

The association between sugar intake during pregnancy and allergies in offspring: a systematic review and a meta-analysis of cohort studies

Adyya Gupta , Ankur Singh, Roshan L. Fernando, Shyamali C. Dharmage, Caroline J. Lodge,[#] and Nilakshi T. Waidyatillake[#]

Context: It has been hypothesized that a mother's diet during pregnancy may modulate her offspring's immune system development and lead to development of allergic diseases among offspring. However, the evidence for this is unclear and inconclusive. **Objective:** This systematic review was undertaken to examine the weight of evidence for causality from cohort studies on the association between maternal free sugar intake during pregnancy and development of allergies in offspring. **Data Sources:** Using a systematic search strategy, PubMed, SCOPUS, and Web of Science databases were searched from inception to May 2020. **Data Extraction:** For the reporting of this systematic review, the PRISMA guideline was followed. Studies examining maternal sugar consumption during pregnancy (using self-reported data) and the development of allergic diseases among offspring (infancy to 5 years) were included. **Data Analysis:** The Newcastle–Ottawa Scale quality assessment tool was used to assess the study quality. Meta-analysis was conducted using a random-effects model to synthesize the findings. Of 159 publications identified from the search, 5 articles with 4 unique cohort studies were included in this systematic review. The limited meta-analysis showed that a mother's increased free sugar intake during pregnancy was associated with an increased risk of developing asthma in offspring (odds ratio 1.07 [95% CI, 1.00 to 1.14; $I^2 = 0\%$]). High free sugar intake by the mother during pregnancy was also associated with increased odds of offspring (to age 7.7 years) developing other common allergies, including allergic rhinitis, atopy and eczema, wheeze, and food allergies. **Conclusion:** From the limited evidence, this review suggests that high free sugar consumption during pregnancy may be associated with the development of allergies in offspring. Clinical guidelines and public health policy recommendations for maternal diet in pregnancy should include advice about reducing free sugar intake

Affiliation: A. Gupta is with the Deakin University, Geelong, Global Obesity Centre, Institute for Health Transformation, School of Health and Social Development, Faculty of Health, Deakin University, Victoria, Australia. A. Singh is with the Center for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia. R.L. Fernando is with the Tri Star Medical Group, Epping, Victoria, Australia. S.C. Dharmage and C.J. Lodge are with the Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia. N.T. Waidyatillake is with the Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia and the Department of Medical Education, Melbourne Medical School, The University of Melbourne, Melbourne, Victoria, Australia.

[#]C.J.L. and N.T.W. contributed equally to this review.

Correspondence: A. Gupta, Institute for Health Transformation, School of Health and Social Development, Deakin University, 221 Burwood Highway, Burwood, Victoria 3125, Australia. E-mail: adyya.gupta@deakin.edu.au.

Key words: allergy, offspring, pregnancy, sugar intake.

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due to a possible association with allergies in offspring. However, recommendations should be made with caution considering other maternal and fetal risk factors.

INTRODUCTION

Noncommunicable diseases (NCDs) such as heart disease, stroke, cancer, diabetes, and chronic lung disease account for almost 70% of all deaths worldwide.¹ Despite being largely preventable,¹ NCDs are highly prevalent. Unhealthy diet, specifically diet high in free sugars, is a leading risk factor for obesity, and type-2 diabetes. According to the World Health Organization (WHO), the term “free sugars” refers to all monosaccharides and disaccharides added to foods by the manufacturer, cook, or consumer, plus the sugars that are naturally present in honey, syrups, and fruit juices.² The World Health Organization recommends that free sugar intake be less than 10% and less than 5% of total energy intake for children and adults, to prevent development of NCDs.² However, the recommendations of national governments vary considerably across countries.³ Furthermore, no specific recommendations exist for sugar intake during pregnancy.

Previous findings suggest that there might be a critical window of exposure to intake of foods and nutrients that include sugar during pregnancy that puts the developing fetus at risk for allergies.⁴ While previous studies have reported equivocal associations between maternal intake of fruits and vegetables,⁵ dairy products,⁶ meat and fish,⁷ and spreadable fats⁷ during pregnancy and the risk of development of allergies in offspring, there is no clear evidence on the association between maternal free sugar intake and the risk of development of allergies in offspring. Some studies suggest an increased risk between the consumption of free sugars in the form of sugar-sweetened beverages and the development of respiratory diseases such as allergic rhinitis, chronic bronchitis, and asthma.^{8–10}

There have been several theories suggesting a mechanistic role of sugar consumption in the development of allergic diseases. Sugar (or specifically fructose) is said to activate a systemic inflammatory response⁹ or trigger symptoms¹¹ leading to development of allergies. Another potential mechanism is through the mediating effect of overweight and obesity that may trigger allergic reactions.¹² There is substantial evidence showing that sugar-sweetened beverage consumption leads to overweight and obesity, both among children and adults.¹³ It has been hypothesized that a mother's diet during pregnancy may modulate her offspring's immune

system development and lead to development of allergic diseases among offspring through overweight and obesity.¹⁴ However, the evidence for these mechanistic pathways remains inconclusive.

To date there is no comprehensive evidence quantifying the plausibility of the association between maternal free sugar intake during pregnancy and the development of offspring's allergic diseases. Importantly, WHO does not provide information on specific limits for (free) sugar consumption for pregnant women. Thus, this systematic review examines the weight of evidence for causality from cohort studies on the association between maternal free sugar intake during pregnancy (from conception until birth) and the development of allergies in offspring.

METHODS

A review protocol was developed a priori and registered in PROSPERO (The International prospective register of systematic reviews; registration number CRD42018115983).¹⁵ For reporting of this systematic review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline was followed¹⁶ (Appendix S1 in the Supporting Information online: PRISMA checklist).

Search strategy

Using a range of key words and MeSH terms based on sugar intake during pregnancy and development of allergies in offspring, the search strategy was first developed for PubMed and then adapted for 2 other databases: SCOPUS and Web of Science. Search terms included: (matern* OR antenatal OR pregnan* OR perinatal) AND (child* OR childhood OR early life OR infan* OR offspring*) AND (sugar OR sweet* OR fructose OR carbonated beverages OR added sugar* OR free sugar*) AND (eczema OR atop* OR asthma* OR hyperreactive* airway OR rhinitis OR hay fever OR allergic rhinitis OR food allergy OR food sensitization OR sensitization) (Table S1 in the Supporting Information online: Search strategy). A manual search through the reference lists of the included articles was also conducted.

Inclusion/exclusion criteria

All peer-reviewed articles published from inception to May 2020 in English were included. To address the research question, study selection criteria were developed using a modified PICOS (population, intervention/exposure, comparison, outcome, and study context) format (Table 1). All articles analyzing cohort data were included. Letters to the editor, conference abstracts, and reviews were excluded. No exclusions were based on race, culture, ethnicity, or geographical location. Articles in which the population being studied was pregnant mothers and offspring (median age from 0–5 years of age) were included. Five years was applied as the upper bound of the age limit for offspring to include pre-school children who are not exposed to diet away from the home and who do not yet have a dietary pattern of their own. But several articles that estimated offspring allergies at different time points beyond 5 years of age were included, and the estimates assessed at the latest age (7 years) were considered in the analysis. No search terms were applied in the search strategy to limit the search to articles with age up to 5 years, instead this was searched at the title and abstract screening stage. Articles that reported free sugar consumption among pregnant women (in any trimester) as exposure were included. In this review, articles with free sugar consumption assessed in the form of table sugar, confectionery food, processed food, fructose, juice, or fizzy drinks as exposure were included in the review. Articles investigating artificial sweeteners were excluded. The outcome measure was development of allergic disease among offspring assessed by any method (parental history, doctor diagnosed, or questionnaire based).

