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REVIEW

ADHD is associated with migraine: a systematic review and meta-analysis

Haitham Salem[1] · David Vivas[2] · Fei Cao[1] · Iram F. Kazimi[2] · Antonio L. Teixeira[1] · Cristian P. Zeni[2]

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Abstract An association between primary headaches and attention-deficit/hyperactivity disorder (ADHD) has long been suggested. Moreover, headache is regarded as a common side effect of stimulants, the most effective treatment for ADHD. So far, no systematic review has evaluated the potential association between ADHD and headache. We performed a systematic review of the literature and a meta-analysis of all reported studies on ADHD and primary headaches. Our analysis showed a positive association between ADHD and migraine (OR 1.322, 95% CI 1.018–1717, *p* value 0.036), but not with tension-type headache. There is a significant association between migraine and ADHD. The mechanisms underlying this association remain to be elucidated, warranting further studies.

Keywords ADHD · Headache · Migraine · Tension-type headache · Meta-analysis · Stimulants

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders affecting children. Lack of attention, impulsivity, and hyperactivity are the main characteristics of ADHD. Many children with ADHD continue to have dysfunctional symptoms as adults [1, 2]. An estimated 5% of children and 2.5% of adults have ADHD in the United States [3, 4]. ADHD has additionally been linked to other psychiatric disorders [5] and somatic conditions such as asthma and obesity [6].

Headache is a frequent complaint among pediatric age groups [7]. The frequency of headache complaints increases progressively from preschool age to adolescence [8]. The most common causes of primary headaches are tension-type headache (TTH) and migraine. The prevalence of migraine, for instance, increases throughout childhood, affecting 1–3% of 3–7-year-old children, 4–11% of 7–11-year-old kids, and 8–28% of teenagers between 13 and 18 years old [9]. It ranges between 16.6 and 22.7% among adults older than 18, with higher prevalence among females (25%) compared to males (11%) [10].

According to hospital-based studies, children with headaches and ADHD have a significant lower quality-of-life scores compared to healthy children [11, 12], as well as higher incidence of other psychiatric disorders. Interestingly, stimulants—the main and most effective pharmacological treatment for ADHD—are reported to induce headache among other side effects [13]. Whether drug induced or not, headache is a common complaint among children with ADHD [14, 15]. It is imperative to assess the strength of the association between ADHD and primary headaches to elucidate possible common pathophysiological pathways, and also to guide treatment.

In this review, we carried out a systematic review of the literature to determine whether there is comorbidity/association between ADHD and primary headaches. In addition, we performed a meta-analysis of the available data.

✉ Cristian P. Zeni
cpzeni@gmail.com

[1] Neuropsychiatry Program, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center, Houston, TX, USA

[2] Pediatric Mood Disorders/ADHD Across Lifespan Programs, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center, 1941 East Road, Suite 3128, Houston, TX 77054, USA

Methods

Three independent literature searches using the keywords "ADHD", "Headache", "Migraine", and "Tension-Type Headache" were performed. The electronic databases *PubMed, ScienceDirect, Google Scholar*, and *PsycINFO* were searched for all published data from January 2000 till January 2017. The specific number of all retrieved, included, and excluded articles at each step of our literature search is provided in Fig. 1, built according to the PRISMA guidelines.

Inclusion criteria

Studies evaluating the comorbidity between migraine, TTH, and ADHD in adults or adolescents were included. ADHD was defined according to ICD-9, 10 or DSM-III, -IV criteria [16, 17]. Different protocols were used to classify individuals as having ADHD: (a) ADHD clinically diagnosed based on the use of semi-structured interviews; (b) ADHD medication use as a proxy for ADHD diagnosis; (c) symptoms of ADHD measured by a validated ADHD symptom rating scale; (d) information on ADHD cases from clinical databases. Peer-reviewed studies published in English, French, Spanish, Portuguese, German, Arabic, and Chinese were included, as those are the languages fluently spoken by the authors of this review. All the studies that classified headache into subtypes (Migraine, TTH) according to the International Classification of Headache Disorders (ICHD) criteria were included [18].

