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Title: Ultra-processed food and chronic non-communicable diseases: A systematic review and meta-analysis of 43 observational studies

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Abstract

This systematic review and meta-analysis investigated the association between consumption of ultra-processed food and non-communicable 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 ultra-processed food was associated with increased risk of overweight (odds ratio: 1.36, 95%CI 1.23 to 1.51, $P<0.001$), obesity (odds ratio: 1.51, 95%CI 1.34 to 1.70, $P<0.001$), abdominal obesity (odds ratio: 1.49, 95%CI 1.34 to 1.66, $P<0.0001$), all-cause mortality (hazard ratio: 1.28, 95%CI 1.11 to 1.48, $P=0.001$), metabolic syndrome (odds ratio: 1.81, 95%CI 1.12 to 2.93, $P=0.015$) and depression in adults (hazard ratio: 1.22, 95%CI 1.16 to 1.28, $P<0.001$) as well as wheezing (odds ratio: 1.40, 95%CI 1.27 to 1.55, $P<0.001$) but not asthma in adolescents (odds ratio: 1.20, 95%CI 0.99 to 1.46, $P=0.065$). In addition, consumption of ultra-processed 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 ultra-processed food consumption and some intermediate risk factors in adults were also highlighted, further studies are required to more clearly define associations in children and adolescents.

Study registration: Prospero ID: CRD42020176752

Keywords: ultra-processed food, NOVA, non-communicable disease, all-cause mortality, meta-analysis

Introduction

NOVA is a food classification system first proposed by Monteiro and colleagues in 2009¹ and is now endorsed by the United Nations and World Health Organization. NOVA categorises food depending on the nature, extent and reasons for food processing.^{2,3} Ultra-processed foods are characterised by NOVA as industrial formulations generated through compounds extracted, derived or synthesised 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 Ultra-processed 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 ultra-processed 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 ultra-processed 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 ultra-processed food, are widely accepted as critical drivers of chronic non-communicable diseases.²⁵

Non-communicable diseases are broadly defined as any health condition of long duration or that has long-term effects and is non-transmissible or non-infectious in its aetiology.^{26,27} According to the World Health Organization, non-communicable diseases account for over 70% of all deaths globally, with more than 85% considered premature. Traditionally, the prevention and management of non-communicable diseases has been limited and targeted toward risk factors such as smoking and blood pressure in diseases like cancer, diabetes, respiratory as well as 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” non-communicable disease framework.^{28,29}

Given the broader definition of chronic diseases (i.e. any non-transmissible 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 ultra-

processed food. Recently published systematic reviews report associations between ultra-processed food consumption and adverse health outcomes.^{30 31} However, in the review by Meneguelli et al. (2020) a number of different food classification systems were used to assess ultra-processed 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 ultra-processed 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 synthesise and provide quantitative analysis of the evidence assessing the association between direct consumption of ultra-processed food, as defined by the NOVA food classification system, and non-communicable diseases, as well as intermediate risk factors and all-cause mortality.

Methods

Search strategy

This review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplementary Figure 1 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 ultra-processed food and NOVA in addition to non-communicable diseases, including mental disorders, metabolic diseases, cardiovascular abnormalities, respiratory tract diseases, neoplasms and frailty (see Supplementary Figure 2 for search terms across the varied databases).

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 ultra-processed food and non-communicable diseases, associated risk factors and all-cause mortality; compared either different levels of ultra-processed food consumption (e.g. lower versus higher) or ultra-processed 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 ultra-processed food (e.g. household availability, access to, price of and purchase of ultra-processed food).

Data extraction

Screening of the publication title and abstract for individual studies was conducted by two authors (ML, JD) with disagreements resolved by consensus. Articles deemed eligible for full-text review were assessed for eligibility independently by two authors (ML, WM). 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, details of NOVA classification), 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 more information was needed, the corresponding author(s) of the original paper were contacted.

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 standardised critical appraisal instruments from the Joanna Briggs Institute.³³ Instrument items ranged from one to eleven 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

Data analysis

Where studies were homogeneous in terms of study design, statistical methods and disease outcome, results were pooled, and meta-analyses conducted. Odds ratios and hazard ratios with 95% CIs for binary outcomes were used. Studies deemed too heterogeneous based on study design, statistical methods and disease outcome were excluded from 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 3.0³⁴ 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-squared 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.

Results

Search results

The search strategy yielded 1324 de-duplicated studies that were screened to identify 43 eligible studies for inclusion.

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 Supplementary Tables 2-7. 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 > 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 (Supplementary Tables 8, 9 and 10). However, limitations included four cross-sectional studies that did not adequately identify confounding factors, nor did they report utilising 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 ultra-processed food and morbidity, mortality and associated risk factors.