Article selection

Two authors (A.G. and N.W.) independently screened article titles and abstracts for detailed review of the eligible articles. Following the removal of the duplicates,

the full texts were retrieved and assessed against the selection criteria. All disagreements were resolved through discussions between A.G. and N.W., and a consensus was reached.

Quality assessment and data extraction

The quality of included articles was assessed using the Newcastle–Ottawa Scale quality assessment tool.¹⁷ Based on the Newcastle–Ottawa Scale, each article's quality was graded as good, fair, or poor quality by scoring it between 0 (lowest methodological quality) and 9 (highest methodological quality) using the tool criteria across 3 domains: selection, comparability, and outcome. The scores were summed for each article across all domains to assess the total score. The article quality was graded as good quality (if articles received 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome domain); fair quality (2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome domain), or poor quality (0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome domain) that represented the overall risk of bias in the article. Additionally, selective reporting was investigated in the included studies by looking into the study itself and within the study protocols (if available). Before data extraction, a Directed Acyclic Graph (DAG) was created to visualize possible confounding factors and mediators for the association between maternal free sugar intake during pregnancy and development of allergies in offspring (Fig. S1 in the Supporting Information online: DAG). Data extracted included information on the first author, publication year, country, study design, sample size, exposure and outcome definitions and ascertainment, details of confounders included in the analysis, study results, and author conclusions. Both the qualitative and quantitative summaries (effect estimates as

Table 1 PICOS criteria for inclusion and exclusion of studies

Parameter	Inclusion criterion	Exclusion criterion
Population	Pregnant mothers (in any trimester) and offspring (median age from 0–5 y of age) of any race, culture, ethnicity, or geographical location	Non-English-language publications
Intervention/exposure	Free sugar consumption (assessed in the form of table sugar, confectionery food, processed food, fructose, juice, or fizzy drinks)	Artificial sweeteners
Comparator(s)/control	None	None
Outcome	Allergic disease among offspring (including eczema, wheeze, atopy, asthma, hyper-reactive airway, allergic rhinitis, hay fever, food allergy, food sensitization)	None
Study context	Cohort studies conducted in any country around the world	Letters to the editor, conference abstracts, and reviews

odds ratios with 95% confidence intervals used for meta-analysis) for the association between the exposure and outcome were extracted from each article and are presented in Table 2.^{18–22}

Data analysis

Meta-analysis was conducted using a random effects model to calculate summary adjusted odds ratio estimates and 95% CIs for the entire sample and for prespecified subgroups, including age of child, type of allergies in offspring, and maternal intake of food containing added and/or free sugar. The I^2 was estimated to assess the heterogeneity of the pooled estimate (>75% was considered to indicate high statistical heterogeneity).²³ Random effects meta-analysis was performed using the Stata 16.0 statistical software package (StataCorp, College Station, Texas, USA).

RESULTS

A total of 159 published articles were identified from database searches (Fig. 1: PRISMA flowchart).^{18–22} Following the removal of duplicates ($n = 42$), title and abstract screening was conducted for 116 articles. Of these, 31 articles underwent full-text review. Of these, 26 articles were excluded on full-text screening because they either did not report specifically on a mother's free sugar intake during pregnancy, or the risk of developing allergy among offspring (infants to 7 years of age). As stated in the protocol, articles in which the median age of offspring was up to 5 years were included, but several articles estimated offspring allergies at different time points beyond 5 years of age, and the estimates assessed at the latest age (7 years) were included. The remaining 5 articles representing 4 unique cohort studies^{18–22} were considered eligible for inclusion in the review. Two articles^{18,21} analyzed the same cohort study – The Avon Longitudinal Study of Parents and Children (ALSPAC), and one article¹⁹ estimated hazard ratios (HRs) for asthma and wheeze, and these estimates were not included in the analysis. This is because HR analyses time to event outcomes, whereas odds ratio does not.²⁴

Overview of included articles

Table 2 shows the characteristics of the 5 articles^{18–22} (representing 4 cohort studies) included in this review. Of these, 2 articles were based on the ALSPAC cohort in the United Kingdom^{18,21} and there was one article from each of: the USA,²² based on Project Viva study; Finland,¹⁹ based on the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study and; Korea,²⁰ based on the COhort for Childhood Origin of

Asthma and allergic diseases (COCOA) study. The mother–child pairs sample size ranged from 1068²² to 14 062.²¹ All the articles reported on maternal diet and/or dietary patterns of consuming foods and drinks containing free sugar during pregnancy using prevalidated food frequency questionnaires (FFQs).

Exposure assessment of the included articles (sugar intake)

There were significant variations in the assessment of a mother's free sugar intake across articles. Data on maternal diet in pregnancy were collected using FFQs covering a range of commonly consumed food items. However, the FFQs differed based on their number of questions (110 questions,²¹ 181 questions¹⁹) and time of administration (26 wks of gestation²⁰ and 32 wks of gestation^{18,21}). Only 2^{19,22} of 5 studies collected maternal sugar intake (exposure) data retrospectively. However, none of the studies collected any exposure data at the same time as the outcome data (development of allergic diseases among offspring). Also, in the articles, the threshold of free sugar consumption frequency varied from less than once per month, to weekly; and was assessed as both a continuous and a categorical variable. Mother's free sugar intake was quantified in various forms such as standard portion sizes; total energy and nutrients as either part of the confectionery diet (high in baked and sugary products),^{19–21} free sugar,¹⁸ sugar-sweetened beverages,²² and fruit juice and fructose.^{19,22}

Outcomes assessment of the included articles (allergic diseases)

The outcome measures included in the articles were doctor-diagnosed/self-reported asthma, wheezing, atopy, eczema, allergic rhinitis, and food allergy, all assessed at different ages. Self-report asthma was defined as a positive response to standardized International Study of Asthma and Allergies in Childhood²⁵ questions on the child's history of allergic symptoms, including doctor-diagnosed asthma. Three articles measured more than 1 outcome.^{18,19,21} Asthma was assessed at 5, 7.5, and 7.7 years in 3 articles.^{18,21,22} Three articles assessed wheezing at 5,¹⁹ 7,¹⁸ and 7.5²¹ years of age; of these, 2 articles (from the 1 cohort study) assessed atopy at 7 years.^{18,21} One article assessed hay fever at 5 years and eczema at 7.5 years,²¹ and 1 article each assessed rhinitis at 7.5 years¹⁹ and food allergy at 1 year of age.²⁰

