



ASSOCIATION BETWEEN MIGRAINE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: SYSTEMATIC REVIEW

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ARTICLE INFO

Received:

01 Dec 2022

Received in revised form:

26 Mar 2023

Accepted:

01 Apr 2023

Available online:

28 Apr 2023

Keywords: ADHD, Headache, Migraine, Systematic review

ABSTRACT

It has long been believed that primary headaches and attention-deficit/hyperactivity disorder (ADHD) are related. In addition, it is believed that stimulants, the most successful treatment for ADHD, frequently cause headaches as a side effect. PubMed, Web of Science, Science Direct, EBSCO, SCOPUS, Wiley, and the Cochrane Library were the search engines that were utilised. Before performing a full-text analysis, study articles were first evaluated using Rayyan QCRI's title and abstract criteria. This analysis includes 12 studies with 209130 ADHD patients in total. The reported studies documented an age range from 5 to 52 years old. Diagnoses of headaches, particularly migraines, were much more common in children with ADHD. In this systematic review, we comprehensively reviewed the available literature on the association between migraine and Attention Deficit Hyperactivity Disorder. Our findings suggested the presence of an association between migraine and ADHD. Higher migraine incidence rates were demonstrated among the pediatric population with ADHD.

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To Cite This Article: Soltan MH, Albalawi RA, Alnawmasi NSM, Alshammari WFD, AlOmari LH, Ibrahim MIFB, et al. Association between Migraine and Attention Deficit Hyperactivity Disorder: Systematic Review. Pharmacophore. 2023;14(2):58-64. <https://doi.org/10.51847/wSrSsrseWK>

Introduction

One of the most prevalent psychiatric conditions affecting children is ADHD [1, 2]. The main traits of ADHD are inattention, impulsivity, and hyperactivity [3, 4]. Many adults who had ADHD as children still experience dysfunctional symptoms [5]. In the US, 2.5% of adults and 5% of children are thought to have ADHD [6]. Additionally, there is a connection between ADHD and other psychiatric disorders [7], as well as somatic diseases like obesity and asthma [8].

There is a dearth of reliable information in the literature about the overlap between primary headaches and ADHD in children. Both conditions frequently progress to the point of being incapacitating for children and their families, as well as resulting in poor academic performance [9], diminished cognitive and emotional functioning [10, 11], and irregular sleep patterns [12], all of which have a significant negative impact on a child's quality of life [13].

It has been established that ADHD and migraine are comorbid with mood and anxiety disorders [14, 15] and that dopaminergic systems are implicated in the pathophysiology of all three types of illnesses [16]. The relationship between attention deficit disorder and certain headaches is unclear [17]. According to studies by Riva *et al.*, attention-related problems were substantially connected with headaches in both migraine and tension-type headaches [18].

Children with headaches performed more frequently atypically on the Conners Continuous Performance Test than did healthy controls, with no differences between migraine and tension-type headaches in terms of hit reaction time mean scores [18]. Villa *et al.* found decreased visual attention in migraine-affected children and proposed that dopamine and

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noradrenaline were responsible. They reasoned that because these neurotransmitters are involved in the pathophysiology of migraine, they may increase the risk of attention deficit disorder in such children [19]. It is crucial to evaluate the strength of the link between ADHD and primary headaches in order to identify any possible similar pathophysiological pathways and inform treatment. This comprehensive review was conducted to assess the relationship between ADHD and migraine.

Materials and Methods

This systematic review was carried out using PRISMA, or Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study Design

This was a systematic Review.

Study Duration

From 1st to 30th January 2023.

Study Condition

This systematic review aims to evaluate the comorbidity/ relationship between migraine and ADHD.

Search Strategy

A thorough search was done across five major databases, including PubMed, Web of Science, Science Direct, EBSCO, Scopus, Wiley, and the Cochrane Library, to find the relevant material. We only searched in English and took into account each database's particular needs. To discover the pertinent research, the following keywords—"attention deficit/hyperactivity disorder," "ADHD," "migraine," and "primary headache"—were transformed into PubMed Mesh terms. We used the Boolean operators "OR" and "AND" to match the required keywords. Publications with full English text, free papers, and human trials were found through the search.

Selection Criteria

Inclusion Criteria

Included studies examined the relationship between migraine and ADHD in adults, kids, or teenagers. There were only open-access, free studies in English.

Exclusion Criteria

The criteria used to determine exclusion were as follows: studies that do not include ADHD as defined under the inclusion criteria include case reports, communications, expert reviews, publications that have not undergone peer review, studies with incomplete or unreported data, pharmacological trials that focus on specific treatment options rather than comorbid disorders, and studies on traumatic events that we believe fall outside the main scope of this review.