Average ultra-processed food consumption and details of exposure variable

Over half of included studies reported the average intake of ultra-processed food expressed as a percentage of total caloric intake (n=28), with proportions ranging from 17% to 56% (see Supplementary Table 1 for more details). The average intake of ultra-processed 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 ultra-processed food consumption were also reported, with some studies using more than one approach, including weight (absolute or percentage grams per day) (n=9),⁴⁹⁻⁵⁷ absolute caloric intake per day (n=6),^{45-47 58-60} servings or times per day (n=5),^{44 61-64} ultra-processed food consumption scores (n=2),^{37 48} and, ultra-processed items consumed per day (n=1).⁵⁸

Figure 1. Bar chart of the average intake of ultra-processed food (% calories) by country

The majority of studies divided ultra-processed food consumption into quartiles (n=19)^{40 44 49 51-54 58 62-69} or quintiles (n=7),^{36-38 43 60 70 71} with the lowest quartile or quintile being the reference group (i.e. lowest consumption). Some reported the mean dietary share of ultra-processed 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 61} Five studies used sex-specific cut-off ranges, four divided the sample by quartiles^{49 66 67 69} and the other study by tertiles.⁴² Other studies treated ultra-processed food consumption as a dichotomous variable (n=5)^{67,69-72} as well as a continuous variable (n=7 for main statistical analyses,^{39 41 47 48 55 59 72} with n=10 for secondary analyses^{36 49 51-53 60 66 68 69}). In the latter, quartiles or quintiles were used for the main statistical analyses. In four studies, ultra-processed

food was analysed as the dependent variable;^{45 73-75} with weight status considered the exposure (see Supplementary Table 1 for more details).

Table 1. Number of individual studies reporting associations versus no associations between ultra-processed food consumption and chronic non-communicable 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	

Population outcome /	Direct association	Inverse association		No association
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			

Population outcome /	Direct association	Inverse association	No association
CVD	2		
Children			
Glucose	1		
Insulin	1		
Insulin Resistance	1		
TC	1		
LDL	1		
NHDL	1		
TG	1		
HDL	1		
Adolescents			
BP	1		
Adults			
BP	1	2	
Sedentary Lifestyle	1		
Framingham Risk Score	1		

Population outcome /	Direct association	Inverse association	No association
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 study³⁸ assessed BMI, obesity and overweight and grouped adolescents aged 10-19 years old with adults aged 20 years (see Adolescents and Adults). BMI: body mass index, body fat %: body fat percentage; OB: obese, OW: overweight, WC: waist circumference, AO: abdominal obesity, ACM: all-cause mortality; MetS: metabolic syndrome, T2DM: type-two diabetes mellitus, IBS: irritable bowel syndrome, IBD: inflammatory bowel disease CVD: cardiovascular disease, TC:

total cholesterol, LDL: low-density lipoprotein cholesterol, VLDL: very-low-density lipoprotein cholesterol, NHDL: non-high-density lipoprotein cholesterol, TG: triglycerides, HDL: high-density lipoprotein cholesterol, BP: blood pressure, CRP: C-reactive protein

Results

1.1 Overweight and Obesity

1.1.1 Adults

Fourteen studies (N=156,276) investigated associations between the consumption of ultra-processed food and measures of overweight and obesity among adults.^{39 40 47 48 54 60 64 68 69 71-75} Twelve were cross-sectional and two studies were prospective^{64 68} (see Supplementary Table 2 for study characteristics).^{39 40 47 48 54 60 69 71-75} The following sections describe the nature of relationships between the consumption of ultra-processed food and varying measures of overweight and obesity.

1.1.1.1 Body mass index ≥ 30 kg/m² - Obesity

Seven studies (N=62,615) examined and defined obesity as BMI ≥ 30 kg/m².^{39 40 60 68 69 71 74} 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 10-19 years old with adults aged at or above 20 years old was also included (N=30,243).³⁸ Meta-analysis found higher consumption of ultra-processed food (ranging from $>29.0\%$ to $\geq 76.2\%$ of calories) was significantly associated with an increased risk of obesity compared to lower consumption of ultra-processed food (ranging from ≤ 13.0 to $\leq 35.2\%$ of calories) (odds ratio: 1.51, 95%CI 1.34 to 1.70, $P < 0.001$; $I^2 = 29\%$; N=61,340) (Figure 2).

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

In the other three of seven studies (not included in the meta-analysis), one was cross-sectional and treated ultra-processed food consumption as a continuous independent variable.³⁹ The authors reported no association between intake of ultra-processed food and obesity (odds ratio: 1.01, 95%CI 1.00 to 1.02).³⁹ Another study was prospective and reported no association between higher intake of ultra-processed food and higher risk of obesity among individuals who were overweight at baseline (relative risk: 1.02, 95%CI 0.85 to 1.21).⁶⁸ The last study was cross-sectional and demonstrated an inverse association between individuals with obesity and their reported consumption of ultra-processed food (beta coefficient: -1.9, 95% CI -3.4 to -0.5).⁷⁴

1.1.1.2 Body mass index ≥ 25 to 29.9 kg/m² - Overweight

Four cross-sectional studies (N=48,614) assessed and defined overweight as BMI ≥ 25.0 to 29.9 kg/m².^{40 60 71 74} One of these reported an inverse association between individuals who were overweight and their reported consumption of ultra-processed food (beta coefficient: -1.0, 95%CI -1.9 to 0.0).⁷⁴ Another study treated ultra-processed food consumption as a continuous independent variable.⁶⁰ The authors reported a ten percent increase in the relative intake of ultra-processed food increased the likelihood of being overweight by 3% (odds ratio: 1.03, 95%CI 1.02 to 1.09).⁶⁰ 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 10-19 years old with adults aged at or above 20 years old (N=30,243).³⁸ Meta-analysis established that higher consumption of ultra-processed food (ranging from >29.0% to $\geq 74.2\%$ of calories) significantly increased the risk of being overweight compared to lower consumption (ranging from $\leq 13.0\%$ to $\leq 36.5\%$ of calories) (1.36, 95%CI 1.23 to 1.51, P<0.001; I²=0%; N=55,197) (Figure 3).