Table 2 Study characteristics of included cohort studies

Study details	Mother's sugar intake (exposure) How the exposure was ascertained	Allergies in offspring (outcome) How the outcome was ascertained	Confounding factors considered during the analysis Additional analysis such as subgroup analysis	Results (qualitative summary)	Results (quantitative summary – effect estimates)	Author conclusion																		
Shaheen et al (2009) ²¹ The ALSPAC study United Kingdom Cohort study Sample size n = 14 062 mother–child pairs	Maternal diet and dietary patterns in pregnancy (Health conscious, Traditional, Processed, Vegetarian or Confectionery) Assessed by: FFQ, which comprised of 110 questions at 32 wks of pregnancy. Dietary pattern scores were expressed in standard deviation units. Dietary patterns were assessed on following parameters: a. "Health conscious" : Salad, fruit, fruit juices, rice, pasta, oat/bran based breakfast cereals, fish, pulses, cheese, non-white bread. b. "Traditional" : vegetables, red meat, poultry.	Early wheezing phenotypes and eczema; wheezing, hay fever, eczema, doctor-diagnosed asthma and atopy. Eczema : Measured at 2.5 y, eczema was defined on the basis of a positive response to the question: "Has your child had an itchy dry skin rash in joints and creases of his/her body (eg, behind the knees, under the arms)?" Wheezing : Measured at 3.5 y, wheezing was obtained by asking the mother "In the last 12 mos, has he/she had any periods when there was wheezing with whistling on his/her chest when he/she breathed?" A similar question at 6 mos of age asked about	Energy intake, maximum smoked, infections, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, pre-pregnancy body mass index, ethnicity, age, parity, history of asthma, eczema, rhinoconjunctivitis, migraine; sex of child, gestational age, breast-fed in first 6 mos, day care at 8 mos, multiple pregnancy, pets in infancy, damp/condensation/mould, child exposed to environmental tobacco smoke at weekends, season of birth, season of FFQ completion, birth weight, head circumference, birth length.	In unadjusted analyses, the "Health conscious" dietary pattern in pregnancy was associated with an increased risk of early and later eczema and atopy. The "Health conscious" dietary pattern was also associated with a lower risk of early wheezing and asthma. In contrast, the "Processed" dietary pattern was associated with an increased risk of early wheezing and was also associated with a lower risk of atopy. On controlling for confounders, the effects were substantially attenuated and became non-significant.	<table><tr><td colspan="2">Risk of asthma at 7.5y: Adjusted (OR ± 95% CI)</td></tr><tr><td>Processed diet</td><td>0.98 (0.90, 1.07)</td></tr><tr><td>Confectionery diet</td><td>1.00 (0.91, 1.08)</td></tr><tr><td colspan="2">Risk of wheezing at 7.5y: Adjusted (OR: 95% CI)</td></tr><tr><td>Processed diet</td><td>0.92 (0.84, 1.01)</td></tr><tr><td>Confectionery diet</td><td>1.02 (0.93, 1.12)</td></tr><tr><td colspan="2">Risk of atopy at 7y: Adjusted (OR: 95% CI)</td></tr><tr><td>Processed diet</td><td>0.93 (0.85, 1.01)</td></tr><tr><td>Confectionery diet</td><td>1.07 (0.99, 1.15)</td></tr></table> ^aEstimates from Health conscious, Traditional, and Vegetarian dietary patterns were purposely not included in this review as these did not exclusively include food and drinks with free sugar(s).	Risk of asthma at 7.5y: Adjusted (OR ± 95% CI)		Processed diet	0.98 (0.90, 1.07)	Confectionery diet	1.00 (0.91, 1.08)	Risk of wheezing at 7.5y: Adjusted (OR: 95% CI)		Processed diet	0.92 (0.84, 1.01)	Confectionery diet	1.02 (0.93, 1.12)	Risk of atopy at 7y: Adjusted (OR: 95% CI)		Processed diet	0.93 (0.85, 1.01)	Confectionery diet	1.07 (0.99, 1.15)	Dietary patterns in pregnancy did not predict asthma or related outcomes in the offspring after controlling for confounders.
Risk of asthma at 7.5y: Adjusted (OR ± 95% CI)																								
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(continued)

Table 2 Continued

Study details	Mother's sugar intake (exposure) How the exposure was ascertained	Allergies in offspring (outcome) How the outcome was ascertained	Confounding factors considered during the analysis Additional analysis such as subgroup analysis	Results (qualitative summary)	Results (quantitative summary – effect estimates)	Author conclusion
	c. "Processed": meat pies, sausages, burgers, fried foods, pizza, chips, crisps, white bread, eggs, baked beans. d. "Vegetarian": meat substitutes, pulses, nuts, herbal tea. e. "Confectionery": chocolate, sweets, biscuits, cakes, puddings.	wheezing since birth. Wheezing; asthma; eczema; hay fever: At 7.5 y, the mothers were asked: "Has your child had any of the following in the past 12 mos: asthma? atopy?" Asthma: At 7.5 y, asthma was diagnosed if mothers responded positively to the question: "Has a doctor ever actually said that your study child has asthma?" and positively to one or both of the questions on wheezing and asthma in the past 12 mos. Atopy: At 7 y, atopy was defined as a positive reaction to <i>Dermatophagoides pteronyssinus</i>, cat or grass.	No additional subgroup analysis was conducted.			

(continued)