Exclusion criteria

The following exclusion criteria were applied: (a) studies not including ADHD as described under inclusion criteria; (b) case reports, communications, opinions, and expert reviews; (c) publications not subjected to peer review; (d) studies with incomplete or unreported data; (e) pharmacological trials focusing on specific treatment options and not on comorbid disorders; (f) studies on traumatic events, as we consider these to be outside the main focus of this review; (g) studies in any other language than those mentioned in the inclusion criteria; and (h) studies that could not be fully retrieved.

Study quality and data analysis

Data were qualified according to the study quality form of the "Guide to Community Preventive Services" [19, 20]. The form has six categories of data classification. These categories are related to potential study problems that can limit the ability to interpret the results, for example, descriptions of the study population or intervention, sampling, measurement, analysis, interpretation of results, and other limitations. After summation of the limitations' number in each category, each study was then scored per the scoring criteria. A study with 0–1 limitation was rated as good execution quality; 2–4 limitations as fair execution quality; and five or more limitations as limited execution quality. In addition, we extracted publication year, study design, assessment tools, geographic location, and demographic data (Table 1).

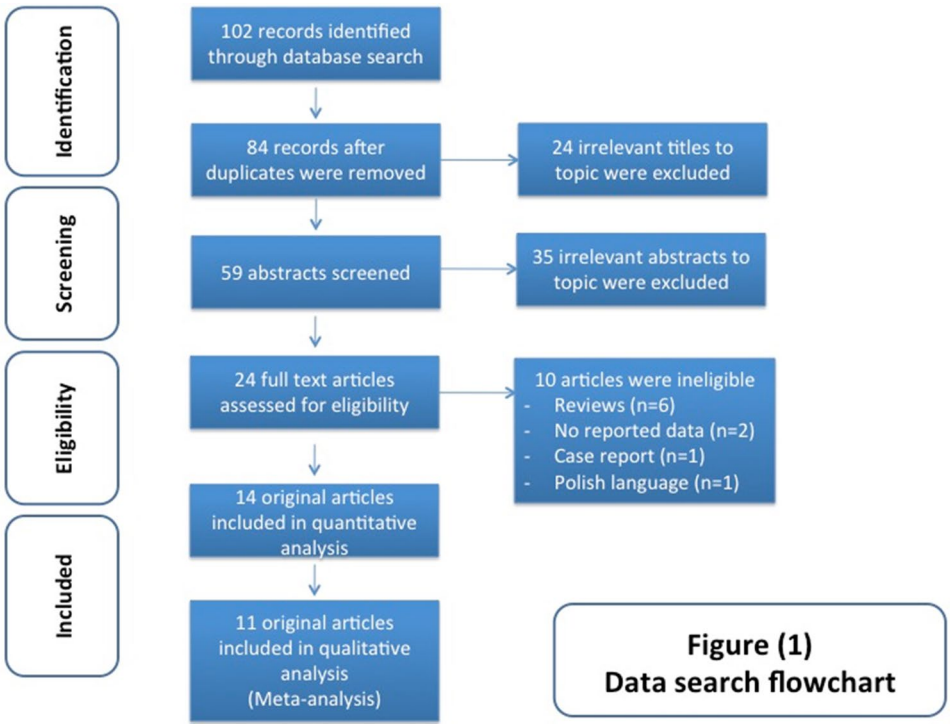

Fig. 1 Data search flow chart (PRISMA guidelines)

