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Sugar consumption, sugar sweetened beverages and Attention Deficit Hyperactivity Disorder: A systematic review and meta-analysis

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ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is a significant neurobehavioral disorder in children and adolescence which may be affected by diet.

Objective: To evaluate the possible relationship between sugar consumption and the development of symptoms of ADHD.

Methods: In March 2020, an exhaustive systematic literature search was conducted using Google Scholar, PubMed, and Scopus. In this meta-analysis of observational studies, odds ratios, relative risks, hazard ratios, and their 95% confidence intervals, which was reported for ADHD regarding SSBS, soft drink consumption, and dietary sugars, were used to calculate ORs and standard errors. At first, a fixed-effects model was used to drive the overall effect sizes using log ORs and SEs. If there was any significant between-studies heterogeneity, the random-effects model was conducted. Cochran's Q test and I^2 were used to measure potential sources of heterogeneity across studies. The Newcastle-Ottawa scale was used to assess the quality of the included articles.

Results: Seven studies, two cross-sectional, two case-control, and three prospective with a total of 25,945 individuals were eligible to include in the current meta-analysis. The association between sugar and soft drink consumption and the risk of ADHD symptoms were provided based on the random-effects model (pooled effect size: 1.22, 95%CI: 1.04-1.42, P = 0.01) (I^2 = 81.9%, $P_{heterogeneity} < 0.0001$).

Conclusion: This meta-analysis indicated a positive relationship between overall sugar and sugar-sweetened beverages consumption and symptoms of ADHD; however, there was heterogeneity among included studies. Future well-designed studies that can account for confounds are necessary to confirm the effect of sugar on ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a significant neurobehavioral disorder that often involves childhood and adolescence (1). Although there are various reports of the prevalence of ADHD, systematic reviews have indicated that the global prevalence of ADHD is between 2 and 7%, with an average of around 5% (2,3). However, it has different rates by age, gender, and ethnicity (4). ADHD is distinguished by inattention, impulsivity, and hyperactivity symptoms (5). ADHD not only could cause a heavy burden on health service and community (6) but also leads to poor academic and social outcomes (7).

The etiology of ADHD has not been determined clearly (8). Both genetic and environmental factors have a contribution to the incidence of ADHD (9). Previous studies have supposed that ADHD is inherited from family (10), while other studies have pointed to environmental factors such as birth weight, preterm birth, alcohol consumption, tobacco, and substance use by parents, especially during pregnancy as

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well as exposure to heavy metals like lead and mercury, as an illustration. (2,11–13).

One of the environmental risk factors which play a pivotal role in ADHD is nutrition and diet (14). In the literature, there was a direct association between the western diet and low adherence to a Mediterranean diet with ADHD symptoms (15,16). Various nutrients have been proposed to have a contribution to neurodevelopment (17). Zinc and Iron are considered to have a potential role via their capacity in metabolic pathways of neurotransmitter production, and a deficiency of them is linked to ADHD symptoms (9,18). Omega-3 fatty acids may also impact on neurotransmission and signaling (19). A meta-analysis by Hawkey et al. indicated that omega-3 s supplementation results in the improvement of ADHD symptoms (19). Furthermore, some special nourishments, such as processed foods, soft drinks, and sugar-sweetened beverages (SSBs) may be associated with the risk of the disorder (20).

Sugar consumption has globally increased in recent years, which is mainly due to the high consumption of SSBs (21). Due to the high sugar content, SSBs could lead to insulin secretion, incite the production of epinephrine and hyperactivity disorders stimulation (22). Besides, SSBs have been accounted as an important source of artificial food colorants and preservatives (23). Sugar, artificial food colorants, and preservatives have been associated with an increased risk of ADHD (24).

Several investigations have evaluated the association between SSB consumption and ADHD (16,20,25–29). However, the conclusion of them has been controversial. To clarify the conflicting evidence, we carried out a systematic review and meta-analysis of observational studies that examined the effect of dietary sugars and SSBs on ADHD.

2. Methods

This review was conducted according to the guideline that previously had been reported for meta-analysis of observational articles (30).