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

1.1.1.3 Body mass index ≥ 25 kg/m² – Overweight and Obesity

Five studies (N=100,419) investigated overweight and obesity defined as BMI ≥ 25 kg/m². This included the two prospective studies,^{64 68} with the other three studies^{39 54 73} 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 ultra-processed food (ranging from >23.0% to >30.8% of calories or 6 servings per day) versus lower consumption (ranging from <11.0% to <17.8% of calories or 2 servings per day) was positively associated with overweight and obesity (risk ratio: 1.20, 95%CI 1.03 to 1.40⁶⁸; hazard ratio: 1.26, 95%CI 1.10 to 1.45⁶⁴; and, 25.9% of total sample, P<0.0001⁵⁴). While the fourth study reported results in the same direction, the association was negligible (odds ratio: 1.01, 95%CI 1.00 to 1.02³⁹). The fifth study (cross-sectional) did not assess overall consumption of ultra-processed food; instead, it determined consumption of ultra-processed 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 ultra-processed dinner products (odds ratio: 1.54, 95%CI 1.04 to 2.30) and fast foods away from home (odds ratio: 3.40, 95%CI 2.26 to 5.11) but not snacks and soft drinks (odds ratio: 1.18, 95%CI 0.81 to 1.71).⁷³ In addition, there were no differences in the proportion of individuals with overweight and obesity versus normal weight categorised as high consumers of ultra-processed 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).⁷³ However, a significantly higher proportion of individuals with overweight and obesity versus normal weight were categorised as high consumers of snacks and soft drinks (54.3% versus 45.1%, P=0.044).⁷³

1.1.1.4 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 68 69 71} Three of 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 69 71} Meta-analysis established that higher consumption of ultra-processed food (ranging from >29.0% to

$\geq 76.2\%$ of calories) was significantly associated with waist circumference or risk of abdominal obesity compared to lower consumption in adults (ranging from $<16.0\%$ to $\leq 36.5\%$) (odds ratio: 1.49, 95%CI 1.34 to 1.66; $P < 0.0001$; $N = 31,097$; $I^2 = 4\%$) (Supplementary Figure 3). The other prospective study, reported that a higher consumption of ultra-processed food was associated with higher risk of both weight gain (1.68 kg per year) (relative risk: 1.27, 95%CI 1.07 to 1.50) and increased waist circumference (2.42cm per year) (relative risk: 1.33, 95%CI 1.12 to 1.58).⁶⁸

BMI was assessed as a continuous variable in seven cross-sectional analyses,^{39 40 47 48 69 71 75} waist circumference in five,^{40 47 48 69 71} body fat percentage in two^{47 72} and visceral fat in one.⁷² One of seven studies examining BMI continuously was prospective in study design; however, the association between ultra-processed food consumption and pre-pregnancy BMI was analysed cross-sectionally, with no association reported (beta coefficient: 0.45 (95%CI -0.02 to 0.92, $N = 189$)).⁷⁵ The other six of seven studies examining BMI continuously were cross-sectional in study design, with half reporting associations with consumption of ultra-processed food ($N = 31,097$),^{40 69 71} 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 69 71} higher consumption of ultra-processed food (ranging from $>29.0\%$ to $\geq 76.2\%$ of calories) versus lower consumption (ranging from $<16.0\%$ to $\leq 36.5\%$ of calories) was associated with higher BMI (beta coefficients: 1.66, 95%CI 0.96 to 2.36⁶⁹; 0.80, 95%CI 0.53 to 1.07⁴⁰; and, 1.61, 95%CI 1.11 to 2.10⁷²). Higher consumption was also associated with greater waist circumference in these three studies (beta coefficients: 3.56, 95%CI 1.79 to 5.33⁶⁹; 1.71, 95%CI 1.02 to 2.40⁴⁰; and, 4.07, 95%CI 2.94 to 5.19⁷²). In contrast, three studies reported no association between ultra-processed food consumption and BMI (beta coefficient: 0.02, 95%CI -0.02 to 0.07³⁹; 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 ultra-processed food was not associated with body fat percentage (beta coefficient: 0.03, 95%CI -0.06 to 0.12⁷²; Pearson correlation coefficient -0.45, $P = 0.57$ ⁴⁷) or visceral fat (beta coefficient: 0.20, 95%CI -4.11 to 4.51⁷²).

1.1.2 Adolescents

Four studies (N=32,311) examined associations between ultra-processed food consumption and overweight and obesity among adolescents,^{38 46 58 76} with one of these grouping adolescents aged 10-19 years old with adults aged 20 and over (previously described).³⁸ One study was prospective⁵⁸ and the other three were cross-sectional (see Supplementary Table 2 for study characteristics).^{38 46 76} Overall, the results were inconsistent. The prospective study reported both an inverse association and no association at different time-points (i.e. baseline, one-year and second-year follow-up).⁵⁸ For the three cross-sectional studies, one reported an inverse association,⁴⁶ one reported no association⁷⁶ and the other reported positive associations.³⁸

The prospective study, more specifically, reported that higher consumption of ultra-processed food versus lower consumption (fourth quartile versus first quartile; not quantified) was inversely associated with BMI at baseline (mean BMI: 21.3kg/m² versus 23.1kg/m², P<0.001) and the one-year (first) follow-up (mean BMI: 21.8kg/m² versus 23.5kg/m², P<0.001) but no association was reported at the second-year (final) follow-up (mean BMI: 22.4kg/m² versus 24kg/m², P=0.40).⁵⁸ In addition, no association was reported for higher versus lower consumption of ultra-processed 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.⁵⁸

