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Non-Nutritive Sweeteners and Metabolic Health Outcomes in Children: A Systematic Review and Meta-Analysis

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Objective To systematically assess and quantitatively synthesize the literature regarding the association of consumption of non-nutritive sweeteners (NNS) during childhood with negative metabolic health outcomes.

Study design Following the PRISMA guidelines, published literature was systematically reviewed. Eligible studies (N = 13) were identified through the screening of over 2500 publications. Random-effects meta-analyses were conducted on the association of NNS consumption with body mass index (BMI) increase. Sensitivity and subgroup analyses by sex were also undertaken.

Results Consumption of NNS during childhood and adolescence was associated with an increase in BMI (OR 1.15, 95% CI 1.06-1.25); the OR was similar in sensitivity analyses. The associations were positive but marginally significant in subanalyses by sex. The qualitative assessment of existing literature showed nonsignificant associations with other components of metabolic disease, such as waist circumference, fat mass accumulation, and type 2 diabetes.

Conclusions Systematic assessment of observational studies showed no association of NNS intake during childhood with fat mass accumulation and waist circumference and a small, but statistically significant association with BMI increase. Inherent methodological weaknesses of to-date published investigations, including mainly underpowered size to explore the hypothesis, call for more research. *(J Pediatr 2018;■■:■■-■■).*

The prevalence of overweight and obesity have significantly risen among children and adolescents.[1] In the US, the prevalence of obesity is estimated as high as 17% among children aged 2-19 years in 2011-2014, with an increasing prevalence among adolescents from 10.5% in 1988-1994 to 20.6% in 2013-2014.[2] Because obesity is strongly implicated in the pathogenesis of severe chronic comorbidities including cardiovascular disease, hypertension, type 2 diabetes, and cancer, identifying strategies to reduce the prevalence of obesity and subsequent health consequences in childhood is a public health priority.[3]

Consumption of sugar-sweetening beverages has been strongly linked to obesity and other negative health outcomes.[4,5] Thus, a growing body of research has been focused on the beneficial effects of non-nutritive artificial sweetener (NNS) substitutes as a means of reducing sugar-sweetening beverage consumption.[6] The total amount of NNS consumed among children aged 2-19 years and the prevalence of consumption nearly tripled over the last decade. Specifically, the prevalence of NNS consumption has risen from 8.2% during the period 2001-2002 to 22.6% during the period 2009-2010 ($P < .001$).[7] However, the biological consequences of NNS remain controversial with some studies suggesting that they may be also associated with the same chronic diseases linked to sugar consumption.[8] Plausible mechanisms that may explain these associations include (1) interference of NNS with learned responses that contribute to control glucose, (2) induction of glucose intolerance through interference of NNS with gut microbiota, and (3) interaction of NNS with sweet-taste receptors involved in glucose absorption and trigger of insulin secretion.[9,10] However, this could also be an example of reverse causation where obese children and adolescents are more likely to choose beverages with NNS in an effort to control weight.

Several systematic reviews have been conducted regarding the metabolic effects of NNS exposure during childhood yielding inconclusive results.[11-15] The aim of this study is to systematically identify, critically appraise, and quantitatively synthesize current evidence regarding the potential association of NNS consumption during childhood and adolescence with negative metabolic outcomes, including obesity and diabetes.

Methods

This systematic review was conducted in accordance with the PRISMA[16] guidelines that recommends that a full electronic search strategy for at least 1 major

BMI	Body mass index
NNS	Non-nutritive artificial sweetener

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database to be presented (**Table I**; available at www.jpeds.com).[17] Medline was searched via PubMed up to February 12, 2017 using the following search algorithm: (nonnutritive OR non-nutritive OR artificial OR low-calorie OR [low AND calorie] OR sweetening OR sweetener* OR sweetened OR beverage* OR stevia OR stevioside OR sucralose OR neotame OR saccharin OR acesulfame OR aspartame OR [sugar AND substitute*]) AND (childhood OR child OR children OR pediatric OR pediatrics) AND ([cardiovascular AND risk] OR (metabolic AND [effect OR outcome]) OR diabetes OR obesity OR obese OR diabetic OR overweight). The reference list of eligible articles and relevant reviews were hand searched ("snowball" procedure) for additional publications. No language or publication year restrictions were applied.