2.1. Search strategy

An exhaustive systematic literature search was conducted on Google Scholar, PubMed, and Scopus for articles published until March 2020. The query syntax was set on the basis of following search terms including MeSH and text words: (ADHD OR "Attention deficit hyperactivity disorder" OR "Attention Deficit Disorder with Hyperactivity"(31) OR "hyperactivity disorder" OR "attention deficit" OR "attention deficit disorder" OR hyperactivity OR "attention problems" OR inattention) AND (sugar OR sugars(31) OR sweets OR "sweetened beverages" OR "sugar-sweetened beverages" OR "sugar sweetened beverages" OR "added sugar" OR "sugary foods" OR "sugary drinks" OR SSBs). Two reviewers with experience in the subject selected the studies independently from the search results based on the established inclusion and exclusion criteria. To accelerate the process of citation screening obtained from databases, all publications were saved into an EndNote library (version X7, for Windows, Thomson Reuters, Philadelphia, PA, USA).

2.2. Selection criteria

The articles that were considered suitable for inclusion were those that showed an association between sugar and soft drinks consumption, and ADHD or hyperactivity, defined as follows: a) had an observational study design including cohort, case-control, and cross-sectional studies, b) English language publications, c) reported either odds ratios (ORs), hazard ratios (HRs), or relative risks (RRs) as well as 95% confidence intervals (95% CIs) for ADHD or hyperactivity in relation to sugar, sweets, and soft drink consumption.

Studies that had a non-observational study design or reported data from the same population, non-English articles, animal studies, letters, conference papers, book chapters, and reviews were excluded.

2.3. Data extraction

The reported risk estimates (ORs or HRs or RRs) and related confidence intervals (CIs) for ADHD or hyperactivity in relation to sugar, sweets, or soft drink consumption were extracted from all the included studies. There were three model of reports in studies: 1. studies just report ORs of sugar and ADHD, 2. studies just report OR of SSBs and ADHD, and 3. studies report OR of sugar, sweets + SSBs and ADHD.

It was tried to extract the most adjusted effect sizes, if available. Some publications reported several exposure items (16,25); therefore, to conduct a meta-analysis on the association between sugars and ADHD, the risk estimates were pooled before data analysis. Informative characteristic of the included studies was extracted as follows: first author's name, date of publication, study origin, study design, age and gender of subjects, the number of participants who took part in the study, the kind of exposure (sugar, sweets, soft drinks), amount of exposure consumption, outcome (ADHD or hyperactivity), methods used for measuring dietary intakes. Furthermore, hyperactivity reported risk estimates related to ADHD and hyperactivity (including ORs, RRs, HRs, as well as their 95% CIs), and the adjusted variables of the study were extracted as well. Extracting relevant data from the included studies were conducted by *two* authors independently*,* and controversy among authors was solved by the principal investigator.

2.4. Study quality assessment

The Newcastle-Ottawa scale (NOS) was used to assess the quality of the included articles (Supplemental Table 1) (32). NOS is based on a star scoring system, which a maximum of nine (for prospective and cross-sectional studies) and ten scores (for case-control studies) can be awarded to each study. Quality assessment was checked independently by two authors, and any disagreements were solved by the third one. Studies that received a score of 6 or above were considered as high quality.

2.5. Statistical analysis

In this meta-analysis of observational studies, odds ratios, relative risks, hazard ratios, and their 95% confidence intervals, which reported for ADHD regarding SSBs, soft drink consumption, and dietary sugars, were used to calculate ORs and standard errors (SE). At first, a fixed-effects model was used to drive the overall effect sizes using log ORs and SEs. If there was any significant between-studies heterogeneity, the random-effects model (DerSimonian-Laird) was conducted. Cochran's Q test and I^2 were used to measure potential sources of heterogeneity across studies. $I^2 > 50$ was taken as an indicator of heterogeneity among studies (33). Subgroup analysis according to the following criteria was conducted using the fixed-effects model: design (cross-sectional / case-control / cohort), age of participants (< 10y and > 10y), studies quality (< 6 and > 6), studies population (< 1000 and > 1000), the method of dietary assessment (prepared questionnaire and food frequency questionnaire) and the exposure (Sugar, SSBs and soft drinks).