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 ultra-processed food (median intake: 1,586.6 versus 1,213.8 absolute calories per day; P<0.001, respectively).⁴⁶ One reported higher consumption of ultra-processed 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 to 1.22) or waist circumference (prevalence ratio: 0.94, 95%CI 0.51 to 1.72).⁷⁶ 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 to 0.96).⁷⁶ In contrast, the one study that assessed a combined cohort of adolescents and adults reported higher consumption of ultra-processed food versus lower consumption (≤13% versus ≥44% of calories) was associated with higher BMI (mean difference: 0.94 kg/m², 95%CI 0.42 to 1.47) (see Figure 2 and 3 above for this study's reported odds ratios and 95%CI for obesity and overweight).³⁸

1.1.3 Children

Two studies (N=511) assessed the relationship between the consumption of ultra-processed food and measures of overweight and obesity in children.^{45 59} One was prospective⁵⁹ and the other was cross-sectional⁴⁵ (see Supplementary Table 2 for study characteristics). Higher consumption of ultra-processed food was associated with higher waist circumference from four to eight years old (beta coefficient: 0.07, 95%CI 0.01 to 0.13).⁵⁹ For every 10% increase in caloric intake from ultra-processed foods, delta waist circumference increased by 0.7cm.⁵⁹ However, higher consumption of ultra-processed 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 to 0.00), or skinfold sum (beta coefficient: 0.05, 95%CI -0.04 to 0.15) from four to eight years old.⁵⁹ The second study reported no difference in means between children with normal versus excess weight in the percentage contribution of ultra-processed food (mean(SE): 48.2% (1.4) versus 49% (2.0), P=0.73).⁴⁵

All-Cause-Mortality

Four prospective studies (N=88,247) examined the link between consumption of ultra-processed food and all-cause mortality in adults (see Supplementary Table 3 for study characteristics).^{44 52 63 77} All four studies were included in a meta-analysis, which showed that higher consumption of ultra-processed 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 to 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 to 1.48; P=0.001; I²=45%) (Supplementary Figure 4). One of these studies (N=11,898) also assessed the association between higher versus lower consumption of ultra-processed 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 to 1.67).

Metabolic Diseases

Four studies investigated the association between ultra-processed food consumption and metabolic syndrome (N=7,708).^{36 56 70 78} All were cross-sectional and one was conducted in adolescents,⁵⁶ with the other three in adults (see Supplementary Table 4 for study characteristics).^{36 56 70 78} In addition, one prospective study assessed the link between consumption of ultra-processed 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.^{70 78} Meta-analysis suggested higher consumption of ultra-processed food significantly increased the risk of metabolic syndrome compared to lower consumption in adults (odds ratio: 1.81, 95%CI 1.12 to 2.93; P=0.015; I²=0%) (Supplementary Figure 5). Higher versus lower consumption of ultra-processed food cut-offs were reported in one study as <40.0 % versus >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)⁷⁸ (see Supplementary Table 1).

Among adolescents, higher consumption of ultra-processed food versus lower consumption ($\geq 1,245$ grams per day versus <1,245 grams 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 >71% versus <40% of calories: 1.28, 95%CI 1.09 to 1.50.³⁶ This study also reported a 10% increase in contribution of ultra-processed food was associated with a 4% increase in the prevalence of metabolic syndrome (prevalence ratio: 1.04, 95%CI 1.02 to 1.07).³⁶

The prospective study in adults examining the association between consumption of ultra-processed food and type 2 diabetes mellitus⁵⁵ reported higher consumption of ultra-processed food was associated with a higher risk of type 2 diabetes mellitus (hazard ratio for 10% increase in proportion of ultra-processed food: 1.15, 95%CI 1.06 to 1.25).⁵⁵

Depression

Two prospective studies (N=41,637) assessing relations between the consumption of ultra-processed food and depression were included in a meta-analysis (see Supplementary Table 5 for study characteristics).^{51 62} This established that higher consumption of ultra-processed food (ranging from between 19.0-76.0% to >33.0% of calories) significantly increased the risk of depression compared to lower consumption in adults (ranging from $\leq 10.0\%$ to <15.0% of calories) (hazard ratio: 1.22, 95%CI 1.16 to 1.28; P<0.001; I²=0%) (Supplementary Figure 6).

Respiratory Diseases

Two cross-sectional studies (N=111,294) that investigated the association between consumption of ultra-processed food and asthma and wheezing were included in a meta-analysis (see Supplementary Table 5 for study characteristics).^{37 43} This established that while higher consumption of ultra-processed 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 to 1.55, $P<0.001$; $I^2=7.58$), it was not associated with asthma (odds ratio: 1.20, 95%CI 0.99 to 1.46, $P=0.065$; $I^2=36\%$; see Supplementary Figures 7 and 8). One of these studies (N=2,190) also reported that higher versus lower consumption of ultra-processed food (50.7% versus 18.4% of calories) was not associated with severe asthma (odds ratio: 1.05, 95%CI 0.59 to 1.86).⁴³ In addition, this study conducted a prospective analysis from age 6 to 11 years old and reported that higher intake of ultra-processed food versus lower intake at age 6 (57.8% versus 26.9% of calories) was not associated with asthma (odds ratio: 0.84, 95%CI 0.58 to 1.21), wheezing (odds ratio: 0.85, 95%CI 0.54 to 1.34) or severe asthma at 11 years (odds ratio: 1.12, 95%CI 0.62 to 2.03).

