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Ultraprocessed food and chronic noncommunicable diseases: A systematic review and meta-analysis of 43 observational studies

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Summary

This systematic review and meta-analysis investigated the association between consumption of ultraprocessed food and noncommunicable disease risk, morbidity and mortality. Forty-three observational studies were included (N = 891,723): 21 cross-sectional, 19 prospective, two case-control and one conducted both a prospective and cross-sectional analysis. Meta-analysis demonstrated consumption of ultraprocessed food was associated with increased risk of overweight (odds ratio: 1.36; 95% confidence interval [CI], 1.23-1.51; P < 0.001), obesity (odds ratio: 1.51; 95% CI, 1.34-1.70; P < 0.001), abdominal obesity (odds ratio: 1.49; 95% CI, 1.34-1.66; P < 0.0001), all-cause mortality (hazard ratio: 1.28; 95% CI, 1.11-1.48; P = 0.001), metabolic syndrome (odds ratio: 1.81; 95% CI, 1.12-2.93; P = 0.015) and depression in adults (hazard ratio: 1.22; 95% CI, 1.16-1.28, P < 0.001) as well as wheezing (odds ratio: 1.40; 95% CI, 1.27-1.55; P < 0.001) but not asthma in adolescents (odds ratio: 1.20; 95% CI, 0.99-1.46; P = 0.065). In addition, consumption of ultraprocessed food was associated with cardiometabolic diseases, frailty, irritable bowel syndrome, functional dyspepsia and cancer (breast and overall) in adults while also being associated with metabolic syndrome in adolescents and dyslipidaemia in children. Although links between ultraprocessed food consumption and some

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intermediate risk factors in adults were also highlighted, further studies are required to more clearly define associations in children and adolescents.

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KEYWORDS

meta-analysis, noncommunicable disease, NOVA, ultraprocessed food

1 | INTRODUCTION

NOVA is a food classification system first proposed by Monteiro et al. in 2009[1] and is now endorsed by the United Nations and World Health Organization. NOVA categorizes food depending on the nature, extent and reasons for food processing.[2,3] Ultraprocessed foods are characterized by NOVA as industrial formulations generated through compounds extracted, derived or synthesized from food or food substrates.[4-6] Such consumables typically contain five or more ingredients per product while scarcely containing intact or unprocessed wholefood.[7] Ultraprocessed foods also commonly contain artificial substances such as colours, sweeteners, flavours, preservatives, thickeners, emulsifiers and other additives used to promote aesthetics, enhance palatability and increase shelf life.[5,7,8] Likely owing to their relatively low-cost, convenience, shelf life and heavy marketing, the consumption of ultraprocessed food has markedly increased over the past several decades.[9-14] More recently, large-scale observational studies across diverse populations show robust dose-response associations between the dietary share of ultraprocessed food and dietary intake of added sugar, saturated fat, sodium and energy,[15-20] with inverse, dose-response associations with dietary intake of protein, fibre and essential vitamins and minerals.[16,17,19-24] Both nutrition in general, and in particular the low nutritional quality and high-energy density profiles common to ultraprocessed food, are widely accepted as critical drivers of chronic noncommunicable diseases.[25]

Noncommunicable diseases are broadly defined as any health condition of long duration or that has long-term effects and is nontransmissible or noninfectious in its aetiology.[26,27] According to the World Health Organization, noncommunicable diseases account for over 70% of all deaths globally, with more than 85% considered premature. Traditionally, the prevention and management of noncommunicable diseases has been limited and targeted towards risk factors such as smoking and blood pressure in diseases like cancer, diabetes, respiratory and cardiovascular disorders.[28] However, as these diseases often co-occur and share many of the same risk factors as both common mental disorders and severe mental illness, there have been recent calls for the integration of mental health into the 'big four' noncommunicable disease framework.[28,29]

Given the broader definition of chronic diseases (i.e., any nontransmissible health condition of long duration) and that it is well established that poorer dietary quality increases the risk of mortality owing to chronic diseases,[29] there is imperative to better understand the link between a more comprehensive disease framework and the relatively novel classification of ultraprocessed food. Recently published systematic reviews report associations between ultraprocessed food consumption and adverse health outcomes.[30,31] However, in the review by Meneguelli et al., a number of different

food classification systems were used to assess ultraprocessed food as an exposure variable, with the authors concluding that these classification differences made comparison between studies difficult.[30] In both reviews, secondary data or indirect measures of ultraprocessed food consumption were included (e.g., national and household availability) and thereby limit inferences.[31] Furthermore, meta-analysis was not conducted in either study. The present systematic review and meta-analysis therefore aims to synthesize and provide quantitative analysis of the evidence assessing the association between direct consumption of ultraprocessed food, as defined by the NOVA food classification system, and noncommunicable diseases, as well as intermediate risk factors and all-cause mortality.

2 | METHODS

2.1 | Search strategy

This review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Figure S1 for PRISMA flowchart).[32] This review was prospectively registered with PROSPERO (CRD42020176752). Since the NOVA food classification system was first proposed in 2009,[1] databases were searched from 2009 to March 2020. Relevant studies were retrieved from MEDLINE complete, EMBASE, Scopus, Cochrane and CINAHL. Search terms were a combination of free-text terms and controlled vocabulary related to ultraprocessed food and NOVA in addition to noncommunicable diseases, including mental disorders, metabolic diseases, cardiovascular abnormalities, respiratory tract diseases, neoplasms and frailty (see Figure S2 for search terms across the varied databases).

2.2 | Study selection, inclusion and exclusion criteria

To be included in this review, studies needed to meet each of the following eligibility criteria: written in English, conducted in humans of any age; used an observational study design (e.g., cross-sectional, prospective, case-control and retrospective designs); investigated the relationship between consumption of ultraprocessed food and noncommunicable diseases, associated risk factors and all-cause mortality; and compared either different levels of ultraprocessed food consumption (e.g., lower versus higher) or ultraprocessed food versus unprocessed or minimally processed food. Studies were excluded if they did not use the NOVA food classification system or did not assess the direct consumption of ultraprocessed food (e.g., household availability, access to, price of and purchase of ultraprocessed food).

2.3 | Data extraction

Screening of the publication title and abstract for individual studies was conducted by two authors (M.L. and J.D.) with disagreements resolved by consensus. Articles deemed eligible for full-text review were assessed for eligibility independently by two authors (M.L. and W.M.). The following parameters were extracted in duplicate: author/date, study design, sample size, sample characteristics (e.g., age, % male and exclusion criteria), dietary data characteristics (e.g., how data were collected and analysed, tool, duration and details of NOVA classification) and confounding variables and details of disease outcomes (e.g., how data were collected and analysed, tool and results). As many of the studies reported results from several analyses (e.g., main statistical models versus sensitivity testing and unadjusted versus adjusted results), those results reported in the studies' abstracts were considered as the main statistical models for extraction unless otherwise indicated by the original authors. In the event that more information was needed, the corresponding author(s) of the original paper were contacted.

2.4 | Critical appraisal assessment

Studies selected for retrieval were assessed for methodological validity using the Critical Appraisal Checklist for Cross-Sectional, Cohort and Case-Control Studies, a set of standardized critical appraisal instruments from the Joanna Briggs Institute.[33] Instrument items ranged from one to 11 and pertained to population characteristics, exposures, confounders, outcomes, follow-up details (where applicable) and statistical analysis. These instruments provide an overall appraisal to include or exclude a study based on the following answers to items: yes, no, unclear or not applicable.[33]

2.5 | Data analysis

Where studies were homogeneous in terms of study design, statistical methods and disease outcome, results were pooled and meta-analyses were conducted. Odds ratios and hazard ratios with 95% confidence intervals (CIs) for binary outcomes were used. Studies deemed too heterogeneous based on study design, statistical methods and disease outcome were excluded from the meta-analysis but formed part of the narrative synthesis of the findings, presented by type of outcome and population characteristics.