Table 1 Extracted data from all the included studies in our review

	Study	Design	Geographic location	Study demographics	ADHD assessment tools	Headache assessment tools	Results	Meta-analysis
1	Genizi et al. [27]	Prospective cohort study	Israel	10th grade students *N* = 279 Males 57% Females 43%	Computerized general health questionnaire (standardized questions on history of previous diagnosis, treatment and school performance) No Face-to-face interviews. Diagnosis is based on computer questionnaire.	ICHD-2	High prevalence rate of headache among adolescents (81%), mostly among girls (88 VS 76%). No significant statistical difference found between the students who reported to have headaches with ADHD (27%), compared to the control group (22.5%)	Included
2	Jameson et al. [31]	Cross-sectional	USA	Schools adolescents (13–18 years old) *N* = 6483 Males 51.2% Females 48.7%	National Comorbidity Replication Survey—Adolescent Supplement, [Adolescent face-to-face interviews and parents self-administered questionnaire (PSAQ)] Face-to-face interviews and diagnosis is based on DSM-IV criteria	ICHD-2	This study provides compelling evidence regarding pervasive comorbidity of ADHD with diverse medical conditions. There was a significantly greater prevalence of specific chronic medical conditions as well as an increased number of medical conditions among those youth with ADHD compared to their unaffected counterparts	Included
3	Arruda and Arruda [23]	Retrospective	Brazil	Public schools children (5–12 years old) *N* = 5671 Males 49.5% Females 50.5%	Strengths and Difficulties Questionnaire (SDQ)—Brazilian version Face-to-face interviews and diagnosis is based on DSM-IV criteria	ICHD-2	Higher prevalence of hyperactivity in preadolescent children with migraine compared with those without headache	Included
4	Genizi et al. [24]	Retrospective	Israel	Children (6–18 years old) in outpatient pediatric neurology clinics in 2009–2010 *N* = 243 Males 44.5% Females 55.6%	Conner's parents and teachers rating scale (CPT) Face-to-face interviews and diagnosis is based on DSM-IV criteria	ICHD-2	There is an association between headaches, ADHD, learning disabilities, and school performance. It is more prevalent in boys than in girls	Not included (lack control group)

Table 1 (continued)

	Study	Design	Geographic location	Study demographics	ADHD assessment tools	Headache assessment tools	Results	Meta-analysis
5	Riva et al. [26]	Prospective	Italy	Children (6–17 years old) from the developmental neurology division of a single institution in 2007–2009 *N* = 62 Males 53.2% Females 46.8%	Conner's parents and teachers rating scale (CPT), Ravine progressive matrices, Face-to-face interviews and diagnosis is based on DSM-IV criteria	ICHD-2	There was no difference between the migraine subtypes and TTH in attention measures	Not included (lacking data)
6	Pavone et al. [25]	Retrospective case–control	Italy	Children (4–14 years old) at university department of Pediatrics *N* = 560 Males 62.5% Females 37.5%	Clinical diagnostic interview (CDI), Child behavior checklist (CBCL) Face-to-face interviews and diagnosis is based on DSM-IV criteria	ICHD-2	There was no significant difference between the primary headache and control group in the prevalence of ADHD or learning disability	Included
7	Fasmer et al. [21]	Cross-sectional	Norway	All population of 2006 *N* = 4640,219 Males = 49.6% Females = 50.4%	Prescription registry rates of anti-migraine and anti-ADHD drugs. No Face-to-face interviews. Diagnosis is based on previous ADHD medications as proxy for ADHD diagnosis	Anti-migraine medications used as a proxy for migraine diagnosis	In the total Norwegian population in the year 2006, there was a positive and significant association between prescription of anti-migraine and anti-ADHD drugs to adult patients	Not Included (No control group)
8	Arruda et al. [32]	Cross-sectional	Brazil	Children (5–12 years old) from 87 cities and 18 states *N* = 5671 Males 50.7% Females 49.3%	Brazilian versions of Multimodal Treatment Study of Children with ADHD—Swanson, Nolan, and Pelham IV (MTA-SNAP-IV) scale. Strengths and Difficulties Questionnaire (SDQ) Face-to-face interviews and diagnosis is based on DSM-IV criteria	ICHD-2	Approximately one-fourth of the preadolescent population has headaches with migraine features Children with migraine are at an increased risk of having impairments in their school performance	Included