Frailty

One prospective study (N=1,822) study assessed the consumption of ultra-processed food and frailty among adults at or above 60 years of age (see Supplementary Table 5 study characteristics).⁶⁷ 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.⁶⁷ Higher consumption of ultra-processed food versus lower consumption (men: 24.3-57.8% versus $\leq 9.6\%$ and women: 27.9%-79.7% versus $\leq 12.0\%$ of calories), expressed as both percentage of total calories and grams per day/body weight, was associated with a higher risk of frailty (percentage of total calories odds ratio: 3.67, 95%CI 2.00 to 6.73 and grams per day/body weight odds ratio: 2.57, 95%CI 1.41 to 4.70).⁶⁷

Functional Gastrointestinal Disorders or Diseases

One prospective study (N=33,343) assessed the consumption of ultra-processed food and functional gastrointestinal disorders in adults, including irritable bowel syndrome as well as functional constipation, diarrhoea and dyspepsia (see Supplementary Table 5 for study characteristics).⁵³ Higher consumption of ultra-processed food versus lower consumption (20.6% versus 9.7% of weight; grams per day) was associated with higher odds of irritable bowel syndrome (odds ratio: 1.25, 95%CI 1.12 to 1.39) and functional dyspepsia (odds ratio: 1.25, 95%CI 1.05 to 1.47).⁵³ However, higher consumption was not associated with odds of functional constipation (odds ratio: 0.98, 95%CI 0.85 to 1.12) or functional diarrhoea (odds ratio: 0.92, 95%CI 0.69 to 1.24).⁵³ One other prospective study (N=105,832) reported that while higher versus lower intake of ultra-processed 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 to 3.12), results did not hold up after adjustments for covariates (relative risk: 1.44, 95%CI 0.70 to 2.94).⁵⁷

Cardiovascular Disease

One prospective study (N=105,159) assessed the association between the consumption of ultra-processed food and cardiovascular diseases in adults (see Supplementary Table 6 for study characteristics).⁴⁹ Higher consumption of ultra-processed food versus lower consumption (men: 22% versus 10.8% and women: 21.8% versus 10.6% of weight; grams per day) was associated with a higher risk of overall cardiovascular disease (hazard ratio for 10% increase in proportion of ultra-processed food: 1.12, 95%CI 1.05 to 1.20), coronary heart disease risk (hazard ratio: 1.13, 95%CI 1.02 to 1.24) and cerebrovascular disease risk (hazard ratio: 1.11, 95%CI 1.01 to 1.21).⁴⁹

Cardiovascular Disease Risk Factors

Seven studies examined the consumption of ultra-processed food and risk factors associated with cardiovascular disease (N=24,880).^{41 42 48 59 61 72 76} Study designs, sample sizes and populations were heterogeneous, including four cross-sectional^{42 48 59 72} and three^{41 61 76} prospective studies. Four studies were conducted in adults,^{42 48 61 72} two in children (N=652)^{41 59} and one in adolescents (N=259)⁷⁶. Two of the adult studies were conducted in individuals without comorbid conditions (N=23,258),^{42 61} whereas one was in hypertensive adults (N=655)⁴⁸ and the other in postmenopausal women diagnosed with rheumatoid arthritis (N=56)⁷² (see Supplementary Table 6 for study characteristics).

Prospective analysis in adults without comorbid conditions at baseline demonstrated that higher consumption of ultra-processed 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 to 1.37).⁶¹ Moreover, a cross-sectional analysis found an association between higher versus lower consumption (absolute calories for men: 823.6 versus 495.5 and women: 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 to 1.24).¹²

In a cross-sectional analysis among adults with hypertension, a small but significant correlation was reported for ultra-processed 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 ultra-processed food consumption and levels of glycated haemoglobin (beta coefficient: 0.04, 95%CI 0.01 to 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 to 0.11).⁷² In the same study, no association was reported for other risk factors, such as adverse levels of glucose, insulin, lipids and blood pressure (see Supplementary Table 6 for study characteristics).⁷² 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).⁷² A stronger inverse association was also reported for low-density lipoprotein cholesterol (beta coefficient: -1.09, 95%CI -1.94 to -0.24).⁷²

Among children, prospective analysis demonstrated that a higher consumption of ultra-processed food at three to four years old was associated with an increase in total cholesterol (beta coefficient: 0.43, 95%CI 0.01 to 0.85) and low-density lipoprotein cholesterol (beta coefficient: 0.37, 95%CI 0.01 to 0.73) at seven to eight 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 eight years old.⁵⁹ When assessed cross-sectionally in an adolescent population, higher consumption of ultra-processed food versus lower consumption (consumption frequency range: <3 - less than weekly versus ≥ 3 - greater than weekly) was not associated with blood pressure (prevalence ratio: 1.55, 95%CI 0.83 to 2.91).⁷⁶

