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Unhealthy Food and Beverage Consumption during Childhood and Risk of Cardiometabolic Disease: A Systematic Review of Prospective Cohort Studies

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A B S T R A C T

Background: Global consumption of unhealthy foods, including ultra-processed foods (UPFs) and sugar-sweetened beverages (SSBs), has increased substantially among pediatric populations. Suboptimal diet during early life can track into adulthood, alongside risk factors for cardiometabolic disease.

Objective: To inform the development of updated WHO guiding principles for complementary feeding of infants and young children, this systematic review sought to examine the association between unhealthy food consumption during childhood and cardiometabolic risk biomarkers.

Methods: PubMed (Medline), EMBASE, and Cochrane CENTRAL were systematically searched, with no language restriction, up to 10 March 2022. Inclusion criteria were randomized controlled trials (RCTs), non-RCTs, and longitudinal cohort studies; children aged ≤10.9 y at exposure; studies reporting greater consumption of unhealthy foods and beverages (defined using nutrient- and food-based approaches) than no or low consumption; studies assessing critical nonanthropometric cardiometabolic disease risk outcomes (blood lipid profile, glycemic control, or blood pressure).

Results: Of 30,021 identified citations, 11 articles from 8 longitudinal cohort studies were included. Six studies focused on exposure to unhealthy foods or UPF, and 4 focused on SSB only. Methodological heterogeneity was too high across studies to meta-analyze effect estimates. A narrative synthesis of quantitative data revealed that exposure to unhealthy foods and beverages, specifically NOVA-defined UPF, in children of preschool age may be associated with a worse blood lipid and blood pressure profile in later childhood (Grading of Recommendations Assessment, Development, and Evaluation [GRADE]: low and very low certainty, respectively). No associations were evident between SSB consumption and blood lipids, glycemic control, or blood pressure (GRADE: all low certainty).

Conclusions: No definitive conclusion can be made because of quality of the data. More high-quality studies that purposefully assess the effects of unhealthy food and beverage exposure during childhood on cardiometabolic risk outcomes are needed. This protocol was registered at https://www.crd.york.ac.uk/PROSPERO/ as CRD42020218109.

Keywords: cardiovascular diseases, cholesterol, children, cohort studies, diabetes, sugar-sweetened beverages, ultra-processed foods

Abbreviations: BP, blood pressure; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IYC, infants and young children; LMIC, low- and middle-income countries; MAP, mean arterial pressure; NCDs, Noncommunicable diseases; PI/ECO, population, intervention or exposure, comparator, outcome, and study design; PWV, pulse wave velocity; RCT, randomized controlled trial; ROBINS-I, risk of bias in nonrandomized studies of interventions; RR, risk ratio; SSB, sugar-sweetened beverage; TAG, triacylglycerol; TC, total cholesterol; UPF, ultra-processed food; %EI, percentage of energy intake.

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Introduction

Noncommunicable diseases (NCDs) impose a substantial socioeconomic burden, particularly in low- and middle-income countries (LMIC) where a large proportion of NCD-related deaths occur prematurely. CVDs are the leading cause of deaths from NCDs worldwide [1]. In parallel, type 2 diabetes (a highly prevalent cardiometabolic disease) is a major risk factor for CVD [1]. Although blood-based clinical markers of cardiometabolic disease risk, including fasting blood lipids and markers of glycemic control, are not routinely assessed among children aged <9 y [2], cut-off values are in place to define dyslipidemia (particularly in terms of cholesterol and triacylglycerol [TAG] concentrations) and diabetes in pediatric and adolescent populations [2–4]. Recommendations also exist for identifying hypertension in nonadult populations [5]. There is increasing evidence that cardiovascular disease risk factors that accelerate the progression of atherosclerotic CVD track from childhood through to adult life [2, 6]. Indeed, a recent narrative systematic review presented evidence linking childhood cardiometabolic risk factors, including hyperlipidemia and hypertension, with subclinical or clinical CVD in adulthood [6]. This is concerning given that US population data indicated that lipid abnormalities were present in ~20% of youth aged 8–17 y, and >1 in 10 had borderline or high blood pressure (BP) [7]. Thus, there is a clear need to understand how modifiable risk factors, such as suboptimal diet, during early life affect cardiometabolic health outcomes.

Poor diet quality is a leading risk factor linked to the overall burden of cardiometabolic diseases [8]. The 2017 Global Burden of Disease study cited suboptimal diet as a significant contributor to mortality worldwide, with CVD and diabetes accounting for >10 million diet-related deaths and 231 million disability-adjusted life years among adults [9]. Over the past decades, global consumption of ultra-processed foods (UPFs), including carbonated sugar-sweetened beverages (SSBs), sweet or savory packaged snacks, confectionery, reconstituted meat products, preprepared meals, and refined grain products, has increased substantially, especially in children and adolescents [10–12]. Additionally, evidence-informed dietary priorities to reduce the burden of cardiometabolic diseases include reducing the intake of processed meats, refined grains as well as nutrients that are abundant in UPF, including starches, added sugars, sodium, and *trans* fat [8].

The WHO guiding principles for feeding infants and young children (IYC) have traditionally focused on indicators for prevention of undernutrition [13, 14]. In recognition of growing concerns over the prevalence of childhood obesity and development of related cardiometabolic disorders in later life, it is now also recommended to include indicators of unhealthy food and beverage consumption in IYC feeding practice assessment [15]. There is a lack of evidence on the cardiometabolic health effects of unhealthy food and beverage consumption among IYC. Additionally, it is widely accepted that the entire childhood period is of concern as suboptimal diet during early life can track into adulthood [16], in parallel with risk factors for cardiometabolic disease [6]. Therefore, to inform the development of updated WHO guiding principles for complementary feeding of IYC, we conducted a systematic review to examine the association between consumption of unhealthy food and beverages (including SSB and UPF) during childhood (≤10.9 y), compared with no or low consumption, and cardiometabolic disease risk markers. We focused on biomarkers of CVD and type 2 diabetes risk, specifically blood lipids, glycemic control, and BP outcomes.

Methods

The current article forms part of a larger WHO-commissioned review, which was conducted to assess, among children aged ≤10.9 y, the risks of greater consumption of unhealthy foods and beverages than no or low consumption on critical outcomes (growth and body composition; diet-related NCDs indicators [specifically, nonanthropometric cardiometabolic disease risk markers]; displacement of healthy foods or breastmilk intake; and dietary quality and diversity) and important outcomes (food or taste preferences later in life; oral health/dental caries; micronutrient deficiencies; and child development) specified by WHO. Critical outcomes are those considered most important from the public health guideline and policy making perspective [17]. In the current article, we focus on synthesizing the evidence base on the associations between unhealthy food and beverage consumption and cardiometabolic disease risk biomarkers, specifically blood lipid profile, glycemic control, and BP outcomes. Outcomes related to risk of overweight and obesity are beyond the scope of the current review and are reported elsewhere [18]. The review was performed in accordance with the PRISMA 2020 reporting guidelines [19]. The protocol was published in the PROSPERO database (www.crd.york.ac.uk/PROSPERO); Registration number: CRD42020218109.