Table 1 (continued)

	Study	Design	Geographic location	Study demographics	ADHD assessment tools	Headache assessment tools	Results	Meta-analysis
9	Fasmer et al. [22]	Cross-sectional	Norway	Genetic study using a national registry of adults (above 18 years old) diagnosed with ADHD in Norway during 1997–2005 *N* = 1247 Males 40.3% Females 59.7%	Wender Utah Rating Scale (WURS), measuring the presence and frequency of childhood ADHD symptoms, the Adult ADHD Self-Report Scale (ASRS) Face-to-face interviews with diagnosis is based on ICD-10 and DSM-IV criteria	Patients/parents self-reports	Adults with persistent ADHD have an increased prevalence of migraine compared to controls from the general population	Included
10	Pitrou et al. [30]	Cross-sectional	France	Primary school children (6–11 years old) *N* = 1308 Males 50.1% Females 49.9%	Strengths and Difficulties Questionnaire (SDQ)—French version Dominic Interactive (DI) Face-to-face interviews with diagnosis is based on DSM-IV criteria	Patients/parents self-reports	The Dominican interactive (DI) psychopathological assessment tool suggested some associations between headaches, and comorbid conditions as ADHD	Included
11	Arruda et al. [33]	Cross-sectional	Brazil	Public school children (5–11 years old) *N* = 1406 Males 52% Females 48%	Brazilian versions of Multimodal Treatment Study of Children with ADHD—Swanson, Nolan, and Pelham IV (MTA-SNAP-IV) scale. Child Behavior Checklist (CBCL/6–18) Face-to-face interviews with diagnosis is based on DSM-IV criteria	ICHD-2	Migraine and TTH are not comorbid to ADHD overall, but are comorbid to hyperactive-impulsive behavior	Included
12	Lateef et al. [29]	Cross-sectional	USA	Children (4–18 years old) who participated in the National Health and Nutrition Examination Surveys. *N* = 10 918 Males 49.8% Females 50.2%	National Health and Nutrition Examination Surveys (1999–2000, 2001–2002, and 2003–2004) No Face-to-face interviews. Diagnosis is based on previous ADHD diagnosis in records	ICHD-2	Confirmed an association between headaches in children and ADHD	Included

Table 1 (continued)

	Study	Design	Geographic location	Study demographics	ADHD assessment tools	Headache assessment tools	Results	Meta-analysis
13	Strine et al. [28]	Cross-sectional	USA	Population based study on healthy children (4–17 years old) *N* = 9264 (No male and female demographics is clearly mentioned)	National Health Interview Survey (NHIS), Strengths and Difficulties Questionnaire—extended version (SDQ-EX) No face-to-face interviews with diagnosis based on previous ADHD diagnosis in records of NHIS	Patients/parents self-reports	Overall, children with frequent headaches were 3.2 times more likely than children without headache to have a high level of difficulties and 2.7 times more likely to have a high level of impairment, suggesting potential mental health issues	Included
14	Mazzone et al. [34]	Cross-sectional	Italy	Children (6–16 years old) referred to the clinic of Child and Adolescent Neuropsychiatry *N* = 114 Males 61% Females 53%	Parent–Child Behavior Checklist (CBCL), Conner's Parent Rating Scale (CPRS) Face-to-face interviews with diagnosis is based on DSM-IV criteria	ICHD-2	Hyperactivity symptoms were elevated among clinically referred children suffering from TTH or migraine compared with normal peers. With the score significantly higher in TTH more than migraine	Included

DSM-IV Diagnostic and statistical Manual-4th edition, *ICHD-2* International Classification on Headache Disorder-2nd edition

The meta-analysis was done with three different settings, using comprehensive meta-analysis Version 3 licensed software (http://www.meta-analysis.com). Continuous data from eligible studies were analyzed, and due to the heterogeneity in rating scales and indices measures reported by different studies, a two-sided random effect model of meta-analysis was applied. Tests for overall effect sizes (*Z*), odds ratios (OR) for associations with their 95% confidence intervals (95% CI), and *p* values were performed. *p* values less than or equal 0.05 in a confidence interval of 95% were considered significant.