Meta-analyses were conducted in Comprehensive Meta-Analysis 3.0[34] using a DerSimonian-Laird random-effects model and the I-squared statistic to assess for heterogeneity between studies.[35] Substantial heterogeneity was defined as an I^2 value greater than 75%. In order to account for heterogeneity between studies, meta-analyses were conducted multiple times with one study removed each time in order to determine whether overall estimates were influenced by outlier studies (i.e., one-study-removed analyses). Data were considered statistically significant if the reported P value was less than 0.05.

3 | RESULTS

3.1 | Search results

The search strategy yielded 1,324 deduplicated studies that were screened to identify 43 eligible studies for inclusion.

3.2 | Study characteristics

A total of 891,723 participants were included in the 43 studies, with sample sizes ranging from 56 to 109,104 participants. The mean age of participants was 39 years (not including seven studies that reported age categories rather than mean age),[36-42] with a mean age of 14.7 years for adolescents and 6.4 years for children. Males accounted for 38% of the samples combined. A detailed summary of study characteristics is outlined in Tables S2 to S7. Selected studies were undertaken in Brazil (*n* = 17), France (*n* = 8), Spain (*n* = 7), Canada (*n* = 3), United States of America (*n* = 3), United Kingdom (*n* = 2), Norway (*n* = 1), Lebanon (*n* = 1) and Malaysia (*n* = 1). A total of 21 cross-sectional, 19 prospective (average follow-up of 6.5 years) and two case-control studies were included. One study conducted both a prospective and cross-sectional analysis.[43] Eligible studies included different age groups, including adults (*n* = 32), adolescents (*n* = 5) children (*n* = 3), older adults greater than 60 years old (*n* = 1) and mixed age groups (i.e., children and adolescents (*n* = 1) and adolescents and adults (*n* = 1)).

Dietary data were either self-reported (*n* = 27) or conducted via interview (*n* = 16). Dietary data were collected using food-frequency questionnaires (FFQ) (*n* = 22), 24-h dietary recalls (R24h) (*n* = 18) and food diaries (*n* = 2), with one study using both an FFQ and R24h.[44] Selected articles were deemed to have satisfactory methodological quality as per the critical appraisal process (Tables S8-S10). However, limitations included four cross-sectional studies that did not adequately identify confounding factors nor did they report utilizing strategies to deal with confounding factors.[45-48] Analytical approaches in these studies were thus considered suboptimal, and none were included in the meta-analyses. See Table 1 below for an overview of the number of studies reporting associations versus no associations between consumption of ultraprocessed food and morbidity, mortality and associated risk factors.

3.3 | Average ultraprocessed food consumption and details of exposure variable

Over half of included studies reported the average intake of ultraprocessed food expressed as a percentage of total caloric intake (*n* = 28), with proportions ranging from 17% to 56% (see Table S1 for more details). The average intake of ultraprocessed food across these 28 studies was 37% of total calories. Averages within countries ranged from 56% in the United States of America (*N* = 22,362), 54% in the United Kingdom (*N* = 8,317), 42% in Canada (*N* = 24,084), 38% in Brazil (*N* = 51,418), 37% in Lebanon (*N* = 302), 32% in France (*N* = 71,778), 24% in Malaysia (*N* = 200) and 23% in Spain (*N* = 45,446) (see Figure 1 below). Various other measurements of ultraprocessed food consumption were also reported, with some studies using more than one approach, including weight (absolute or percentage grammes per day) (*n* = 9),[49-57] absolute caloric intake per day (*n* = 6),[6,45-47,58,59] servings or times per day (*n* = 5),[44,60-63] ultraprocessed food consumption scores (*n* = 2)[37,48] and ultraprocessed items consumed per day (*n* = 1).[6]

The majority of studies divided ultraprocessed food consumption into quartiles (*n* = 19)[6,40,44,49,51-54,61-68] or quintiles (*n* = 7),[36-38,43,59,69,70] with the lowest quartile or quintile being the reference group (i.e., lowest consumption). Some reported the mean dietary share of ultraprocessed food across groups, whereas others presented above and below cut-off ranges. Three studies used tertiles, with the lowest tertile being the reference and also referring to lowest consumption.[42,57,60] Five studies used sex-specific cut-off ranges, four divided the sample by quartiles[49,65,66,68] and the other study by tertiles.[42] Other studies treated ultraprocessed food consumption as a dichotomous variable (*n* = 5)[66,68-71] as well as a continuous variable (*n* = 7 for main statistical analyses,[39,41,47,48,55,58,71] with *n* = 10 for secondary analyses[36,49,51-53,59,65,67,68]). In the latter, quartiles or quintiles were used for the main statistical analyses. In four studies, ultraprocessed food was analysed as the dependent variable,[45,72-74] with weight status considered the exposure (see Table S1 for more details).

4 | RESULTS

4.1 | Overweight and obesity

4.1.1 | Adults

Fourteen studies (*N* = 156,276) investigated associations between the consumption of ultraprocessed food and measures of overweight and obesity among adults.[39,40,47,48,54,59,63,67,68,70-74] Twelve were cross-sectional, and two studies were prospective[63,67] (see Table S2 for study characteristics).[39,40,47,48,54,59,68,70-74] The following sections describe the nature of relationships between the consumption of ultraprocessed food and varying measures of overweight and obesity:

Body mass index greater than or equal to 30 kg/m^2: Obesity

Seven studies (*N* = 62,615) examined and defined obesity as body mass index (BMI) ≥ 30 kg/m^2.[39,40,59,67,68,70,73] Out of these seven, four were cross-sectional with homogeneous data and were thus included in a meta-analysis. In addition to these four studies, one other cross-sectional study that grouped adolescents aged 10 to 19 years old with adults aged at or above 20 years old was also included (*N* = 30,243).[38] Meta-analysis found higher consumption of ultraprocessed food (ranging from >29.0% to ≥76.2% of calories) was significantly associated with an increased risk of obesity compared with lower consumption of ultraprocessed food (ranging from ≤13.0

TABLE 1 Number of individual studies reporting associations versus no associations between ultraprocessed food consumption and chronic noncommunicable diseases, mortality and associated risk factors

Population/outcome	Direct association	Inverse association	No association
Children			
BMI			1
Weight			1
WC	1		
Adolescents			
BMI		1	1
Body fat %		1	1
Weight		1	
WC			1
Adolescents and adults			
BMI	1		
OB	1		
OW			1
Adults			
BMI	3		4
OB	4	1	2
OW	3	1	
OW and/or OB	5		
WC	4		2
AO	2		1
ACM	4		
Adolescents			
MetS	1		
Respiratory disease	1		1
Adults			
MetS	3		
T2DM	1		
Depression	2		
Frailty	1		
IBS	1		
IBD			1
CVD	2		
Children			
Glucose			1
Insulin			1
Insulin resistance			1
TC	1		
LDL	1		
NHDL			1
TG			1
HDL			1
BP			1
Adults			
BP	1		2
Sedentary lifestyle	1		

(Continues)

TABLE 1 (Continued)

Population/outcome	Direct association	Inverse association	No association
Framingham risk score	1		
Glycated haemoglobin	1		
Glucose			1
Insulin			1
TC			2
LDL			1
VLDL			1
TG			2
HDL			1
CRP	1 (women only)		2
Cancer overall	1		
Cancer breast	2		
Cancer prostate			2
Cancer colorectal			1

Note. one study[38] assessed BMI, obesity and overweight and grouped adolescents aged 10 to 19 years old with adults aged 20 years (see Adolescents and Adults).

Abbreviations: ACM, all-cause mortality; AO, abdominal obesity; BMI, body mass index; body fat %, body fat percentage; BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LDL, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NHDL, nonhigh-density lipoprotein cholesterol; OB, obese; OW, overweight; T2DM, type-two diabetes mellitus; TC, total cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein cholesterol; WC, waist circumference.