Search strategy

Three major databases were used for the systematic literature searches (PubMed [Medline], EMBASE, Cochrane CENTRAL). The literature search strategy was developed by the review team and checked by an independent academic librarian. Scoping searches were conducted to refine the search strategy to ensure that relevant studies had been identified with the search syntax. The search syntax was first developed for PubMed using database-specific indexing terms and then adapted to the requirements of the other 2 databases. The 3 initial searches were conducted between 17 and 23 December 2020, followed by an updated search up to 10 March 2022. The full search strategies for the initial search of all databases are presented in Supplemental Table 1. The search results were imported into web-based Covidence software platform for title, abstract and full-text screening. PubMed alerts were set up to notify the authors of any new potentially relevant publications. The reference lists of review papers identified in our search and included papers were also scrutinized for additional publications. Where necessary, experts in the field were contacted for additional relevant studies. Grey literature was not included in the review because of time and budgetary constraints.

Study eligibility criteria

As outlined in Supplemental Table 2, study eligibility criteria were established by the population or participant, intervention or exposure, comparator, outcome, and study design (PI/ECOS) framework. We included quantitative studies of human infants and children (girls and boys) in which the baseline age was from

birth to ≤10.9 y from any ethnicity or location. Records published from January 1971 onward were included. No country or language restrictions were applied.

Unhealthy foods and beverages were defined using both nutrient- and food-based approaches. Because there was no single classification system or criteria for unhealthy foods that covered all relevant exposures, we used the following 4 main measures to classify foods and beverages as unhealthy: *1*) UPF based on the NOVA classification system [20], which categorizes foods and beverages based on the nature, extent, and purpose of industrial processing (i.e., the physical, biological and chemical processes) that food items and beverages undergo; *2*) unhealthy foods and beverages defined in IYC feeding indicators from the WHO guide to assess infant and young child feeding practices, namely (i) sweet beverages (i.e., commercially produced and packaged sweetened drinks, 100% fruit juice drinks, and home-made drinks with sweeteners added) and (ii) sentinel unhealthy foods (i.e., sweet foods and fried/salty foods) [15]; *3*) foods high in 1 or more of the following: added sugars, free sugars, artificial sweeteners, and salt; and *4*) foods rich in saturated and/or *trans* fats. In addition to the 4 classifications above, we included studies in which authors used terminologies denoting unhealthy foods namely: "junk food," "fast food," "snack food," "extra food," "noncore food," and "convenience food." Although these are not precise definitions, they were considered to meet inclusion criteria based on the likelihood of containing either UPF; unhealthy foods; and foods high in free sugars, saturated or *trans* fat. Free sugars included "all added sugars in any form; all sugars naturally present in fruit and vegetable juices, purées and pastes and similar products in which the structure has been broken down; all sugars in drinks (except for dairy-based drinks); and lactose and galactose added as ingredients" [21]. Sugars naturally present in "milk and dairy products, fresh and most types of processed fruit and vegetables and in cereal grains, nuts and seeds" were not included in the definition of free sugars [21]. We included sugars from all beverages (including 100% fruit juices) in our classification on the basis that beverages have the potential to provide higher amounts of total/free sugars and may not be as satietogenic when compared with solid foods [21]. To be deemed eligible for inclusion, studies were required to provide information at the food item/food group level, such as total intake of free sugars/added sugars from food and/or beverages included on our unhealthy food list (see Supplemental Table 3). If, however, studies only reported nutrients (e.g., total saturated fats, total free sugar intake, total added sugar intake, etc.) and did not quantify consumption of unhealthy foods and beverages, they were excluded. This approach was taken because the planned WHO dietary recommendations for IYC are food-based, rather than nutrient-based, and the systematic review was conducted to inform future guidelines. The detailed criteria for defining unhealthy foods and beverages are presented elsewhere [18].

Study selection

Duplicate records were identified automatically by Covidence software (Veritas Health Innovation) before screening. Half of the identified duplicates were checked to ensure that no incorrect duplicates were identified. A multiple-pass method was used to review the articles identified in the database searches. Where necessary, non-English language title and abstracts or full-text stage were screened with the assistance of a native speaker with health- or nutrition-related expertise. Before screening commencement, the review team underwent training by screening a random test sample of 25 retrieved records. This process helped improved clarity of the eligibility criteria and consistency among the reviewers. We had originally set aged <10 y at baseline as an inclusion criterion. However, it was necessary to refine the age criteria in our review protocol to include children aged ≤10.9 y and exclude children aged >10.9 y. This protocol amendment, registered on PROSPERO, ensured consistency in screening across reviewers and was more inclusive of evidence as per guidance [22], i.e., if studies were ambiguous in their reporting of childhood age inclusion criteria or sample characteristics. Inclusion/exclusion criteria guidance notes were updated based on feedback from reviewers.

The first pass involved 2 independent reviewers (OM, RP, SG, PLG, EKR, NP, KB, or MS) screening every title and abstract to exclude clearly irrelevant articles. Any disagreements were resolved via an additional third reviewer (RP or NP). If the third reviewer was unsure, the relevant record was considered by a fourth reviewer (EKR). For the second pass, 2 reviewers independently screened records included at the full-text stage (OM, RP, SG, PLG, EKR, NP, KB, or MS). Following screening of the first 50 records, the review team discussed decisions and any eligibility uncertainties. Further details were added to the inclusion/exclusion criteria guidance based on these discussions e.g., multicomponent intervention. All subsequent disagreements were discussed and resolved by a third reviewer (RP, NP, or EKR). Reasons for exclusions at full-text screening were recorded. Studies that met all criteria for study entry but reported data for a wider age range (e.g., 8–13 y) were included at full-text stage. The authors of relevant studies were subsequently contacted by the review team to request disaggregated data for participants aged ≤10.9 y or the raw data. Two reviewers each checked 2 distinct random 10% samples of excluded records at title/abstract and full-text stage (OM, RP, SG, or EKR).