Table 2 Continued

Study details	Mother's sugar intake (exposure) How the exposure was ascertained	Allergies in offspring (outcome) How the outcome was ascertained	Confounding factors considered during the analysis Additional analysis such as subgroup analysis	Results (qualitative summary)	Results (quantitative summary – effect estimates)	Author conclusion																																										
Erkkola et al (2012) ¹⁹ Type 1 nutrition study Finland Cohort study Sample size n = 2441 Mother–child pairs	Maternal food consumption during pregnancy (fruit juice, chocolate) Assessed by a validated self-administered, semi-quantitative 181-item FFQ Designed especially for the DIPP nutrition study and reflecting the diet of Finnish women of child-bearing age Mothers received the FFQ by mail after delivery and retrospectively recorded the foods they had eaten during the month preceding their pregnancy leave, that is, the eighth month of pregnancy. The FFQ assessed the use of foods and food groups and their consumption frequency (less than once per month, number of times per month, week, or day).	Asthma: Measured using ISAAC questionnaire Wheeze: Defined as parental “yes” answer on whether the child has had any of the following during the last 12 mos: Wheezy sound in respiration; wheezy sound in respiration in connection with physical activity; difficulties in respiration in the morning on waking up; wheezy respiration without having the sniffles or respiratory infection; dry cough at nights not associated with common colds or respiratory infections. At 5 y, allergic rhinitis: Defined as sneezing, nasal congestion, or rhinitis other than with respiratory infections, accompanied by itching of the eye and tearing during the previous 12 mos.	Infants susceptible to type 1 diabetes were enrolled. Sex, place of birth, duration of gestation, maternal age at delivery, maternal basic education, smoking during pregnancy, mode of delivery, number of siblings at the time of the child's birth, parental asthma, parental allergic rhinitis, atopic eczema by 6 mos of age, pets at home by 1 y of age, duration of breast-feeding, and day care at 1 y of age. <i>Additional subgroup analysis</i> When excluding the women with history of allergy and children with eczema by 6 mos of age, from the analysis, the results remained the same.	No statistically significant associations were found between maternal food consumption during pregnancy and asthma in children by age 5. High maternal total consumption of fruit and berry juices was positively associated with allergic rhinitis in the offspring in the adjusted model. Low consumption of chocolate was positively associated with wheeze in the offspring.	<table><tr><td colspan="2">Risk of asthma at 5y: Adjusted HR (95% CI)</td></tr><tr><td>Chocolate: Lowest</td><td>1.37 (0.85, 2.22)</td></tr><tr><td>Mid-half</td><td>1</td></tr><tr><td>Highest</td><td>0.09 (0.66, 1.81)</td></tr><tr><td>Fruit juice: Lowest</td><td>1.08 (0.67, 1.74)</td></tr><tr><td>Mid-half</td><td>1</td></tr><tr><td>Highest</td><td>0.71 (0.45, 1.13)</td></tr><tr><td colspan="2">Risk of allergic rhinitis at 5y: Adjusted HR (95% CI)</td></tr><tr><td>Chocolate: Lowest</td><td>1.18 (0.85, 1.63)</td></tr><tr><td>Mid-half</td><td>1</td></tr><tr><td>Highest</td><td>1.24 (0.90, 1.70)</td></tr><tr><td>Fruit juice: Lowest</td><td>0.96 (0.70, 1.33)</td></tr><tr><td>Mid-half</td><td>1</td></tr><tr><td>Highest</td><td>1.40 (1.03, 1.90)</td></tr><tr><td colspan="2">Risk of wheeze at 5y: Adjusted OR (95% CI)</td></tr><tr><td>Chocolate: Lowest</td><td>1.36 (1.07, 1.74)</td></tr><tr><td>Mid-half</td><td>1</td></tr><tr><td>Highest</td><td>1.12 (0.88, 1.43)</td></tr><tr><td>Fruit juice: Lowest</td><td>0.97 (0.77, 1.23)</td></tr><tr><td>Mid-half</td><td>1</td></tr><tr><td>Highest</td><td>1.27 (1.00, 1.61)</td></tr></table>	Risk of asthma at 5y: Adjusted HR (95% CI)		Chocolate: Lowest	1.37 (0.85, 2.22)	Mid-half	1	Highest	0.09 (0.66, 1.81)	Fruit juice: Lowest	1.08 (0.67, 1.74)	Mid-half	1	Highest	0.71 (0.45, 1.13)	Risk of allergic rhinitis at 5y: Adjusted HR (95% CI)		Chocolate: Lowest	1.18 (0.85, 1.63)	Mid-half	1	Highest	1.24 (0.90, 1.70)	Fruit juice: Lowest	0.96 (0.70, 1.33)	Mid-half	1	Highest	1.40 (1.03, 1.90)	Risk of wheeze at 5y: Adjusted OR (95% CI)		Chocolate: Lowest	1.36 (1.07, 1.74)	Mid-half	1	Highest	1.12 (0.88, 1.43)	Fruit juice: Lowest	0.97 (0.77, 1.23)	Mid-half	1	Highest	1.27 (1.00, 1.61)	Development of allergic diseases in preschool children may be influenced by intrauterine exposure to maternal diet.
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(continued)

Table 2 Continued

Study details	Mother's sugar intake (exposure) How the exposure was ascertained	Allergies in offspring (outcome) How the outcome was ascertained	Confounding factors considered during the analysis Additional analysis such as subgroup analysis	Results (qualitative summary)	Results (quantitative summary – effect estimates)	Author conclusion								
			intakes and after exclusion of mothers with diabetes (whose offspring will have experienced high fetal exposure to glucose). To correct for potential loss to follow-up bias, inverse probability weighting was conducted and to each woman a weight was assigned that was the inverse of the probability of her selection for given values of covariates.											
Wright et al (2018) ²² Project Viva study USA Cohort study Sample size n = 1068 mother-child pairs	Maternal prenatal (first and second trimester) and early childhood (median age, 3.3 y) intake of sugar-sweetened beverages and fructose Mother's consumption of beverages during pregnancy was assessed using a semi-quantitative FFQ. Children's dietary intakes using an	Current asthma in mid-childhood (median age, 7.7 y): assessed based on asthma questions from the ISAAC. Current asthma in mid-childhood defined as the mother's affirmative response to her child's ever having a doctor's diagnosis of asthma, plus either report of wheezing or	diameter of any detectable wheal) to <i>Dermaphagoides pteronyssinus</i> , cat or grass (after subtracting positive saline reactions from histamine and allergen wheal's and excluding children unreactive to 1% histamine).	Higher maternal pregnancy intake of sugar-sweetened beverages and total fructose were associated with greater odds of mid-childhood current asthma.	<table><tr><th colspan="2">Risk of asthma at 7.7 y: Adjusted OR (95% CI)</th></tr><tr><td>Sugar-sweetened beverages</td><td>1.18 (0.96, 1.45)</td></tr><tr><td>Juice</td><td>1.12 (0.95, 1.33)</td></tr><tr><td>Total fructose</td><td>1.18 (0.94, 1.50)</td></tr></table>	Risk of asthma at 7.7 y: Adjusted OR (95% CI)		Sugar-sweetened beverages	1.18 (0.96, 1.45)	Juice	1.12 (0.95, 1.33)	Total fructose	1.18 (0.94, 1.50)	Higher sugar-sweetened beverage and fructose intake during pregnancy and in early childhood was associated with childhood asthma development independent of adiposity.
Risk of asthma at 7.7 y: Adjusted OR (95% CI)														
Sugar-sweetened beverages	1.18 (0.96, 1.45)													
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Study details	Mother's sugar intake (exposure) How the exposure was ascertained	Allergies in offspring (outcome) How the outcome was ascertained	Confounding factors considered during the analysis Additional analysis such as subgroup analysis	Results (qualitative summary)	Results (quantitative summary – effect estimates)	Author conclusion			
Kim et al (2019) ²⁰ Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) study Korea Birth cohort study Sample size n = 1628 infants	88-item semi-quantitative child FFQ previously validated among preschool-aged children, which was completed by the mothers when their children were in early childhood	asthma medication use in the past 12 mos, based on the mid-childhood questionnaire	exposures and covariates						
	A previously validated semi-quantitative FFQ was self-administered at 26 wks of pregnancy to assess maternal dietary intake.	All mothers were asked to complete a questionnaire regarding food allergies in their children at 1 y of age. All children at 1 y of age visited an allergy clinic at one of the institutions and were examined for the presence of food allergies by a pediatric allergy specialist. If there was a positive response to any of the seven questions, the pediatric allergy specialists asked more detailed questions to verify the allergic symptoms.	Maternal characteristics (maternal age, allergic history, and smoking history, including indirect contact and delivery methods) and infant characteristics (birth season, sex, presence of siblings, and atopic dermatitis at 6 mos). <i>No additional subgroup analysis was conducted.</i>	A maternal confectionery diet characterized by a high intake of baked and sugary products during pregnancy was associated with a higher prevalence of food allergies in infants.	<table><tr><th colspan="2">Risk of food allergy at 1y: Adjusted OR (95% CI)</th></tr><tr><td>Increased confectionery intake</td><td>1.52 (1.07, 2.15)</td></tr></table>	Risk of food allergy at 1y: Adjusted OR (95% CI)		Increased confectionery intake	1.52 (1.07, 2.15)
Risk of food allergy at 1y: Adjusted OR (95% CI)									
Increased confectionery intake	1.52 (1.07, 2.15)								

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; DIPP, Diabetes Prediction and Prevention; FFQ, food frequency questionnaire; HR, hazard ratio; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio.

