Early Exposure to Nonnutritive Sweeteners and Long-term Metabolic Health: A Systematic Review

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abstract

CONTEXT: Nonnutritive sweetener (NNS) consumption is increasing among children, yet its long-term health impact is unclear, particularly when exposure occurs during early life.

OBJECTIVE: To synthesize evidence from prospective studies evaluating the association of early-life NNS exposure and long-term metabolic health.

DATA SOURCES: Medline, Embase, and Cochrane Library (inception to July 2015).

STUDY SELECTION: We aimed to include randomized controlled trials (RCTs) evaluating NNS-based interventions and prospective cohort studies reporting NNS exposure among pregnant women, infants, or children (<12 years of age), with a minimum study duration of 6 months.

DATA EXTRACTION: The primary outcome was BMI; secondary outcomes included growth velocity, overweight/obesity, adiposity, and adverse metabolic effects. Study quality and risk of bias were evaluated using validated assessment tools.

RESULTS: We identified 6 eligible cohort studies and 2 RCTs (n = 15 641 children). Half of the cohorts reported increasing weight gain or fat mass accumulation with increasing NNS intake, and pooled data from 2 cohorts showed a significant correlation with BMI gain (weighted mean correlation 0.023, 95% confidence interval 0.006 to 0.041). RCTs reported contradictory effects on weight change in children receiving NNSs. No eligible studies evaluated prenatal or infant NNS exposure.

LIMITATIONS: Meta-analysis was limited because of the small number of eligible studies and heterogeneity of populations and outcomes.

CONCLUSIONS: There is limited and inconsistent evidence of the long-term metabolic effects of NNS exposure during gestation, infancy, and childhood. Further research is needed to inform recommendations for the use of NNSs in this sensitive population.

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Ms Reid drafted the initial protocol and the initial manuscript; Ms Reid and Dr Azad extracted data and performed quality assessments; Ms Reid and Drs Lys, Copstein, Mann, and Azad screened citations and assessed studies for eligibility; Drs Chauhan, Abou-Setta, and Zarychanski provided methodological expertise in knowledge synthesis; Drs Chauhan and Abou-Setta resolved disagreements regarding study eligibility or quality assessments; Drs Chauhan, Abou-Setta, MacKay, McGavock, Wicklow, and Zarychanski critically reviewed the manuscript; Drs Chauhan, Abou-Setta, and Zarychanski critically revised the manuscript; Dr Rabbani

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Obesity and its associated comorbidities, including type 2 diabetes and cardiovascular disease, continue to be among the most important public health concerns worldwide. One-third of children and two-thirds of adults in developed countries are overweight or obese,[1–3] with attributable medical costs estimated at $147 billion annually in the United States[4] and €33 billion annually in the European Union.[5,6] Childhood obesity has more than doubled in the past 30 years,[2] and children who are overweight or obese are at a greater risk for adverse health outcomes including obstructive sleep apnea, hypertension, dyslipidemia, metabolic syndrome, type 2 diabetes, and cardiovascular disease.[2,7]

There is strong evidence that consumption of sugar-sweetened foods and beverages promotes development of obesity and related complications,[2,4,8,9] prompting population-wide recommendations to reduce added-sugar intake.[10,11] Sugar replacements or nonnutritive sweeteners (NNSs) have thus gained enormous popularity owing to their low caloric value and perceived health benefits.[10,12] The consumption of beverages and foods containing NNSs has increased markedly in recent decades,[10] particularly in children,[13] yet their long-term impact on human health is unclear, and current recommendations for NNS use during pregnancy and childhood are conflicting. Although the American Dietetic Association maintains that NNSs are safe in pregnant women and children within acceptable daily intakes,[14] the Institute of Medicine does not support NNS use in children, citing "a paucity of evidence on long-term health effects … from [NNSs], particularly resulting from exposure initiated in childhood."[15]