Cancer

Three studies ($N=109,008$) investigated the relationship between consumption of ultra-processed food and cancer among adults.^{65 66 79} One study prospectively assessed risk of overall cancer as well as breast, prostate and colorectal cancer.⁶⁶ The other two were case-control studies and assessed breast cancer and prostate cancer separately (see Supplementary Table 7 for study characteristics).^{65 79} In the prospective study, higher consumption of ultra-processed

food versus lower consumption (men: 23.3% versus 11.8% and women: 23.4% versus 11.8% of weight; grams per day) was associated with a higher risk of overall cancer (hazard ratio for 10% increase in proportion of ultra-processed food: 1.12, 95%CI 1.06 to 1.18) and breast cancer (hazard ratio: 1.11, 95%CI 1.02 to 1.22).⁶⁶ However, no association was reported for prostate (hazard ratio: 0.98, 95%CI 0.83 to 1.16) or colorectal cancer in this cohort (hazard ratio: 1.13, 95%CI 0.92 to 1.38).⁶⁶

The case-control study examining breast cancer risk alone assessed ultra-processed food consumption as a dichotomous variable; less than five days per week versus more than five days per week (considered as less than regular versus regular consumption, respectively).⁷⁹ Regular consumption was associated with higher odds of breast cancer (odds ratio: 2.35, 95%CI 1.08 to 5.12).⁷⁹ The second case-control study investigating prostate cancer alone reported no significant associations between higher versus lower consumption of ultra-processed food (33% versus 18% of calories) and prostate cancer (odds ratio: 0.92, 95%CI 0.72 to 1.17).⁶⁵

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 ultra-processed 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 ultra-processed 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 ultra-processed food is associated with numerous chronic diseases. Our results are consistent with the large body of evidence demonstrating 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 index⁸⁰) and traditional or culturally-specific diets (e.g. the Mediterranean diet⁸¹).

Although significant associations across varying non-communicable 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.

1.2 Sample characteristics and analytical approaches in adults

Despite an association between ultra-processed food consumption and hypertension reported in adults (hazard ratio 1.21 (95% CI 1.06 to 1.37, N=14,790),⁶¹ there was insufficient evidence supporting an association between the consumption of ultra-processed and other cardiometabolic risk factors. For example, while two studies reported associations between ultra-processed 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 to 0.11) and 0.04 (95% CI 0.01 to 0.08, N=56)),⁷² 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 72} 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 post-menopausal women diagnosed with rheumatoid arthritis.⁷² In addition, although higher levels of C-reactive protein were reported in otherwise healthy women consuming higher amounts of ultra-processed food, the association lost significance when adjusted for BMI (arithmetic mean ratio: 1.00, 95% CI 0.84 to 1.02, N=8,468).⁴²

Contrasting evidence was reported in adults for the association between consumption of ultra-processed food and continuous measures of BMI,^{39 40 47 48 69 71} waist circumference,^{40 47 48 69 71} body fat percentage^{47 72} and visceral fat.⁷² For example, three of six studies reported associations,^{40 69 71} 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 percent of the combined sample size for those reporting associations (N=31,097).^{40 69 71} Moreover, two of the three studies reporting 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 non-communicable diseases and their related risk factors.⁸² Thus, it remains to be established if more consistent associations would have been found had a principled confounder selection framework been utilised. In order to address the possible presence of confounding factors, future studies are encouraged to use appropriate analytical approaches, including adjusted models.

1.2.1 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 ultra-processed 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 ultra-processed food was linked with higher waist circumference⁵⁹ and dyslipidaemia in children⁴¹ 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,^{58 59 76} waist circumference,⁷⁶ waist to height ratio⁵⁹ skinfold sum⁵⁹ and body fat percentage⁵⁸) and other metabolic risk factors (i.e. elevated levels of glucose,⁵⁹ insulin,⁵⁹ triglycerides,⁴¹ non-high-density and high-density lipoprotein cholesterol⁴¹ and blood pressure⁷⁶). Similarly, cross-sectional analysis of children and adolescents with normal weight versus excess weight showed either no difference in the consumption of ultra-processed food between groups⁴⁵ or higher consumption among those with normal weight.^{46 58} These findings suggest that consistent intake of ultra-processed food over time is needed for any deleterious effects of ultra-processed food on sub-clinical cardiovascular disease to manifest later in the lifespan (e.g. early adulthood).^{59 46}

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 ultra-processed 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.⁵⁸ It is well-established that physical activity is a principal determinant of cardiometabolic outcomes.⁸³ Physical activity may attenuate the association between ultra-processed 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 59 76} where physical activity levels may be greater than in higher-income communities.⁷⁶ 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.⁸⁴ 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,⁸⁵ preventative efforts ought to consider targeting ultra-processed food consumption in younger individuals.

1.2.2 Total caloric intake

A recent experimental study in humans has shown a causal relationship between the consumption of ultra-processed food and excess caloric intake, body weight and fat gain.⁸⁶ 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).⁸⁷ However, total caloric intake can confound associations between disease risk and the nutrient composition of macro and micronutrients.⁸⁸ In the present review, only one of four studies in adolescents adjusted for total caloric intake⁴⁶ (with none in children). Adolescents within normal weight ranges versus those in higher weight ranges reported greater consumption of ultra-processed food.⁴⁶ It is plausible that the impact of ultra-processed food on weight outcomes in younger populations may be mediated by the caloric value of ultra-processed food. In contrast, only one⁴⁰ of fourteen studies in adults (assessing associations between ultra-processed food consumption and overweight and obesity) made additional adjustment for total energy intake, with the main findings remaining statistically significant (i.e. higher ultra-processed food consumption was associated with various measures of overweight and obesity).⁴⁰ This suggests that other aspects of ultra-processed food may be driving observed relations, such as nutritional quality. Given 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 Willet's residual method.⁸⁸

