

Review article

Dietary patterns and attention deficit/hyperactivity disorder (ADHD): A systematic review and meta-analysis



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ABSTRACT

Background: The Attention Deficit Hyperactivity Disorder (ADHD) is a neurobiological disorder characterized by persistent symptoms of inattention, impulsivity and hyperactivity. The diet during childhood has been investigated as a factor potentially involved in the ADHD etiology.

Objective: To review systematically the evidence of the association between dietary patterns and ADHD.

Methods: Two independent literature searches were carried out in PubMed, LILACS and PsycINFO databases. The studies included were only those that assessed dietary patterns and ADHD in children and adolescents. Due to heterogeneity between the studies random-effects models were used to pool the estimates.

Results: We included fourteen observational studies (four cohorts, five case-control and five cross-sectional studies). In the pooled analysis, healthy dietary patterns were protective against ADHD (OR: 0.65; 95% CI: 0.44 – 0.97), while unhealthy dietary patterns were found as risk to ADHD (OR: 1.41; 95% CI: 1.15–1.74). After stratifying the studies by design (cohort/case control or cross-sectional), continent (Europe or Asia/Oceania) and sample size (≥ 1000 or < 1000) the effects remained.

Limitations: Absence of randomized controlled trials at the literature on this subject and scarce evidence from more robust designs, such as cohort and case-control studies.

Conclusion: This study suggests that a diet high in refined sugar and saturated fat can increase the risk, whereas a healthy diet, characterized by high consumption of fruits and vegetables, would protect against ADHD or hyperactivity. Nevertheless, giving the number and the design of most of the studies available in the literature, the current evidence is weak. More studies using longitudinal design need to be performed to reinforce this evidence.

1. Introduction

The Attention Deficit Hyperactivity Disorder (ADHD) is a neurobiological disorder characterized by persistent symptoms of inattention, impulsivity and hyperactivity (Association AP, 2013). The ADHD begins at childhood and frequently persists until adulthood, causing low educational achievement, as well as cumulative losses throughout life (Barkley and Roizman, 2002), such as family and interpersonal difficulties. The etiology of the disorder is multifactorial, resulting from the interaction between the sex of the child (Arnold, 1996) and genetic and environmental factors, such as intrauterine exposures (Bekkhus et al., 2010) and parent's mental health (Anselmi et al., 2010).

The role of diet in the prevention and/or treatment of ADHD was firstly investigated in the 1980s and 1990s, resulting in a series of studies, mostly experimental, focusing on the effect of additives and sugars on the attention deficit and/or hyperactivity (Wolraich et al., 1995). As a result, dietary therapies were proposed at that time, which

mainly included restriction of sugar, additives, food coloring agents and antigens. Later studies showed the protective effect of increased iron intake (Konofal et al., 2008; Konofal et al., 2004), zinc (Akhondzadeh et al., 2004; Arnold et al., 2005), iodine (Yüksek et al., 2016) and polyunsaturated fatty acids (Johnson et al., 2009; Sinn and Bryan, 2007; Richardson and Montgomery, 2005), and in contrast, adverse effect of excessive ingestion of food coloring agents (Bateman et al., 2004; Rowe and Rowe, 1994), preservatives (McCann et al., 2007) and sugar (Park et al., 2015; Wiles et al., 2009).

Recent studies assessing diet effect on the development of diseases have focused their analysis on dietary patterns, instead of specific nutrients consumption. The analysis of dietary patterns emerged as a complementary approach in the study of the relationship between diet and chronic diseases (Hu, 2002). Thus, the effects of overall diet combinations are evaluated, incorporating complex interactions that occur between nutrients (Hu, 2002). Dietary patterns represent a wider vision of nutrient and food intake and may be more appropriate for the

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study of the relationship between dietary factors and diseases, (Hu, 2002) as ADHD. Therefore, the purpose of this study was to review systematically the evidence about the relationship between dietary patterns and ADHD. Our hypothesis was that healthy dietary patterns would be protective whereas unhealthy dietary patterns would increase the risk of ADHD.

2. Methods

In March 2019, we searched indexed articles in *PubMed*, *LILACS* and *PsycINFO* databases using the following combination of descriptors: (“diet” OR “eating pattern” OR “eating patterns” OR “food pattern” OR “food patterns” OR “dietary pattern” OR “dietary patterns” OR “dietary behaviors” OR “dietary behaviours” OR “dietary habits”) AND (“attention deficit hyperactivity disorder” OR “adhd” OR “adh” OR “hyperactive” OR “hyperactivity” OR “inattentive” OR “inattention” OR “hyperactive behaviors” OR “hyperactive behaviours” OR “externalizing behavior problems” OR “externalizing behaviour problems” OR “behavior problems” OR “behaviour problems”). In addition, we searched reference lists of the articles identified.

The review process was performed in pairs. Disagreements were solved by the reviewers’ consensus. The studies included were those that assessed the exposure (dietary pattern) and the outcome of interest (ADHD and/or hyperactivity). The selected papers were analyzed methodologically through the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) tool, that assesses, among other criteria, sample representativeness, appropriateness of the design, presence of blinding for evaluating outcomes, training and measures of standardization, use of appropriate instruments for exposure and outcome assessment, appropriate statistical analysis, control for confounding factors, and power calculation (Vandenbroucke et al., 2014). We considered to this review, a minimal set of confounders: sex, socioeconomic variables and maternal schooling.

As the studies included in the review explored the effects of different dietary patterns, for the meta-analysis we selected the most frequently analyzed patterns that presented the food description, thus allowing the characterization of the dietary pattern. Two dietary patterns attended those requirements and were analyzed: a healthy pattern (characterized predominantly by foods of plant origin sources of vitamins and minerals and which did not include processed or ultra-processed food, sources of saturated or hydrogenated fat, low quality sugars and chemical additives) and an unhealthy pattern (processed or ultraprocessed foods, sources of saturated or hydrogenated fat, low-quality sugars and additives such as colorants, flavorings and preservatives, and which did not include food of plant origin). Hence, two meta-analysis were performed, one to assess the effect of healthy food consumption on ADHD and another to assess the same effect of unhealthy foods. Pooled effects were calculated using fixed and random-effects models. Heterogeneity among studies was assessed using the Q-test and I-square; if either test suggested that the variability between studies was higher than expected, the random-effects model was used. A Forest plot was used to present the results of the meta-analysis and the comparison of the studies. The publication bias was formally tested by the Egger test. The review was registered on PROSPERO—International Prospective Register of Ongoing Systematic Reviews (CRD42018111822).

3. Results

Initially, the 1260 references found in the *Pubmed* and the 562 found in the other databases (*LILACS* and *PsycINFO*) were exported to an *EndNote* library. A total of 271 duplicates were identified. Next, we selected the titles, resulting in 31 abstracts to be assessed by the reviewer 1 and 44 by the reviewer 2.

After this, reviewer 1 excluded 16 manuscripts based in the following reasons: no assessment of the exposure of interest (like food

coloring agents, additives and vitamin supplements) ($n = 2$); theoretical papers or reviews ($n = 6$); experimental studies with use of diet on ADHD treatment ($n = 3$); ADHD evaluated as the exposure and diet as the outcome ($n = 5$). Of the fifteen papers left for full reading, tree did not meet the inclusion criteria previously set (evaluated as exposure the intake of additives, the influence of different diets in children with ADHD or the quality of diet rather than dietary patterns) and were subsequently excluded. One paper was included from the references’ list, remaining thirteen articles that met the inclusion criteria to compose the systematic review.

The reviewer 2 excluded 29 manuscripts after the abstract reading based in the following reasons: no assessment of the exposure of interest ($n = 14$), theoretical papers or reviews ($n = 7$) and experimental studies with use of diet on ADHD treatment ($n = 8$). Of the fifteen papers left for full reading, two did not meet the inclusion criteria previously set (the influence of different diets in children with ADHD). Thus, thirteen papers were selected for the systematic review.

In the last step, comparing the selected publications, ten were consensus and six discordant. Finally, two manuscripts were excluded by consensus, because they evaluated the effect of diet on ADHD treatment. Thus, fourteen references were included by agreement to the systematic review (Fig. 1).

The selected studies used an observational design and had been published in the last eight years. Five studies had a cross-sectional design (Azadbakht and Esmailzadeh, 2012; Howard et al., 2011; Park et al., 2012; Oellingrath et al., 2014; Kim and Chang, 2011; Yan et al., 2018), four were cohorts (Wiles et al., 2009; Howard et al., 2011; Peacock et al., 2011; Kohlboeck et al., 2012) and five, case-control (Woo et al., 2014; Ríos-Hernández et al., 2017; Zhou et al., 2016; Abbasi et al., 2019; Chou et al., 2018). Sample size varied from 375 (Azadbakht and Esmailzadeh, 2012) to 16,831 participants (Kim et al., 2018) and the analyses were adjusted at least for the minimal set of confounding factors.