Sensitivity analysis was performed to elucidate the stability of findings and to ascertain whether final pooled effect sizes were affected by a single or a couple of publications. A minimum of ten studies is needed to ensure adequate power and assess publication bias. The number of studies was insufficient for assessing publication bias (34). Data analyses were done applying the platform of Stata, version 12 (Stata Corp, College Station, TX). P values were regarded as significant at the level of < 0.05.

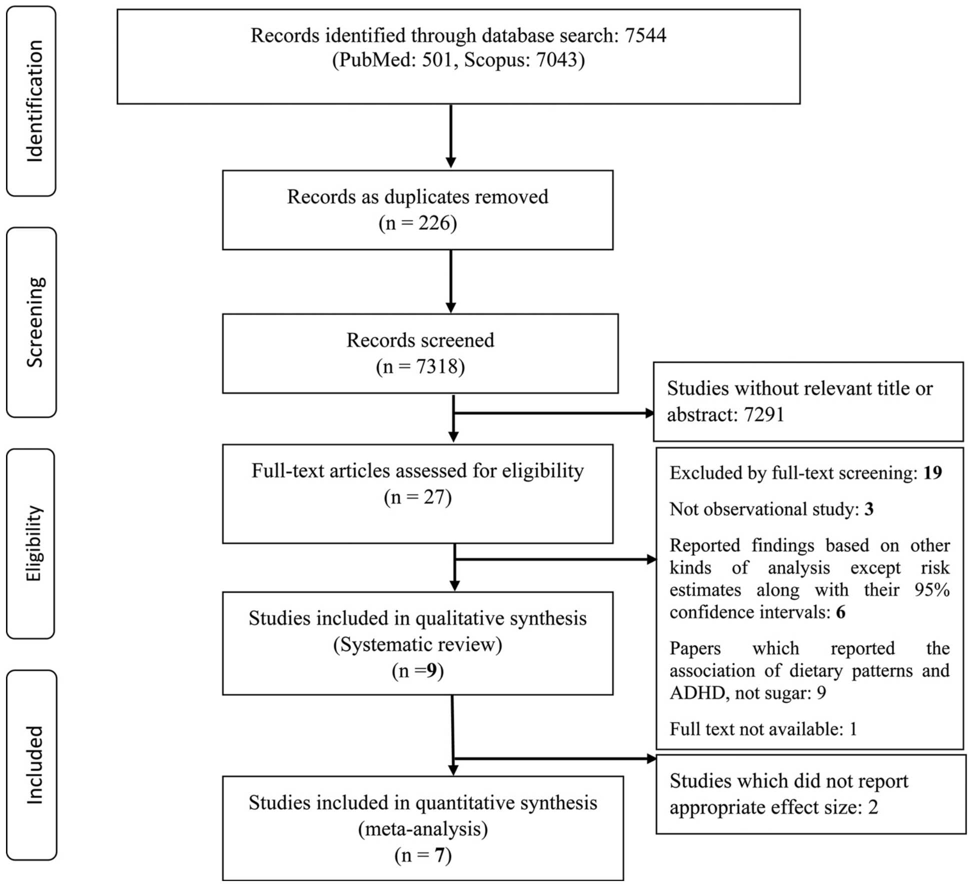

Fig. 1. The flow chart of the literature search.

3. Results

3.1. Findings from a systematic review

The initial search retrieved 7544 publications. After removing duplicates, 7318 publications remained for the title and abstract screening. After the exclusion of 7291 records, including short communication, letters, books, reports, review articles, and animal studies, 27 articles remained for full-text evaluation. Nine studies that investigated the association of sugars and ADHD were identified. Nevertheless, two of them did not report odds ratios. Therefore, these two articles failed to be included in the meta-analysis (35,36). Finally, seven eligible articles selected for inclusion in this study in which three of them were a cohort, two case-control and, two of them had a cross-sectional design (Fig. 1).