1.2.3 Nutritional quality

One common explanation for the observed associations between consumption of ultra-processed food and risk of non-communicable diseases is that ultra-processed foods typically have poorer nutritional quality than unprocessed or minimally processed foods.⁸⁹ Dietary patterns high in ultra-processed food have not only been associated with excessive intake of calories, but also added sugars, sodium and trans and saturated fat.^{22 39 89-91} Excessive added sugar intake has been independently associated with cardiovascular mortality risk and accelerated pathogenesis of vascular disease.^{90 92} Likewise, high sodium intake has been

associated with cardiovascular deaths⁹³ and elevated risk for some cancers, such as stomach cancer.⁹⁴ 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 ultra-processed food with high levels of added sugar and sodium include sugary beverages and processed meats, respectively.⁹⁵ Sugar sweetened beverages may also have the added effect of promoting excessive energy intake by disrupting the internal satiety trigger.⁹⁶

The characteristically scarce levels of fibre common to ultra-processed food should also be considered, with a separate systematic review and meta-analysis,⁹⁷ as well as an umbrella review of such studies,⁹⁸ reporting an inverse association between fibre and risk of all-cause mortality.^{97 98} 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).⁹⁸ 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,⁹⁹ respiratory conditions³⁷ and reduced levels of serotonin and dopamine involved in regulating neurological reward circuitry and mood.¹⁰⁰ In sum, ultra-processed 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,⁸⁹ 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 ultra-processed 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 ultra-processed food and risk of depression,⁵¹ type-two diabetes mellitus,⁵⁵ overall cardiovascular disease,⁴⁹ coronary heart disease,⁴⁹ cerebrovascular disease,⁴⁹ overall cancer⁶⁶ and breast cancer,⁶⁶ with all studies documenting unchanged positive associations. This underscores the notion that other components of ultra-processed 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 ultra-processed food and adverse health outcomes could be explained by lower consumption of non-ultra-processed food. Several studies in the present review made adjustment for consumption of non-ultra-processed foods, such as unprocessed or minimally processed food,⁴⁰ fruits and vegetable intake,^{37 38 61 64} adherence to national

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dietary recommendations,^{52 53} adherence to the Mediterranean diet,⁶² 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 ham⁵⁷). However, for all but one study⁵⁷ assessing inflammatory bowel disease, adjustment for non-ultra-processed food did not attenuate any of the observed relations, including the association between consumption of ultra-processed food and risk of overweight and obesity,^{38 40 64} all-cause mortality,⁵² depression,⁶² irritable bowel syndrome and functional dyspepsia,⁵³ asthma and wheezing³⁷ and hypertension.⁶¹

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,⁷⁶ metabolic syndrome in adults,⁷⁸ cardiovascular risk factors in adults⁷² and prostate cancer in men.⁶⁵ With respect to BMI, these findings are consistent with a recent randomised, controlled trial, where the consumption of an unprocessed versus ultra-processed diet led to reduced energy intake as well as lower body weight and fat mass.⁸⁶ This was despite the fact that the presented diets were closely matched for sugar, sodium, fat, protein and fibre content.⁸⁶ It is also important to note that six studies^{49 51-54 66} in the present review used the percentage of weight in grams per day of ultra-processed food rather the percentage of total calories. The percentage of weight in grams per day of ultra-processed food was noted as the preferred measure to account for ultra-processed 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 ultra-processed food may not be the only relevant factor explaining observed relations, which is an important consideration for future studies.

1.3 Underlying mechanisms

1.3.1 The food matrix and artificial food additives

Beyond nutritional quality, several other qualities of ultra-processed food may explain associations, including the effect of processing on the food matrix. The food matrix is characterised as the nutrient and non-nutrient components of food and their molecular interactions.¹⁰¹ 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 potential¹⁰² as well as the gut microbiota;^{5 103} all of which may influence the risk of non-communicable diseases.

Other constituents of ultra-processed food, such as artificial food additives may also play a part in the observed relations. Pre-clinical 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.¹⁰⁴ Both emulsifiers and non-caloric artificial sweeteners have been linked to alterations to the gut microbiota,¹⁰⁴⁻¹⁰⁶ with gut microbiota being associated with many metabolic aberrations,¹⁰⁷ including insulin resistance.^{108 109} Our recent systematic review of ultra-processed very low-energy diets (≤ 900 kilocalories 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.¹¹⁰ We concluded this was counterintuitive given the significant weight loss noted across studies and the well-established advantageous impact of weight loss dietary interventions on inflammation.¹¹⁰ In contrast, one cross-sectional study in the present review concluded associations between the consumption of ultra-processed 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.¹¹¹ Thus, elevated inflammation may be a possible underlying mechanism in the association between ultra-processed food consumption and chronic disease. This concept may be supported by the previously noted experimental study in humans by Hall et al. (2019).⁸⁶ While this study demonstrated a causal relationship between an ultra-processed diet and excess caloric intake, body weight and fat gain compared to 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 ($P=0.014$).⁸⁶ However, no between-group difference at endpoint was reported ($P=0.072$).⁸⁶ Further research is needed to more clearly delineate the role of inflammation in non-communicable diseases.