Data Extraction

To find duplicates in the search method's output, we used Rayyan (QCRI) [20]. The researchers used a set of inclusion and exclusion criteria to refine the combined search results in order to evaluate the relevance of the titles and abstracts. The reviewers thoroughly looked through each manuscript that met the criteria for admission. The authors talked about how to resolve conflicts. A data extraction form was created, and the authorised study was uploaded using it. The researchers gathered information on the studies' names, authors, years, study plans, nations, populations, participant counts, median ages, genders, ADHD and migraine diagnostic tools, and primary outcomes.

Strategy for Data Synthesis

Summary tables were created using the data acquired from the applicable research to offer a qualitative review of the outcomes and elements of the included study. After the data for the systematic review had been extracted, the most efficient method for using the data from the included study articles was chosen. Studies that met the criteria for full-text inclusion but did not discuss the relationship between migraine and ADHD were ignored.

Risk of Bias Assessment

The included papers' quality was evaluated using the ROBINS-I risk of bias assessment approach for non-randomised trials of therapies [21]. Confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and choice of the reported result were the seven themes that were evaluated.

Results and Discussion

Search Results

After removing 42 duplicates from the search results, a total of 382 study articles were found. After screening 340 studies for titles and abstracts, 293 studies were rejected. Out of the 47 reports that were sought for retrieval, only seven articles were not located. A total of 40 papers were eventually screened for full-text evaluation; 10 were rejected due to inaccurate study results, 9 for having unavailable ADHD and migraine data, and 9 for having the wrong population type. In this systematic review, 12 relevant study papers were included. A description of the selection process for the studies is shown in **Figure 1**.

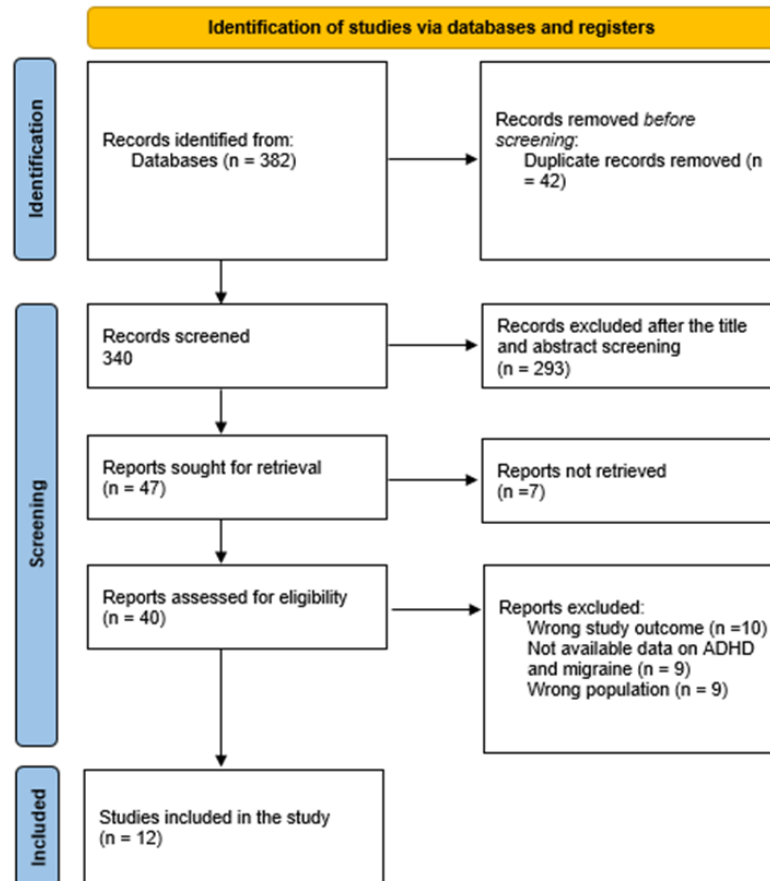


Figure 1. PRISMA flowchart summarizes the study selection process.

Characteristics of the Included Studies

Table 1 includes the sociodemographic characteristics. A total of twelve studies with 209130 patients were included. Three studies were conducted in Brazil [22-24], two in Norway [25, 26], one in Denmark [27], one in Israel [28], one in Turkey [29], one in Sir Lanka [30], one in France [31], one in Taiwan [32], and one in Italy [18]. Four studies comprised the adult population with ADHD [25-27, 31] and eight studies with a pediatric population [18, 23, 24, 28-30, 32]. The reported studies documented an age range from 5 to 52 years old.