Emerging data indicate that NNSs may have adverse effects on glucose metabolism,[16] gut microbiota,[16] and appetite control.[17] In adults, NNS intake has paradoxically been associated with weight gain, incident obesity, and increased fat mass.[11,18,19] However, long-term studies of prenatal or early-life NNS exposure are rare,[20,21] and a systematic review in 2010[22] was inconclusive regarding metabolic effects of NNSs in children. Moreover, that review[22] did not focus on long-term effects or assess study quality, and several studies have since been published.[23–25] The purpose of the current systematic review is to identify, critically appraise, and synthesize evidence from studies documenting the long-term metabolic effects of NNS exposure occurring during gestation, infancy, and childhood.

METHODS

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[26] following a registered protocol.[27] Our primary research question was "Does exposure to NNSs during gestation, infancy, or childhood have adverse long-term metabolic effects?"

Study Selection

We included randomized controlled trials (RCTs) and prospective observational cohort studies of NNS exposure in pregnant women, infants, or children (≤12 years; age limit applied to capture primarily prepubertal exposures) (Supplemental Table 3). We considered all NNSs consumed as ingredients or additives to foods or beverages. Eligible comparators were nutritive sweeteners, placebo, or the participants' regular diet. To exclude short-term studies of acute effects and allow time for long-term metabolic outcomes to develop, we required a minimum study duration of 6 months. To ensure that NNS exposures reported in observational studies preceded metabolic outcomes of interest, we required that associations with baseline NNS intake (not only changes in intake) were reported. Our primary outcome of interest was change in BMI or BMI *z*-score. BMI *z*-scores are recommended in pediatric populations because BMI varies with age and gender in growing children[28]; a BMI *z*-score is adjusted for age and gender relative to a reference standard and represents the number of SD units above or below the mean (eg, a *z*-score of +2 refers to a value that is 2 SD units above the mean). Our secondary outcomes included the following parameters reflecting metabolic health: birth weight (for prenatal exposure studies), growth velocity, incidence of overweight/obesity, change in total adiposity (eg, percentage body fat or skinfold thickness) or central adiposity (eg, waist circumference or waist-to-hip ratio), and incidence of impaired glucose tolerance, metabolic syndrome, insulin resistance, or type 2 diabetes.

Search Strategy

Our search strategy was developed in consultation with an information specialist (Ms Fiander) and was designed to overcome the limitations of a previous NNS review.[29] Because not all studies reporting NNS consumption include NNS-specific terms in their searchable fields, a broader search strategy was applied to capture relevant studies overlooked in previous reviews. Our Medline (OVID) strategy (Supplemental Table 4) was peer-reviewed by an independent information specialist and translated for Embase (OVID) and the Cochrane Central Database of Controlled Trials (Wiley). The following terms, among others, were included: nonnutritive sweeteners, aspartame, saccharin, sucralose, cyclamate, xylitol, stevia, mannitol, carbonated beverages, calories, food frequency, and sweetening agents. We did not

limit the search strategy using terms related to outcomes of interest. Searches were conducted from database inception to July 1, 2015, with no language restrictions. We also searched conference proceedings from the following societies from 2010 to 2015: American Society for Nutrition, American Diabetes Association, and the Obesity Society. Reference lists of pertinent reviews and included studies were hand-searched for relevant citations, and a gray-literature search of OpenSIGLE and Google Scholar was performed. Reference management was performed in EndNote (version x6, Thompson Reuters, New York, NY), and search results were exported to the web-based systematic review software, DistillerSR (version 2, Evidence Partners, Ottawa, ON, Canada) for screening and data extraction.