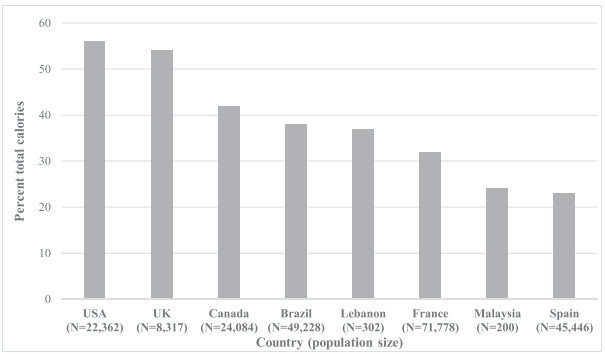

FIGURE 1 Bar chart of the average intake of ultraprocessed food (% calories) by country

to ≤35.2% of calories) (odds ratio: 1.51; 95% CI, 1.34-1.70; $P < 0.001$; $I^2 = 29\%$; $N = 61,340$) (Figure 2).

In the other three of seven studies (not included in the meta-analysis), one was cross-sectional and treated ultraprocessed food consumption as a continuous independent variable.[39] The authors reported no association between intake of ultraprocessed food and obesity (odds ratio: 1.01; 95% CI, 1.00-1.02).[39] Another study was prospective and reported no association between higher intake of ultraprocessed food and higher risk of obesity among individuals who were overweight at baseline (relative risk: 1.0; 95% CI 0.85-1.21).[67] The last study was cross-sectional and demonstrated an inverse association between individuals with obesity and their reported consumption of ultraprocessed food (beta coefficient: −1.9; 95% CI, −3.4 to −0.5).[73]

BMI greater than or equal to 25 to 29.9 kg/m^2: Overweight

Four cross-sectional studies ($N = 48,614$) assessed and defined overweight as BMI ≥ 25.0 to 29.9 kg/m^2.[40,59,70,73] One of these reported an inverse association between individuals who were overweight and their reported consumption of ultraprocessed food (beta coefficient: −1.0; 95% CI −1.9 to 0.0).[73] Another study treated ultraprocessed food consumption as a continuous independent variable.[59] The authors reported a 10% increase in the relative intake of ultraprocessed food increased the likelihood of being overweight by 3% (odds ratio: 1.03; 95% CI, 1.02-1.09).[59] The other two studies with homogeneous study designs and data were included in a meta-analysis as well as one other cross-sectional study (previously described) that grouped adolescents aged 10 to 19 years old with adults aged at or above 20 years old ($N = 30,243$).[38] Meta-analysis established that higher consumption of ultraprocessed food (ranging from >29.0% to ≥74.2% of calories) significantly increased the risk of being overweight compared with lower consumption (ranging from ≤13.0% to ≤36.5% of calories) (1.36, 95% CI, 1.23-1.51; $P < 0.001$; $I^2 = 0\%$; $N = 55,197$) (Figure 3).

BMI greater than or equal to 25 kg/m^2: Overweight and obesity

Five studies ($N = 100,419$) investigated overweight and obesity defined as BMI ≥ 25 kg/m^2. This included the two prospective studies,[63,67] with the other three studies[39,54,72] being cross-sectional. No studies were included in a meta-analysis given the heterogeneous study designs and statistical approaches as well as data reported below.

Three reported higher consumption of ultraprocessed food (ranging from >23.0% to >30.8% of calories or six servings per day) versus lower consumption (ranging from <11.0% to <17.8% of calories or two

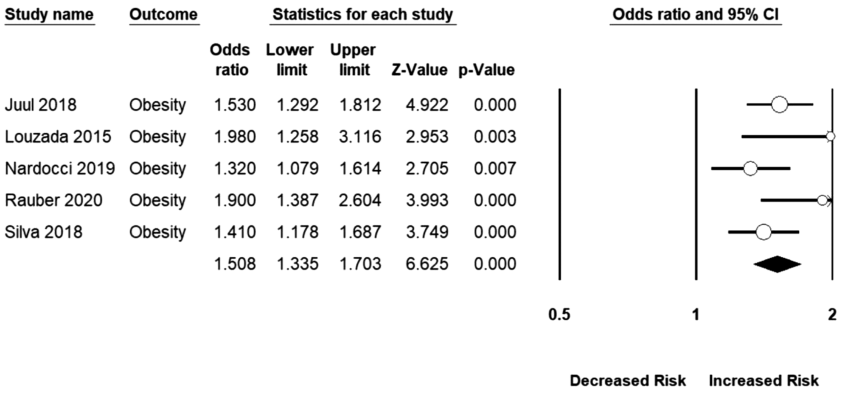

FIGURE 2 Forest plot of meta-analysis for cross-sectional studies assessing association between higher versus lower consumption of ultraprocessed food and obesity risk in adults

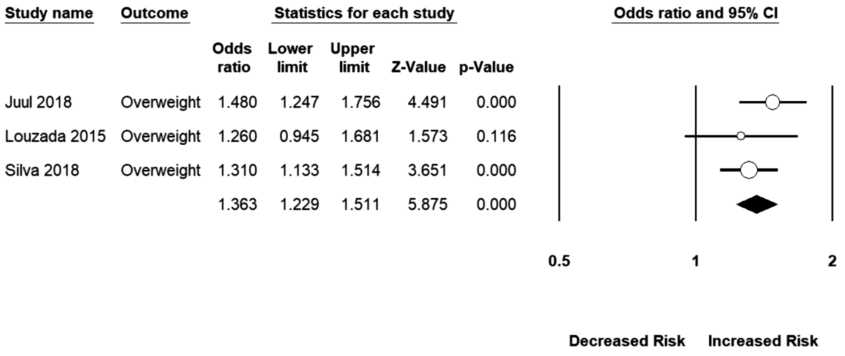

FIGURE 3 Forest plot of meta-analysis for cross-sectional studies assessing association between higher versus lower consumption of ultraprocessed food and overweight risk in adults

servings per day) was positively associated with overweight and obesity (risk ratio: 1.20; 95% CI, 1.03-1.40[67]; hazard ratio: 1.26; 95% CI, 1.10-1.45[63]; and 25.9% of total sample, $P < 0.0001$[54]). While the fourth study reported results in the same direction, the association was negligible (odds ratio: 1.01; 95% CI, 1.00-1.02[39]). The fifth study (cross-sectional) did not assess overall consumption of ultraprocessed food; instead, it determined consumption of ultraprocessed dinner products, sweet/salty snacks and soft drinks, and fast food prepared away from home. Individuals with overweight and obesity versus normal weight had higher odds of consuming ultraprocessed dinner products (odds ratio: 1.54; 95% CI, 1.04-2.30) and fast foods away from home (odds ratio: 3.40; 95% CI, 2.26-5.11) but not snacks and soft drinks (odds ratio: 1.18; 95% CI, 0.81-1.71).[72] In addition, there were no differences in the proportion of individuals with overweight and obesity versus normal weight categorized as high consumers of ultraprocessed dinner products (52.8% versus 46.8%, $P = 0.190$) or fast foods away from home (49.2% versus 40.6%, $P = 0.059$, respectively).[72] However, a significantly higher proportion of individuals with overweight and obesity versus normal weight were categorized as high consumers of snacks and soft drinks (54.3% versus 45.1%, $P = 0.044$).[72]

Other weight measures

Four studies ($N = 42,924$) assessed other measures of overweight and obesity, including categorical variables of weight gain and waist circumference or abdominal obesity.[40,67,68,70] Three of the four studies were cross-sectional with homogeneous data and were thus included in a meta-analysis (waist circumference ≥102 cm for men and ≥88 cm for women).[40,68,70] Meta-analysis established that higher consumption of ultraprocessed food (ranging from >29.0% to ≥76.2% of calories) was significantly associated with waist circumference or risk of abdominal obesity compared with lower consumption in adults (ranging from <16.0% to ≤36.5%) (odds ratio: 1.49; 95% CI, 1.34-1.66; $P < 0.0001$; $N = 31,097$; $I^2 = 4\%$) (Figure S3). The other prospective study reported that a higher consumption of ultraprocessed food was associated with higher risk of both weight gain (1.68 kg per year) (relative risk: 1.27; 95% CI, 1.07-1.50) and increased waist circumference (2.42 cm per year) (relative risk: 1.33; 95% CI, 1.12-1.58).[67]