Three prospective (20,27,29), two case-control (16,26), and two cross-sectional (25,28) studies were selected for inclusion in the current meta-analysis. Characteristic of these studies is provided in Table 1. The publication date varied between 2006 and 2019. Four of the included studies were conducted in Europe (16,20,27,28), one in Asia (26), and two in the Americas (25,29). All studies were conducted on both genders, however, two studies (28,29) reported risk estimates for girls and boys separately and, we pooled these risk estimates for final analysis. The studies' sample size ranged from 120 to 12942. In total, 25945 subjects, aged ≥ seven, were entered in the current systematic review. Four studies used a food frequency questionnaire (FFQ) to determine dietary intakes (16,20,27,29), and three others used a prepared questionnaire (PQ) (25,26,28). Four articles assessed the risk of hyperactivity and ADHD in relation to sugar consumption (16,20,27,29), four regarding soft drinks and SSBs (16,25,26,28). There are some tools to assess ADHD. Based on a systematic review, it revealed that ADHD was assessed by different assessment tools in the included studies, three by strengths and difficulties questionnaire (SDQ) (20,25,27), and others with HSCL-10 (28), Swanson, Nolan and Pelham, fourth revision questionnaire (SNAP-IV) (26) the ADHD rating scale-IV (ADHD RS-IV) (16) and Development and Well-Being Assessment (DAWBA) (29).

Three studies showed no significant association between sugar consumption and ADHD (20,27,29). One study showed a significant positive association between sugar consumption and the risk of ADHD (16). Moreover, one study revealed no association between sweets consumption and the risk of ADHD (25). Lien et al. study showed no significant association between soft drinks and ADHD in girls (28).

3.2. Findings from meta-analysis

In total, seven studies (two cross-sectional, two case-control, and three prospective) were eligible to conduct a meta-analysis regarding sugar and soft drinks consumption. If the study reported the risk estimate separately for ADHD and hyperactivity, the reported risk estimates were pooled. Due to an inadequate number of studies, cohort studies were pooled to another type of studies which investigated the association between dietary sugars and ADHD. A total of 25945 individuals were considered in the current meta-analysis.

The association between sugar and soft drink consumption and the risk of ADHD symptoms based on fixed-effects model (pooled effect size: 1.075, 95%CI: 1.028-1.125, $P = 0.002$) ($I^2 = 81.9\%$, $P_{heterogeneity} < 0.0001$)) and random-effects model (pooled effect size: 1.22, 95%CI: 1.04-1.42, $P = 0.013$) ($I^2 = 81.9\%$, $P_{heterogeneity} < 0.0001$) (Fig. 2) were provided. Both the fixed-effect and random-effects model presented a positive association between sugars and sugary drinks consumption and the risk of ADHD. However, based on subgroup analysis, there was no association between just dietary sugar and ADHD. Moreover, based on the findings

Table 1
Characteristics of the included studies on the association between dietary intake of sugar and soft drinks and the risk of ADHD.

