,[39 40] with follow-up to monitor progress and adjust advice.[41] Multidisciplinary primary care teams, including physicians, nurses, nutritionists, and community health workers, may support the implementation of UPF-reduction strategies and patient-centred multimorbidity management.[42]

Beyond individual-level interventions, population-level strategies are needed to reduce widespread consumption of UPFs. Government-mandated front-of-package warning labels may provide a scalable and equitable approach. Evidence from Chile suggests that labelling and marketing regulations identifying products high in sugar, sodium, and saturated fat were associated with sustained reductions in household purchases of energy, sugar, and sodium, alongside product reformulation.[43] More targeted labelling systems may address specific UPF subtypes. For example, Singapore's Nutri-Grade system classifies beverages by sugar content into Grades A (≤1 g/100 mL), B (>1–5 g/100 mL), C (>5–10 g/100 mL), and D (>10 g/100 mL), with mandatory front-of-pack labels for Grades C–D and advertising restrictions for Grade D, encouraging reformulation below the 5 g/100 mL threshold.[44] Evidence from randomised controlled trials (RCT) in the UK further suggests that such warning labels improve consumer awareness and reduce the selection of unhealthy options.[45] Together, these actions may support healthier dietary choices and reduce reliance on individual clinical encounters to address poor dietary patterns.

Strengths and limitations

This study has several strengths. First, the large sample size (n=8 819 894) and inclusion of 51 prospective cohort studies enhanced statistical power and the precision of effect estimates. Second, we employed a one-stage dose-response meta-regression with robust error estimation, utilising the full exposure gradient across three metrics—% of total daily weight/energy intake, g/day, and servings/week—which allowed direct comparison of proportional vs absolute intake measures. Third, the long follow-up duration (range: 2–32 years) allowed sufficient time to capture the development

of chronic disease outcomes. Fourth, by examining a broad spectrum of health outcomes—including cardiovascular, metabolic, cancer, mental health, and mortality—this study provides a more integrated assessment of UPFs exposure across conditions that commonly co-occur, offering insight into its potential role as a shared upstream determinant in populations with multimorbidity.

However, several limitations should be considered. First, all studies relied on self-reported dietary assessments, which may not fully capture processing characteristics, ingredient composition, or UPF subtypes, leading to exposure misclassification and measurement error that likely attenuate associations.[46] Second, exclusion of individuals <18 years limits generalisability to younger populations. Third, publication bias could not be assessed for outcomes with fewer than 10 studies, and limited data likely contributed to heterogeneity and imprecision for outcomes such as depression, overweight, and cancer.[47] Fourth, most cohorts were from Europe and the Americas, with few from Asia, and several large cohorts had a predominance of female participants, potentially limiting generalisability and introducing sex-related bias. Fifth, subclinical outcomes (eg, dyslipidaemia and sleep disorders) were not included. Finally, converting intake of UPFs into standard 50g servings and the small number of studies for some dose-response classifications may have introduced additional imprecision. Residual confounding also remains possible because all included studies were observational. Intake of UPFs often co-occurs with broader lifestyle and behavioural patterns that are difficult to fully adjust for and may influence long-term health risks, including mortality.

CONCLUSION

Evidence suggests that higher consumption of UPFs is associated with higher risks of multiple chronic health outcomes, including cardiovascular events, cancer events, obesity/overweight, MetS/diabetes, depression/anxiety, digestive diseases, and all-cause mortality, with dose-response evidence supporting positive exposure-risk relationships. These associations may vary according to how exposure to UPFs is quantified, with relative measures reflecting the contribution of UPFs within the overall diet showing more consistent patterns across outcomes. Given that UPF related chronic diseases often cluster as multimorbidity, reducing consumption of UPFs and replacing them with minimally processed alternatives may be relevant for chronic disease prevention and primary care management. Future studies should adopt harmonised and subtype-specific UPF exposure metrics, improve dietary assessment methods, and clarify clinically meaningful intake thresholds across diverse populations.

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