Results

Search results

Of the 102 hits in the initial search, 84 records remained after duplicates were removed, from which 24 titles were deemed irrelevant after screening. The remaining 59 abstracts were screened for title/abstract and 35 of them were irrelevant to the topic. The full text of 24 articles was read. Ten manuscripts were not eligible (one was in Polish, two did not report data results, one was a case report, and six were reviews), while 14 original articles fulfilled all the inclusion criteria (Fig. 1; Table 1).

Review of the study designs of the included articles

All included studies ($n = 14$) are summarized in Table 1. The studies included 43,244 participants with the exception of one study [21] that included the full national registry of the Norwegian population ($n = 4{,}640{,}219$). Most studies ($n = 12$) included only adolescents, one study included an adult only sample [22], and one study included an all population registry [21].

Nine studies (64%) used a cross-sectional design. Three studies used a retrospective analysis [23–25], and only two studies did a prospective evaluation [26, 27]. Eight studies (57%) had more males than females, while five (35.7%) of them included more females. One study did not report the numbers of male and female populations [28]. Twelve studies included control groups, while two studies lacked a control group [21, 24].

Methods of ADHD assessment in the studies

Ten studies (71.4%) used direct face-to-face interviews with different assessment tools for the diagnosis of ADHD based upon DSM-IV criteria (Table 1). The rest of the studies ($n = 4$) did not use direct interviews. One study used a self-administered computer-based assessment questionnaire for the diagnosis of ADHD [27], two studies relied on the information extracted from national data registries on previous diagnosis of ADHD [28, 29], and one study used the national prescription registry of ADHD medications as a proxy for ADHD diagnosis [21].

Methods of headache assessment in the studies

Ten studies (71.4%) used the ICHD for the diagnosis of headache among their sample (Table 1). Three studies (21.4%) relied on patient/parent self-reports of primary headache [22, 28, 30]. One study used a national prescription registry of anti-migraine medications as a proxy for migraine diagnosis [21].

Eight studies (57.1%) evaluated migraine—as a clearly diagnosed headache subtype by ICHD criteria—in relation to ADHD (Fig. 3) [22, 23, 25, 27, 31–34].

Five studies (35.7%) evaluated TTH—as a clearly diagnosed headache subtype by the ICHD criteria—in relation to ADHD (Fig. 4) [23, 25, 32–34].

Methodological considerations and limitations of the studies

Several limitations were identified in each 1 of the 14 studies under review. Apart from the heterogeneity of the diagnostic techniques and samples used, one of the main overall limitations was that 57.1% of the studies ($n = 8$) focused on the association between ADHD and headache, while 42.9% of the studies ($n = 6$) did not focus merely on this association but also investigated other comorbidities which could potentially be a source of confounding bias.

The absence of control groups was another major limitation in two studies [21, 24]. The absence of detailed results in one study was considered a limitation [26]. Relying on patient/parent subjective reports for the clinical diagnosis of headaches was another limitation in three studies [22, 28, 30].

Moreover, using medication databases as a proxy for ADHD and migraine diagnoses [21] is also prone to considerable bias; the traditional medications for ADHD and migraine may have been prescribed for other conditions; and self-medication, with over-the-counter analgesics, could be present.

Interestingly, most studies ignored the reports that linked stimulants to headache as a side effect and those that concluded that patients treated with stimulants for ADHD might develop headache as a medication side effect and not have it a comorbid condition [35, 36].

A technology consideration also arises from entirely depending on computer-based surveys for a diagnosis of ADHD. One of the studies had a significant discrepancy in results [27], thus raising concerns about the validity of computer-based questionnaire techniques.