The features of the included studies are shown in **Table 2**. There were six cross-sectional studies [23, 25, 27, 29, 30, 32] one population-based research study [26], three retrospective studies [22, 24, 28], one cohort study [31], and one prospective study [18]. For the diagnosis of ADHD and migraine, the International Classification of Headache Disorders (ICHD) was most frequently employed, coupled with face-to-face interviews and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The papers that were reviewed found a correlation between ADHD and migraines. Children with ADHD had a significantly higher prevalence of headache diagnoses, particularly migraines. Children and mothers who have ADHD frequently have migraines.

Table 1. Sociodemographic characteristics of the included participants

Study	Country	Population type	Participants (n)	Age range	Males (%)
Arruda <i>et al.</i> , 2020 [22]	Brazil	School-age children	5671	5-12	NA
Hansen <i>et al.</i> , 2018 [27]	Denmark	Adult population	26456	30-52	14209 (53.7%)
Genizi <i>et al.</i> , 2013 [28]	Israel	10th-grade students	243	6-18	108 (44%)
Arruda <i>et al.</i> , 2010 [23]	Brazil	Public school children	1856	5-11	959 (51.7%)
Kutuk <i>et al.</i> , 2018 [29]	Turkey	School-age children	117	6-18	96 (82.1%)

Fasmer <i>et al.</i> , 2011 [25]	Norway	Adult population	572	30.7 (mean)	290 (50.7%)
Attygalle <i>et al.</i> , 2020 [30]	Sri Lanka	School-age children	226	5-14	112 (50.2%)
Carpenet <i>et al.</i> , 2019 [31]	France	Adult population	4816	20.3 ± 2.8 (mean)	1178 (24.5%)
Hsu <i>et al.</i> , 2022 [32]	Taiwan	School-age children	81441	9.0 ± 4.1 (mean)	58,461 (71.8%)
Fasmer <i>et al.</i> , 2012 [26]	Norway	General population	81225	NA	NA
Arruda and Arruda, 2014 [24]	Brazil	Preadolescent children	6445	5-12	3259 (50.7%)
Riva <i>et al.</i> , 2012 [18]	Italy	School-age children	62	6-17	33 (53.2%)

Table 2. Characteristics and outcomes of the included studies.

Study	Study design	ADHD diagnostic tool	Migraine diagnostic tool	Key findings	ROBIN-I
Arruda <i>et al.</i> , 2020 [22]	Retrospective	SDQ and face-to-face evaluations and diagnosis are based on DSM-IV standards	ICHD-2	ADHD is associated with migraines, including frequent migraines. The burden that the relationship places on the children and their families should be the main topic of future investigations.	Moderate
Hansen <i>et al.</i> , 2018 [27]	Cross-sectional	ADHD Self-Report Scale (ASRS)	SQM	Migraine and ADHD are co-occurring disorders; the link with ADHD was strongest in people who also experienced migraine with visual abnormalities.	Moderate
Genizi <i>et al.</i> , 2013 [28]	Retrospective	The computerized general health questionnaire	ICHD-2	Children and adolescents who are directed to a neurological evaluation because of primary headaches (44% of whom had migraines) are more likely to have learning difficulties and ADHD than children and adolescents in the general pediatric population.	High
Arruda <i>et al.</i> , 2010 [23]	Cross-sectional	DSM-IV	ICHD-2	Although migraine does not generally co-occur with ADHD, it does with hyperactive-impulsive conduct. The association should be known to providers and educators.	Moderate
Kutuk <i>et al.</i> , 2018 [29]	Cross-sectional	DSM-5	ICHD-3	Children with ADHD had considerably higher rates of headache diagnoses and particular migraines. Migraine is a significant component of the comorbidity of ADHD in both mothers and children.	Moderate
Fasmer <i>et al.</i> , 2011 [25]	Cross-sectional	ASRS and face-to-face interviews with the diagnosis are based on ICD-10 and DSM-IV	Self-report	Compared to controls from the general community, adults with chronic ADHD have a higher rate of migraines.	Moderate
Attygalle <i>et al.</i> , 2020 [30]	Cross-sectional	Swanson, Nolan, and Pelham (SNAP) Questionnaire (SNAP-IV) along with personal interviews based on DSM-5	ICHD-3	Children with migraines are more prone than children without migraines to display traits of hyperactivity, impulsivity, and inattentiveness. Clinically diagnosed ADHD and screen time did not correlate; however, migraine was linked to more daily screen time.	Moderate
Carpenet <i>et al.</i> , 2019 [31]	Cohort study	ASRS-V	ICHD-3	The strongest associations between the hyperactivity domain and migraineurs with aura, but no correlations with headaches that are not migraines.	Moderate
Hsu <i>et al.</i> , 2022 [32]	Cross-sectional	ICD-9-CM	ICHD-2	Compared to matched controls, children and adolescents with ADHD had a higher incidence of migraine. Young adults with ADHD did not exhibit an elevated risk.	Moderate
Fasmer <i>et al.</i> , 2012 [26]	Population-based study	NA	NA	There is a comorbidity between migraine and ADHD, according to the prescription trends for these medications among adult patients.	Moderate