Data extraction process

A data extraction form was developed in Excel and piloted by all data extractors using a selection of 6 included articles covering different review outcomes from the wider WHO-commissioned report. Following the first pilot, the form was revised, and a second pilot data extraction was performed, with all reviewers extracting data from a single article. After further revisions, the data extraction form was finalized. One reviewer independently extracted data for each article (OM, RP, SG, BB, or EKR). Any data extraction queries were discussed among the review team. A second reviewer (EKR) checked 50% of all records extracted for completeness and accuracy. Full details of the information extracted from eligible studies are presented in Supplemental Table 4. In brief, the following details were extracted: study ID, title, authors, study location, study design, aim, study funding sources, conflicts of interest, randomization process, participant selection and characteristics, sample size, duration of intervention or exposure, exposure measures (including type of food consumption data and dietary assessment tool), and outcomes (including assessment method, any adjustment for confounding and measures of intervention effect). Data were extracted on all ages of follow-up with no upper age limit. Where multiple articles from the same study were included, we extracted data that were unique to each article (e.g., where

different outcomes or different exposures from the same study were reported in separate articles). If the same data were reported in >1 article, we extracted data from the article that most closely addressed the review question.

Risk-of-bias assessment

Two reviewers (OM, RP, SG, BB, or EKR) independently assessed the risk of bias of included articles (all prospective cohort studies) in Covidence software using the risk of bias in nonrandomized studies of interventions (ROBINS-I) tool [22, 23]. Each of the 7 domains of bias (confounding, selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of reported results) in the ROBINS-I tool were rated as being at low, moderate, serious, or critical risk of bias, or no information [23] with inclusion of notes to justify the judgment. Reviewers checked study protocols, clinical trial registrations, and supplemental files for required information where necessary. The 2 reviewers then compared independent ratings, discussed inconsistencies, and reached consensus on each domain. If agreement could not be reached, a third reviewer (RP or EKR) assessed the judgments and supporting statements for the 2 reviewers to make a consensus assessment. After completing consensus on the 7 domains in the tool, the overall risk of bias for each study was assessed using the criteria in Supplemental Table 5. Using these criteria, overall risk of bias was rated as low, moderate, serious, critical, or no information. Risk of bias figures for individual studies and summary of risk of bias tables were prepared using the Risk-Of-Bias VISualization tool [24].

Data synthesis and narrative review

Findings were synthesized using the PI/ECOS framework. Studies were initially grouped by outcome and then by exposure. For synthesis relating to participant characteristics, we stratified by age groups (0 to <2 y; 2 to <5 y; and 5 to ≤10.9 y) when there were sufficient studies available. Measures of effect were tabulated based on the availability and type of data. For completeness, we included all estimates in summary tables of results, including studies with critical risk of bias. In line with guidance [23, 25], we did not report results from studies assessed as having a critical risk of bias in the narrative synthesis.

Exposures were synthesized using 2 overarching groups of unhealthy foods and beverages based on the need for requirements for evidence to make recommendations: Unhealthy foods and beverages (for details see [18] and Supplemental Table 3). In line with our a priori protocol for the quantitative synthesis, we tabulated the predefined interventions (exposures) for each of the specified outcomes to identify which studies were eligible for synthesis. Following tabulation, the exposures were insufficiently comparable across studies to meta-analyze effect estimates. Methodological differences included variability across studies in the measurement of exposure (including the dietary assessment methods, recall period, definition of food items/food groups, or units of measurement). Data reporting varied from dichotomous, multiple categories, or continuous measures of consumption. Therefore, we conducted a narrative synthesis of quantitative data, according to synthesis without meta-analysis (SWiM) guidance [25]. We extracted the measures of effect (e.g., mean differences; ORs, beta coefficients (β), relative risks with 95% CIs and/or *P* value) for all studies providing data on the effect of exposure on the outcome of interest. We extracted data from fully adjusted models where available. If unadjusted effect measures only were reported, these were extracted.

Certainty of evidence evaluation

The GRADE approach was used to assess the 5 domains (risk of bias across studies, inconsistency, imprecision, indirectness, and publication bias) and rate the certainty of evidence as high, moderate, low, or very low [17]. Statements defining the certainty for each grade are provided in Supplemental Table 6 (see further details on the grading of evidence approach in Rousham et al. [18]). Evidence profile tables were produced using GradePro software (GRADEpro Guideline Development Tool), in line with published recommendations [17]. Two independent reviewers (OM, SG, or EKR) graded the evidence and individual ratings were agreed through discussion and consensus. Included observational studies were initially graded as high certainty of evidence in accordance with Cochrane guidance when using ROBINS-I [22]. A GRADE evidence profile was produced to assess the certainty of evidence for each critical outcome. Effects of exposures (interventions) are reported following Cochrane standard reporting statements [26]. Individual studies assessed as at critical risk of bias were excluded from GRADE evidence profile tables as the evidence was deemed too unreliable.