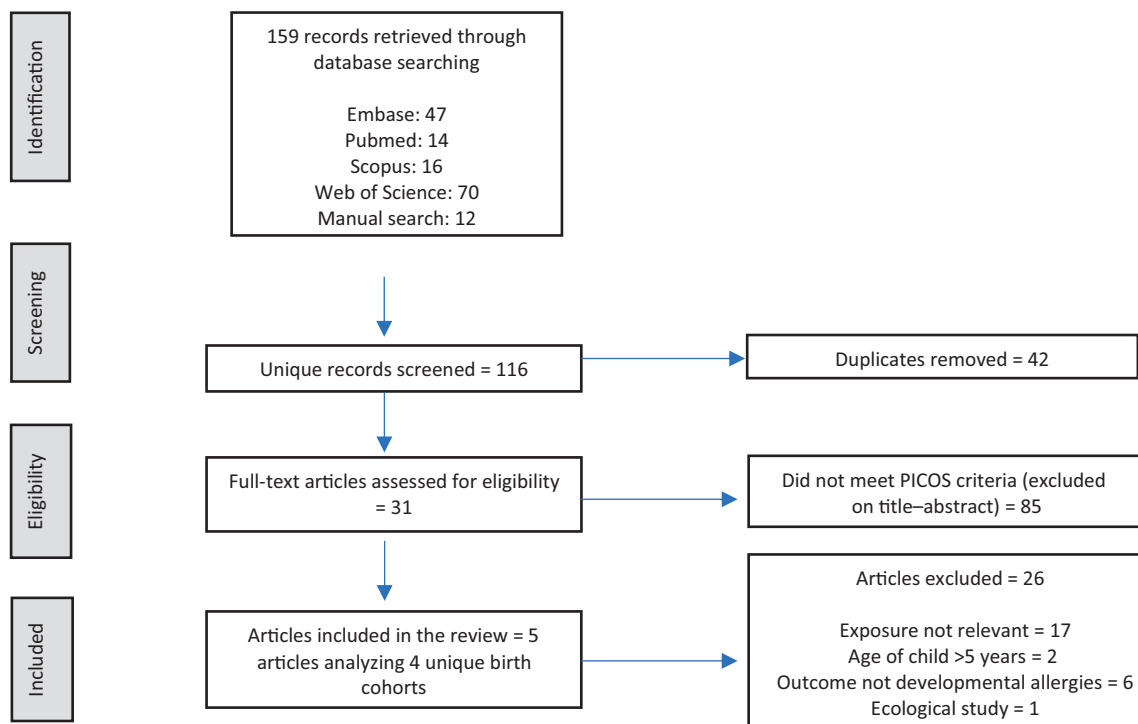


Figure 1 PRISMA flow chart.

Quality of the included articles

The risk of bias assessment resulted in 2 articles (from the 1 cohort study) scoring an overall good^{18,21} and the remaining 3 articles scoring poor ratings.^{19,20,22} The articles that scored poor ratings (≤ 6) performed poorly across 3 criteria: ascertainment of exposure, assessment of outcome, and adequacy of follow-up (Table S2 in the Supporting Information online: Quality assessment). No evidence of selective reporting was found in the included studies, as all outcomes measured were appropriately reported.

Overall findings from included articles (results of the meta-analysis)

Five articles^{18–22} assessed the association between maternal free sugar intake during pregnancy and allergies in the offspring. Overall pooled estimates for the association of maternal free sugar intake during pregnancy and allergies in the offspring was only calculated for asthma due to high heterogeneity between the studies. The pooled odds ratio of maternal increased free sugar intake during pregnancy and asthma from 2 articles^{18,22} representing 2 cohort studies was odds ratio 1.07 (95% CI, 1.00 to 1.14; $I^2 = 0\%$), suggesting that increased maternal free sugar intake during pregnancy is associated with increased odds of developing asthma in the offspring (Fig. 2).^{18,22} Among 2 other cohort studies, both deemed to have lower quality evidence due to risk of bias and confounding, the Finnish

study¹⁹ [Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Nutrition Study] using Cox proportional hazards regression found no statistically significant associations between maternal food consumption during pregnancy and asthma in offspring at 5 years of age. However, the same study found high maternal total consumption of fruit and berry juices to be positively associated with allergic rhinitis in the offspring at 5 years of age in the adjusted model. Also, this study found less consumption of chocolate to be positively associated with wheeze in the offspring at 5 years of age. The other birth cohort study in Korea²⁰ [Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) study] found a maternal Confectionery diet (characterized by a higher intake of baked and sugary products) during pregnancy to be associated with a higher prevalence of food allergies in infants [odds ratio 1.52 (95% CI, 1.07 to 2.15)].

Pooled estimates for the association of maternal free sugar intake during pregnancy and other allergies in offspring were not calculated for 3 reasons: (1) only 4 studies assessed allergic outcomes; (2) each study reported estimates for multiple outcomes, which would have overestimated the pooled results, and (3) there was high heterogeneity in the exposure and outcomes measurements (Fig. 3).^{18–22} However, visual representations (forest plots) of odds ratios of maternal increased free sugar intake (in various forms, including Confectionery diet, Processed diet, sugar-containing beverage, and free sugar) during pregnancy and allergic outcomes are