The included studies were conducted in Europe (Norway, England, Australia, and Germany) (Wiles et al., 2009; Howard et al., 2011; Oellingrath et al., 2014; Peacock et al., 2011; Kohlboeck et al., 2012), Asia (China, Iran and Korea) (Azadbakht and Esmailzadeh, 2012; Park et al., 2012; Kim and Chang, 2011; Yan et al., 2018; Woo et al., 2014; Zhou et al., 2016; Abbasi et al., 2019; Chou et al., 2018) e Oceania (Howard et al., 2011). Table 1 presents a detailed description of the studies included in this review. The effect of healthy and unhealthy patterns over ADHD or hyperactivity was analyzed in twelve and thirteen studies, respectively (one study explored exclusively the effect of a healthy pattern; two studies explored exclusively the effect of unhealthy patterns; and eleven studies explored both effects).

3.1. Cohort and case-control studies

The first study was conducted by Wiles et al. (Wiles et al., 2009), with data from a British cohort (ALSPAC), including 4000 children, that assessed the relationship between diet at 4.5 years and behavior at seven years of age. A Food Frequency Questionnaire (FFQ) was applied to mothers to assess diet. Dietary patterns were constructed using principal component analysis (PCA), identifying three dietary patterns. This study used only one of them, “junk food”, associated to the highest consumption of ultra-processed foods, high concentration of sugar and fat foods and nutritional low-quality foods. The outcome, behavior disorders, was assessed by Strengths and Difficulties Questionnaire (SDQ). The pattern “junk food” was associated to hyperactivity, even after adjusting for sex, maternal smoking (during pregnancy and when the children were four years old), maternal age at child’s birth, number of siblings, socioeconomic variables (maternal education, house ownership, household overpopulation, and car ownership), birth weight, gestational age and maternal depression and anxiety (at 33 months).

Peacock et al. (2011) using data from the ALSPAC cohort, investigated whether a “junk food” diet at 81 months of age was

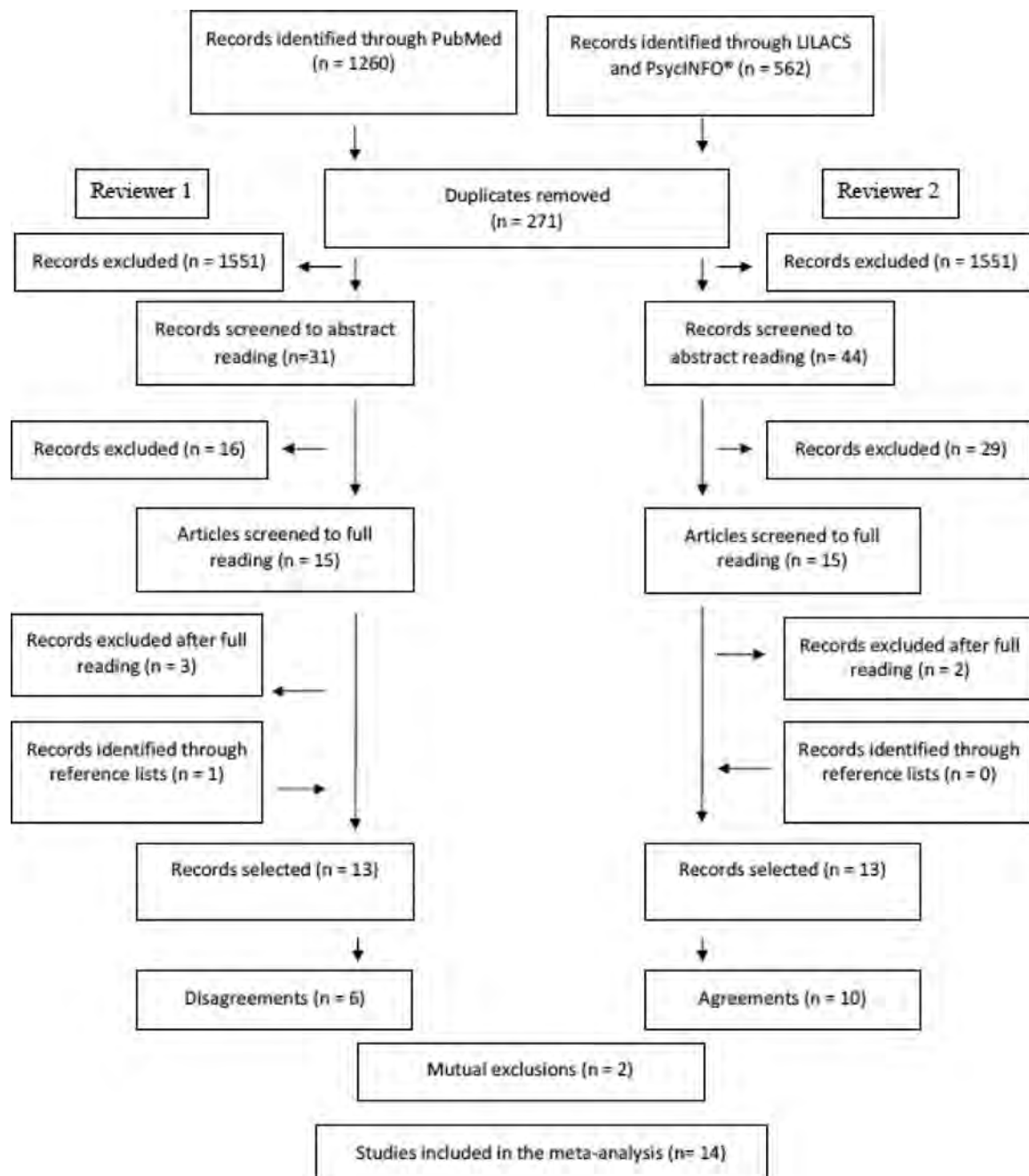


Fig. 1. Diagram reporting studies selection process.

associated with the development of behavioral problems over the following sixteen months. The participant's diet was assessed by FFQ and three dietary patterns were identified using PCA: “Junk food”, “health-conscious” and “traditional”. However, just the “junk food” pattern, associated to higher consumption of saturated fat, sugar and sodium was analyzed. As in the study by Wiles et al. (2009) at the same cohort, behavioral problems were measured using the SDQ. The analysis was adjusted for possible maternal confounders when the child was six years old (smoking, age, depression and anxiety), children's confounders (sex, birth weight, gestational age and eight years IQ) and socio-demographic confounders at seven years old (maternal education, income stratum, living conditions, and if the family owned a car). No association was found between “junk food” pattern and behavioral problems (OR: 1.01; 95% CI: 0.92–1.10).

In an Australian birth cohort, Howard et al. (2011) analyzed 1799

adolescents. The food information was collected by FFQ and two dietary patterns were identified by PCA, the “Western” and the “Healthy” pattern. The “Western” pattern was positively associated to high saturated fat, sugar and sodium consumption, and inversely associated to Omega3, fiber and folic acid intake. The “Healthy” pattern was positively associated to Omega3, fiber and folic acid, and inversely associated to saturated fat, sugar and sodium. To assess the outcome, the adolescent was asked if he had ever received a medical diagnosis of ADHD. Those with a positive response were evaluated by a clinician, to confirm or refute the diagnosis based on the International Classification of Diseases, Ninth Revision (ICD-9). The analysis was adjusted by total energy intake, gestational variables and adolescent's characteristics (physical activity, sedentary lifestyle, family structure, and income). After adjusting, the highest consumption of the “Western” pattern was associated to ADHD (OR: 2.21; 95% CI: 1.18–4.13), whereas the

Table 1
Selected characteristics of the included studies.