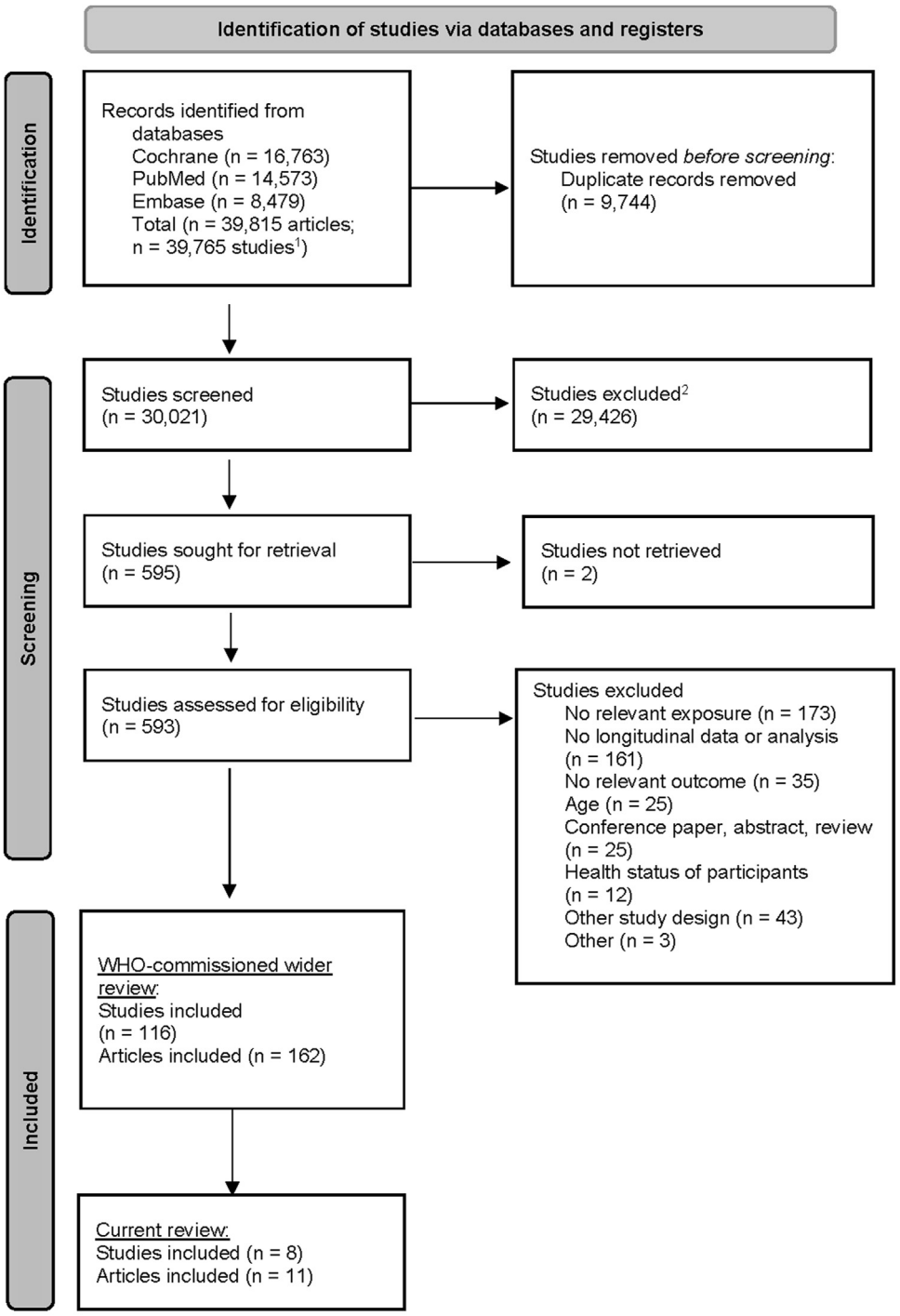
Results

Study selection

The detailed steps of the literature search and screening process are presented in Figure 1. In brief, the search for the wider review retrieved 39,765 studies of which 9744 duplicate records were detected by the Covidence software platform. Of the 30,021 screened studies, a total of 162 articles from 116 studies were included in the wider review after full-text screening. A total of 11 articles from 8 studies met the criteria for inclusion in the current systematic review. Although the review was not limited to cohort studies, all studies retrieved that met the inclusion criteria had longitudinal study design. Only English language studies were identified for inclusion. A total of 1 study (3 articles) could not be included because it was not possible to disaggregate data for participants aged ≤10.9 y at baseline [27–29].

Participant and study characteristics

Details of the 7 included prospective cohort studies, including characteristics of the study participants, country, setting, baseline age, exposure details, outcomes assessed, and details of adjustment for confounding factors in multivariate models are presented in Supplemental Table 7, and Table 1 with the sources of funding and conflicts of interests of authors for each of the included studies listed in Supplemental Table 8. Study publication dates ranged from 2001 to 2020. Mean baseline age of participants ranged from 13 mo to 9.57 y, with follow-up duration ranging from 12 to 59 mo. All studies included girls and boys. Three of the 8 studies were conducted in a middle-income country (all Brazil [30–32]) and the remaining 5 were conducted in high-income countries (UK [33], South Korea [34], Spain [35], The Netherlands [36], or the US [37]), based on the current Gross National Income per capita [38]. Of the 7 studies that reported setting, all were conducted in an urban location [30–32, 34, 35, 37].



[1]This term is used throughout this flowchart as Covidence software calculated numbers at the study level.
[2]No automation tools were used, all screened by review team.

FIGURE 1. Flowchart of study search and selection for the review of the effects of unhealthy food and beverage consumption in children aged ≤10.9 y on cardiometabolic disease risk biomarkers.

Of the included studies, 4 reported on consumption of 1 or more SSB (sodas, fruit-flavored drinks, cordials, powdered sweet drinks, juice with added sugar, and caffeinated drinks with sugar added) [31, 34, 36, 37], and 6 reported on consumption of unhealthy food and beverage or UPF exposure [30–35] (Table 1).

Risk-of-bias assessment

The 8 included studies were nonrandomized studies and were therefore assessed using the ROBINS-I tool. As summarised in Supplemental Figure 1, the main contributors to the overall risk of bias across studies were bias because of confounding (D1) and

TABLE 1
Synthesis of results of unhealthy food and beverage consumption among children aged ≤10.9 y and nonanthropometric cardiometabolic disease risk outcomes[1]

Reference, country, cohort	Baseline age (mean or range)	Follow-up duration	n[2]	DAT	Exposure	Intake unit	Comparator	Relevant outcomes	Result[3]	Adjustment	Overall RoB
SSB											
0 to <2 y											
Leermakers et al., 2015 [36] the Netherlands, Generation R study	13 mo	59 mo	1383	1-m SFFQ (211 item)	SSB included fruit juices, fruit concentrates, lemonades, soft drinks, and sports drinks	sv/wk	T3 vs. T1; T2 vs. T1	SBP; DBP; PWV; HDL-C; TAG; insulin	No significant associations: T3 v T1: SBP: 0.02; 95% CI −0.08, 0.13 mmHg; DBP: 0.09; 95% CI −0.02, 0.19 mmHg; PWV: −0.01; 95% CI −0.13, 0.11 m/s; HDL-C: −0.12; 95% CI −0.25, 0.01 mmol/L; TAG: 0.12; 95% CI −0.01, 0.25 mmol/L; Insulin: 0.03; 95% CI −0.10, 0.16 pmol/L	Age, sex, total energy intake, maternal age, BMI, education level, smoking during pregnancy, folic acid supplement use during pregnancy, breastfeeding of the child, diet quality score, and hours of TV watching at age 2 y.	Moderate
2 to <5 y											
Costa et al., 2019 (31) Brazil	4 y	4 y	307	Two 24-h dietary recalls	SSB included soda, sweetened juice, and sport drinks	%EI	Continuous	Glucose; insulin; HOMA-IR	No significant associations: Glucose: β: 0.01; 95% CI: −0.01, 0.03 mmol/L; insulin: β: 0.01; 95% CI: −0.01, 0.02 μU/mL; HOMA-IR: β: 0.01; 95% CI: −0.01, 0.03.	Group status in the early phase (intervention and control), prepregnancy BMI, sex, birth weight, breastfeeding, family income, maternal schooling, and total screen duration.	Moderate
5 to ≤10.9 y											
Van Rompay et al., 2015 [37] US	9.57 y	12 mo	127	7-d SFFQ (72 item)	SSB included regular sodas, non-100% fruit juices/drinks, and other beverages e.g., sweetened teas	times/wk	Continuous across 4 categories: nonconsumer; >0 but <2, ≥2 but <7; and ≥7 sv/wk	HDL-C; TAG	No significant associations for HDL-C but significant associations for TAG[4]: HDL-C (≥7 sv/wk vs. nonconsumer): β: 1.35; 95% CI: −2.75, 5.44 mg/dL, $P = 0.517$ TAG: >0 but <2 sv/wk vs. nonconsumer: β: 13.5; 95% CI: −0.2,	Baseline age, sex, race/ethnicity, lipid concentration, pubertal status, BMI *z*-score, sedentary time, and changes in intakes of total energy, fruits/vegetables, and	Serious