BMI was assessed as a continuous variable in seven cross-sectional analyses,[39,40,47,48,68,70,74] waist circumference in five,[40,47,48,68,70] body fat percentage in two[47,71] and visceral fat in one.[71] One of seven studies examining BMI continuously was prospective in study design; however, the association between ultraprocessed food consumption and prepregnancy BMI was analysed cross-sectionally, with no association reported (beta coefficient: 0.45; 95% CI, −0.02 to 0.92; $N = 189$).[74] The other six of seven studies examining BMI continuously were cross-sectional in study design, with half reporting associations with consumption of ultraprocessed food ($N = 31,097$)[40,68,70] and the other half reporting no associations ($N = 3,029$).[39,47,48]

More specifically, in three of seven studies reporting BMI as a continuous variable,[40,68,70] higher consumption of ultraprocessed food (ranging from >29.0% to ≥76.2% of calories) versus lower consumption (ranging from <16.0% to ≤36.5% of calories) was associated with higher BMI (beta coefficients: 1.66, 95% CI, 0.96-2.36[68]; 0.80, 95% CI, 0.53-1.07[40]; and 1.61, 95% CI, 1.11-2.10[22]). Higher consumption was also associated with greater waist circumference in these three studies (beta coefficients: 3.56, 95% CI, 1.79-5.33[68]; 1.71, 95% CI, 1.02-2.40[40]; and 4.07, 95% CI,

2.94-5.19[22]). In contrast, three studies reported no association between ultraprocessed food consumption and BMI (beta coefficient: 0.02; 95%CI, −0.02 to 0.07[39]; Spearman correlation coefficient: −0.12, $P = 0.78$[48]; Pearson correlation coefficient: 0.04, $P = 0.95$[47]), with two of these reporting no association with waist circumference (Spearman correlation coefficient 0.01, $P = 0.90$[48]; Pearson correlation coefficient 0.025, $P = 0.75$[47]). Similarly, two studies reported that higher versus lower consumption of ultraprocessed food was not associated with body fat percentage (beta coefficient: 0.03; 95% CI, −0.06 to 0.12[71]; Pearson correlation coefficient −0.45, $P = 0.57$[47]) or visceral fat (beta coefficient: 0.20; 95% CI, −4.11 to 4.51[71]).

4.1.2 | Adolescents

Four studies (N = 32,311) examined associations between ultraprocessed food consumption and overweight and obesity among adolescents,[6,38,46,75] with one of these grouping adolescents aged 10 to 19 years old with adults aged 20 years and over (previously described).[38] One study was prospective,[6] and the other three were cross-sectional (see Table S2 for study characteristics).[38,46,75] Overall, the results were inconsistent. The prospective study reported both an inverse association and no association at different time-points (i.e., baseline, first-year and second-year follow-up).[6] For the three cross-sectional studies, one reported an inverse association,[46] one reported no association[75] and the other reported positive associations.[38]

The prospective study, more specifically, reported that higher consumption of ultraprocessed food versus lower consumption (fourth quartile versus first quartile; not quantified) was inversely associated with BMI at baseline (mean BMI: 21.3 kg/m^2 versus 23.1 kg/m^2, $P < 0.001$) and the 1-year (first) follow-up (mean BMI: 21.8 kg/m^2 versus 23.5 kg/m^2, $P < 0.001$) but no association was reported at the second-year (final) follow-up (mean BMI: 22.4 kg/m^2 versus 24 kg/m^2, $P = 0.40$).[6] In addition, no association was reported for higher versus lower consumption of ultraprocessed food and body fat percentage at baseline (mean body fat percentage: 21.9 versus 25.1, $P = 0.088$), with a significant inverse association at the second follow-up (mean body fat percentage: 22.1 versus 25.9, $P < 0.001$); no assessment of body fat percentage was undertaken at the first follow-up.[6]

For the cross-sectional studies, one reported adolescents with normal weight versus excess weight (i.e., percentile <85 versus percentile ≥85, respectively) presented higher consumption of ultraprocessed food (median intake: 1,586.6 versus 1,213.8 absolute calories per day; $P < 0.001$, respectively).[46] One reported higher consumption of ultraprocessed food versus lower consumption (consumption frequency range: <3 [less than weekly] versus ≥3 [greater than weekly]) was not associated with BMI (prevalence ratio: 0.76; 95% CI, 0.47-1.22) or waist circumference (prevalence ratio: 0.94; 95% CI, 0.51-1.72).[75] However, higher consumption of minimally processed food versus lower consumption was inversely associated with lower BMI (i.e., Z-score of BMI-for-age less than 1 standard deviation) (prevalence ratio: 0.61; 95% CI, 0.39-0.96).[75] In contrast, the one study that assessed a combined cohort of adolescents and adults reported higher consumption of ultraprocessed food versus lower consumption (≤13% versus ≥44% of calories) was associated with higher BMI (mean difference: 0.94 kg/m2; 95% CI, 0.42-1.47) (see Figures 2 and 3 above for this study's reported odds ratios and 95% CI for obesity and overweight).[38]

4.1.3 | Children

Two studies (N = 511) assessed the relationship between the consumption of ultraprocessed food and measures of overweight and obesity in children.[45,58] One was prospective,[58] and the other was cross-sectional[45] (see Table S2 for study characteristics). Higher consumption of ultraprocessed food was associated with higher waist circumference from 4 to 8 years old (beta coefficient: 0.07; 95% CI, 0.01-0.13).[58] For every 10% increase in caloric intake from ultraprocessed foods, delta waist circumference increased by 0.7 cm.[58] However, higher consumption of ultraprocessed food was not associated with BMI (beta coefficient: 0.00; 95% CI, −0.02 to 0.01), waist-to-height ratio (beta coefficient: 0.00; 95% CI, 0.00-0.00) or skinfold sum (beta coefficient: 0.05; 95% CI, −0.04 to 0.15) from 4 to 8 years old.[58] The second study reported no difference in means between children with normal versus excess weight in the percentage contribution of ultraprocessed food (mean [SE]: 48.2% [1.4] versus 49% [2.0], $P = 0.73$).[45]

4.1.4 | All-cause-mortality

Four prospective studies (N = 88,247) examined the link between consumption of ultraprocessed food and all-cause mortality in adults (see Table S3 for study characteristics).[44,52,62,76] All four studies were included in a meta-analysis, which showed that higher consumption of ultraprocessed food (ranging from >35.7% to >36.0% of calories or from 5.2 to <29.8 times per day) significantly increased risk of all-cause mortality compared with lower consumption in adults (ranging from 14.1% to <21.6% of calories or <2.6 times per day) (hazard ratio: 1.28; 95% CI, 1.11-1.48; $P = 0.001$; $I^2 = 45\%$) (Figure S4). One of these studies (N = 11,898) also assessed the association between higher versus lower consumption of ultraprocessed food (<2.6 times per day versus 5.2 to <29.8 times per day) and cardiovascular disease mortality but reported no association (hazard ratio: 1.10; 95% CI, 0.74-1.67).

4.1.5 | Metabolic diseases

Four studies investigated the association between ultraprocessed food consumption and metabolic syndrome (N = 7,708).[36,56,69,77] All were cross-sectional and one was conducted in adolescents,[56] with the other three in adults (see Table S4 for study characteristics).[36,56,69,77] In addition, one prospective study assessed the link

between consumption of ultraprocessed food and type 2 diabetes mellitus in an adult population (N = 104,707).[55]

Two cross-sectional studies in adults (combined N = 1,113) with homogeneous data were included in a meta-analysis.[69,77] Meta-analysis suggested higher consumption of ultraprocessed food significantly increased the risk of metabolic syndrome compared with lower consumption in adults (odds ratio: 1.81; 95% CI, 1.12-2.93; P = 0.015; I^2 = 0%) (Figure S5). Higher versus lower consumption of ultraprocessed food cut-offs were reported in one study as less than 40.0% versus greater than 71.0%.[36] However, cut-offs for the second study were not reported other than low adherence (first quartile) was compared against medium/high adherence (second, third and fourth quartiles)[77] (see Table S1).