Author, year, country	Design	Population age	Outcome instrument	Main exposure	Main results	(STROBE) Evaluation
Willes et al. (2009), England	Cohort (ALSPAC)	4000 Seven years old children	Screening for hyperactivity/ inattention: SDQ	Dietary patterns—FFQ-PCA <i>Junk food</i> (fat and sugar)	<i>Junk food</i> pattern was associated with increase of hyperactivity at 7 years (OR: 1.13; 95% CI: 1.01–1.15).	24/34
Howard et al. (2011), Australia	Cohort	1799 Adolescents 14 years old	ADHD Clinical diagnosis: CID-9	Dietary patterns—FFQ-PCA Western (saturated fat, refined sugar and sodium) - <i>Healthy</i> (Omega3, fiber, folic acid)	Western pattern was associated with ADHD (OR: 2.21; 95% CI: 1.18–4.13). <i>Healthy</i> was not associated (OR: 1.02; 95% CI: 0.61–1.70)	24/34
Peacock et al. (2011) England	Cohort (ASPAC)	7727 Eight years old children	Screening for hyperactivity/ inattention: SDQ	Dietary patterns—FFQ-PCA <i>Junk food</i> (fat and sugar)	<i>Junk food</i> was not associated with ADHD (OR: 1.01 ; 95% CI: 0.92–1.10).	26/34
Park et al. (2012), Korea	Cross-sectional	986 Children aged 8 to 11	ADHD Clinical diagnosis: DISC-IV	Dietary patterns established a priori FFQ <i>Dairy products</i> (milk or dairy product) <i>High-protein diet</i> (meat, fish, egg, bean or tofu) <i>Vegetables</i> (vegetables) <i>Fruits</i> (fruit or fruit juice) <i>Fried foods</i> (fried or stir-fried) <i>Fatty meats</i> (bacon, ribs, eel, etc.) <i>Sweetened desserts</i> (ice-cream, cake, snacks and soda)	<i>Vegetables</i> pattern was not associated with ADHD (OR:0.94; 95% CI:0.42–2.12) <i>Fruits</i> pattern was not associated with ADHD (OR:0.94; 95% CI:0.42–2.12) <i>Field foods</i> pattern was not associated with ADHD 1.96 (0.74, 5.16) <i>Fatty meats</i> pattern was not associated with ADHD (OR:1.85; 95% CI:0.78–4.37) <i>Sweetened desserts</i> pattern was not associated with ADHD (OR:0.86; 95%CI:0.36–2.08)	25/34
Azadbakht and Esmailizade (2012), Iran	Cross-sectional	375 Eight years old schoolchildren	ADHD Clinical diagnosis: DSM-IV	Dietary patterns—FFQ-AF - <i>Healthy</i> (fruits, vegetables, vegetable oils, whole grains and dairy products) - <i>Western</i> (high in processed meat, red meat, butter, eggs, pizza, snacks, animal fat, and hydrogenated fat) - <i>Sweet</i> (highly loaded with ice cream, refined grains, sweet desserts, sugar, and soft drinks) - <i>Fast food</i> (high in processed meat, commercially produced fruit juices, pizza, snacks, sauces and soft drinks).	<i>Healthy</i> pattern was not associated with ADHD (OR 0.84; 95% CI 0.28–2.21) (Q5 vs. Q1). <i>Western</i> pattern was not associated with ADHD (OR: 1.34; 95% CI: 0.58–4.29) (Q5 vs. Q1). <i>Sweet</i> pattern consumption presented risk to ADHD, comparing the highest quintile to the lowest (OR 3.96; 95% CI 1.16–15.31) (Q5 vs. Q1). <i>Fast-food</i> pattern presented risk to ADHD (OR 3.21; 95% CI: 1.05–10.90) (Q5 vs. Q1).	21/34
Kohlboeck et al. (2012), Germany	Cohort	3361 children 10 years old	Screening for hyperactivity/ inattention: SDQ	Dietary patterns established a priori FFQ <i>Dairy and dairy products</i> (milk, cheese, yoghurt) <i>Fats and oils</i> (butter, vegetable oils, margarine) <i>Fruits and vegetables</i> (apples, carrots, mushrooms, nuts and seeds) <i>Confectionery</i> (chocolate, candy, chewing gum) <i>Cereals and cereal products</i> (rice, pasta, breakfast cereals) <i>Bakery wares</i> (bread, rolls, cakes, cookies) <i>Meat and meat products</i> (fresh and	The dietary patterns <i>fruits and vegetables</i> , <i>confectionery</i> , <i>beverages and ready-to-eat savories</i> were not associated with hyperactivity/inattention [(OR: 0.87; 95% CI: 0.72–1.02); (OR: 1.06; 95% CI: 0.96–1.17); (OR:1.04; 95% CI:0.91–1.19); (OR:1.08; 95% CI:0.89–1.28)] <i>Meat and meat products</i> pattern was associated with ADHD (OR: 1.17; 95% CI: 1.01–1.35)	25/34

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Table 1 (continued)

Author, year, country	Design	Population age	Outcome instrument	Main exposure	Main results	(STROBE) Evaluation
Oellingrath et al. (2013), Norway	Cross-sectional	1095 Adolescents aged 12 and 13 years	Screening for hyperactivity/inattention: SDQ	processed meat, sausages) <i>Fish and fish products</i> <i>Eggs and egg products</i> Beverages (soft and energy drinks, fruit juices/nectars, water-based flavored drinks, tea) <i>Ready-to-eat savories</i> (snacks: crisps) Dietary patterns—FFQ-PCA <i>Varied Norwegian</i> (unrefined plant foods, fish, water) <i>Junk/convenient</i> (high-energy processed fast foods, refined grains, cakes and sweets) <i>Snacking</i> (sugar-rich snack items and drinks, low intake of vegetables and brown bread, low frequency of eating breakfast and dinner and high frequency of eating between meals)	<i>Varied Norwegian</i> pattern was protection for hyperactivity (OR:0.4; 95% CI: 0.2–0.8). <i>Junk/convenient</i> pattern presented risk to ADHD (OR:3.4; 95% CI:1.3–8.6) <i>Snacking</i> pattern was not associated with ADHD (OR:1.6; 95% CI:0.7–3.5)	23/34
Woo et al. (2014), Korea	Case-control	117 cases 202 controls Children and adolescents, 7–12 years old	ADHD Clinical diagnosis: DSM-IV	Dietary patterns—24 h recall-PCA <i>Traditional</i> (condiments, vegetables, tofu/soymilk, and mushrooms) <i>Seaweed-egg</i> (seaweeds, fats/oils, sweets, and eggs) <i>Traditional-healthy</i> (kimchi, grains, bonefish) <i>Snack</i> (high intakes of snacks and processed meat and a low intake of noodles)	<i>Traditional</i> was not associated with ADHD comparing the second to the first tertile (OR: 0.43; 95% CI: 0.18–1.04) <i>Traditional-healthy</i> pattern showed protective effect comparing the third to the first tertile (OR:0.32; 95% CI: 0.13–0.77) <i>Snack</i> pattern was risk to ADHD comparing the second to the first tertile (OR: 2.93; 95% CI:1.22–7.05)	19/34
Zhou et al. (2016) China	Case-control	293 pares de crianças e adolescentes de 6 a 14 anos, recrutados em clínicas pediátricas	ADHD Clinical diagnosis: CID10 e DSM IV	Dietary patterns—FFQ-AF <i>Vegetable-Fruit</i> (leafy vegetables, fruiting vegetables, tuber vegetables, fruits, and root vegetables) <i>Fish-White meat</i> (shellfish, deep water fish, white meat, freshwater fish, organ meat, and fungi and algae) <i>Grain-Bean</i> (process grains, soya beans, grains, and other beans) <i>Fast food-Sweet</i> (fast food, ice cream, sweets, snacks, and red meat, but low loadings for dairy products)	<i>Vegetable-Fruit</i> was not associated with ADHD comparing the third to the first tertile (OR: 0.69; 95% CI:0.42–1.13) <i>Fast food-Sweet</i> was not associated with ADHD comparing the third to the first tertile (OR: 1.25; 95% CI:0.76–2.06)	24/34
Ríos-Hernández et al. (2017) Spain	Case-control	60 matched children and adolescents from 6 to 16 years were recruited at the ADHD Unit of the Department of Child and Adolescent Psychiatry and Psychology of the Hospital of Sant Joan de Deu in Barcelona. 42 patients with ADHD treated in the outpatient Department of Child Psychiatry at Chang Gung	ADHD Clinical diagnosis: DSM IV	Dietary patterns—FFQ-AF <i>Mediterranean Diet</i> (healthy and balanced diet)	The lower adherence to a <i>Mediterranean</i> diet was associated with ADHD (OR: 7.07; 95% CI: 2.65–18.84), even after adjustment for potential confounding factors.	25/34
Chou et al. (2017) China	Case-control		ADHD Diagnostic tool ADHD-RS based on DSM-IV	Dietary patterns established a priori by FFQ <i>Grains</i> <i>Refined grains</i>	Healthy eating patterns <i>Vegetable and Fruit</i> were not associated with ADHD (measure of effect not presented by the authors)	24/34

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Table 1 (continued)

Author, year, country	Design	Population age	Outcome instrument	Main exposure	Main results	(STROBE) Evaluation
Kim et al. (2018) Korea	Cross-sectional	Children's Hospital in Taiwan and 36 healthy control children.	16,831 school children aged 6–12 years	Meat (including seafood) Vegetable Fruit Dairy Oil Nuts/seeds/legumes Dietary patterns established a priori by FFQ Fast food Soft drinks Instant noodles Vegetables Fruit Milk	Refined grains consumption was lower among controls compared to children with ADHD (OR: 0.19; 95% CI: 0.04–0.93) Children who consumed fast food, soft drinks and instant noodles more frequently showed higher odds for ADHD risk compared to children who 'never' consumed these foods (referent) [(OR: 1.54; 95% CI: 1.13–2.09); (OR: 1.72; 95% CI: 1.38–2.15); (OR: 1.64; 95% CI: 1.30–2.08)]. Children who never consumed fruits and vegetables showed higher odds for ADHD compared to children who consumed these foods 'more than 3 times per day' (referent) [(OR: 2.51; 95% CI: 1.96–3.22); (1.83; 95% CI: (1.14–2.95)]	18/34
Yan et al. (2018) China	Cross-sectional	14,912 children aged 3–6 years old	Screening for attention and hyperactivity problems: Conners abbreviated symptom questionnaire (C-ASQ)	Dietary patterns—FFQ-PCA Processed (fried vegetables, fried rice and wheat, smoked foods, fried meat, processed foods, western fast foods) Vegetarian (preserved fruit, coarse food grain, wheat and wheat foods, beans in various forms, green vegetables, other vegetables, fresh fruit/vegetable juice) Snack (sweets, chocolate, snack-biscuits or cake-, puffed food, milk-based puddings and custard) Beverage (puffed food, milk-based puddings and custard, fruit juice, flavored milk drinks, carbonated beverages, yogurt, preserved fruit) Protein (rice and processed, products, red meat, poultry, egg, fish and other fishery products, fruits)	After adjustment for potential confounders, preschoolers with scores in the top quintile for the processed snack (OR = 1.56; 95% CI: 1.31–1.86) and snack (OR = 1.76; 95% CI: 1.49–2.07) were at increased risk of presenting ADHD symptoms. Children in the top quintile for the vegetarian pattern intake were less likely to have ADHD symptoms (OR = 0.67; 95% CI: 0.56–0.79). The beverage dietary pattern was not associated with ADHD symptoms (OR: 1.18; 95% CI: 0.99–1.41)	22/34
Abbasi et al. (2019) Iran	Case-control	Children aged 4 to 12 years old 200 with ADHD were selected from psycho-therapy clinics in Isfahan 300 healthy were recruited from preschool and elementary schools in Isfahan	ADHD Clinical diagnosis: DSM-V	Dietary patterns—FFQ-AF Healthy (vegetable, fruit, nut, cereals, dairy low fat, pickles, olives, dough, fish, natural fruit juice, dried fruit, vegetable oil, whole cereals, poultry, without skin, fruit can, spices, potato) Western (refined cereals, red meat, entrails, coffee, garlic, dairy high fat, poultry with skin, dessert, sugar, sweets, salt, broth, hydrogenated fat, processed meat, soft drinks, egg)	After adjustment, the Western dietary pattern was associated with a higher risk of having ADHD (OR: 3.45; 95% CI: 1.17–18.3). The highest quintile of the Healthy pattern was negatively associated with risk of ADHD after adjusting for potential confounding factors (OR: 0.46; 95% CI: 0.38–0.91).	19/34