(*continued on next page*)

TABLE 1 (*continued*)

Reference, country, cohort	Baseline age (mean or range)	Follow-up duration	n[2]	DAT	Exposure	Intake unit	Comparator	Relevant outcomes	Result[3]	Adjustment	Overall RoB
									27.3 mg/dL; P = 0.054; ≥2 but <7 sv/wk vs. nonconsumer: β: 17.9; 95% CI: 4.4, 31.5 mg/dL; P = 0.010; ≥7 sv/wk vs. nonconsumer: β: 21.0: 95% CI: 5.7, 36.4 mg/dL; P = 0.008 (Overall P-trend: 0.02)	discretionary solid fats.	
Hur et al., 2015 [34] South Korea, Korean Child-Adolescent Cohort	9.9 y	4 y	345	Modified 3-d diet record	SSB included fruit juice, fruit and vegetable drinks, carbonated beverages, sports drinks, coffee, sweet tea, soy milk, energy drinks, and other beverages	g/d	Continuous	Metabolic syndrome score components: glucose; HDL-C; TAG concentration; MAP	MAP: β: −0.61, SE: 0.30 mmHg; P < 0.05. Glucose, HDL-C, TAG: no significant associations: β: 0.10, SE: 0.27 mg/dL; P > 0.05; β: −0.004, SE: 0.02 mg/dL; P > 0.05 and β: −0.46, SE: 0.40 mg/dL; P > 0.05, respectively.	Baseline total energy intake, sex, age, and household income.	Serious
Unhealthy foods (including UPF)											
0 to <2 y											
Cowin et al., 2001 [33] UK, Avon Longitudinal Study of Pregnancy and Childhood Cohort	~18 mo	~13 mo	372	3-d unweighed diet record	Biscuits; chocolate; butter	g/d; consumed/not consumed last 24-h (biscuit exposure only)	Consumed vs. not consumed	TC; HDL-C	Consumed vs. not consumed: TC (mean ± SE): biscuits (boys): 4.19 ± 0.63 vs. 3.86 ± 0.67 mmol/L; P = 0.011. Chocolate (boys) TC: 4.22 ± 0.67 vs. 3.99 ± 0.57 mmol/L; P = 0.012. HDL-C: butter (boys): 0.91 ± 0.26 vs. 0.83 ± 0.19; P = 0.047. TC and HDL-C: no significant associations among girls: NR	NA	Critical
2 to <5 y											
Leffa et al., 2020 [30] Brazil	3.2 y	~3 y	308	Two 24-h dietary recalls	UPF[5]	%EI	T2 vs. T1; T3 vs. T1	TC; LDL-C; HDL-C; TAG	T3 vs. T1: TC: β: 0.22 mmol/L, 95% CI : 0.04, 0.39; TAG : β: 0.11 mmol/L, 95% CI: 0.01, 0.20. LDL-C and HDL-C: no	Sex, group status in the early phase (intervention and control), family income, prepregnancy	Moderate

(*continued on next page*)

TABLE 1 (*continued*)

Reference, country, cohort	Baseline age (mean or range)	Follow-up duration	n[2]	DAT	Exposure	Intake unit	Comparator	Relevant outcomes	Result[3]	Adjustment	Overall RoB
									significant associations: T3 vs. T1: 0.09 mmol/L, 95% CI:–0.06, 0.23 and 0·05 mmol/L, 95% CI: -0.06, 0.15, respectively.	BMI, child birth weight, BMI *z*-score and total energy and fat intake at 3 y follow-up.	
Rauber et al., 2015 [32] Brazil	3-4 y	4 y	305	Two 24-h dietary recalls	UPF[5] included bread, savory, biscuits, sweets, soft drinks, processed meat, mayonnaise, dressing, and sauces	%EI	Continuous	TC; LDL-C; HDL-C; non–HDL-C; TAG	TC and LDL-C: for every 1% increase in EI from UPF, change in TC increased by β: 0.430 mg/dL, 95% CI: 0.008, 0.853 and LDL-C increased by β: 0.369 mg/dL, 95% CI: 0.005, 0.733. No significant change in HDL-C, non–HDL-C and TAG: β: 0.125 mg/dL, 95% CI: −0.026, 0.277; β: 0.319 mg/dL, 95% CI: −0.059, 0.697 and β: −0.465 mg/dL, 95% CI: −0.955, 0.025, respectively.	Sex, group status in the early phase (intervention and control), birth weight, family income, maternal schooling, and BMI *z*-score and total energy intake at age 7 y.	Moderate
Costa et al., 2019 [31] Brazil	4 y	4 y	307	Two 24-h dietary recalls	Total UPF[5] included biscuits (crackers and cookies); breakfast cereal; powdered chocolate; processed meats; savory snacks; sugary milk beverages; sweets (candy, chocolate, and ice cream); others (instant noodles, dehydrated soup, mayonnaise, dressing and sauces)	%EI	Continuous	Glucose; insulin; HOMA-IR	No significant associations: Glucose: β: 0.00 mmol/L; 95% CI: −0.01, 0.00; insulin: β: 0.00 μU/mL; 95% CI: −0.00, 0.01; HOMA-IR: β: 0.00; 95% CI: −0.01, 0.01.	Group status in the early phase (intervention and control), prepregnancy BMI, sex, birth weight, breastfeeding, family income, maternal schooling, and total screen duration.	Moderate
Bawaked et al., 2020 [35]	4 y	7 y	832	12-m SFFQ (105 item)	Total UPF[5] included	sv/d	Continuous	SBP and DBP *z*-score	SBP *z*-score: No significant association	Age, sex, cohort, maternal	Serious

(*continued on next page*)

TABLE 1 (*continued*)