Screening, Data Extraction, and Management

Search results were independently screened in duplicate, and 2 reviewers assessed each potentially eligible full-text article according to our predetermined inclusion and exclusion criteria (Supplemental Table 3) (Ms Reid and Drs Azad, Lys, Copstein, and Mann). Disagreements were resolved by discussion between the 2 reviewers or by third-party adjudication (Dr Abou-Setta). A standardized data extraction form was developed and deployed in DistillerSR. The form was pilot-tested on a sample of studies before finalization. Two reviewers (Ms Reid and Dr Azad) independently extracted the following data: bibliographic data (author, journal, date, language, country, and year of publication), funding source, study design, population (including main inclusion and exclusion criteria), baseline characteristics (age, gender, body composition, metabolic conditions), NNS intervention and comparator (for RCTs) or NNS exposure and confounders/covariates (for cohort studies), type, dose and duration of NNS exposure; duration of follow-up, and metabolic outcomes of interest (as described above). If multiple follow-up periods were reported for an individual study, the longest follow-up was included. For cohort studies, NNS effect estimates were extracted in 2 possible formats: (1) ratio comparing the highest versus lowest category of NNS intake (extreme quantiles as defined by study authors) or (2) linear association quantifying effects per unit NNS intake (intake unit as defined by study authors). Adjusted effect estimates were extracted; if multiple adjusted estimates were reported for a single outcome, the estimate from the statistical model including the largest number of covariates was extracted.

Analysis

Data from RCTs and prospective cohorts were analyzed separately using random effects models (Comprehensive Meta-Analysis Software, version 2.2.064, Biostat, Englewood, NJ). Because NNS intake units differed between cohort studies, reported β estimates were converted to *t*-values (β/SE) to generate a standardized metric.[30] A pooled weighted mean correlation >0 suggests a positive association in which increasing NNS intake correlates with increasing BMI. Statistical heterogeneity was quantified by using the I^2 statistic. All tests of statistical inference reflect a 2-sided α of 0.05. Subgroup analyses were planned a priori to explore heterogeneity and determine summary effect estimates in several prespecified strata including gender, age, and body composition at baseline; type of NNS; type of comparator; study quality; NNS dose and duration of exposure; and follow-up.[27]

Assessment of Methodological Quality

Methodological quality was assessed by using the Cochrane Handbook of Systematic Reviews of Interventions.[31] RCTs were assessed by using the Cochrane Collaboration Risk of Bias tool,[31,32] and cohort studies were evaluated by using the 9-point Newcastle-Ottawa Scale (NOS).[33] NOS requires certain evaluation criteria to be customized by the investigators. For the purpose of this review, we defined "adequate follow-up duration" as ≥1 year and "adequate retention" as >70%. We also designated 2 "critical confounders": body composition at baseline (BMI or other measure of body composition) and diet (total energy or sugar intake, or a diet pattern or quality score).

RESULTS

From 10 746 citations identified, 844 potentially eligible full-text articles were reviewed, and 8 studies met our inclusion criteria: 2 RCTs[23,24] and 6 prospective observational cohort studies[11,25,34–37] involving a total of 15 641 children (Tables 1 and 2, Fig 1). No eligible studies evaluated NNS exposure among pregnant women or infants. Included studies reported a range of body composition measures including BMI[25,34,35,37] or BMI *z*-score,[23,24,36] weight,[34] weight-for-age *z*-score,[24] adiposity,[11,23,25] and incidence of overweight/obesity.[35] The remaining secondary outcomes that we aimed to explore, including birth weight, insulin resistance, metabolic syndrome, and type 2 diabetes, were not evaluated in the reviewed literature.

Study Quality

Both RCTs were judged to be at unclear risk of bias (Tables 1 and Supplemental Table 5), and the majority of cohort studies were of moderate quality (Tables 2 and Supplemental Table 6). Half of the cohort studies had inadequate or unclear loss-to-follow up,[11,34,36] and 4 evaluated specific groups of children

TABLE 1 Summary of Included RCTs Evaluating NNS Interventions and Long-term Metabolic Health in Children