1.3.2 Carcinogenic compounds

Other possible explanatory constituents of ultra-processed food include carcinogenic compounds produced via the heat treatments of intensive food processing, such as acrylamide and acrolein.^{49 112} Both compounds have been associated with higher risk of cardiovascular diseases,^{113 114} with systematic reviews reporting modest association between acrylamide

consumption and risk of cancer in non-smokers (i.e. kidney and endometrial cancer).¹¹⁵ Pre-clinical 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.^{116 117} Relatedly, a recent observational study in adolescents reported higher versus lower consumption of ultra-processed food was associated with higher DNA oxidative damage as measured by urinary concentrations of 8-hydroxy-2'-deoxyguanosine.¹¹⁸ Indeed, the initiation and development of cancer has been associated with oxidative stress via DNA mutation and damage.¹¹⁹ Finally, meta-analytical studies have reported bisphenol A, a compound used to make plastics and resins, was associated with elevated cardiometabolic risk,¹²⁰ including obesity and type two diabetes mellitus.¹²¹ Such compounds are suspected of migrating into products from the plastic packaging of many ultra-processed foods,⁴⁹ disrupting endocrine signalling and adversely affecting hormonally regulated metabolic processes.¹²² Although the emerging evidence pertaining to the impact of artificial compounds commonly contained within ultra-processed 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 ultra-processed foods could mitigate their adverse effects.

1.4 Limitations

This systematic review and meta-analysis has a number of limitations. Firstly, 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 ultra-processed 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 exists regarding inadequate estimation of the between-study variance.¹²³ 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. $\leq 36.5\%$ of total calories was categorised as the lowest cut-off in one study,⁷¹ whereas $>29\%$ was the highest in another⁴⁰). These disparities limit conclusions about how much ultra-processed food in the diet is needed to initiate adverse health consequences. In order to improve evidence, we propose *posteriori* as well as standardised analytical approaches that consider data presented in the current review. More specifically, while the majority of studies divided ultra-processed food consumption into quartiles or quintiles, pre-defined cut-off ranges for lowest versus highest consumption that consider geographical location and population characteristics are needed.

Secondly, the observational nature of the studies eligible for inclusion in our review demonstrate associations rather than causation. There has only been one randomised, controlled trial to date that has assessed the effect of ultra-processed food consumption on health outcomes.⁸⁶ While this study found a causal relationship between ultra-processed food in the diet and excess caloric intake as well as body weight and fat gain,⁸⁶ 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 non-ultra-processed food.¹²⁴ It was beyond the scope of our review to investigate such factors. However, it is important to reemphasise that the NOVA system is endorsed by United Nations and World Health Organization.²³ Compared to 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

Conclusions

The present review and meta-analysis provides evidence associating higher consumption of ultra-processed food with a 20% to 81% increased risk of various non-communicable 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 ultra-processed 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 ultra-processed consumption and intermediate risk factors. Nevertheless, the weight of evidence is sufficient, especially given the precautionary principle, to address consumption of ultra-processed food in diverse preventive and treatment efforts.

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Figure 1: Bar chart of ultra-processed food consumption by country

Figure 2: Forest plot of meta-analysis for cross-sectional studies assessing association between higher versus lower consumption of ultra-processed 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 ultra-processed food and overweight risk in adults

Table 1: Number of individual studies reporting associations versus no associations between ultra-processed food consumption and chronic non-communicable diseases, mortality and associated risk factors

Supplementary Information

Figure 1: PRISMA flowchart

Figure 2: Search terms

Figure 3: Forest plot of meta-analysis for consumption of ultra-processed food and risk of abdominal obesity

Figure 4: Forest plot of meta-analysis for consumption of ultra-processed food and risk of all-cause mortality

Figure 5: Forest plot of meta-analysis for consumption of ultra-processed food and risk of metabolic syndrome

Figure 6: Forest plot of meta-analysis for consumption of ultra-processed food and risk of depression

Figure 7: Forest plot of meta-analysis for consumption of ultra-processed food and risk of wheezing

Figure 8: Forest plot of meta-analysis for consumption of ultra-processed food and risk of wheezing

Table 1: Details of exposure variable and average ultra-processed food consumption across studies according to chronic disease and population

Table 2: Study characteristics and key findings for overweight and obesity separated by age (children, adolescents and adults)

Table 3: Study characteristics and key findings for all-cause mortality in adults

Table 4: Study characteristics and key findings for metabolic diseases separated by age (adolescents and adults)

Table 5: Study characteristics and key findings for depression, frailty, functional gastrointestinal disorders and respiratory diseases separated by age (children, adolescents and adults)

Table 6: Study characteristics and key findings for cardiovascular diseases and risk factors separated by age (children, adolescents and adults)

Table 7: Study characteristics and key findings for cancer in adults

Table 8: Critical Appraisal Checklist for Cohort Studies

Table 9: Critical Appraisal Checklist for Cross-Sectional Studies

Table 10: Critical Appraisal Checklist for Case-Control Studies

Figure 1. Bar chart of the average intake of ultra-processed food (% calories) by country

Figure 2. Meta-analysis of cross-sectional studies assessing association between higher versus lower consumption of ultra-processed food and obesity risk in adults

OBR_13146_Figure 2_Meta-analysis of UPF and risk of obesity.tif

Figure 3. Forest plot and meta-analysis of cross-sectional studies assessing association between higher versus lower consumption of ultra-processed food and overweight risk in adults

OBR_13146_Figure 3 Meta-analysis of UPF and risk of overweight.tif

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