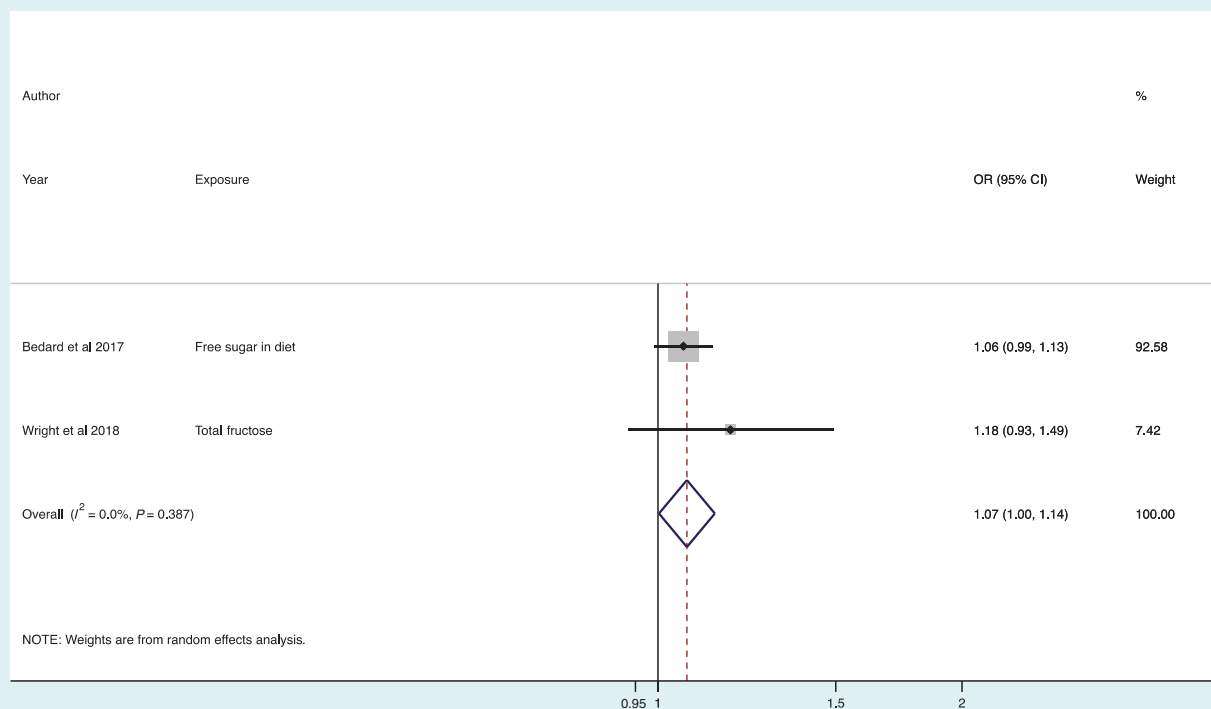


Figure 2 Meta-analysis: association between mother's sugar intake during pregnancy and asthma in offspring.

presented in Fig. 3. Furthermore, as only 4 unique cohort studies were included in the review, a statistical test to assess publication bias was not conducted.

DISCUSSION

Albeit limited by the low number and quality of the included studies, overall, this review found some evidence that maternal increased free sugar intake during pregnancy is associated with a risk of developing allergies, including allergic rhinitis, atopy and eczema, and asthma and wheeze among offspring assessed at different ages (infancy to 7.7 years).

Several theories are proposed to explain how an individual's increased free sugar intake may lead to the development of allergies. One explanation is that the free sugar content in sugar-sweetened beverages and other sugar-containing foods may lead to asthma, either through increasing adiposity, or adiposity-related pulmonary restriction and inflammation, or through adiposity-independent mechanisms.^{26–28} Another explanation is that the association could be related to the free sugar composition (sucrose, fructose), rather than the amount of free sugar intake, inducing inflammation leading to allergic reactions.^{29–31} Fructose is a major component of added sugars and is present naturally in fruit juice and in sweetened drinks (in the form of added sucrose or isolated fructose), and it has been linked with asthma in children.^{12,32}

Also, in a mouse model study, it was shown that a high-fat or high-fructose diet led to asthma through adiposity-independent mechanisms.³³ A third hypothesis to explain the link between an individual's increased free sugary-food intake and development of food allergies could be the presence of additives in the sugary food, for example sodium benzoate or sulphites. These additives have been previously shown to cause urticaria and contact dermatitis, which can trigger asthma and allergic rhinitis.³⁴ Though there is no clear indication of the mechanistic pathways explaining the relationship between maternal sugar intake during pregnancy and development of child allergies, it is plausible that in utero exposure to maternal sugar intake (either directly on the fetus or via epigenetics) could increase the risk of allergy developing in offspring.³⁵

Overall, this review suggests that maternal diet high in sugar during pregnancy may increase the risk of offspring developing allergies, particularly asthma. This is in line with previous studies that have reported that energy-dense dietary patterns (such as increased consumption of fast food, high-fat snacks, and candy) affect the development of eczema and asthma.^{36,37} It is important to note that most of the previous literature focuses on the relationship between energy-dense dietary patterns and the development of asthma and atopy through excessive weight gain, especially during pregnancy, leading to an inflammatory response of adipose tissue

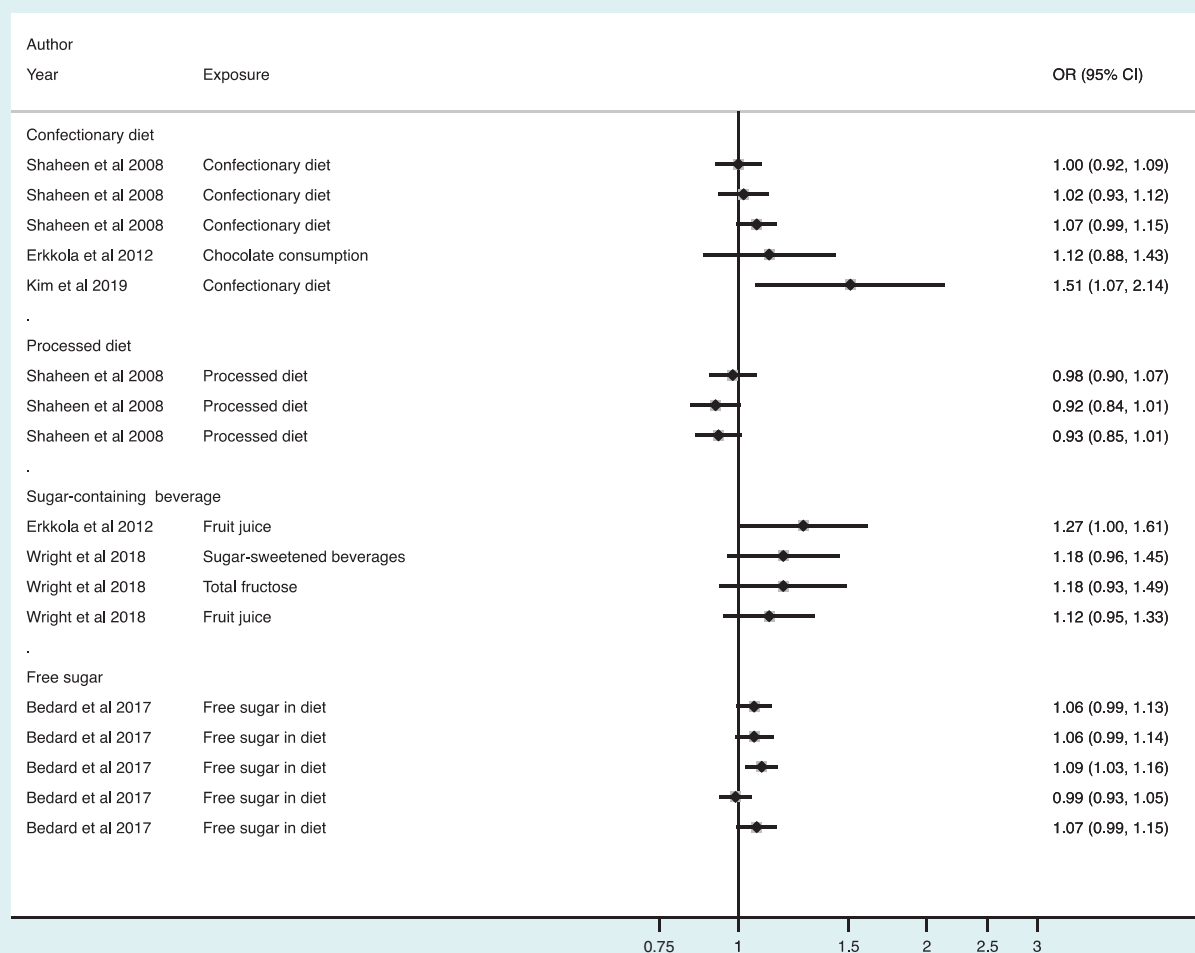


Figure 3 Forest plot showing odds ratios of mother's increased free sugar intake (in various forms) during pregnancy and allergies in offspring.