Among adolescents, higher consumption of ultraprocessed food versus lower consumption (≥1,245 g per day versus <1,245 g per day) was associated with a higher prevalence of the metabolic syndrome (prevalence ratio: 2.49, P = 0.012).[56] A comparable association was found in an adult sample with prevalence ratio for greater than 71% versus less than 40% of calories: 1.28; 95% CI, 1.09-1.50.[36] This study also reported that a 10% increase in contribution of ultraprocessed food was associated with a 4% increase in the prevalence of metabolic syndrome (prevalence ratio: 1.04; 95% CI, 1.02-1.07).[36]

The prospective study in adults examining the association between consumption of ultraprocessed food and type 2 diabetes mellitus[55] reported that higher consumption of ultraprocessed food was associated with a higher risk of type 2 diabetes mellitus (hazard ratio for 10% increase in proportion of ultraprocessed food: 1.15; 95% CI, 1.06-1.25).[55]

4.1.6 | Depression

Two prospective studies (N = 41,637) assessing relations between the consumption of ultraprocessed food and depression were included in a meta-analysis (see Table S5 for study characteristics).[51,61] This established that higher consumption of ultraprocessed food (ranging from between 19.0% and 76.0% to >33.0% of calories) significantly increased the risk of depression compared to lower consumption in adults (ranging from ≤10.0% to <15.0% of calories) (hazard ratio: 1.22; 95% CI, 1.16-1.28; P < 0.001; I^2 = 0%) (Figure S6).

4.1.7 | Respiratory diseases

Two cross-sectional studies (N = 111,294) that investigated the association between consumption of ultraprocessed food and asthma and wheezing were included in a meta-analysis (see Table S5 for study characteristics).[37,43] This established that while higher consumption of ultraprocessed food (ranging from 50.7% of calories or ≥5 days per week versus 18.4% of calories or <2 days per week) was associated with wheezing (odds ratio: 1.40; 95% CI, 1.27-1.55, P < 0.001; I^2 = 7.58), it was not associated with asthma (odds ratio: 1.20; 95% CI, 0.99-1.46, P = 0.065; I^2 = 36%; see Figures S7 and S8). One of these studies (N = 2,190) also reported that higher versus lower consumption of ultraprocessed food (50.7% versus 18.4% of calories) was not associated with severe asthma (odds ratio: 1.05; 95% CI, 0.59-1.86).[43] In addition, this study conducted a prospective analysis from age 6 to 11 years old and reported that higher intake of ultraprocessed food versus lower intake at age 6 years (57.8% versus 26.9% of calories) was not associated with asthma (odds ratio: 0.84; 95% CI, 0.58-1.21), wheezing (odds ratio: 0.85; 95% CI, 0.54-1.34) or severe asthma at 11 years (odds ratio: 1.12; 95% CI, 0.62-2.03).

4.1.8 | Frailty

One prospective study (N = 1,822) study assessed the consumption of ultraprocessed food and frailty among adults at or above 60 years of age (see Table S5 study characteristics).[66] Frailty was defined as having three or more of the following five phenotypic criteria: (1) exhaustion, (2) muscle weakness, (3) low physical activity, (4) slow walking speed, and (5) unintentional weight loss.[66] Higher consumption of ultraprocessed food versus lower consumption (men, 24.3%-57.8% versus ≤9.6%, and women, 27.9%-79.7% versus ≤12.0%, of calories), expressed as both percentage of total calories and grammes per day/body weight, was associated with a higher risk of frailty (percentage of total calories odds ratio: 3.67; 95% CI, 2.00-6.73; and grammes per day/body weight odds ratio: 2.57; 95% CI, 1.41-4.70).[66]

4.1.9 | Functional gastrointestinal disorders or diseases

One prospective study (N = 33,343) assessed the consumption of ultraprocessed food and functional gastrointestinal disorders in adults, including irritable bowel syndrome as well as functional constipation, diarrhoea and dyspepsia (see Table S5 for study characteristics).[53] Higher consumption of ultraprocessed food versus lower consumption (20.6% versus 9.7% of weight; grammes per day) was associated with higher odds of irritable bowel syndrome (odds ratio: 1.25; 95% CI, 1.12-1.39) and functional dyspepsia (odds ratio: 1.25; 95% CI, 1.05-1.47).[53] However, higher consumption was not associated with odds of functional constipation (odds ratio: 0.98; 95% CI, 0.85-1.12) or functional diarrhoea (odds ratio: 0.92; 95% CI, 0.69-1.24).[53] One other prospective study (N = 105,832) reported that while higher versus lower intake of ultraprocessed food (using tertiles; not quantified) was associated with incident irritable bowel disease among adults in a univariate analysis (relative risk: 1.81; 95% CI, 1.05-3.12), results did not hold up after adjustments for covariates (relative risk: 1.44; 95% CI, 0.70-2.94).[57]

4.1.10 | Cardiovascular disease

One prospective study (N = 105,159) assessed the association between the consumption of ultraprocessed food and cardiovascular diseases in adults (see Table S6 for study characteristics).[49] Higher

consumption of ultraprocessed food versus lower consumption (men [22% versus 10.8%] and women [21.8% versus 10.6%] of weight; grammes per day) was associated with a higher risk of overall cardiovascular disease (hazard ratio for 10% increase in proportion of ultraprocessed food: 1.12; 95% CI, 1.05-1.20), coronary heart disease risk (hazard ratio: 1.13; 95% CI, 1.02-1.24) and cerebrovascular disease risk (hazard ratio: 1.11; 95% CI, 1.01-1.21).[49]

4.1.11 | Cardiovascular disease risk factors

Seven studies examined the consumption of ultraprocessed food and risk factors associated with cardiovascular disease (N = 24,880).[41,42,48,58,60,71,75] Study designs, sample sizes and populations were heterogeneous, including four cross-sectional[42,48,58,71] and three[41,60,75] prospective studies. Four studies were conducted in adults,[42,48,60,71] two in children (N = 652)[41,58] and one in adolescents (N = 259).[75] Two of the adult studies were conducted in individuals without comorbid conditions (N = 23,258),[42,60] whereas one was in hypertensive adults (N = 655)[48] and the other in postmenopausal women diagnosed with rheumatoid arthritis (N = 56)[71] (see Table S6 for study characteristics).