Reference, country, cohort	Baseline age (mean or range)	Follow-up duration	n[2]	DAT	Exposure	Intake unit	Comparator	Relevant outcomes	Result[3]	Adjustment	Overall RoB
Spain, Spanish INMA birth cohort study					carbonated drinks, processed meat, biscuits (cookies), candy (confectionery), 'instant' packaged soups and noodles, sweet or savory packaged snacks, and sugared milk and fruit drinks				(low vs. high intake: β: –0.04; 95% CI: –0.16, 0.08). DBP *z*-score: High intake of UPF was associated with higher DBP *z*-score (low vs. high intake: β: −0.15; 95% CI: −0.29, −0.01).	education, maternal prepregnancy BMI, and, for outcomes at 7 y, the corresponding value at 4 y and follow-up time.	
5 to ≤10.9 y											
Hur et al., 2015 [34] South Korea, Korean Child-Adolescent Cohort Study	9.9 y	4 y	345	Modified 3-d diet record	'Other sugar' included sweets, sweetened grains, sweetened dairy products, sugars, syrup and natural sugar from vegetables and grains	g/d	Continuous	Metabolic syndrome score components: Glucose; HDL-C; TAG concentration; MAP	Glucose, HDL-C, TAG and MAP: no significant associations: β: 0.05, SE: 0.92 mg/dL; $P >$ 0.05; β: −0.03, SE: 0.07 mg/dL; $P > 0.05$ and β: −0.40, SE: 1.38 mg/dL; $P > 0.05$ and β: 0.33, SE: 1.04 mmHg; $P > 0.05$, respectively.	Baseline total energy intake, sex, age, and household income.	Serious

[6]Reporting different outcomes from the same study.

[1] AOR, adjusted OR; DAT, dietary assessment tool; DBP, diastolic blood pressure; EI, energy intake; SFFQ, semiquantitative FFQ; HDL-C, HDL cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, LDL cholesterol; MAP, mean arterial pressure; NA, not applicable; NR, not reported; RoB, risk of bias; PWV, pulse wave velocity; SBP, systolic blood pressure; Sv, serving; SSB, sugar-sweetened beverages; T, tertile; TAG, triacylglycerol; TC, total cholesterol; UPF, ultra-processed foods; WC, waist circumference; %EI, percentage of energy intake.

[2] Minimum analytical sample size.

[3] Adjusted, unless otherwise stated.

[4] Data presented are from a subcohort aged ≤10.9 y, with permission from Friedman School of Nutrition Science and Policy, Tuft's University.

[5] Intake quantified by the authors according to the NOVA classification system (Group 4) [20].

bias because of missing data (D5). Full details of the risk-of-bias assessment for each study and domain are presented in Supplemental Figure 2. Four studies (50.0%) had a moderate overall risk of bias [30–32, 36], 3 studies (37.5%) had a serious overall risk of bias [34, 35, 37], and 1 study (12.5%) had a critical overall risk of bias across the 7 bias domains [33].

Narrative synthesis

Six studies investigated the association between unhealthy food (including UPF) consumption and cardiometabolic risk markers (for details, see Table 1). One study was assessed as being at critical risk of bias and the results are not described further [33]. Two studies included children aged <2 y [33, 36]; 3 included children aged 2 to <5 y [30, 32, 35] and 2 studies included children aged 5 to ≤10.9 y at baseline [34, 37]. Across all age groups, 4 studies assessed SSB exposure [31, 34, 36, 37] and 5 assessed other unhealthy food exposures, including UPF [30–35]. Six studies assessed the blood lipid profile [30, 32–34, 36, 37], 3 studies assessed markers of glycemic control [31, 34, 36], and 2 studies assessed systolic and diastolic BP [35, 36] (outcomes of critical importance, according to the GRADE approach [17]).

SSB exposure

Four studies examined the association between SSB consumption and cardiometabolic disease risk indicators [31, 34, 36, 37]. In The Generation R study, Leermakers et al. [36] studied the association of SSB intake in Dutch children at 13 mo of age with cardiometabolic health outcomes at the age of 6 y. The authors reported no association between SSB intake (according to high compared with low and medium compared with low tertile) and individual risk factors, including HDL cholesterol, TAG, insulin, BP (systolic and diastolic), and carotid-femoral pulse wave velocity (moderate risk of bias) [36]. However, the authors reported an association between higher SSB intake at aged 13 mo and a higher cardiometabolic risk factor score (which combined body fat percentage, systolic and diastolic BP, insulin, HDL cholesterol, and TAG) at 6 y (0.13 SD: 95% CI 0.01, 0.25; highest compared with the lowest tertile) [36]. Among Brazilian children, Costa et al. [31] investigated the association between UPF consumption at preschool age (4 y) and glucose profile at age 8 y. The authors found that glucose, insulin, and HOMA-IR were not associated with the % EI from SSB (moderate risk of bias) [31]. In The Korean Child-Adolescent Cohort Study, Hur et al. [34] examined SSB consumption to a combined metabolic syndrome score (calculated based on fasting blood glucose, HDL cholesterol, TAG concentrations, mean arterial pressure [MAP], and waist circumference) among children with a mean baseline age of 9.9 y. After a 4-y follow-up, no association was observed between the metabolic syndrome score and SSB consumption (serious risk of bias) [34]. In the subanalysis of individual metabolic syndrome components, SSB consumption had a negative association with MAP (β: −0.61; SE: 0.30 mmHg; $P < 0.05$), but no associations were found with fasting blood glucose, HDL cholesterol, or TAG. In the fourth study, the longitudinal association between SSB intake and plasma HDL cholesterol and TAG concentrations over 12 mo was assessed in an ethnically diverse cohort of US children aged 8–15 y. A subcohort of data from children aged ≤10.9 y at baseline were analyzed by the review team [37]. No association was evident between mean SSB consumption and changes in HDL cholesterol over 12 mo in the subcohort, which was similar to what was reported longitudinally for the full cohort ($n = 380$) (serious risk of bias) [37]. However, there was an overall effect of SSB consumption on change in TAG concentrations in the subcohort (P-trend: 0.02), which was significant for ≥2 but <7 serving/wk (sv/wk) compared with nonconsumer: β: 17.9; 95% CI: 4.4, 31.5 mg/dL; $P = 0.010$; ≥7 sv/wk compared with nonconsumer: β: 21.0; 95% CI: 5.7, 36.4 mg/dL; $P = 0.008$, but not 0 but <2 sv/wk compared with nonconsumer: β: 13.5; 95% CI: –0.2, 27.3 mg/dL; $P = 0.054$.