Authors (Year)	Type of study	Country	Mean age (range)	Gender	Sample size	Outcome	Outcome assessment	Exposure	Consumed amount	OR (95%CI)*	Adjustments ¥	Exposure assessment
Lien et al (2006) (26)	Cross-sectional	Norway	15.50 (15-16)	Boys Girls Both	2646 2717	Hyperactivity	HSCL-10	Soft drink	> 4 glass/wk	1.99 (1.23-3.24) 0.99 (0.47-2.10)	1-9	PQ
Wiles et al (2009) (18)	Cohort	UK	7 (7)	Both	4430	Hyperactivity	SDQ	Sugar	577 g/wk	1.04 (0.97-1.10)	10-21	FFQ
Peacock et al (2011) (25)	Cohort	UK	8.08 (97 months)	Both	12942	Hyperactivity	SDQ	Sugar	494 ± 185 g/wk	1.01 (0.92-1.10)	5, 6, 10-13, 15- 18, 21-24	FFQ
Schwartz et al (2015) (23)	Cross-sectional	USA	12.38 (11-14)	Both	1649	Hyperactivity	SDQ	Sweets SSBs	1.51 type/d 2.24 type/d	1.17 (0.95-1.45) 1.14 (1.04-1.25) 1.14 (1.04-1.25)	4, 6, 12, 25-27	PQ
Yu et al (2016) (24)	Case-control	Taiwan	9.20 (6-12)	Both	332	ADHD	SNAP-IV	SSBs	> 7 serving/d	3.69 (1.29-16.60)	2, 5, 12, 28-31	PQ
Rios-Hernandez et al (2017) (14)	Case-control	Spain	9.30 (6-12)	Both	120	ADHD	ADHD RS-IV	Sugar Cola Soft drink		3.25 (1.28-8.25) 3.55 (1.40-9.01) 3.89 (1.53-9.87)	5, 10, 32-36	FFQ
Del-Ponte et al (2019) (29)	Cohort	Brazil	(6-11)	Boys Girls	578 531	ADHD	DAWBA	Sugar		0.7 (0.3-2.0) 2.5 (0.3-23.5)	4, 9, 12, 14, 17	FFQ

- UK, United Kingdom; USA, United States of America; ADHD, Attention Deficit Hyperactivity Disorder; HSCL-10, 10-item Hopkins Symptom Checklist; SDQ, Strengths and Difficulties Questionnaire; SNAP-IV, Swanson, Nolan and Pelham, Fourth Revision questionnaire; ADHD RS-IV, the ADHD rating scale-IV; DAWBA, Development and Well-Being Assessment; SSBs, sugar-sweetened beverages; OR, odds ratio; CI, confidence interval; PQ, prepared questionnaire; FFQ, food frequency questionnaire.

* Effect sizes are presented for the association between various sugary materials and the risk of ADHD. Finally, the pooled effect size of each study was used for performing a meta-analysis.

¥ Consumption of potato chips (1), consumption of sweets and chocolates (2), consumption of fruits (3), regular consumption of lunch and breakfast (4), parental education level (5), family structure (6), perceived social support (7), history of intoxication (8), smoking status (9), maternal smoking (10), SDQ score (11), sex (12), maternal age at delivery (13), number of siblings (14), socio-economic status (15), birth weight (16), gestational age (17), maternal depression and anxiety (18), maternal enjoyment score (19), single parent household (20), Intelligent Quotient (21), housing tenure and crowding (22), family car use (23), single parent (24), age (25), race/ ethnicity (26),sugary food consumption (27), consumption of milk/meat/vegetables (28), family history of nervous system diseases (29), maternal alcohol consumption during pregnancy (30), gene polymorphism of DRD4 at rs752306 (31), body mass index (32), level of physical activity (33), breastfeeding (34), biological father living with family (35), and parents divorced (36).

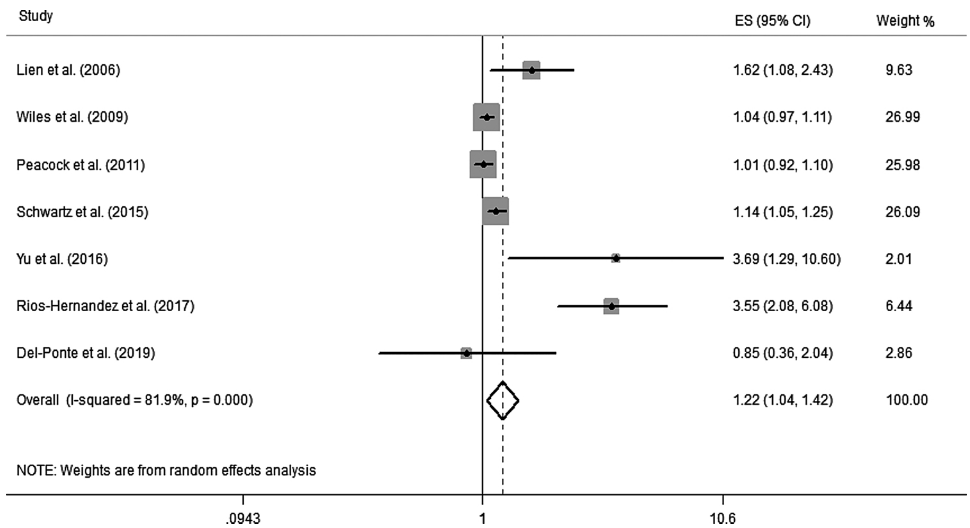

Fig. 2. Forest plot for the association between sugars consumption and the risk of ADHD using a random-effects model.