Prospective analysis in adults without comorbid conditions at baseline demonstrated that higher consumption of ultraprocessed food versus lower consumption (5 versus 2.1 energy-adjusted servings per day) was linked with higher risk of developing hypertension (hazard ratio: 1.21; 95% CI, 1.06-1.37).[60] Moreover, a cross-sectional analysis found an association between higher versus lower consumption (absolute calories for men is 823.6 versus 495.5 and for women is 718.8 versus 444.9) and elevated levels of C-reactive protein among women but only when adjusting for sociodemographic characteristics and health-related behaviours (i.e., findings lost statistical significance when models were also adjusted for BMI) (arithmetic mean ratio: 1.14; 95% CI, 1.04-1.24).[12]

In a cross-sectional analysis among adults with hypertension, a small but significant correlation was reported for ultraprocessed food consumption and a sedentary lifestyle (Spearman correlation coefficient: 0.10, P = 0.01), with no evidence of a relationship being reported for systolic blood pressure (Spearman correlation coefficient: −0.01, P = 0.85), diastolic blood pressure (Spearman correlation coefficient: −0.03, P = 0.45), total cholesterol (Spearman correlation coefficient: 0.06, P = 0.39) or triglycerides (Spearman correlation coefficient: 0.01, P = 0.87).[48] In a cross-sectional analysis among postmenopausal women with rheumatoid arthritis, weak evidence was reported for the association between ultraprocessed food consumption and levels of glycated haemoglobin (beta coefficient: 0.04; 95% CI, 0.01-0.08) and Framingham risk score, which is derived from a linear combination of factors including age, total cholesterol, high-density lipoprotein, smoking, systolic blood pressure and use of antihypertensive drugs (beta coefficient: 0.06; 95% CI, 0.00-0.11).[71] In the same study, no association was reported for other risk factors, such as adverse levels of glucose, insulin, lipids and blood pressure (see Table S6 for study characteristics).[71] In contrast, higher consumption of unprocessed or minimally processed foods was inversely, but weakly, associated with lower 10-year risk of developing cardiovascular diseases (beta coefficient: −0.05; 95% CI, −0.09 to −0.003).[71] A stronger inverse association was also reported for low-density lipoprotein cholesterol (beta coefficient: −1.09; 95% CI, −1.94 to −0.24).[71]

Among children, prospective analysis demonstrated that a higher consumption of ultraprocessed food at 3 to 4 years old was associated with an increase in total cholesterol (beta coefficient: 0.43; 95% CI, 0.01-0.85) and low-density lipoprotein cholesterol (beta coefficient: 0.37; 95% CI, 0.01-0.73) at 7 to 8 years old.[41] However, higher consumption was not associated with glucose profiles (beta coefficient: 0.00; 95% CI, −0.01 to 0.00), insulin profiles (beta coefficient: 0.00; 95% CI, −0.00 to 0.01) or insulin resistance (beta coefficient: 0.00; 95% CI, −0.01 to 0.01) at 8 years old.[58] When assessed cross-sectionally in an adolescent population, higher consumption of ultraprocessed food versus lower consumption (consumption frequency range: <3 [less than weekly versus] to ≥3 [greater than weekly]) was not associated with blood pressure (prevalence ratio: 1.55; 95% CI, 0.83-2.91).[75]

4.1.12 | Cancer

Three studies (N = 109,008) investigated the relationship between consumption of ultraprocessed food and cancer among adults.[64,65,78] One study prospectively assessed risk of overall cancer as well as breast, prostate and colorectal cancer.[65] The other two were case-control studies and assessed breast cancer and prostate cancer separately (see Table S7 for study characteristics).[64,78] In the prospective study, higher consumption of ultraprocessed food versus lower consumption (men, 23.3% versus 11.8%, and women, 23.4% versus 11.8%, of weight; grammes per day) was associated with a higher risk of overall cancer (hazard ratio for 10% increase in proportion of ultraprocessed food: 1.12; 95% CI, 1.06-1.18) and breast cancer (hazard ratio: 1.11; 95% CI, 1.02-1.22).[65] However, no association was reported for prostate (hazard ratio: 0.98; 95% CI, 0.83-1.16) or colorectal cancer in this cohort (hazard ratio: 1.13; 95% CI, 0.92-1.38).[65]

The case-control study examining breast cancer risk alone assessed ultraprocessed food consumption as a dichotomous variable; less than 5 days per week versus more than 5 days per week (considered as less than regular versus regular consumption, respectively).[78] Regular consumption was associated with higher odds of breast cancer (odds ratio: 2.35; 95% CI, 1.08-5.12).[78] The second case-control study investigating prostate cancer alone reported no significant associations between higher versus lower consumption of ultraprocessed food (33% versus 18% of calories) and prostate cancer (odds ratio: 0.92; 95% CI, 0.72-1.17).[64]

5 | DISCUSSION

We presented a systematic review and meta-analysis in 891,723 humans across the lifespan and various chronic conditions as well as

their related risk factors. Meta-analytic data showed that higher consumption of ultraprocessed food was associated with a greater risk of overweight and obesity, abdominal obesity, all-cause mortality, metabolic syndrome and depression in adults as well as wheezing but not asthma in adolescents. In addition, systematic review of the literature showed that in adults, higher consumption of ultraprocessed food was associated with higher risk of type two diabetes mellitus, frailty, irritable bowel syndrome, functional dyspepsia, cardiovascular diseases (and some but not all associated risk factors), breast cancer and overall cancer while also being associated with metabolic syndrome in adolescents and dyslipidaemia in children. This review provides evidence that consumption of ultraprocessed food is associated with numerous chronic diseases. Our results are consistent with the large body of evidence that demonstrates that unprocessed or minimally processed dietary patterns are linked with reduced risk of chronic disease, including, for example, diets with low inflammatory potential (determined by the dietary inflammatory index[79]) and traditional or culturally specific diets (e.g., the Mediterranean diet[80]).

Although significant associations across varying noncommunicable diseases, morbidity and mortality were reported, no increase in risk of cardiovascular disease mortality, inflammatory bowel disease, colorectal cancer or prostate cancer in adults was found. In addition, the following factors ought to be considered when interpreting results.

5.1 | Sample characteristics and analytical approaches in adults

Despite an association between ultraprocessed food consumption and hypertension reported in adults (hazard ratio 1.21 (95% CI, 1.06-1.37, *N* = 14,790),[60] there was insufficient evidence supporting an association between the consumption of ultraprocessed and other cardiometabolic risk factors. For example, while two studies reported associations between ultraprocessed food consumption and a sedentary lifestyle (Spearman correlation coefficient: 0.10, *P* = 0.01; *N* = 655),[48] Framingham risk score and glycated haemoglobin (beta coefficients: 0.06 [95% CI, 0.00-0.11] and 0.04 [95% CI, 0.01-0.08], *N* = 56),[71] effect size estimates and sample sizes were small. These two studies also reported no associations for various other metabolic risk factors in adults, including elevated blood pressure and levels of glucose, insulin and lipids.[48,71] Null results may be partly due to the noted issues surrounding power as well as population characteristics, which included individuals with underlying clinical conditions that may distort estimates; one study was conducted in hypertensive adults,[48] with the other in postmenopausal women diagnosed with rheumatoid arthritis.[71] In addition, although higher levels of C-reactive protein were reported in otherwise healthy women consuming higher amounts of ultraprocessed food, the association lost significance when adjusted for BMI (arithmetic mean ratio: 1.00; 95% CI, 0.84-1.02; *N* = 8,468).[42]

Contrasting evidence was reported in adults for the association between consumption of ultraprocessed food and continuous measures of BMI,[39,40,47,48,68,70] waist circumference,[40,47,48,68,70] body fat percentage[47,71] and visceral fat.[71] For example, three of six studies reported associations,[40,68,70] with the other half reporting no associations.[39,47,48] This inconsistency may also be partly explained by issues pertaining to power. The combined sample size of studies reporting null results (*N* = 3,029)[39,47,48] was less than 10% of the combined sample size for those reporting associations (*N* = 31,097).[40,68,70] Moreover, two of the three studies that reported null results undertook bivariate correlational analysis.[47,48] Bivariate correlations do not account for confounding factors, which are important considerations given the multifactorial nature of noncommunicable diseases and their related risk factors.[81] Thus, it remains to be established if more consistent associations would have been found had a principled confounder selection framework been utilized. In order to address the possible presence of confounding factors, future studies are encouraged to use appropriate analytical approaches, including adjusted models.