Publication; Study	Country, Enrollment Years	Subjects Randomized (% Completed)	Mean Age at Baseline, y (SD)	Study Duration, mo	Weight Status at Baseline	NNS Intervention and Comparator	Relevant Outcomes Reported	Effects Reported	Risk of Bias
de Ruyter et al, 2012[23]; Double-Blind Randomized Intervention Study in Kids (DRINK)	Netherlands, 2009–2011	641 (74)	8.2 ± 1.8	18	18% overweight; BMI *z*-score 0.03	Sweetened beverages: 34 mg sucralose + 12 mg acesulfame K vs 26 g sucrose	BMI *z*-score, weight:height ratio, fat mass, sum of skinfolds, waist circumference, % body fat	Reduced weight gain and fat accumulation in NNS group; difference in BMI *z*-score change from baseline for NNS versus comparator: −0.13 (95% CI −0.20 to −0.06; *P* = .001)	Unclear
Taljaard et al, 2013,[24] BeForMi Study	South Africa, 2010	414 (96)	8.2 ± 1.1	8.5	14% underweight; BMI *z*-score −0.58	Sweetened beverages: 25 mg sucralose vs 21 g sucrose	BMI *z*-score, weight-for-age *z*-score	No effect on BMI *z*-score, but higher weight-for-age *z*-score with NNS: +0.07 (95% CI 0.14 to 0.002, *P* = .03)	Unclear

Risk of bias was assessed using the Cochrane Risk of Bias tool.[32]

that may not represent the general population.[25,34,36,37]

RCTs

The 2 included RCTs (Table 1) were published in 2012 and 2013 in peer-reviewed journals[23,24] and enrolled children of both genders with a mean age of 8 years. De Ruyter et al[23] provided sweetened beverages (sucralose versus sucrose) to 641 Dutch children in an 18-month obesity prevention trial. Taljaard et al[24] provided sweetened micronutrient-fortified beverages (sucralose and acesulfame K versus sucrose) to 398 South African children for 9 months, aiming to improve growth and cognition. Neither study had health-related inclusion criteria, yet the baseline BMI of enrolled participants differed substantially, with the Dutch trial evaluating primarily healthy and normal-weight children (18% overweight, mean BMI *z*-score 0.03)[23] and the South African trial investigating primarily undernourished children (14% underweight, mean BMI *z*-score −0.58).[24] Notably, these studies used different reference datasets to calculate BMI *z*-scores: de Ruyter et al[23] used national reference data from the Netherlands, whereas Taljaard et al[24] used international reference data from the World Health Organization.

Both RCTs reported significant but contradictory effects on weight gain. De Ruyter et al[23] reported significantly lower weight gain and fat accumulation among children receiving the NNS-sweetened beverage: their change in BMI *z*-score over 18 months was 0.13 SD units lower (95% confidence interval [CI] −0.20 to −0.06) than children receiving the sugar-sweetened comparison beverage. In contrast, Taljaard et al[24] reported that children receiving NNSs had a significantly greater increase in weight-for-age *z*-score: +0.07 SD units (95% CI 0.002 to 0.14). Results for change in BMI *z*-score were similar but did not reach statistical significance: +0.07 (−0.03 to +1.16). The authors speculated that in their undernourished population, the sugar-containing beverages made children more energetic and consequently lowered their weight gain. Given the significant clinical heterogeneity between study populations (healthy Dutch children versus undernourished South African children), we did not pool data from these trials.

Prospective Cohort Studies

The 6 included prospective cohort studies (Table 2) were published in peer-reviewed journals between 2001 and 2014.[11,25,34–37] All were conducted in the United States[25,34–37] or United Kingdom,[11] with baseline NNS intake assessments performed between 1987[25] and 1997.[11] These studies enrolled generally healthy children of both genders with no specific requirements for metabolic health at baseline. The mean age at enrollment ranged from 2[34] to 11[35] years, and duration of follow-up ranged from 6 months[34] to 12 years.[25] All 6 studies evaluated intake of artificially sweetened beverages without specifying the type of NNS. Three studies collected dietary

TABLE 2 Summary of Included Prospective Cohort Studies Evaluating NNS Exposure and Long-term Metabolic Health in Children