Table 2
Subgroup analysis based on fixed-effects models for the association of sugars consumption and ADHD.

Subgroup	Effect sizes (n)	Effect size (95% CI)	I^2	P Heterogeneity	P Within[1]	P Between[2]
Overall	7	1.08 (1.03, 1.12)	81.9	< 0.0001	0.002	-
Study design						
Cross-sectional	2	1.16 (1.06, 1.26)	63.7	0.097	0.001	< 0.0001
Case-control	2	3.58 (2.22, 5.77)	0	0.949	< 0.0001	
Cohort	3	1.03 (0.97, 1.08)	0	0.799	0.309	
Study population						
> 1000	5	1.06 (1.01, 1.11)	53.2	0.074	0.008	< 0.0001
< 1000	2	3.58 (2.22, 5.77)	0	0.949	< 0.0001	
Participant's age						
> 10 year	2	1.16 (1.06, 1.26)	63.7	0.097	0.001	0.046
< 10 year	4	1.04 (0.99, 1.10)	84.8	< 0.0001	0.111	
Food assessment tool						
Prepared questionnaire	3	1.17 (1.07, 1.27)	72.9	0.025	< 0.0001	0.027
FFQ	4	1.04 (0.99, 1.10)	85.5	< 0.0001	0.141	
Study quality						
> 6 score	6	1.07 (1.03, 1.12)	82.0	< 0.0001	0.002	0.022
< 6 score	1	3.69 (1.29, 10.58)	-	-	0.015	
Exposure						
SSBS	2	1.80 (1.23, 2.63)	51.1	0.153	0.002	0.001
Sugar	3	1.03 (0.97, 1.08)	0	0.7999	0.309	
Sugar & SSBS	2	1.17 (1.08, 1.28)	94	< 0.0001	< 0.0001	

-FFQ; food frequency questionnaire, SSBS; sugar-sweetened beverages.
[1] Test for heterogeneity in sub-groups.
[2] Overall Test for heterogeneity between sub-groups by fixed-effect model.

of subgroup analysis, type, and a population of studies was detected as potential sources of heterogeneity (Table 2). Due to conducting all studies in both genders, we were unable to conduct subgroup analysis for gender. Besides, findings of sensitivity analysis demonstrated that the association between sugars intake and the risk of ADHD did not rely on a single or a couple of publications (Supplementary Fig. 1).

Three studies were added after performing trim and fill analysis, in which these nine studies showed a non-significant association between sugars consumption and risk of ADHD symptoms (pooled effect size: 1.03, 95%CI: 0.98-1.08, P = 0.799).

4. Discussion

The current systematic review and meta-analysis of observational studies highlighted the association between sugar intake and ADHD symptoms in children over seven years old. Based on the results, there was a significant positive association between overall sugar intake and SSBs and symptoms of ADHD, after adjusting for important potential confounders. However, further analysis showed significant heterogeneity of this finding. Interestingly, the sub-group analysis revealed that dietary sugars alone did not increase the risk of developing ADHD symptoms, nevertheless, higher SSBs consumption was associated with a 40% greater odds of ADHD symptoms in the study population compared with their lower intake counterparts.