5.1.1 | Sample characteristics and analytical approaches in children and adolescents

It is important to note that, while numerous cardiometabolic parameters were repeatedly associated with consumption of ultraprocessed food in adults, such as overweight, obesity, abdominal obesity and metabolic diseases, data in children and adolescents were less clear. Indeed the increased consumption of ultraprocessed food was linked with higher waist circumference[58] and dyslipidaemia in children[41] as well as metabolic syndrome in adolescents.[56] However, both prospective and cross-sectional data showed either no association or inverse association across varying measures of excess weight (i.e., BMI,[6,58,75] waist circumference,[75] waist-to-height ratio,[58] skinfold sum[58] and body fat percentage[6]) and other metabolic risk factors (i.e., elevated levels of glucose,[58] insulin,[58] triglycerides,[41] nonhigh-density and high-density lipoprotein cholesterol[41] and blood pressure[75]). Similarly, cross-sectional analysis of children and adolescents with normal weight versus excess weight showed either no difference in the consumption of ultraprocessed food between groups[45] or higher consumption among those with normal weight.[6,46] These findings suggest that consistent intake of ultraprocessed food over time is needed for any deleterious effects of ultraprocessed food on subclinical cardiovascular disease to manifest later in the lifespan (e.g., early adulthood).[46,58]

Nevertheless, the absence of clear associations in children and adolescents may be partly explained by physical developmental changes that take place during these vital stages of the human life cycle, which has the potential, for example, to delay or offset the effects of ultraprocessed food on measures of weight. In addition, only one of the abovementioned studies controlled for physical activity and the underreporting of dietary intake as potential confounders.[6] It is well established that physical activity is a principal determinant of cardiometabolic outcomes.[82] Physical activity may attenuate the association between ultraprocessed food consumption and cardiometabolic outcomes in children and adolescents. Another

possible explanation is that the majority of samples were from low-income communities (four of five studies),[41,45,58,75] where physical activity levels may be greater than in higher-income communities.[75] The underreporting of dietary intake, a common and well-known source of measurement error in dietary assessment, may also explain the incongruent findings in adolescents. With respect to children, parents reported dietary intake on their behalf, where underreporting and the introduction of error is higher than in adult populations alone.[83] On the other hand, all of the studies in the present review pertaining to children, adolescents and cardiometabolic outcomes were conducted in one region (i.e., Brazil). There is a need to replicate these results in other children and adolescent populations before drawing inferences. However, as it is widely accepted that dietary intake and behaviours in childhood and adolescence influence the risk of chronic diseases in adulthood,[84] preventative efforts ought to consider targeting ultraprocessed food consumption in younger individuals.

5.1.2 | Total caloric intake

A recent experimental study in humans has shown a causal relationship between the consumption of ultraprocessed food and excess caloric intake, body weight and fat gain.[85] It is well established that a sustained imbalance between caloric intake and energy expenditure undoubtedly contributes to the development of overweight and obesity (i.e., caloric intake over what is exerted by physical activity, resting metabolic rate and thermogenesis).[86] However, total caloric intake can confound associations between disease risk and the nutrient composition of macronutrients and micronutrients.[87] In the present review, only one of four studies in adolescents adjusted for total caloric intake[46] (with none in children). Adolescents within normal weight ranges versus those in higher weight ranges reported greater consumption of ultraprocessed food.[46] It is plausible that the impact of ultraprocessed food on weight outcomes in younger populations may be mediated by the caloric value of ultraprocessed food. In contrast, only one[40] of 14 studies in adults (assessing associations between ultraprocessed food consumption and overweight and obesity) made additional adjustment for total energy intake, with the main findings remaining statistically significant (i.e., higher ultraprocessed food consumption was associated with various measures of overweight and obesity).[40] This suggests that other aspects of ultraprocessed food may be driving observed relations, such as nutritional quality. Given that associations with individual nutrients occur independently of caloric intake and are pertinent in epidemiological studies, future studies are encouraged to account for total caloric intake by using the residual method of Willet et al.[87]

5.1.3 | Nutritional quality

One common explanation for the observed associations between consumption of ultraprocessed food and risk of noncommunicable diseases is that ultraprocessed foods typically have poorer nutritional quality than unprocessed or minimally processed foods.[88] Dietary patterns high in ultraprocessed food have not only been associated with excessive intake of calories but also added sugars, sodium and trans and saturated fat.[22,39,88-90] Excessive added sugar intake has been independently associated with cardiovascular mortality risk and accelerated pathogenesis of vascular disease.[89,91] Likewise, high sodium intake has been associated with cardiovascular deaths[92] and elevated risk for some cancers, such as stomach cancer.[93] A recent systematic review and meta-analysis of prospective studies assessing the association between specific food groups and all-cause mortality risk reported common sources of ultraprocessed food with high levels of added sugar and sodium include sugary beverages and processed meats, respectively.[94] Sugar-sweetened beverages may also have the added effect of promoting excessive energy intake by disrupting the internal satiety trigger.[95]

The characteristically scarce levels of fibre common to ultraprocessed food should also be considered, with a separate systematic review and meta-analysis,[96] as well as an umbrella review of such studies,[97] reporting an inverse association between fibre and risk of all-cause mortality.[96,97] In particular, the latter review also reported an inverse association with risk of cardiovascular disease and cardiovascular disease-related mortality, coronary artery disease and cancer (i.e., pancreatic and gastric cancer).[97] Similarly, excessive intake of fat contributes to weight gain and increased risk of overweight and obesity, all of which are implicated as major risk factors for cardiovascular diseases,[98] respiratory conditions[37] and reduced levels of serotonin and dopamine involved in regulating neurological reward circuitry and mood.[99] In sum, ultraprocessed foods typically contain higher levels of sugar, sodium and trans and saturated fat, coupled with lower levels of fibre relative to unprocessed or minimally processed food,[88] which may in turn promote the risk of developing diverse chronic diseases and related mortality.

Several studies in the present review made additional adjustment for the nutritional quality of ultraprocessed food, including adjustment for sugar, sodium and saturated fat intake. These additional adjustments were made in studies assessing the association between higher versus lower consumption of ultraprocessed food and risk of depression,[51] type-2 diabetes mellitus,[55] overall cardiovascular disease,[49] coronary heart disease,[49] cerebrovascular disease,[49] overall cancer[65] and breast cancer,[65] with all studies documenting unchanged positive associations. This underscores the notion that other components of ultraprocessed food aside from poor nutritional composition may be driving associations.

Related to the confounding potential of nutrient composition is the hypothesis that the observed relations between ultraprocessed food and adverse health outcomes could be explained by lower consumption of nonultraprocessed food. Several studies in the present review made adjustment for consumption of nonultraprocessed foods, such as unprocessed or minimally processed food,[40] fruits and vegetable intake,[37,38,60,63] adherence to national dietary recommendations,[52,53] adherence to the Mediterranean diet,[61] and a 'healthy' dietary pattern (i.e., positively correlated with vegetables,

fruits, dried fruits, nuts, wholegrain products, legumes, unsweetened beverages including water, broths and vegetable fat consumption and negatively correlated with meat and ham[57]). However, for all but one study[57] assessing inflammatory bowel disease, adjustment for non-ultraprocessed food did not attenuate any of the observed relations, including the association between consumption of ultraprocessed food and risk of overweight and obesity,[38,40,63] all-cause mortality,[52] depression,[61] irritable bowel syndrome and functional dyspepsia,[53] asthma and wheezing[37] and hypertension.[60]

In contrast, the present review also identified the possible protective effect of unprocessed or minimally processed food, as demonstrated by its inverse association with BMI in adolescents,[75] metabolic syndrome in adults,[77] cardiovascular risk factors in adults[71] and prostate cancer in men.[64] With respect to BMI, these findings are consistent with a recent randomized controlled trial, where the consumption of an unprocessed versus ultraprocessed diet led to reduced energy intake as well as lower body weight and fat mass.[85] This was despite the fact that the presented diets were closely matched for sugar, sodium, fat, protein and fibre content.[85] It is also important to note that six studies[49,51-54,65] in the present review used the percentage of weight in grammes per day of ultraprocessed food rather the percentage of total calories. The percentage of weight in grammes per day of ultraprocessed food was noted as the preferred measure to account for ultraprocessed foods and beverages that do not provide energy (e.g., artificially sweetened drinks) and to better assess properties directly related to food processing (e.g., neo-formed contaminants and changes to the food matrix). Taken together, these data suggest that the nutritional quality of ultraprocessed food may not be the only relevant factor explaining observed relations, which is an important consideration for future studies.