Eligible were considered observational (case-control or cohort) studies on the association of NNS consumption in children/adolescents with risk of obesity and diabetes. The term "non-nutritive artificial sweeteners" included any artificially sweetened item consumed during childhood. Excluded were randomized clinical trials, case reports, case series, in vitro studies, and animal studies due to their different methodological approach. Eligible studies were evaluated for potential overlap, based on geographic location, data sources, diagnostic period, age range, and number of cases. Two pairs of reviewers, blinded to each other, completed the study selection, whereas disagreements were resolved by team consensus.

Extracted data included publication details (year, first author, title, journal), information on study characteristics (study design and geographic area, mean age/age range, percentage of male subjects, sample-size, ascertainment of cases, and comparison groups), type and assessment of exposure, control for potential confounding factors, ascertainment of outcome, and statistical analysis variables (methodology, results). Authors were also contacted for missing data.

Eligible studies were evaluated on quality with the Newcastle-Ottawa Scale.[18] Quality criteria included the follow-up period which was considered adequate at a minimum of 1 year and >80% percentage of completeness. Pairs of reviewers conducted blindly the data extraction and quality assessment; thereafter, consensus was reached for disagreements.

Statistical Analyses

A quantitative synthesis of results was available only for studies exploring the association of NNS consumption (any vs no consumption) with body mass index (BMI) increase treated as an ordinal variable (per annual increase in BMI in kg/m^2). Because effect estimates for NNS intake differed between cohort studies, reported β estimates and t values were converted to ORs and 95% CIs to generate a standardized metric.[19] The ORs and 95% CI of the included studies were pooled and summary effect estimates were calculated. The random-effects (DerSimonian–Laird) model[20] was implemented; between-study heterogeneity was measured by I^2 and Cochran Q,[21] with $P < .10$ set as significance level.

Sensitivity analyses, that is repetitions of the primary meta-analyses substituting alternative assumptions, were performed, retaining only the high quality studies, namely those missing <2 points in the Newcastle-Ottawa Scale evaluation and the studies presenting adjusted effect estimates. Subanalyses, namely analyses including a smaller group of studies, on the association of NNS consumption and BMI increase by sex were also conducted.

Meta-analyses were not feasible for the remaining exposures and outcomes because of the highly heterogeneous group of available studies in terms of inherent characteristics (multiple NNSs, variable doses and routes of NNS administration, multiple disease outcomes), selection of an appropriate control group, use of adjusting factors, and alternative methods of statistical analysis; thus, a qualitative synthesis of published data was performed.

An Egger test was used for the evaluation of publication bias[22] (significance level was set at $P < .05$) and respective funnel plots were designed.

Statistical meta-analysis was performed using the Stata software v 13.0 (StataCorp, College Station, Texas).

Results

The initial search strategy yielded 2809 results, whereas 15 additional articles were identified via snowball. After screening the full-text of 91 potentially eligible articles, 13 met the preset eligibility criteria[23-35]; the flow chart of the selection process is graphically presented in **Figure 1**.

The characteristics of the eligible studies are summarized in **Table II**. All included articles were cohort studies with the majority of them conducted in the US[24-30,32-36] and 2 in the United Kingdom,[23,31] yielding a grand total of 37 966 cases. The mean age at enrollment ranged from 2 to 17 years and duration of follow-up from 6 months to 10.5 years. Consumption of NNS was assessed through validated food frequency questionnaires during a record period varied from 24 hours to 30 days before the interview time.

The quality of cohort studies was satisfactory (no cumulative loss >2 points in Newcastle-Ottawa Scale). Factors that mainly compromised study quality were the unadjusted effect estimates and incompleteness of follow-up (**Table III**; available at www.jpeds.com).

"Any" compared with "no" consumption of NNS during childhood and adolescence was positively associated with increase in BMI (OR 1.15, 95% CI 1.06-1.25; **Figure 2**) based on the synthesis of 9 highly heterogeneous studies without evidence for publication bias ($P = .09$, **Figure 3**; available at www.jpeds.com). Sensitivity analyses by study quality (6 study arms; $OR_{high\text{-}quality}$ 1.07, 95% CI 1.00-1.14) and level of adjustment (7 study arms; $OR_{adjusted}$ 1.18, 95% CI 1.07-1.30) yielded similar results (results not tabulated). The association was positive, but marginally significant when subanalyses by sex were performed (OR_{male} 1.16, 95% CI 0.93-1.46; 3 study arms/ OR_{female} 1.48, 95% CI 0.76-2.90; 3 study arms).

Among the 2 studies, which could not be quantitatively synthesized, an analysis[35] of the data from the National Health and Nutrition Examination Survey 1999-2002 on children 2-5 years old (N = 1572) found a significant association of soda intake with energy intake ($P < .001$) but not with BMI ($P = .88$).

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