macrophages.^{38,39} However, weight gain as an explanatory factor was not explored as part of this review, but could be a possible pathway explaining the relationship between maternal sugar intake during pregnancy and development of child allergies. Furthermore, children of parents who eat a high-density/high-sugar diet are more likely to eat such a diet themselves, leading to weight gain followed by the risk of developing allergies.

Strengths and limitations of the review

Among the strengths, this review presents the most updated and collective evidence on the association between maternal increased free sugar intake during pregnancy and allergies in offspring, because the articles published from inception to May 2020 were identified using a robust search strategy and included in the review. Second, the results must be viewed with an

understanding that cohort studies can suffer with systematic sources of bias (selection, information, and confounding) that may undermine confidence in causal relationship. Creating different forest plots according to different allergic diseases (stratified by age) enabled us to better understand the age at which different allergic diseases appear. Of these, the most appropriate forest plot [presenting the odds ratios of maternal increased free sugar intake (in various forms) during pregnancy and allergies in offspring] was selected (Fig. 3).

This review has several limitations. The overall pooled results on the association of maternal increased free sugar intake during pregnancy with the development of allergic disease among offspring (except for asthma) were not calculated for 3 reasons: (1) few articles ($n=5$) were included in the review; (2) the articles were included multiple times if they reported more than one allergic outcome within the meta-

analysis, and that would have overestimated the pooled estimates; and (3) there was high heterogeneity in the exposure and outcome measurements. Thus, it was considered appropriate to not calculate pooled estimates for allergies other than asthma. Also, all studies primarily relied on parental recollection of whether their child had ever been diagnosed with asthma by a doctor. Only 2 studies^{19,22} indicated that they assessed children's asthma based on questions from the International Study of Asthma and Allergies in Childhood.²⁵ This may have led to overestimation or underestimation of true associations depending on the differential or non-differential misclassification of the exposure. Therefore, the above limitation must be taken into consideration when drawing inferences from this study. Further, as 3 of the 5 included studies were of low quality, the overall findings of this review should be interpreted with caution. Several confounding factors and mediators (Fig. S1 in the Supporting Information online: DAG) such as childhood dietary habits and maternal weight, which could possibly influence the association between maternal sugar intake and allergic outcomes, were not accounted for in individual studies. These must also be taken into consideration when interpreting the results of this review and should be explored in future studies. It is also important to consider that there was considerable heterogeneity in the measurement of free sugar intake (eg, as part of the Processed diet and the Confectionery diet, chocolate consumption, fruit juice consumption, fructose consumption, per quintile increase in free sugar consumption, and sugar-sweetened beverages consumption), and hence inferences should be drawn with some caution.

Research and policy implications

This review provides moderate quality evidence that maternal increased free sugar intake during pregnancy is associated with the development of allergic disease outcome among offspring. However, more studies on maternal increased free sugar intake during pregnancy and its possible impact on the risk of allergy outcomes in the offspring are needed. It is important that future studies collect and report exposure and outcome measures in a consistent pattern in order to make clear inferences. Increasing sugar intake among mothers during pregnancy may be associated with changes in other dietary and lifestyle characteristics. Hence, this could be a potential new area of future research. Given the high prevalence of free sugar consumption worldwide,⁴⁰ it is imperative to implement population-level measures to reduce the high free sugar intake to help prevent poor health outcomes both among children and adults. Additionally, initiating and providing equitable support

measures to vulnerable groups such as pregnant mothers to help reduce their free sugar intake to prevent allergies in offspring would be beneficial.

CONCLUSION

In conclusion, within the limitations of the present review, the results suggest that there may be an association between mother's increased free sugar intake during pregnancy and child allergic diseases. Further longitudinal research exploring the potential mechanisms for the influence of mothers' increased free sugar intake during pregnancy on child allergic disease development is warranted to strengthen the evidence. In the absence of an internationally accepted recommendation, the findings of this review are critical for informing the development of future recommendations regarding free sugar consumption during pregnancy to help prevent the development of allergies in offspring, and other sugar-related health complications.

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Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

[Appendix S1 PRISMA checklist](#)

[Figure S1 Directed Acyclic Graph \(DAG\)](#)

[Table S1 Search strategy](#)

[Table S2 Quality assessment](#)

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PRISMA 2009 Checklist

Appendix S1: The association between sugar intake during pregnancy and allergies in offsprings: A systematic review and a meta-analysis of Cohort studies

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page and Page 1,2 (main document)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2 (main document)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3 (main document)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4,5, Table 1 (main document)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4,5 and Table 2 (main document)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4 (main document)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4 (main document), Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4,5,6 (main document)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5,6 (main document)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5,6 (main document)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5,7 (main document), Appendix C
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6 (main document)



PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6 (main document)
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Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5,7 (main document), Appendix C
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6, Figure 1 (main document)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 6,7, Table 2 (main document)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 7, Appendix C
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 8-11, Table 2 (main document)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 7,8, Table 2 (main document)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 7, 8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 9-10 (main document)
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 10 (main document)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 10 (main document)
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page