5.2 | Underlying mechanisms

5.2.1 | The food matrix and artificial food additives

Beyond nutritional quality, several other qualities of ultraprocessed food may explain associations, including the effect of processing on the food matrix. The food matrix is characterized as the nutrient and nonnutrient components of food and their molecular interactions.[100] Emerging evidence suggests that changes to the food matrix through extensive food processing, including the structure and size of food particles, affects nutrient bioavailability, digestion kinetics and glycaemic, satiety, antioxidant or alkalinising potential[101] as well as the gut microbiota,[5,102] all of which may influence the risk of non-communicable diseases.

Other constituents of ultraprocessed food, such as artificial food additives, may also play a part in the observed relations. Preclinical animal and cellular studies suggest emulsifiers such as carboxymethylcellulose and polysorbate-80, used as antimicrobial agents,[5,8] may be implicated in inducing inflammation and cardiometabolic disturbances in mouse models.[103] Both emulsifiers and noncaloric artificial sweeteners have been linked to alterations to the gut microbiota,[103-105] with gut microbiota being associated with many metabolic aberrations,[106] including insulin resistance.[107,108] Our recent systematic review of ultraprocessed very low-energy diets (≤900 kcal per day) in individuals with obesity reported alterations to the gut microbiota composition but null effects on certain inflammatory biomarkers, such as interleukin-6, interleukin-8, alanine aminotransferase and C-reactive protein.[109] We concluded that this was counterintuitive given the significant weight loss noted across studies and the well-established advantageous impact of weight loss dietary interventions on inflammation.[109] In contrast, one cross-sectional study in the present review concluded associations between the consumption of ultraprocessed food and C-reactive protein levels were sex-specific and mediated by adiposity in women.[42] Systemic chronic inflammation is implicated in the aetiology of most, if not all, chronic diseases covered in the present review.[110] Thus, elevated inflammation may be a possible underlying mechanism in the association between ultraprocessed food consumption and chronic disease. This concept may be supported by the previously noted experimental study in humans by Hall et al.[85] While this study demonstrated a causal relationship between an ultraprocessed diet and excess caloric intake, body weight and fat gain compared with an unprocessed diet, a significant within-subject reduction in highly sensitive C-reactive protein from baseline to endpoint was also reported when participants were allocated to the unprocessed diet (P = 0.014).[85] However, no between-group difference at endpoint was reported (P = 0.072).[85] Further research is needed to more clearly delineate the role of inflammation in noncommunicable diseases.

5.2.2 | Carcinogenic compounds

Other possible explanatory constituents of ultraprocessed food include carcinogenic compounds produced via the heat treatments of intensive food processing, such as acrylamide and acrolein.[49,111] Both compounds have been associated with higher risk of cardiovascular diseases,[112,113] with systematic reviews reporting modest association between acrylamide consumption and risk of cancer in nonsmokers (i.e., kidney and endometrial cancer).[114] Preclinical animal and cell models also report the implication of sodium nitrate (used as a preservative to increase shelf life) and titanium dioxide (used as white food pigment) in carcinogenesis.[115,116] Relatedly, a recent observational study in adolescents reported that higher versus lower consumption of ultraprocessed food was associated with higher DNA oxidative damage as measured by urinary concentrations of 8-hydroxy-2′-deoxyguanosine.[117] Indeed, the initiation and development of cancer have been associated with oxidative stress via DNA mutation and damage.[118] Finally, meta-analytical studies have reported that bisphenol A, a compound used to make plastics and resins, was associated with elevated cardiometabolic risk,[119] including obesity and type-two diabetes mellitus.[120] Such compounds are suspected of migrating into products from the plastic packaging of many ultraprocessed foods,[49] disrupting endocrine signalling and adversely affecting hormonally regulated metabolic processes.[121]

Although the emerging evidence pertaining to the impact of artificial compounds commonly contained within ultraprocessed food on health outcomes is compelling and warrants further investigation in humans, data from tightly controlled animal or cell models ought to be interpreted with caution. Moreover, it remains to be established if the reformulation of ultraprocessed foods could mitigate their adverse effects.

5.3 | Limitations

This systematic review and meta-analysis has a number of limitations. First, approximately half of the included studies were cross-sectional by design and the reported dietary intake at the time of measurement may not be representative of habitual dietary intake (e.g., a possible discrepancy exists between individuals with excess weight undertaking a healthier or weight-loss diet at the time of measurement versus the diet that led to their current weight status). More longitudinal research with repeated measurements of diet is required to better capture habitual dietary intake and infer directionality.

There are various between-study differences within the included studies, particularly with respect to analytical approaches and the distribution of ultraprocessed food consumption. For example, given the wide range of statistical methods used, a limited subset of studies (with more homogeneous approaches) were included in several of our meta-analyses. This meant that for outcomes such as obesity, overweight and metabolic syndrome, a smaller number of studies than what was available were included in the syntheses. This also meant that for outcomes such as cancer, meta-analysis was not possible. It is also worth noting the small number of studies included in our meta-analyses for metabolic syndrome, depression, wheezing and asthma (for all outcomes, $n = 2$). When the synthesis is based on a small number of studies, a potential issue exits regarding inadequate estimation of the between-study variance.[122] Thus, results from these meta-analyses ought to be considered as preliminary, with more studies within these disease domains being necessary. In addition, due to a significant gap in the literature, future studies are encouraged to investigate associations in other common mental disorders and/or severe mental illnesses outside of depression.

Meta-analyses of obesity, overweight and abdominal obesity also included quartiles and quintiles with overlapping below and above sample-based cut-off ranges for categories of lowest versus highest consumption (e.g., ≤36.5% of total calories was categorized as the lowest cut-off in one study,[70] whereas >29% was the highest in another[40]). These disparities limit conclusions about how much ultraprocessed food in the diet is needed to initiate adverse health consequences. In order to improve evidence, we propose a posteriori as well as standardized analytical approaches that consider data presented in the current review. More specifically, while the majority of studies divided ultraprocessed food consumption into quartiles or quintiles, predefined cut-off ranges for lowest versus highest consumption that consider geographical location and population characteristics are needed.

Second, the observational nature of the studies eligible for inclusion in our review demonstrates associations rather than causation. There has only been one randomized controlled trial to date that has assessed the effect of ultraprocessed food consumption on health outcomes.[85] While this study found a causal relationship between ultraprocessed food in the diet and excess caloric intake as well as body weight and fat gain,[85] mechanisms are still uncertain, with more exemplar experimental studies being needed. Observational studies run the risk of residual confounding by many factors, such as socioeconomic status. While the majority of studies in the present review adjusted for potential covariates, residual confounding remains possible.

Lastly, it has been argued that the widespread success and adoption of the NOVA food classification system depends on sensitivity to factors impacting consumer choices, including the time, effort and expense required to prepare nonultraprocessed food.[123] It was beyond the scope of our review to investigate such factors. However, it is important to reemphasize that the NOVA system is endorsed by United Nations and World Health Organization.[2,3] Compared with traditional approaches that have typically focused on isolated nutrients, the NOVA system provides a novel area of research into the possible effects of the nature, extent and reasons for food processing, including the food matrix and artificial food additives.[2]

6 | CONCLUSIONS

The present review and meta-analysis provides evidence associating higher consumption of ultraprocessed food with a 20% to 81% increased risk of various noncommunicable diseases when assessed cross-sectionally and a 22% to 28% increased risk of depression and mortality when examined prospectively in adults. However, evidence for an association between ultraprocessed food consumption and adverse health outcomes in children and adolescents was limited. Further rigorously executed studies that address the noted limitations and between-study disparities are required to investigate and more clearly define associations between ultraprocessed consumption and intermediate risk factors. Nevertheless, the weight of evidence is sufficient, especially given the precautionary principle, to address consumption of ultraprocessed food in diverse preventive and treatment efforts.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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