CID-9: International Classification of Diseases, Ninth Revision; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; SDQ: Strengths and Difficulties Questionnaire; DISC-IV: Diagnostic Interview Schedule for Children version—IV; PCA: Principal component analysis; FFQ: Food Frequency Questionnaire; FA: Factor analysis; MDA: Mini-dietary assessment; ADHD Rating Scale (K-ARS); ADHD-RS:

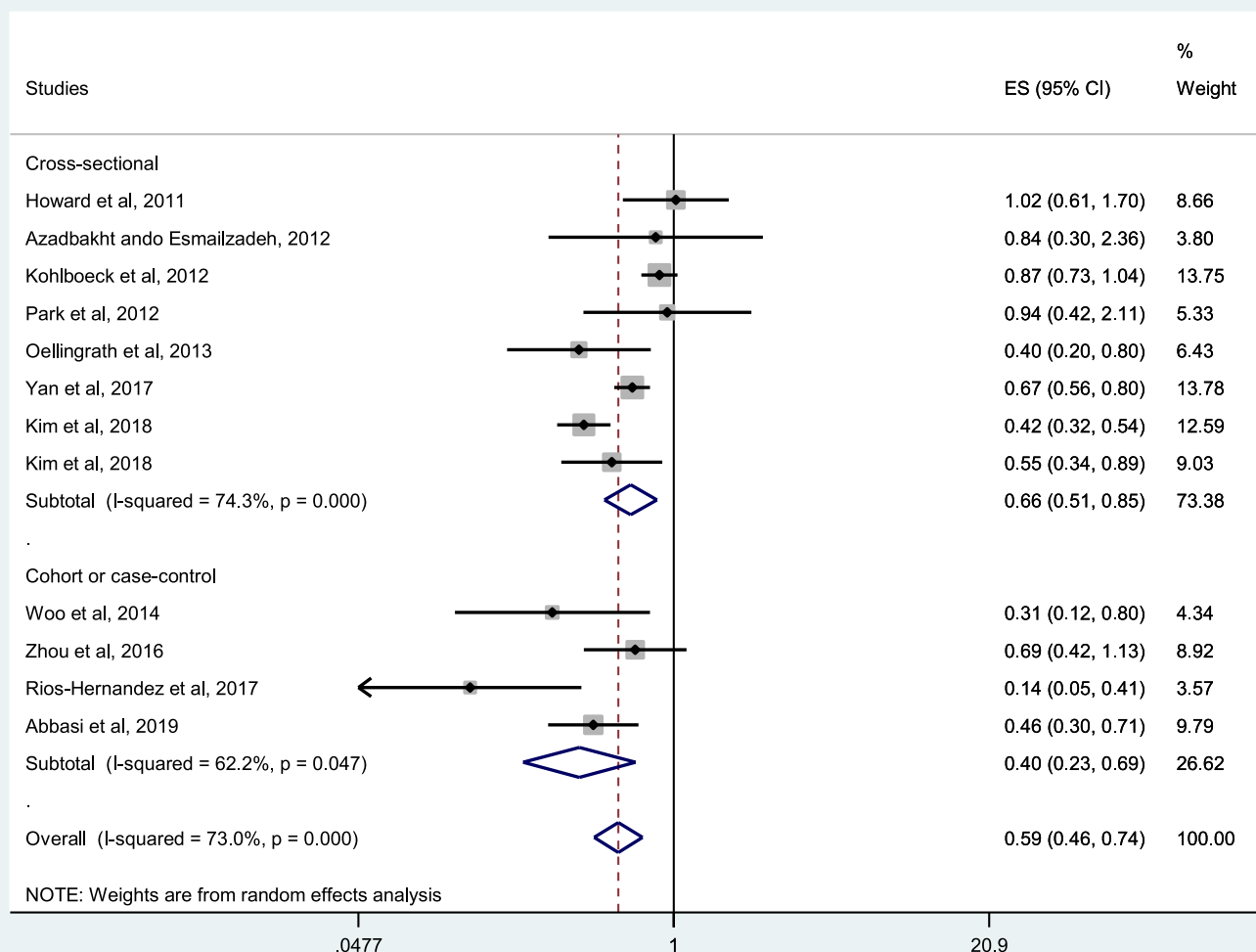


Fig. 2. Healthy dietary patterns and ADHD's Forest plot stratified by study design.

“Healthy” pattern did not show association (OR: 1.02; 95% CI: 0.61–1.70).

Kohlboeck et al. (2012) in a birth cohort from Germany evaluated the effect of diet on hyperactivity/inattention. A total of 3361 children who presented complete outcome and exposure information were evaluated. The instrument to evaluate hyperactivity/inattention was SDQ. The dietary patterns were established *a priori* from FFQ: “Dairy and dairy products” (milk, cheese, yoghurt), “Fats and oils” (butter, vegetable oils, margarine), “Fruits and vegetables” (apples, carrots, mushrooms, nuts and seeds), “Confectionery” (chocolate, candy, chewing gum), “Cereals and cereal products” (rice, pasta, breakfast cereals), “Bakery wares” (bread, rolls, cakes, cookies), “Meat and meat products” (fresh and processed meat, sausages), “Fish and fish products”, “Eggs and egg products”, “Beverages” (soft and energy drinks, fruit juices/nectars, water-based flavored drinks, tea), and “Ready-to-eat savories” (snacks: crisps). The dietary patterns “Fruits and vegetables”, “Confectionery”, “Beverages” and “Ready-to-eat savories” were not associated with hyperactivity/inattention [(OR: 0.87; 95% CI: 0.72–1.02), (OR: 1.06; 95% CI: 0.96–1.17), (OR: 1.04; 95% CI: 0.91–1.19), and (OR: 1.08; 95% CI: 0.89–1.28)], respectively], while, “Meat and meat products” pattern was associated with ADHD (OR: 1.17; 95% CI: 1.01–1.35).

A case-control study carried by Woo et al. (2014) in Korea, selected a total of 117 ADHD cases, diagnosed by psychiatrists based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition

(DSM-IV). Age- and sex-matched controls were recruited from three university hospitals. To assess dietary intake, three non-consecutive 24-hour dietary recall (HR) interviews were employed and 32 predefined food groups were considered in a PCA. Four major dietary patterns were identified. The “traditional”, composed by condiments, vegetables, tofu/soymilk, and mushrooms; the “traditional-healthy”, consisting by consumption of kimchi, grains, bonefish, and low intakes of fast foods and beverages; the “seaweed-egg” pattern characterized by consumption of seaweeds, fats/oils, sweets, and eggs; and the “snack” pattern, consisted by high intakes of snacks and processed meat and a low intake of noodles. All analyses were adjusted for birth weight, birth order, gestational age and sex of the child, schooling and paternal occupation, maternal age, and family income. When comparing the third tertile (highest consumption) with the first tertile (reference), the “traditional-healthy” pattern had a protective effect over the occurrence of ADHD (OR: 0.31; 95% CI: 0.12–0.79). On the other hand, the highest consumption of the “snack” pattern (third tertile) increased the risk for ADHD when compared to the second and first tertiles (less consumption) (OR: 2.93; 95% CI: 1.22–7.05). The other dietary patterns were not associated to ADHD.