Unhealthy food or UPF exposure

Across all age groups, 5 articles (from 4 studies) examined the association between a range of unhealthy foods items and cardiometabolic risk biomarkers. Three Brazilian-based studies reported specifically on exposure to UPF (as assessed according to the NOVA classification system) [30–32]. One study reported a significant association between higher UPF intake (%EI) at aged 3.2 y and increased total cholesterol (TC) (tertile 3 compared with tertile 1; β: 0·22 mmol/L; 95% CI: 0·04, 0·39) and TAG concentrations at age 6 y (tertile 3 compared with tertile 1; β: 0·11 mmol/L; 95% CI: 0·01, 0·20) than those in the lowest tertile (moderate risk of bias) [30], but not LDL cholesterol or HDL cholesterol concentrations. A second study examined UPF consumption as a %EI among aged 3–4 y old children and followed-up at 7–8 y of age [32]. Changes in TC and LDL cholesterol concentrations were significantly associated with UPF intake (β: 0.430; 95% CI: 0.008, 0.853; $P = 0.046$; β: 0.369; 95% CI: 0.005, 0.733; $P = 0.047$, respectively), but not HDL cholesterol, non-HDL cholesterol, or TAG concentrations (moderate risk of bias) [32]. An additional study, however, found no significant association between UPF consumption (%EI) at age 4 y and circulating glucose, insulin and HOMA-IR in children aged 8 y (moderate risk of bias) [31]. In the Spanish INMA (Infancia y Medio Ambiente [Environment and Childhood]) birth cohort study, Bawaked et al. [35] estimated the association between NOVA-defined UPF intake in children aged 4 y and BP following a 3-y follow-up. The authors found that there was an overall association between UPF intake and diastolic BP z-score (P-trend = 0.05), which was significant for low compared with high intake (β: –0.15; 95% CI: –0.29, –0.01) but not for medium compared with high intake (β: –0.17: 95% CI: –0.31, 0.03) (serious risk of bias). No significant association between systolic BP z-score and UPF intake was observed [35]. In additional analysis from The Korean Child-Adolescent Cohort Study, consumption of "other sugars" (calculated from total sugar minus sugars from fruit, milk, and SSB) at a mean baseline age of 9.9 y was not associated with a metabolic syndrome score, or individual risk components, including fasting circulating glucose, HDL cholesterol and TAG concentrations and MAP at the age 13–14 y (serious risk of bias) [34].

Certainty of evidence

GRADE evidence profiles for the effects of SSB and unhealthy food or UPF consumption and cardiometabolic risk markers are presented in Supplemental Tables 9 and Table 10, respectively. Because of lack of sufficient studies, it was not possible to disaggregate evidence by age group. All studies were observational. Risk of bias across studies was assessed as very serious because the nonrandomization in observational studies was

considered to lead to confounding and selection bias. This was the main contributor to low certainty of evidence. Inconsistency was judged as not serious for all outcomes; however it was noted that interventions and comparators were different across studies. Indirectness and imprecision were judged as not serious. The certainty of evidence of the effects of SSB consumption in children aged ≤10.9 y on cardiometabolic disease risk outcomes was low for studies reporting blood lipid profiles, glucose and insulin concentrations, and BP (Supplemental Table 9). The certainty of evidence of the effects of unhealthy or UPF consumption in children aged ≤10.9 y on cardiometabolic disease risk outcomes was low for studies reporting blood lipid profiles, glucose, and insulin concentrations and very low for BP (Supplemental Table 10).

Discussion

To our knowledge, the current study is the first to systematically review available studies that examined the association between unhealthy food and beverage consumption, during childhood with nonanthropometric cardiometabolic disease risk outcomes. Studies deemed suitable for inclusion in our review focused on unhealthy food, including UPF exposure, or SSB consumption only. Of the limited available evidence, our narrative systematic review presents evidence, which indicates that unhealthy food consumption, specifically intake of NOVA-defined UPF, during childhood may worsen the blood lipid and BP profile (low and very low certainty, respectively), but not glycemic control (low certainty). No associations were evident between SSB consumption and blood lipids, glycemic control, or BP outcomes (all low certainty). These findings must be carefully interpreted because of low or very low certainty of evidence, small sample size of the evidence base, and lack of common core outcome set.

In recent decades, the global food system has shifted significantly toward increased intake of highly processed foods. This includes the rapidly increasing sales of UPF in LMIC, which are displacing traditional dietary patterns based on whole or minimally processed foods [39]. Nationally representative data indicate that youths in Chile, the UK, and US receive 37.9%–64.6% of their total energy intake from UPF [10–12], with total sales of UPF in middle-income countries likely to be equivalent to those in high-income countries by 2024 [40]. Emerging studies have highlighted that UPF consumption may be adversely linked to cardiometabolic health outcomes, including the blood lipid profile. Circulating lipid concentrations are influenced by the quantity and quality of fat and carbohydrate in the diet, as well as food source and degree of processing [41]. A systematic review and meta-analysis of cross-sectional studies conducted in adults recently indicated that the highest UPF consumption was possibly associated with cardiometabolic health outcomes, including reduced levels of HDL cholesterol, overweight/obesity, and the metabolic syndrome, but not hyperglycemia or hypertension [42]. In line with this, we found no association between SSB consumption and glycemic control (low certainty), but our findings indicate that higher UPF intake in children of preschool age is possibly linked to a poorer blood lipid and BP profile later in childhood [31, 32] (low and very low certainty, respectively). This is of concern given that food choices and dietary patterns established in early life have been shown to significantly track into adulthood [16], alongside cardiometabolic disease risk factors [6]. Furthermore, findings from the prospective Framingham Offspring and NutriNet-Santé cohort studies both highlight that intake of UPF is positively associated with risk of incident CVD [43, 44]. This emphasizes the importance of developing effective strategies to prevent excessive consumption of discretionary foods likely to be classified as UPF during childhood. This is particularly important for children in LMIC who are already experiencing a large problem of NCD-related premature deaths [45, 46] associated with increased consumption of energy-dense, nutrient-poor UPF, and SSB which often displace macro- and micronutrient-rich whole foods and contribute to multiple forms of malnutrition (i.e., presence of undernutrition and micronutrient deficiencies alongside overweight/obesity) [47]. NCD risk in adult life is exacerbated among those exposed to the double burden of malnutrition (early undernutrition followed by the onset of overweight in later life) in LMIC populations [48], including an increased presence of dyslipidemia, higher BP, and insulin resistance [49].

Biological mechanisms through which UPF affect energy intake and cardiometabolic disease risk are not fully understood, but are likely to be multifactorial (for detailed review, see [41]). Beyond their nutrient profile (e.g., high energy density, presence of free sugars, saturated or *trans* fats, low fiber content), the health effects of these foodstuffs may be influenced by their physical structure (i.e., absence of a natural food matrix), chemical (e.g., additives, artificial sweeteners, neo-formed contaminants, glycemic index, and load) content and packaging materials [41]. For example, heat-related ultra-processing of foods produces neo-formed contaminants, including acrylamide and acrolein, which could also be implicated in the development of CVD [42]. However, some contend that the health effects of excessive intake of UPF, including discretionary foods, may be because of their energy-dense, nutrient-poor composition, rather than the nature and degree of processing [50]. Indeed, further investigation is warranted to understand if the concept of UPF can inform dietary guidelines beyond traditional approaches to the study of diet and NCD risk [51, 52].