Remarkably, most of the published data resulted from cross-sectional ($n = 9$) and retrospective studies ($n = 3$), rendering it difficult to infer the causality between headaches and ADHD. Only two studies had a prospective design, with only one cohort study among them [27]. This can be attributed to the higher cost of conducting cohorts. Accordingly, there is still a need for these types of studies.

Meta-analysis

Data from 11 studies were used for meta-analysis. Three studies were not included in the analysis as two articles lacked a control group, and one article did not report its full data as per inclusion criteria (Table 1).

Not all studies identified headache subtypes, i.e., migraine or TTH. Migraine was fully defined in 8 studies and TTH in only 5 out of the 11 studies.

Accordingly, we categorized our data for analysis in three strata. In the first-level stratification, we used all studies ($n = 11$) as a general headache reference and analyzed them together. The first-level results showed a non-significant association between headache, in general, and ADHD (OR 1.009, 95% CI 0.501–2.034, p value 0.980) (Fig. 2). In the second-level analysis, we used the studies diagnosing migraine ($n = 8$), revealing a significant positive association between migraine and ADHD (OR 1.322, 95% CI 1.018–1717, p value 0.036) (Fig. 3). In the third-level analysis, we used the studies diagnosing TTH ($n = 5$) that showed a non-significant association between TTH and ADHD (OR 1.068, 95% CI 0.994–1.312, p value 0.679) (Fig. 4).

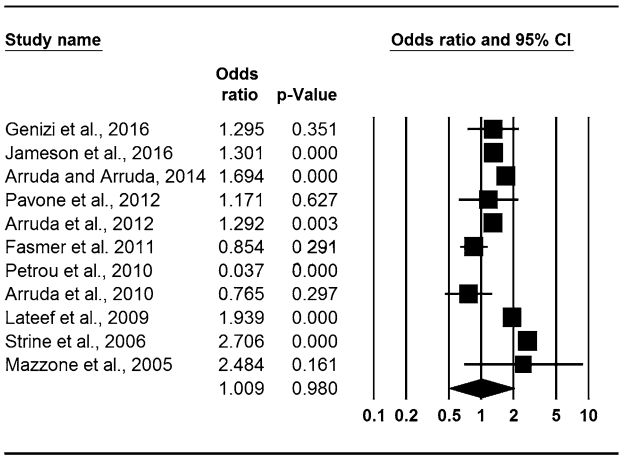

Fig. 2 Meta-analysis of the comorbidity between ADHD and headache (produced by CMA software)

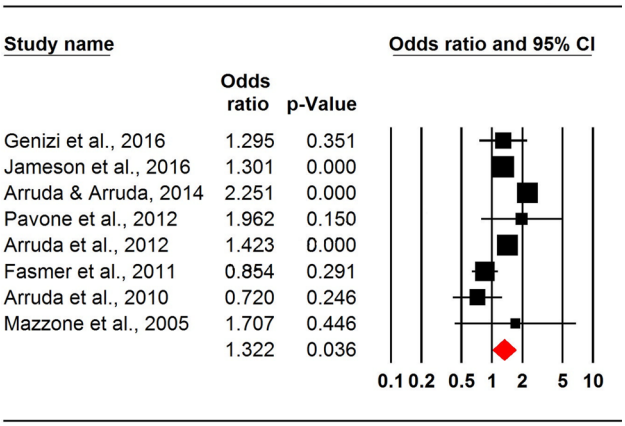

Fig. 3 Meta-analysis of the comorbidity between ADHD and migraine (produced by CMA software)

Discussion

To our knowledge, this is the first systematic review and meta-analysis evaluating the association between ADHD and headache. Historically, Leviton was one of the first authors to report that out of 150 elementary-school children who were referred to his clinic for recurrent headaches; approximately 40% of them had academic difficulties [37]. His results came in accordance with later studies that reported a higher incidence of hyperactivity and impulsivity symptoms in children with headache in comparison to healthy peers [38, 39].