Arruda and Arruda (2014) [24]	Retrospective	SDQ and face-to-face interviews and DSM-IV criteria are used to make the diagnosis	ICHD-2	Preadolescent adolescents with migraines have a higher rate of hyperactivity than children without headaches.	Moderate
Riva <i>et al.</i>, 2012 [18]	Prospective	Conner's parents' and teachers' rating scale (CPT), face-to-face interviews, and diagnosis are based on DSM-IV criteria.	ICHD-2	The conclusion that there were no significant differences in attentional performance between the three clinical groups adds credibility to the notion that migraine may be on a continuum and share common pathophysiological mechanisms.	High

According to one of history's earliest writers, of the 150 elementary school pupils who were referred to Leviton's clinic for persistent headaches, 40% had academic issues [33]. His results supported subsequent research that revealed headache-affected children had a higher prevalence of hyperactivity and impulsivity symptoms than their healthy peers [34].

Several studies have shown a relationship between ADHD and several other comorbidities [35-37]. It's still unclear how ADHD and headaches are related specifically. In this systematic review, we are documenting and investigating the published literature on the comorbidity between ADHD and migraine. All of the included studies reported that ADHD and migraines usually co-occur. Similarly, Salem *et al.* reported a significant link between migraine and ADHD. However, to date, it is unknown what causes such an association, so more research is necessary [38].

Because most of the currently available studies are cross-sectional, a causal relationship between ADHD and migraines cannot be proven. A shared pathophysiology, according to some scientists, may explain why there is a connection between ADHD and migraine. For instance, Villa and colleagues suggested that dopamine and noradrenaline were to blame for the decreased visual attention seen in children with migraine. Given that these neurotransmitters are also involved in the pathophysiology of migraine, it has been suggested that these kids may be more susceptible to attention deficit disorder [19]. The pathophysiology of both conditions is also thought to involve other neurotransmitters, such as GABA [39, 40]. According to a different theory, having frequent headaches increases irritability and distractibility, particularly in kids who already have a short attention span, adding to the difficulty of learning. A study that discovered a connection between neuropsychological deficiencies and the frequency of headache episodes [41] lends support to this. Additionally, a genome-wide analysis study [42] led to the hypothesizing of a genetic background theory.

This study also reported that diagnoses of headaches, particularly migraines, were much more common in children with ADHD. Both mothers and children who have ADHD frequently experience migraines. Childhood migraine affects the quality of life [43], school attendance [44], and academic achievement [45], and it is linked to behavioral, emotional, and social issues [46].

However, there is still disagreement over how to categorize headaches in children. The primary factor for this is that headache phenotypes frequently evolve, and various headache diagnoses may instead reflect a continuum of headache symptoms than distinct entities [47]. Dopaminergic system dysfunction, iron deficiency in the brain, and shared genetic pathways are some of the hypothesized pathophysiological connections between ADHD and headache [29]. The ubiquitous malfunction of the sleep-wake and arousal systems may have an impact on how pain is processed, and internalising symptoms and sleep issues may also play a mediation role in the association between ADHD and headaches [1, 12]. Unfortunately, there is currently no evidence-based guidance on how to treat headaches in kids with ADHD, how migraine prophylaxis using valproate, amitriptyline, and flunarizine affects ADHD symptoms [19], or medication hierarchies for people with ADHD who experience headaches.

Conclusion

In this systematic review, we comprehensively reviewed the available literature on the association between migraine and ADHD. Our findings suggested the presence of an association between migraine and ADHD. Higher migraine incidence rates were demonstrated among the pediatric population with ADHD.

Acknowledgments: Many thanks to Dr. Mostafa Hussein Soltan; Consultant of Psychiatry, King Salman Military Hospital, Tabuk, Saudi Arabia, for his continuous help, support, and encouragement to complete this work.

Conflict of interest: None

Financial support: None

Ethics statement: None

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