Zhou et al. conducted a case-control study with 293 pairs of children and adolescents aged six to fourteen years, recruited at pediatric clinics (Zhou et al., 2016). The outcome, ADHD, was assessed clinically, based on the ICD-10 and on the Diagnostic and Statistical Manual of Mental

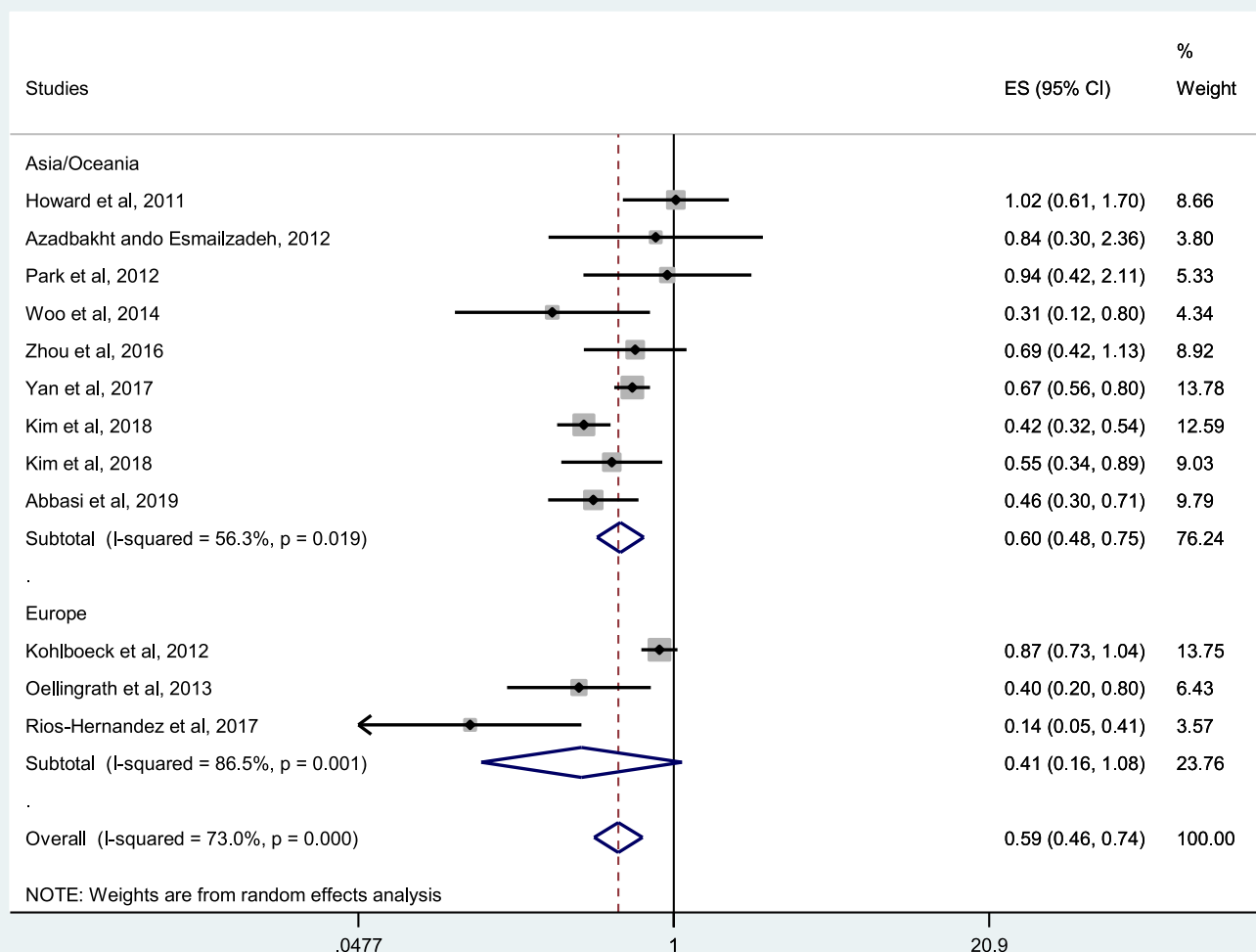


Fig. 3. Healthy dietary patterns and ADHD's Forest plot stratified by contine.

Disorders-Fourth Edition Revised (DSM-IV-R). The food intake was measured using FFQ. The dietary patterns generated by factor analysis were “Vegetable-fruit” (fruits and vegetables), “Fish-white meat” (fish and white meat), “Grain bean” (grains), and “Fast food-sweet” (fast-food, ice cream, sweets, snacks, and red meat). The analyses were adjusted for body mass index (BMI), daily energy intake, family history of ADHD, household composition, maternal smoking during pregnancy, paternity smoking during pregnancy, postpartum paternal smoking, previous maternal obstetric history of abortion, maternal age at birth, parental education, family income, clinical complications at birth, birth weight, twin birth, gestational age, breastfeeding, emotional abuse, and family conflicts. Comparing the second and third tertiles of consumption to the first (lower consumption), the “Fish-white meat” pattern was inversely associated with ADHD (OR: 0.57 95% CI: 0.38–0.85 and OR: 0.55; 95% CI: 0.37–0.82, respectively). In addition, the second and third tertiles of consumption of the other healthy dietary pattern, “Grain bean”, were inversely associated with ADHD (OR: 0.65; 95% CI: 0.43–0.96 and OR: 0.62; 95% CI: 0.42–0.92, respectively), when compared to the first tertile (lower consumption). The “Fast food-sweet” pattern was not associated to ADHD (Zhou et al., 2016).

A small case-control study in Spain with 60 pairs of children and adolescents from 6 to 16 years old assessed the effect of the Mediterranean diet on ADHD. The cases were recruited at a psychiatric outpatient clinic of a university hospital in Barcelona and the controls

were classmates of patients with ADHD and patients attending other hospital services. The ADHD diagnoses was clinical, based on the DSM-IV-R. Diet was assessed using FFQ, which allowed the construction of a Mediterranean diet adherence score. The lower adherence to the Mediterranean diet was associated to ADHD (OR: 7.07; 95% CI: 2.65–18.84, Ríos-Hernández et al., 2017).

Chou et al. (2018) conducted a case-control study with 42 patients with ADHD treated in the outpatient Department of Child Psychiatry at Chang Gung Children's Hospital in Taiwan and 36 healthy control children. The outcome, ADHD, was assessed clinically, using the ADHD Diagnostic tool ADHD-RS based on the DSM-IV. Dietary patterns were established *a priori* and eight dietary patterns were investigated through FFQ: “Grains”, “Refined grains”, “Meat (including seafood)”, “Vegetable”, “Fruit”, “Dairy”, “Oil”, and “Nuts/seeds/legumes”. Healthy eating patterns “Vegetable” and “Fruit” were not associated with ADHD. Refined grains consumption was lower among controls compared to children with ADHD (OR: 0.19; 95% CI: 0.04–0.93).

A case control study (Abbasi et al., 2019) was carried out in Iran with children aged 4 to 12 years old. Two hundred children with ADHD were selected from psychotherapy clinics in Isfahan and 300 healthy children were recruited from preschool and elementary schools in Isfahan. The diagnosis of ADHD was made through the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V). The Diet was assessed by FFQ and the food standards established by factorial