Several studies have demonstrated an association between ADHD and several other comorbidities [40–46]. However, the specific association between ADHD and headache remained debatable. In our current systematic review and meta-analysis, the data provide compelling evidence of an association between ADHD and migraine.

During the past 2 decades, few studies have focused on ADHD with headache as a comorbidity. Most of the

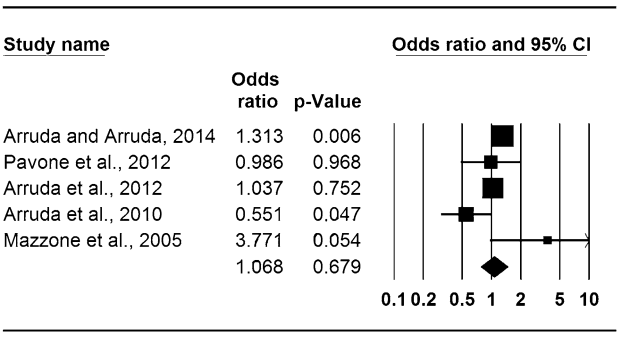

Fig. 4 Meta-analysis of the comorbidity between ADHD and TTH (produced by CMA software)

studies included in our review reported a positive association between ADHD and headache, while a few did not report any association [25, 26, 33]. The variability of results can be attributed to several factors, including discrepancy in diagnostic protocols, non-representative samples, and heterogeneity of assessment tools.

The causal relationship between ADHD and migraine could not be determined, since most currently available studies are cross-sectional. However, some authors tried to speculate that a relationship between ADHD and migraine emerges from a common underlying pathophysiology. For instance, Villa and colleagues described impaired visual attention in children with migraine and suggested that this is dependent on neurotransmitters such as dopamine and noradrenalin. Such neurotransmitters are also involved in the pathophysiology of migraine, thus suggesting that this might predispose those children to attention deficit [47]. Other neurotransmitters such as GABA are also implicated in the pathophysiology of both conditions [48–50]. A different hypothesis was that frequent headaches independently increase distractibility and irritation especially in children with a primary short attention span, thus imposing a further burden on the challenge of learning. This is supported by a study that found a correlation between neuropsychological deficits and frequency of headache episodes [51]. Moreover, a genetic background theory was hypothesized based on a genome-wide analysis study [52].

ADHD is associated with other conditions with a strong genetic component. For instance, epilepsy [53–56] and vasovagal syncope [57–59] are commonly comorbid with migraine. However, we have not identified any meta-analyses confirming the association between ADHD and epilepsy or ADHD and vasovagal syncope. Further studies should take into consideration that the genetic and pathologic underpinnings of these heterogeneous syndromes may overlap, promoting a better understanding of common neural pathways. As an example, structural and functional abnormalities in corticosubcortical brain networks found to be central in both migraine and ADHD pathophysiology [60, 61] also play an important role in obesity. Obesity is also associated with cognitive problems leading to decline in intellectual performance [62–64], which can be mistaken as ADHD. This is particularly important when obesity in children has become an epidemic. Another area that should be explored further is the cognitive profile of children affected by headaches/migraine. Cognitive abilities, particularly verbal skills, reaction time, and information speed processing may be impaired in children with headaches [65, 66]. We hope that these findings are quickly incorporated into the clinical assessment of patients with ADHD.

Finally, as supported by recent results, the adverse effects of stimulants could be a causative factor for the complaint of headaches among patients with ADHD [67–70]. Data from randomized clinical trials on methylphenidate support at least in part this assumption [71–74]. On the other hand, Genizi and colleagues found no difference in headache prevalence rates among students with ADHD who took medications such as methylphenidate and those who were not taking medications for ADHD [27].

Conclusion

In this manuscript, we provided a comprehensive review together with a meta-analysis of the available data on the association between headache and ADHD. Our results confirmed that there is a significant association between migraine and ADHD. However, the pathogenesis of such an association remains unknown to date, warranting further studies.

Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interests associated and that no funding of any kind is associated with this work.

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