doi:10.1371/journal.pmed1000097

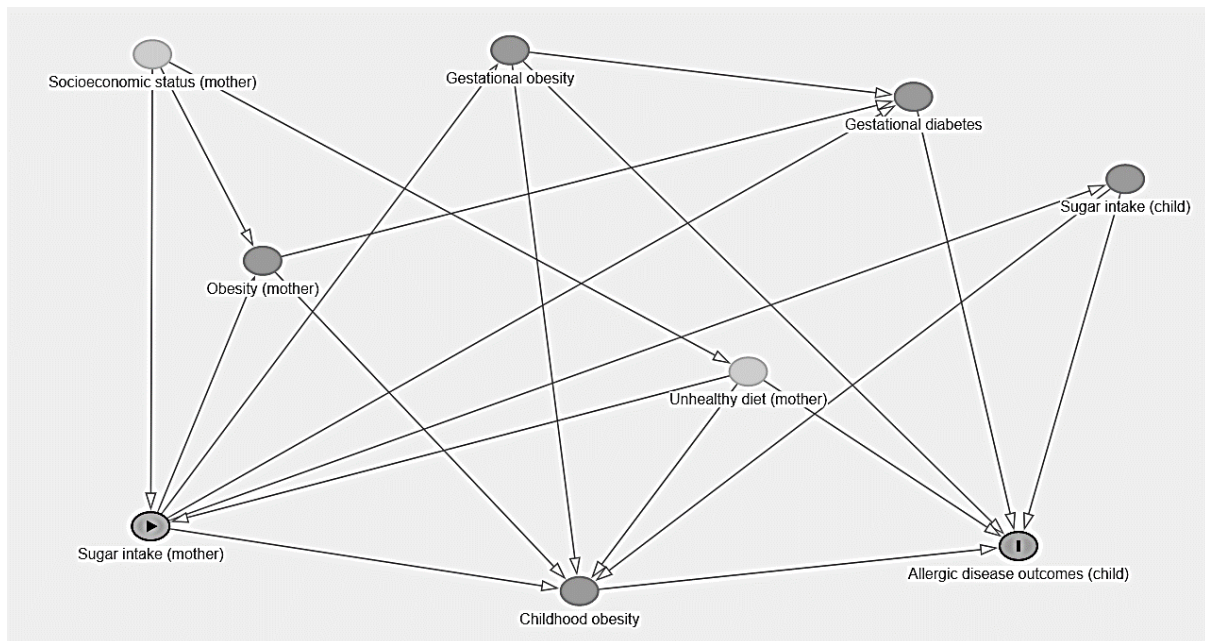
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Figure S1: Directed Acyclic Graph (DAG)

Directed Acyclic Graph (DAG) for the association between maternal free sugar intake during pregnancy and development of allergies in offspring



Exposure: Sugar intake during pregnancy (mother)

Outcome: Allergic disease outcomes (child)

Confounder: Unhealthy diet (mother), socioeconomic status (mother)

Mediators: Obesity (mother), childhood obesity, gestational obesity, gestational diabetes, sugar intake (children)

Table S1: Search Strategy

Hedge 1 (population)	AND	Hedge 2 (population)	AND	Hedge 3 (sugar intake)	AND	Hedge 3 (childhood allergic diseases)
matern* OR antenatal OR pregnan* OR perinatal	AND	child* OR childhood OR early life OR infan* OR offspring*	AND	sugar OR sweet* OR fructose OR carbonated beverages OR added sugar* OR free sugar*	AND	eczema OR atop* OR asthma* OR hyperreactiv* airway OR rhinitis OR hay fever OR allergic rhinitis OR food allergy OR food sensitization OR sensitization

PUBMED

(matern*[Title/Abstract] OR antenatal[Title/Abstract] OR pregnan*[Title/Abstract] OR perinatal[Title/Abstract]) AND (child*[Title/Abstract] OR childhood[Title/Abstract] OR early life[Title/Abstract] OR infan*[Title/Abstract] OR offspring*[Title/Abstract]) AND (sugar[Title/Abstract] OR sweet*[Title/Abstract] OR fructose[Title/Abstract] OR carbonated beverages[Title/Abstract] OR added sugar*[Title/Abstract]) AND (eczema[Title/Abstract] OR atop*[Title/Abstract] OR asthma*[Title/Abstract] OR hyperreactive* airway[Title/Abstract] OR rhinitis[Title/Abstract] OR hay fever[Title/Abstract] OR allergic rhinitis[Title/Abstract] OR food allergy[Title/Abstract] OR food sensitization[Title/Abstract] OR sensitization[Title/Abstract])

SCOPUS

TITLE-ABS (Matern*) OR TITLE-ABS (antenatal) OR TITLE-ABS (pregnan*) OR TITLE-ABS (perinatal) AND TITLE-ABS (child*) OR TITLE-ABS (childhood) OR TITLE-ABS (early life) OR TITLE-ABS (infan*) OR TITLE-ABS (offspring*) AND TITLE-ABS (sugar) OR TITLE-ABS (sweet*) OR TITLE-ABS (fructose) OR TITLE-ABS (carbonated beverages) OR TITLE-ABS (added sugar*) AND TITLE-ABS (eczema) OR TITLE-ABS (atop*) OR TITLE-ABS (asthma*) OR TITLE-ABS (hyper reactive* airway) OR TITLE-ABS (hay fever) OR TITLE-ABS (allergic rhinitis) OR TITLE-ABS (food allergy) OR TITLE-ABS (food sensitization) OR TITLE-ABS (sensitization)

WEB OF SCIENCE

TS= (matern* OR antenatal OR pregnan* OR perinatal) AND TS= (child* OR childhood OR early life OR infan* OR offspring*) AND TS= (sugar OR sweet* OR fructose OR carbonated beverages OR added sugar*) AND TS= (eczema OR atop* OR asthma* OR hyper reactive airway OR rhinitis OR hay fever OR allergic rhinitis OR food allergy OR food sensitization OR sensitization)

Table S2: Quality Assessment

Newcastle-Ottawa scale for assessment of quality of included studies – Cohort studies (each asterisk represents if individual criterion within the subsection was fulfilled)													
Quality assessment criteria	Selection				Comparability		Outcome			Overall Quality Score (Maximum = 9)	Good quality*	Fair quality**	Poor quality***
	Representativeness of sample	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study controls for age/sex?	Study controls for at least 3 additional risk factors?	Assessment of outcome	Was follow-up long enough/adequate for outcomes to occur	Adequacy of follow-up of cohorts				
Shaheen et al. (2008) ^{S1}	*	*	*	*	*	*		*	*	8	GOOD		
Erkkola et al. (2012) ^{S2}	*	*		*	*	*		*		6			Poor
Bedard et al. (2017) ^{S3}	*	*		*	*	*		*	*	7	GOOD		
Wright et al. (2017) ^{S4}	*	*	*	*	*	*		*		7			Poor
Kim et al. (2019) ^{S5}	*	*		*	*	*		*		6			Poor

***Good quality:** 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

****Fair quality:** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

*****Poor quality:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

SUPPLEMENTAL REFERENCES

- S1. Shaheen SO, Northstone K, Newson RB, Emmett PM, Sherriff A, Henderson AJ. Dietary patterns in pregnancy and respiratory and atopic outcomes in childhood. *Thorax*. **2009**;64(5):411-7.
- S2. Erkkola M, Nwaru BI, Kaila M, Kronberg-Kippilä C, Ilonen J, Simell O, et al. Risk of asthma and allergic outcomes in the offspring in relation to maternal food consumption during pregnancy: a Finnish birth cohort study. *Pediatr Allergy Immunol*. **2012**;23(2):186-94.
- S3. Bédard A, Northstone K, Henderson AJ, Shaheen SO. Maternal intake of sugar during pregnancy and childhood respiratory and atopic outcomes. *European Respiratory Journal*. **2017**;50(1).
- S4. Wright LS, Rifas-Shiman SL, Oken E, Litonjua AA, Gold DR. Prenatal and Early Life Fructose, Fructose-Containing Beverages, and Midchildhood Asthma. *Annals of the American Thoracic Society*. **2018**;15(2):217-24.
- S5. Kim YH, Kim KW, Lee SY, Koo KO, Kwon SO, Seo JH, et al. Maternal perinatal dietary patterns affect food allergy development in susceptible infants. *The journal of allergy and clinical immunology In practice*. **2019**.