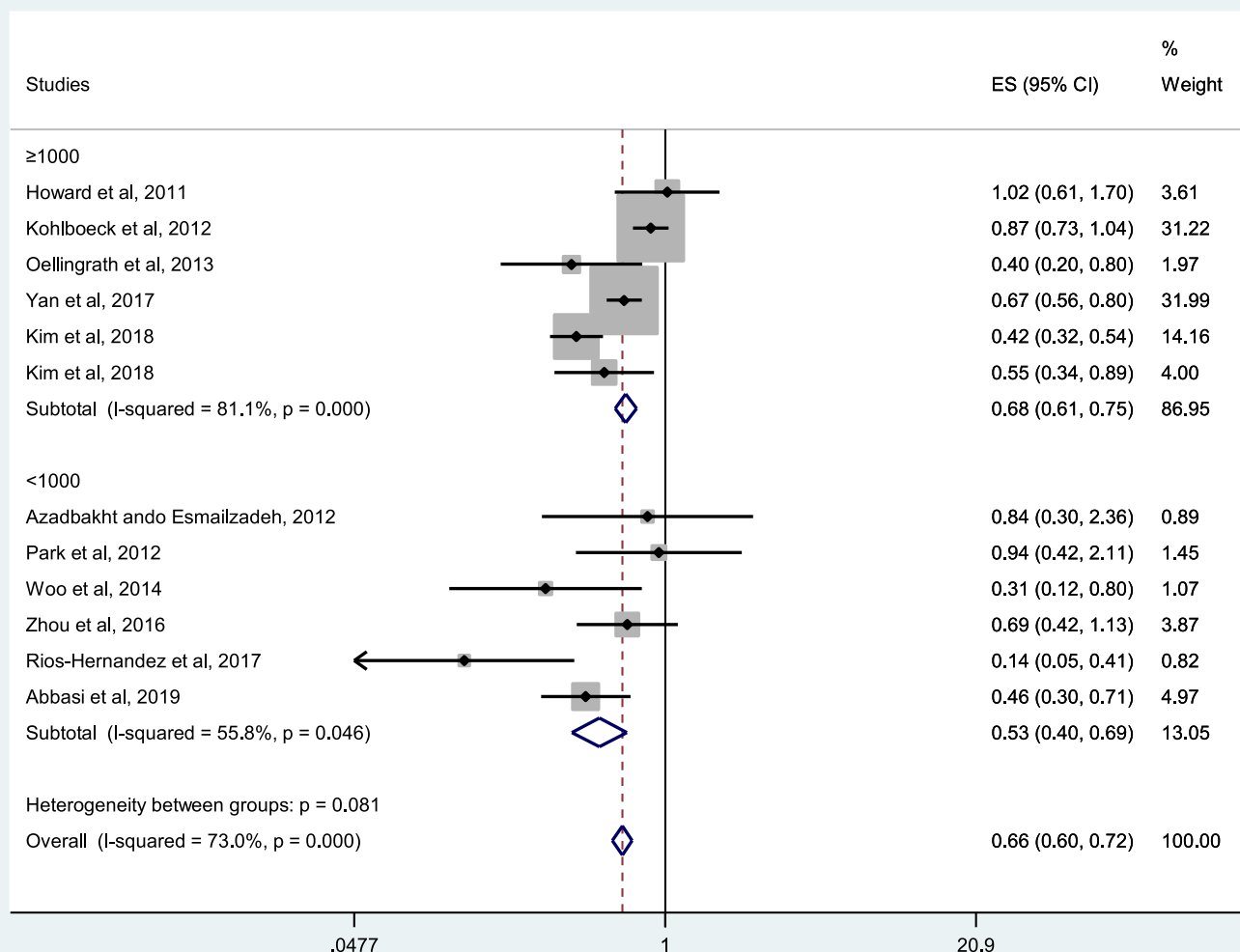


Fig. 4. Healthy dietary patterns and ADHD's Forest plot stratified by sample size.

analysis. Two eating patterns were identified: “Healthy” (vegetable, fruit, nuts, cereals, dairy low fat, pickles, olives, dough, fish, natural fruit juice, dried fruit, vegetable oil, whole cereals, poultry without skin, fruit can, spices, and potato) and the “Western” (refined cereals, red meat, entrails, coffee, garlic, dairy high fat, poultry with skin, dessert, sugar, sweets, salt, broth, hydrogenated fat, processed meat, soft drinks, and egg). In adjusted analysis, the “Western” dietary pattern was associated with a higher risk of ADHD (OR: 3.45; 95% CI: 1.17–18.3) and the highest quintile of consumption of the “Healthy” pattern (when compared to the lowest quintile) was negatively associated with risk of ADHD (OR: 0.46; 95% CI: 0.38–0.91).

3.2. Cross-sectional studies

In Iran, a cross-sectional study carried out by Azadbakht and Esmailzadeh (2012) with 375 schoolchildren aged in average eight years old, food consumption was assessed using FFQ and dietary patterns were generated through factorial analysis. Four dietary patterns were identified: “healthy” (fruits, vegetables, vegetable oils, whole grains, and dairy products), “Western” (high in processed meat, red meat, butter, eggs, pizza, snacks, animal fat, and hydrogenated fat), “sweet” (highly loaded with ice cream, refined grains, sweet desserts, sugar, and soft drinks), and “fast food” (high in processed meat, commercially produced fruit juices, pizza, snacks, sauces, and soft drinks).

The ADHD diagnosis was clinical, based on the DSM-IV). The analyses were adjusted for confounders (total energy intake, sex, socioeconomic status, and family history of ADHD). The dietary patterns were stratified in quintiles. After adjusting for confounders, children at the 5th superior quintile of the “sweet” (OR = 3.95; 95% CI: 1.16–15.31) and the “fast food” pattern consumption (OR = 3.21; 95% CI: 1.05–10.90) presented higher prevalence of ADHD, in comparison to children in the lowest tertile of consumption. The Healthy pattern was not associated with ADHD (OR 0.84; 95% CI: 0.28–2.21).

Park et al. (2012) conducted a cross-sectional study with 986 Korean children aged 8 to 11 years old. The children's eating habits were investigated through the Mini-dietary Assessment (MDA), a food survey tool built for the Korean population, which derives food patterns *a priori*. Participants were classified in three consumption groups (frequently, usual and rarely). The definitive or probable diagnosis of ADHD (presence of hyperactivity, attention deficit and impulsivity) was assessed by the Diagnostic Interview Schedule for Children-Version IV (DISC-IV). The analyses were adjusted for gender, age, IQ, BMI, parental schooling, family socioeconomic status, and housing area. Ten dietary patterns were generated and none of them were associated with the definitive or probable diagnosis of ADHD.

Oellingrath et al. (2014) evaluated the association between dietary patterns and hyperactivity in a cross-sectional study with 1095 Norwegian adolescents aged 12 and 13 years old, using FFQ with 25 food

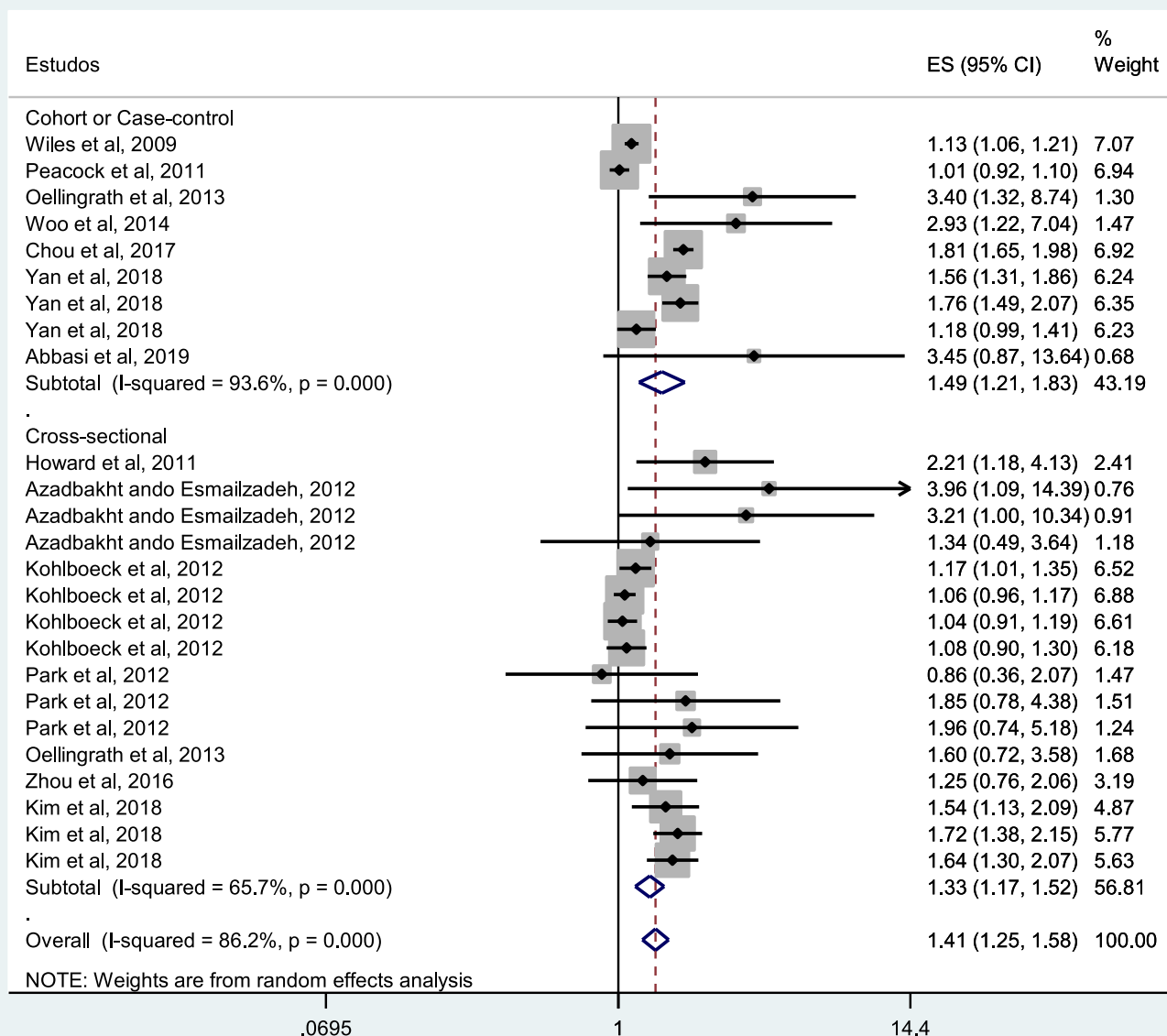


Fig. 5. Unhealthy dietary patterns and ADHD's Forest plot stratified by study design.

items and PCA to construct the dietary patterns. Four dietary patterns were generated (“junk-food/convenience”, “varied Norwegian”, “snacking”, and “dieting”). The outcome, hyperactivity, was assessed by SDQ. The analyses were adjusted for maternal and paternal education, family income, family structure, physical activity, BMI, and sex of the child. The “varied Norwegian” pattern was protective (OR: 0.4; 95% CI: 0.2–0.8) and the “junk/convenient” pattern increased the risk of hyperactivity (OR:3.4; 95% CI:1.3– 8.6). The other patterns were not associated to ADHD.