In the literature, there are conflicting reports regarding the association between sugar intake and ADHD. Michels et al. (35) reported a significant relationship between hyperactivity and the consumption frequency of sweet foods in preadolescent children. Amani et al. in a study of 7 to 9 years old school-age children found that high consumption of sugar is associated with increased severity of ADHD in school girls (37). In the trial study of Hoover et al., mothers of 5- to 7-year-old boys in the sugar expectancy condition reported their children as significantly more hyperactive (38). The possible explanation in which sugar consumption could cause behavioral problems is that sugar ingestion might induce gastrointestinal discomfort, reactive hypoglycemia, and/or insufficient intake of some essential micronutrients (39).

Meanwhile, Wolraich et al. (40), in a meta-analysis and literature review conducted on clinical trials, concluded that sugar consumption is not a significant risk factor for ADHD symptoms. The current meta-analysis, in line with the recent study, could not find any significant relationship between non-SSB sugar sources and symptoms of ADHD. The discrepancy between reports could be attributed to the different study designs, diagnostic tools, and adjustment of confounding variables, sample sizes, and population characteristics.

In the current study, we found some heterogeneity in concern with questionnaires, which was used by studies to assess the sugar intake of the individuals. This was probably due to the fact that food questionnaires that estimate the past food intake are usually limited by issues such as recall problems and the person who completes the questionnaire e.g, self/family report or using an interview. Furthermore, the period which was used by studies to determine the sugar intake was different to some extent, and it also can be considered as a heterogeneity source. Population size was another source of heterogeneity between the included studies. The diversity of study designs probably affected the results, which were reported by different investigators. Additionally, there was heterogeneity in sub-group analysis in the participant's age. Most research supports the theory that ADHD is a physiological condition and is therefore present at birth. An American Addiction Centers Resource indicates that a noticeable beginning of ADHD symptoms typically occurs early in childhood, which may be challenging to diagnose. Therefore the average age of diagnosis is 8-10 years (41). Also, It seems that different data sources (parent or another childcarer) that were used for subjects aged less than ten years old had impacts on dietary exposure assessments.

The observed relationship between SSBs intake and increased odds for ADHD symptoms is consistent with previous studies (42,43). This finding was also supported by Wesnes et al.'s (44) study, which reported that substituting breakfast for a sugary drink could impair attention and adversely affect memory in children. However, Kim et al. (36) in Korean school children from both genders did not found a significant association between the consumption of beverages and hyperactivity. The observed negative effects of sugar intake from SSBs that were reported by some studies should be interpreted with caution because there are existing confounding factors, such as ethnicity and race, socioeconomic status, as well as factors that have a more significant impact on childhood ADHD including attachment, parenting styles, and family structure, that could not be studied by this meta-analysis due to the limited number of studies assessing certain factors. These factors could drive both an increase in sugar intake and ADHD and that the relationship between them is accounted for in part by these factors. In fact, it is suggested that food coloring, preservatives or, even caffeine in SSBs might induce adverse effects on ADHD symptoms; consequently, these items should be considered as significant confounding variables in future studies (25,45). The controversy in findings of different studies may be explained by adjustment of confounding factors and diversity in beverages which considered to estimate sugar intake from SSBs.

This meta-analysis and systematic review had some limitations. Initially, there were a limited number of observational studies with various designs and epidemiologic power to determine the causality relationship. Secondly, the studies were used different criteria to determine ADHD risk in children. Some studies compared the sugar intake between ADHD diagnosed cases and healthy children, where others only estimated the risk of ADHD in children. Moreover, different studies used a different approach to evaluate ADHD risk, which must be discussed in further studies. Other than these, some sweetened beverages may also contain other substances such as caffeine which we were unable to distinguish their possible conflicting effect on ADHD along with sugar (25,45).

5. Conclusions

According to the current observational evidence, there is a positive relationship between total sugar intake from SSBs and dietary sources and symptoms of ADHD. Although, sugar intake from SSBs might be associated with increased the ADHD risk in children over seven years old; but, there is no relationship between dietary sugars consumption alone ADHD symptoms. Considering the possible involvement of other substances of SSBs, further controlled studies are warranted to accurately determine the cause and effect relationship between sugar and ADHD. At the same time, there should be more well-designed surveys and longitudinal studies to support the effect of sugar on ADHD.

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Appendix A. Supplementary data

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