Study	Country	Year of Baseline NNS Intake	Subjects Analyzed	Age at Baseline NNS Intake, y	Follow-up Duration	Weight Status at Baseline	NNS Type, Measure, Method of Assessment	Major Confounders Considered[a]	Outcomes Reported	Associations Reported	Quality Score (of 9)
Berkey et al, 2004,[37] Growing Up Today Study (GUTS)	US	1996	16 771 children; offspring from the Nurses' Health Study	9–14	2 y	20% overweight	NNS soda, servings/day, validated FFQ	Baseline BMI, total energy intake, physical activity, puberty, race, age, gender	BMI	NNSs associated with BMI increase in boys but not girls: β ± SE 0.12 ± 0.05 kg/m^2; p = .02 (boys); 0.05 ± 0.04; p = .16 (girls)	7
Blum et al, 2005[36]	US	1992	166 children	9.3 ± 1.0	2 y	29% overweight	NNS soda, ounces/day, 24-h dietary recall	Baseline BMI, total energy intake, age, gender	BMI *z* score	No association of baseline NNS intake and change in BMI *z*-score[b]	7
Hasnain et al, 2014,[25] Framingham Cohort Offspring	US	1987	98 non-Hispanic white children	3–9	12 y	Not reported	NNS beverages, ounces/day, 3-d food record	Baseline BMI and body fat %, % energy from fat, other beverage intake, screen time, maternal education, age, gender	BMI, waist circumference, sum of skinfolds, body fat %	No association of NNS intake and final body composition[b] but NNSs associated with increasing body fat accumulation over time (p = .04 for highest versus lowest tertile)	8
Johnson et al, 2007,[11] Avon Longitudinal Study of Parents and Children (ALSPAC)	UK	1997	1432 children	5.2 ± 0.1	4 y	15% overweight	NNS beverages, servings/day, food diary	Baseline BMI, total energy intake, physical activity, gender	Body fat %	NNS intake associated with increase in fat mass: β (95% CI) 0.26 kg (−0.004 to 0.52); p = .05	8
Ludwig et al, 2001,[35] Planet Health intervention and evaluation project	US	1995	780 children	11.7 ± 0.8	19 mo	27% obese	NNS soda, servings/day, validated FFQ	Baseline BMI, total energy intake, physical activity, puberty, race, age, gender	BMI, overweight or obesity	No association of baseline NNS intake and change in BMI (*P* = .10) or incident overweight/obesity (*P* = .69)[b]	9
Newby et al, 2004,[34] North Dakota Supplemental Nutrition Program for Women, Infants, and Children (WIC)	US	1996	1345 low-income children	2.9 ± 0.7	6–12 mo	21% at risk for overweight	NNS soda, ounces/day, validated FFQ	Baseline BMI, total energy intake, race, socioeconomic status, age, gender	BMI, weight	No association of NNS intake and change in BMI or weight (β ± SE): BMI: 0.01 ± 0.02 kg/m^2/y; *P* = .68; weight: 0.01 ± 0.06 lb/y; *P* = .82	6

Values are expressed as mean ± SD or range. FFQ, food frequency questionnaire.

[a] Major confounders defined a priori include baseline BMI, baseline body composition, total energy, sugar intake, diet quality, physical activity, puberty, race, age, gender, and socioeconomic status.

[b] Effect estimates not reported and unavailable from study authors. Study quality assessed using NOS.[33]