Kim et al. (2018) conducted a cross-sectional study with 16,831 school children aged 6–12 years presenting ADHD. The Diagnostic tool based on the ADHD Rating Scale (K-ARS) was used to establish the outcome. Dietary patterns were defined *a priori* by FFQ: “Fast food”, “Soft drinks”, “Instant noodles”, “Vegetables”, “Fruit”, and “Milk”. Children who consumed “fast food”, “soft drinks” and “instant noodles” more frequently showed higher odds for ADHD risk, compared to children who “never” consumed these foods (referent) [(OR: 1.54; 95% CI: 1.13–2.09), (OR: 1.72; 95% CI: 1.38–2.15) and (OR:1.64; 95%

CI:1.30–2.08), respectively]. Those who never consumed “fruits” and “vegetables” showed higher odds for ADHD risk, compared to children who consumed these foods ‘more than 3 times per day’ (referent) [(OR: 2.51; 95% CI: 1.96–3.22) and (1.83; 95% CI: (1.14–2.95), respectively].

Yan et al. (2018) evaluated 14,912 Korean children aged 3–6 years old. Attention and hyperactivity problems were assessed through the Conners Abbreviated Symptom Questionnaire (C-ASQ). Food consumption was appraised using FFQ and five dietary patterns were generated by PCA: “Processed” (fried vegetables, fried rice and wheat, smoked foods, fried meat, processed foods, western fast foods), “Vegetarian” (preserved fruit, coarse food grain, wheat and wheat foods, beans in various forms, green vegetables, other vegetables, fresh fruit/vegetable juice), “Snack” (sweets, chocolate, snack -biscuits or cake-, puffed food, milk-based puddings, and custard), “Beverage” (puffed food, milk-based puddings and custard, fruit juice, flavored milk drinks, carbonated beverages, yogurt, preserved fruit), “Protein” (rice and processed products, red meat, poultry, egg, fish and other fishery products, fruits). After adjustment for potential confounders, the likelihood of having ADHD

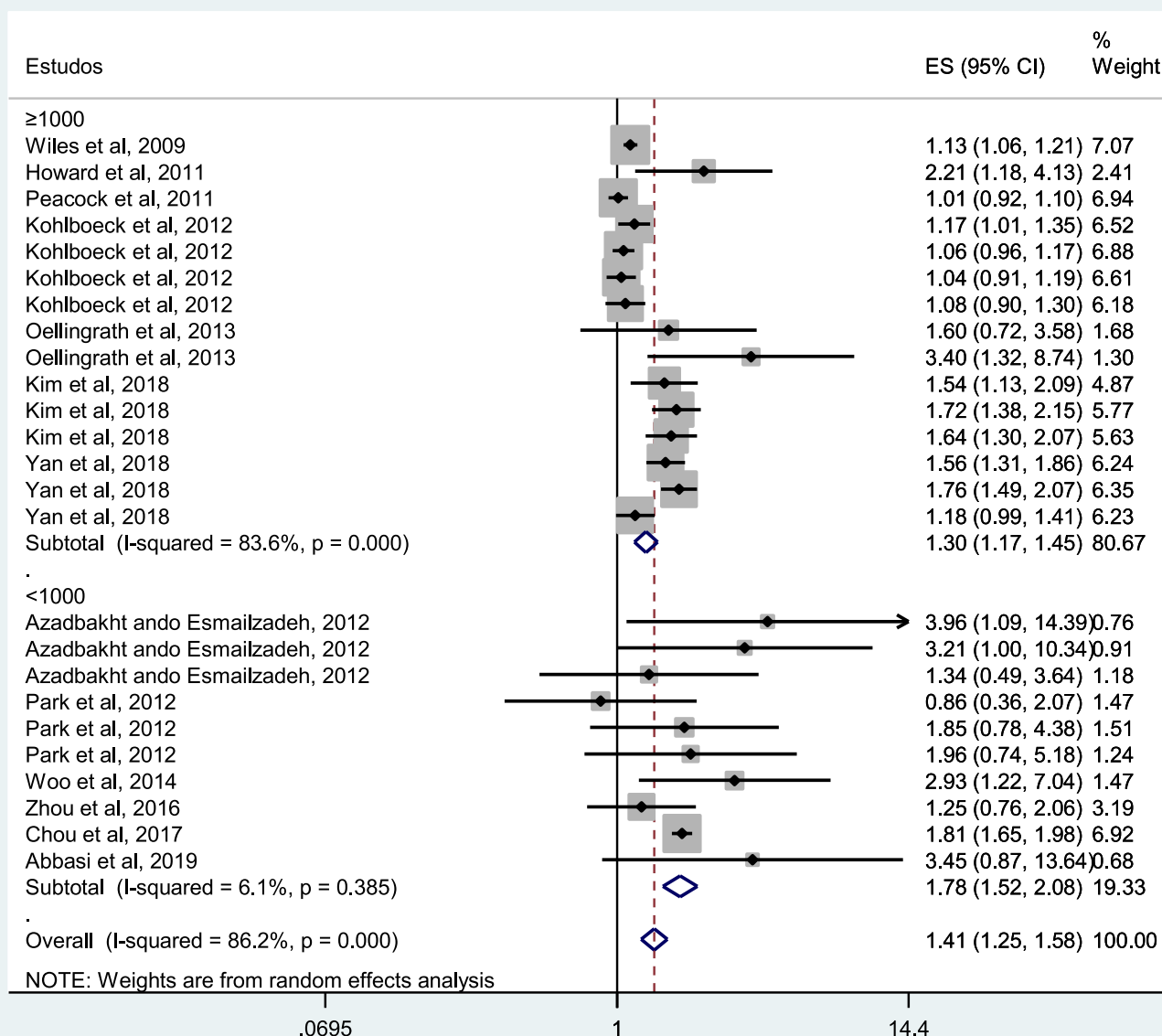


Fig. 6. Unhealthy dietary patterns and ADHD's Forest plot stratified by continent.

symptoms was higher among those in the top quintile of consumption of “processed” (OR = 1.56; 95% CI: 1.31–1.86) and “snack” (OR = 1.76, 95% CI: 1.49–2.07) patterns. Children in the top quintile of consumption of “vegetarian” pattern were less likely to present ADHD symptoms (OR = 0.67, 95% CI: 0.56–0.79). The “beverage” dietary pattern was not associated with ADHD symptoms (OR: 1.18; 95% CI: 0.99–1.41)

3.3. Pooled effect of healthy and unhealthy dietary patterns

We performed two meta-analyses, one to assess the effect of unhealthy food consumption the other to assess the effect on healthy food patterns consumption on ADHD. In both meta-analyses, the chi-square and I^2 test indicated the presence of heterogeneity between the studies, suggesting the need of using the random-effects model.

Pooling the studies altogether the highest consumption of a healthy pattern indicated a protective effect (OR: 0.66; 95% CI: 0.60–0.72) (Fig. 2), while the highest consumption of an unhealthy pattern was

associated with increased risk of ADHD (OR: 1.41; 95% CI: 1.15–1.74) (Fig. 5). After stratifying the studies by design (cohort/control case or cross-sectional studies), continent (Europe or Asia/Oceania) and sample size (≥ 1000 or < 1000), the effects remained significant (Figs. 2–7). The Egger test showed that publication bias was not likely in the studies investigating the association of healthy ($p = 0.054$) and unhealthy dietary patterns with ADHD ($p = 0.205$).

4. Discussion

In the reviewed papers we found two most frequently consumed dietary patterns, and both indicated dietary effects on ADHD. The healthy patterns characterized predominantly by the consumption of fruits, vegetables and whole grains showed a protective effect against hyperactivity or ADHD, while unhealthy dietary patterns, characterized predominantly by the consumption of saturated fat and refined sugar was associated with increased risk of hyperactivity or ADHD occurrence. However, the possibility of reverse causality and information