Strengths and limitations

Strengths of this work include focusing on a less-extensively studied age group, the a priori–deposited protocol, the comprehensive literature search of 3 databases with no language restrictions, use of ROBINS-I for risk of bias assessment, and the GRADE certainty of evidence judgment. Several limitations also warrant discussion. There was an absence of suitable randomized controlled trials (RCTs). However, although well-conducted RCTs could be viewed as the optimal design for minimizing confounding and selection bias, subjecting participants to dietary treatments that have suspected adverse effects might be considered unethical, particularly in vulnerable childhood populations. Additionally, the certainty of evidence for the limited number of prospective cohort studies was rated as low or very low. Thus, the results should be interpreted cautiously. It was not possible to carry out a meta-analysis on specific cardiometabolic disease risk outcomes because methodological heterogeneity was too high across the limited included studies; the main issues were different dietary assessment methods, different recall period, different units of measurements, and definition of the exposure (typology of food item/food group). Although we aimed to minimize typical bias in grading by using standardized methods and transparent reporting, we acknowledge that

assessment of risk of bias and certainty of evidence is subjective. Finally, NOVA classification of foods presents challenges; it may be affected by insufficient detail collected about food items in conventional dietary assessment methods and is influenced by subjective coding of foods [50–52]. Therefore, misclassification of foods and potential under- or over-estimation of UPF exposure in the observational studies included in our review cannot be excluded.

Implications and future directions

More research is needed in this area to improve our understanding of the impact of childhood intake of unhealthy foods, particularly UPF, on cardiometabolic health outcomes. To improve the certainty of evidence, future longitudinal studies should be specifically designed to assess the effects of UPF consumption in childhood populations, with longer exposure periods, and a common agreed set of fasting clinical outcomes related to cardiometabolic disease risk, including blood lipid profile (TC, HDL cholesterol, LDL cholesterol, and TAG concentrations), markers of glycemic control (glucose, insulin, and HOMA-IR), and (systolic and diastolic) BP. The standardization of criteria and exposure measures to classify processed foods on a group-by-group level should also be considered because this approach would help to identify specific UPF groups that are most detrimental to cardiometabolic health [53]. In support of this, it was reported that the association between UPF consumption and cardiometabolic disease risk markers differed significantly depending on the food processing-based classification system used to analyze data from the PREDIMED-Plus Cohort [54]. The unit of measure also requires consideration in future studies. As acknowledged by Srour et al [44], there is no ideal weighting method for UPF. The authors [44] used a weight ratio (% g/d), rather than an energy ratio because this approach accounted for low-energy/nonenergy–yielding UPF like artificially-sweetened beverages and nonnutritional attributes of these foodstuffs (e.g., additives, physical structure, neo-formed contaminants). In agreement with Srour et al. [44] it is proposed that studies should also conduct sensitivity analysis to assess energy ratio (%EI). To capture long-term dietary intake of UPF, it is recommended that observational studies should conduct repeated dietary assessment over time to capture variation in habitual dietary intake. Wider implementation of the STROBE Nutritional Epidemiology reporting guidelines is warranted to enhance future evidence syntheses [55].

Further understanding of the relative harm related to the nutritional composition, food additives, physical structure, and other characteristics of UPF, and what mechanisms might underlie the effects that are observed, is needed to help optimize levels of processing and product reformulation [41]. Because the progression and development of cardiometabolic disorders is complex and involves multiple pathways, further investigation is warranted to examine the impact of UPF, and their above mentioned characteristics, on vascular function, systemic inflammation, oxidative stress and gut microbiome composition and barrier function [41]. Although it may not be feasible to conduct RCTs with hard end points in young populations because of ethical constraints, these investigations may be feasible in healthy adult populations (for example, [56]). The incorporation of "omics" technology into traditional nutritional epidemiology (i.e., adoption of a systems epidemiology approach) should also be considered [57] because this approach may help to identify biological mechanisms through which UPF may potentially influence cardiometabolic health beyond traditional dietary risk factors.

Measures to promote consumption and better access to unprocessed or minimally processed foods are warranted (e.g., subsidy strategies). As recently highlighted by Tobias and Hall [58] policies aimed at reducing or eliminating UPF from the global food system may be unrealistic. Indeed, ultra-processing has potential to reduce public health risks related to food safety and security [58, 59], which are of particular concern in LMIC. For example, industrial food processing can improve palatability, extend product shelf-life, reduce waste, the need for access to refrigeration and cooking facilities and associated costs, enhance the nutrient profile (food fortification) and reduce the risk of microbial contamination [20, 50, 60]. It is imperative for public health policies focused on industrial food processing to consider the heterogeneity of UPF and prioritize some food categories over others [58]. A balanced policy approach that encourages beneficial food processing while reducing intake of UPF that have little nutritional value is needed, particularly in LMIC that face an increasing double (or triple) burden of malnutrition [61, 62]. Global public health actions should include targeted product reformulation, as well as taxation and front-of-pack product labeling of UPF or discretionary foods with limited nutritional value (including SSB), and restriction of promotions and marketing strategies to advertise these foodstuffs, particularly those targeted at children [53, 58, 63]. Finally, the environmental impact of UPF has also recently been highlighted. It is of utmost importance to develop public policies and actions to reduce production and consumption of UPF with limited nutritional value from a human and planetary health perspective [64].

In conclusion, a greater consumption of unhealthy foods and beverages, specifically NOVA-defined UPF, during childhood may worsen the blood lipid and BP profile (low and very low certainty, respectively). Further investigation is needed to define associations between childhood intake of UPF and dyslipidemia and BP with stronger level of certainty. However, public health actions should aim to reduce exposure to discretionary foods likely to be classified as UPF during early life, given that dietary patterns and cardiometabolic disease risk factors have been shown to track into adulthood. No association was evident between unhealthy food and beverage consumption and glycemic control indicators (low certainty). However, because of limited number of studies and observational study designs, these findings should be interpreted with caution. This review highlights the need for more high-quality RCTs and prospective cohort studies that purposefully assess the effects of unhealthy food and beverage exposure during childhood on cardiometabolic disease risk biomarkers. Evidence from low-income countries is also warranted.

Data Availability

Data described in the manuscript will be made available upon request pending.

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Appendix A. Supplementary data

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