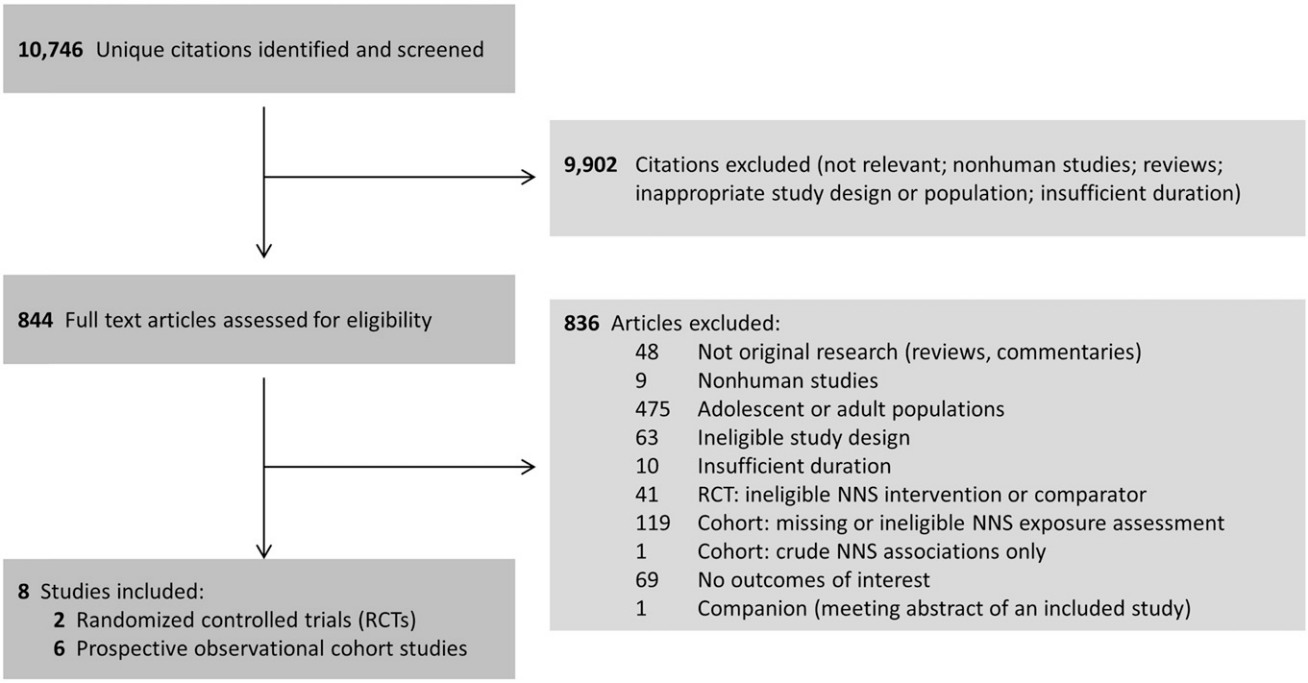

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow diagram.

information with validated food frequency questionnaires[34,35,37]; the others used a food diary,[11] 24-hour recall[36] or a 3-day food record.[25] All studies controlled for gender and adjusted for age, baseline body composition, and total energy intake[11,34–37] or sugar-sweetened beverage intake and percent energy from fat.[25] Four studies adjusted for physical activity,[11,25,35,37] and 2 adjusted for socioeconomic status.[25,34]

Five cohort studies reported associations of NNS intake and subsequent change in BMI or BMI *z*-score[25,34–37]; however, only 2 of those studies reported extractable effect estimates.[34,37] Pooled data from Berkey et al[37] and Newby et al[34] show that NNS intake is significantly correlated with subsequent BMI gain (Fig 2; weighted mean correlation 0.023, 95% CI 0.006 to 0.041, $P <$ .01). With only 2 studies eligible for meta-analysis, planned subgroup analyses were not possible. Meta-analysis of secondary outcomes was not possible because no single outcome was reported by >1 study. Individual study results are summarized below and in Table 2.

Three of 6 cohort studies identified a significant association between NNS exposure and subsequent BMI gain or fat mass accumulation.[11,25,37] Among schoolchildren in the US Growing Up Today Study, Berkey et al[37] reported a significant association between diet soda consumption and BMI gain over 2 years in boys (+0.12 ± 0.05 kg/m^2 per daily serving of diet soda, p = .02), but found no association in girls (+0.05 ± 0.04 kg/m^2, p = .16).