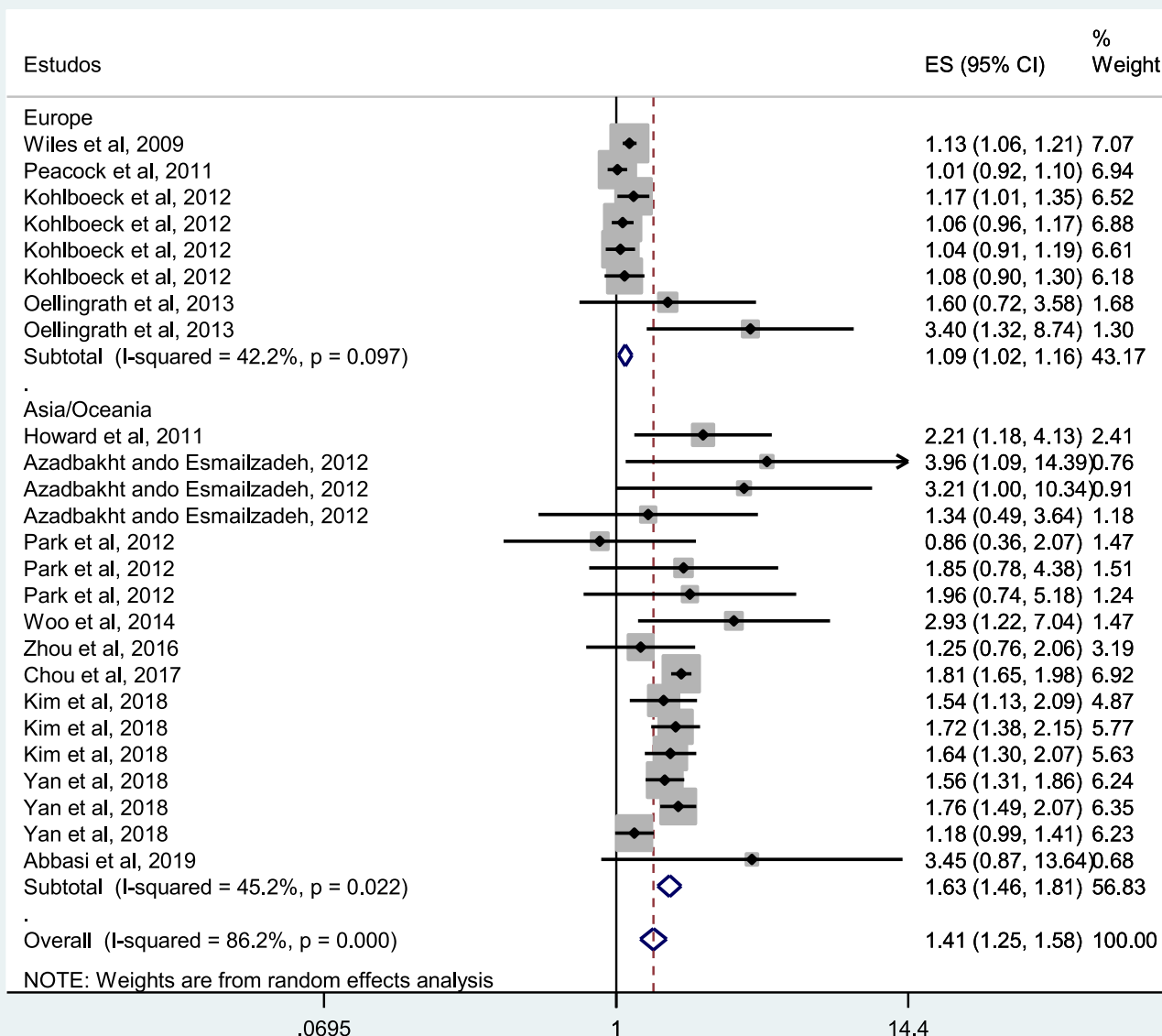


Fig. 7. Unhealthy dietary patterns and ADHD's Forest plot stratified by sample size.

bias cannot be ruled out, because ten of the fourteen studies that found an association between the dietary patterns and ADHD had cross-sectional or case-control design. In such study designs, food information and outcome were collected at the same time (cross-sectional) or referring to a past time (case-control), thus impairing the temporality of the association and carrying possible memory bias, respectively. Thus, it might be possible that the consumption of unhealthy foods is a consequence, rather than a determinant of ADHD, because some types of foods, especially those with high content of sugar, are activators of the reward system (Johnson et al., 2011). Previous studies have shown a higher prevalence of binge eating behavior in individuals with ADHD (Cortese et al., 2007; Docet et al., 2012; Seitz et al., 2013).

The mechanisms that would link the diet to the etiology of ADHD have not yet been fully elucidated. A systematic review published on 2011 including evidences over 30 years about the relationship of additives and coloring agents with ADHD, concluded that although diets free of coloring agents and additives decrease the symptoms of ADHD, there is not enough evidence to attribute a causal relationship between

them (Stevens et al., 2011). Wolraich et al. conducted a meta-analysis, including only experimental studies, with the objective of assessing the effect of sugar on ADHD and concluded that there was no association (Wolraich et al., 1995). Subsequently, other studies evaluated the same relationship and the results were inconsistent (Dykman and Dykman, 1998; Kim and Chang, 2011; Lien et al., 2006). More recently, in a birth cohort, the highest sugar consumption at 6 years old was associated with higher prevalence of ADHD in a cross-sectional analysis; however, when a longitudinal analysis was performed with exposure measured at 6 and the outcome at 11 years old, there was no effect of highest sugar consumption on the incidence of ADHD (Del-Ponte et al., 2019).

On the other hand, evidence for the protective effect of healthy food patterns is supported by the fact that some specific nutrients, such as iron, zinc, iodine, and long chain fatty acids are considered protective against ADHD, mainly because individuals with the disorder have low blood levels of these nutrients (Yüksek et al., 2016; Zhou et al., 2016; Akhondzadeh et al., 2004; Konofal et al., 2004). In addition, children supplemented with zinc had a reduction in ADHD symptoms compared

to those receiving placebo (Akhondzadeh et al., 2004; Bilici et al., 2004). Other studies evaluated the effect of Omega3 and Omega6 supplementation and observed reduction and improvement of ADHD symptoms (Sinn and Bryan, 2007; Richardson and Montgomery, 2005). The lack of specific nutrients in the human body impacts mental health through different biological pathways (O'Neil et al., 2014). Iron, for instance, is a precursor for the production of dopamine and nor-epinephrine, which play an essential role in the etiology of the disorder. Similarly, zinc is required for many metal-enzyme complex, most of them located in the nervous system (Toren et al., 1996), being essential for the conversion of dietary pyridoxine into active pyridoxine, that is necessary for the conversion of tryptophan to serotonin, which has a close relationship with ADHD (Quist et al., 2001). Moreover, zinc is basic for the production and modulation of melatonin, that helps to regulate dopamine function, important in the pathophysiology of ADHD (Arnold and DiSilvestro, 2005; Kirby et al., 2001).

This study presents strengths and limitations. Among the limitations are some of the methodological aspects of the studies included in the review. For instance, FFQ is subjected to memory bias and imprecision in the quantification of diet. However, its use in epidemiological studies is the most indicated when compared to 24 h dietary recalls or dietary records, because when we want to assess diet as an exposure for health outcomes, it does not matter what the individual consumes in a single day, but rather over time.

Another limitation refers to the statistical techniques used by the authors for the derivation of dietary patterns (PCA and factorial analysis), which are complex and arbitrary, from the formation of food groups to the retention and interpretation of the patterns. In addition, the dietary patterns identified in a population are hardly the same as those generated in another population, a fact that impairs comparability between the findings. Despite these limitations, dietary patterns have been recommended by the World Health Organization as the best method to assess diet, because it involves the global consumption of foods, taking into account the interaction between them (Organization, 2002). Finally, the absence of randomized controlled trials which is not exactly a limitation of this study, but of the literature on the subject. Randomized clinical trials found in the literature tested the effects of specific foods or nutrients in ADHD trials.

Among the strengths of this review and meta-analysis, its writing followed the guidelines for reporting meta-analysis of observational studies (Meta-analysis of observational studies in epidemiology—MOOSE) (Stroup et al., 2000). Additionally, in all the studies included in the review, both the exposure and the outcome were evaluated with instruments that allowed comparability between the findings. Most of the dietary patterns were constructed retrospectively, with the dietary information obtained through FFQ (Wiles et al., 2009; Azadbakht and Esmailzadeh, 2012; Howard et al., 2011; Oellingrath et al., 2014; Yan et al., 2018; Kohlboeck et al., 2012; Woo et al., 2014; Abbasi et al., 2019; Kim et al., 2018; Chou et al., 2018) and generated by PCA (Wiles et al., 2009; Oellingrath et al., 2014; Yan et al., 2018; Peacock et al., 2011; Woo et al., 2014) or factor analysis (Azadbakht and Esmailzadeh, 2012; Howard et al., 2011; Abbasi et al., 2019). The outcome of hyperactivity was assessed by SDQ (Wiles et al., 2009; Oellingrath et al., 2014; Peacock et al., 2011) and ADHD by a specific instrument for assessing child mental health (DISC-IV) (Park et al., 2012) or by diagnostic criteria based on manuals of clinical guidelines, such as the DSM-IV (Azadbakht and Esmailzadeh, 2012; Woo et al., 2014) and the CID-9. (Howard et al., 2011) In addition, only one study did not adjust the analyses for the appropriate minimum set of confounding factors.

As a conclusion, this study provides evidence about association between diet and ADHD, suggesting that a diet high in refined sugar and saturated fat can increase the risk of ADHD or hyperactivity, whereas a healthy diet, characterized with the high consumption of fruits and vegetables, would protect against these outcomes. New studies need to be performed using longitudinal designs, because the

strength of the current evidence is supported only by nine studies, five of which are cross-sectional.

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Conflict of interest

The authors have no potential conflicts of interest to disclose.

CRediT authorship contribution statement

Bianca Del-Ponte: Conceptualization, Data curation, Writing - original draft, Writing - review & editing. **Gabriela Callo Quinte:** Data curation, Writing - original draft, Writing - review & editing. **Suélien Cruz:** Conceptualization, Writing - original draft, Writing - review & editing. **Merlen Grellert:** Data curation, Writing - original draft, Writing - review & editing. **Iná S. Santos:** Data curation, Writing - original draft, Writing - review & editing.

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