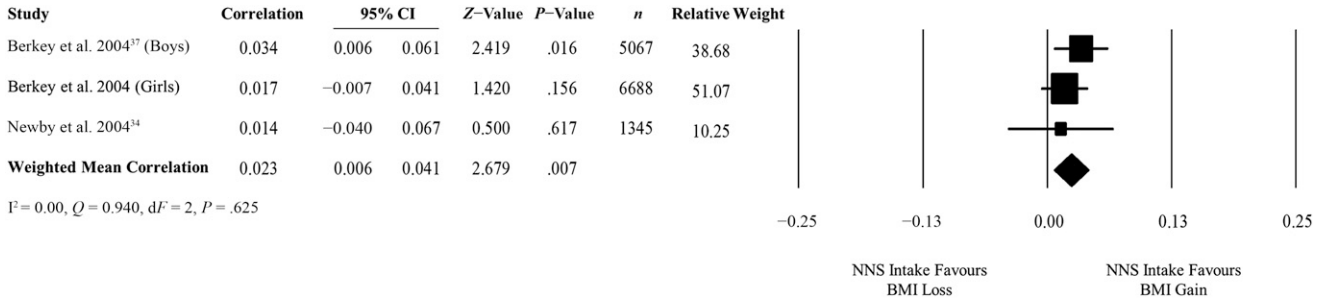

FIGURE 2
NNS intake in children and subsequent BMI change in prospective cohort studies. Squares represent the mean correlation within each study, with 95% CIs represented by horizontal lines. Square size is proportional to the weight of each study. The diamond represents the weighted group mean correlation using a random effects model. A value >0 indicates a positive correlation between NNS intake and BMI increase.

Comparable results were found by Johnson et al[11] among 5-year-old children in the UK Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, in which low-energy drink consumption was associated with fat mass accumulation by 9 years of age: +0.26 kg fat per daily serving of low-energy drinks (95% CI 0.00 to 0.52, $p = .05$). Hasnain et al[25] evaluated the earliest exposure period and the longest duration of follow-up, reporting diet beverage intake and changes in body composition from age 3 to 15 years in the Framingham Children's Study. Although NNS intake in early childhood was not associated with body fat at age 15, longitudinal trajectory analyses revealed that preschool children in the highest tertile of diet beverage intake had increased accumulation of body fat (sum of skinfolds) beginning at 7 years of age ($P = .04$ compared with the lowest tertile of diet beverage intake). The remaining 3 cohort studies reported no association between baseline NNS intake and subsequent change in BMI,[34,35] BMI *z*-score,[36] weight,[34] or fat mass.[11] Ludwig et al was the only study to report incident overweight and obesity, finding no association with baseline NNS intake over 2 years of follow-up.[35]

DISCUSSION

Key Findings

Despite widespread availability and increasing consumption, few studies have evaluated the long-term effect of early-life NNS exposure on metabolic health. We identified 2 eligible RCTs demonstrating significant but opposite associations between NNS exposure and weight gain in children from vastly different populations. Three of 6 eligible cohorts reported positive associations between NNS intake and weight gain or fat accumulation, and 2 with extractable data showed a significant positive correlation between NNS intake and subsequent BMI gain. Nearly all studies were at unclear risk of bias or of moderate quality. Secondary outcomes including growth velocity, metabolic syndrome, and type 2 diabetes were not reported, and no eligible studies evaluated NNS exposure during gestation or infancy.

Comparison With Previous Studies

A 2010 review concluded that evidence from prospective cohort studies support an association between NNS intake and weight gain in children, whereas RCTs failed to show either beneficial or adverse metabolic effects.[22] We provide a timely update to this review, including several additional studies for analysis[23–25,34] and focusing specifically on long-term effects. A recent meta-analysis of NNS studies in both adults and children reported that RCTs demonstrated potential health benefits, including modest weight loss and weight maintenance, whereas observational studies showed a small but significant association with increasing BMI.[12] That review was conducted in the absence of an a priori protocol, and the published search strategy was incomplete.[29] Our review addressed these limitations and aimed to evaluate a broader scope of metabolic health outcomes (beyond weight gain and body composition) focusing on long-term effects and including prenatal exposures. With stringent requirements for long-term outcomes after early NNS exposure (before 12 years of age) and NNS-specific longitudinal analyses demonstrating clearly prospective relationships (baseline NNS exposures associated with subsequent metabolic outcomes), some studies included in previous reviews were excluded from ours because of insufficient duration and evaluation of adolescent populations,[38,39] multifaceted interventions,[40] or unclear temporality of exposure.[41,42] Even with our search strategy improvements, evaluation of new studies, and strict inclusion criteria to reduce heterogeneity and address our modified research question, we have found insufficient evidence to clearly determine whether an association exists between early-life NNS exposure and long-term metabolic health.

Strengths and Weaknesses

The strengths of our systematic review include our rigorous methodology, following an a priori registered protocol,[27] and sensitive peer-reviewed search strategy. Additionally, we targeted a comprehensive set of metabolic health outcomes and focused on a unique early-life exposure period that has not been specifically investigated in previous reviews. We applied strict inclusion criteria to identify high-quality studies (RCTs and prospective cohorts with ≥6 months' follow-up) addressing our research question and evaluated study quality with validated assessment tools. The main limitation of this review is that meta-analysis was not possible because of the limited number of eligible studies, unreported effect estimates, and heterogeneity of study populations, NNS exposure measurements, and outcomes. A limitation of individual cohort studies included in this review is the subjective and likely incomplete ascertainment of total NNS exposure from self-reported data; all studies evaluated artificially sweetened beverage consumption before 1997, yet NNS are widespread in many foods besides beverages, and consumption patterns have changed considerably since the 1990s.[10]

Opportunities for Future Research

We found that only 2 RCTs[23,24] have been appropriately designed to evaluate causal long-term metabolic effects of NNSs in children, and

those studies reported contradictory associations. Notably, they were conducted in extremely different settings and used different reference data to generate BMI *z*-scores. New RCTs and extended follow-up of existing trials will be required to clarify the long-term metabolic effects of NNS exposure in childhood. Prospective cohort studies are also needed and should use comprehensive assessment tools to accurately capture modern NNS consumption patterns. Cohort studies will be particularly important to evaluate very early NNS exposure, since randomization may not be acceptable in pregnant women or infants, and our review identifies a critical lack of evidence in these populations. NNS exposure during gestation or infancy could have long-term effects because predisposition to metabolic disease can be acquired or "programmed" early in life.[21] For example, children born to mothers with gestational diabetes or high caloric intake are at increased risk of developing metabolic conditions later in life.[21,43] Interestingly, perigestational NNS exposure in animals also predisposes offspring to obesity[21]; however, our review indicates that no human studies to date have investigated this association. Recent data show that NNSs are commonly detected in human milk,[44] suggesting another route of early-life NNS exposure with unstudied clinical implications.

CONCLUSIONS

The effect of NNS exposure on metabolic health in children is uncertain, with conflicting evidence suggesting potentially adverse effects on BMI gain and fat accumulation. No studies to date have investigated this association among pregnant women or infants. Further research is required to understand the long-term metabolic impact of NNS exposure during gestation, infancy, and childhood and to inform evidence-based recommendations for NNS use in this sensitive population.

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ABBREVIATIONS

CI: confidence interval
NNS: nonnutritive sweetener
RCT: randomized controlled trial

performed statistical analyses; Drs Rabbani, Lys, Copstein, and Mann and Ms Fiander reviewed the manuscript; Ms Fiander developed search strategies; Drs MacKay, McGavock, and Wicklow provided content expertise in nutrition and metabolic health; Dr Azad conceptualized the study, led and coordinated the review, reviewed and revised the protocol and manuscript, and agrees to be accountable for all aspects of the review; and all authors approved the final manuscript as edited.

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