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Prevalence of bone fractures among children and adolescents with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is a significant neurodevelopment disorder among children and adolescents, with 5 % prevalence. Bone fractures account for 25 % of accidents and injuries among all children and adolescents. Considering the characteristics of inattention, hyperactivity, and impulsivity in children with ADHD, it is critical to examine bone fractures among these children. The objective of our meta-analysis was to determine the prevalence of bone fractures among children and adolescents with ADHD.

Methods: We completed a systematic review and meta-analysis using an electronic search of the following databases: CINAHL, EMBASE, PsycINFO, PubMed, and Scopus. The search terms used were: “attention deficit hyperactivity disorder OR attention deficit disorder” and “bone fracture*.” We included studies examining patients 18 years or younger who were diagnosed with ADHD and tracked (prospectively or retrospectively) for five or more years. Effect size (es), using a random effects model, was calculated. We registered the review protocol with PROSPERO (CRD42019119527).

Results: From 445 records retrieved, 31 full text articles were reviewed and 5 articles met inclusion criteria for meta-analysis. The summary es revealed the prevalence of bone fractures among children and adolescents with ADHD to be 4.83 % (95 % CI: 3.07–6.58 %). The location of bone fractures, using a subset of data, showed a distribution of 69.62 %, 22.85 %, and 7.53 % in the upper limbs, lower limbs, and other anatomical regions, respectively. Another subset of studies revealed a 2.55-fold increase in the prevalence of fractures among the children with ADHD compared to their counterparts.

Conclusions: Awareness of these findings is critical to physicians, parents, and policy makers to create safe environments and provide supports in order to optimize the health and safety of children and adolescents with ADHD.

Keywords: Attention-deficit/hyperactivity disorder, Bone fracture, Children, Adolescents, Injury, Accident

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Background

Attention-deficit/hyperactivity disorder (ADHD) can be described as a neurodevelopment disorder of impairing inattention, motor hyperactivity, and impulsivity with an onset in childhood and difficulties continuing into adulthood [1]. There has been great variability in the reported prevalence of ADHD between studies, explained mainly by differences in their methodology [2]. One such methodological variation is differences in the definition of ADHD used, such as those between the Diagnostic and Statistical Manual of Mental Disorders (DSM) versus the International Classification of Diseases (ICD) classifications. Other reasons for the discrepancy originate from the demographic characteristics of the population under study, such as age and gender, as well as the source of information [3]. Overall, according to DSM-5 [4], the prevalence of ADHD is estimated to be 5% and the male to female ratio is nearly 2:1 among children.

Bone fractures account for nearly 25% of all accidents and injuries among children, with fractures of the distal radius being the most common [5]. Overall, extremity fractures are one of the most common reasons of children's hospital admission [6]. The three main causes of children's extremity fractures are accidental trauma, non-accidental trauma (that is, child abuse), and pathological bone conditions [7]. Among the accidental reasons of these fractures are falling from a height or falling while running, motor vehicle accidents (such as being hit by a car as a pedestrian), fighting, and recreational activities (such as riding a bicycle) [7].

One may assume that symptoms of ADHD, such as hyperactivity, ought to predispose children and adolescents diagnosed with ADHD to a greater number of accidental injuries [8]. This notion is supported by evidence from Brehaut, Miller, Raina, and McGrail [9] who report a 1.5-fold increase in the risk of injury in children with behavioral disorders.

Considering the increased risk of injuries among children with ADHD and the high prevalence of bone fractures among children, it is essential to examine bone fractures in children and adolescents with ADHD. To the authors' knowledge, no review of these findings has been conducted. The purpose of this review is to systematically assess the available studies and to synthesize their findings as a meta-analysis.

Methods

The authors have adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines in completing this systematic review and meta-analysis [10]. The review has also been registered with PROSPERO (CRD42019119527).

Search strategy

The Cochrane Library and PROSPERO were searched to ensure that the systematic review of fractures among children and adolescents with ADHD had not previously been completed. Then, an electronic search of the following databases was conducted to retrieve studies: CINAHL, EMBASE, PsycINFO, PubMed, and Scopus. The following search terms were used: "attention deficit hyperactivity disorder OR attention deficit disorder" and "bone fracture*." There were no restrictions set on language or publication dates of retrieved articles. To supplement the electronic search, reference lists from key articles and other systematic reviews on the topic of ADHD and injuries were identified and assessed for articles meeting the systematic review criteria.

Eligibility criteria

In order to fulfill inclusion requirements, studies had to meet five general criteria. First, the age range for the population under study was set at 18 years old and younger. If a study's population age range had 60% or greater overlap with this age range, it would be included. For example, a study whose population was ages six to 17 years would qualify but a study whose population was 40 years or younger would be excluded.

The second criterion for inclusion was a diagnosis of ADHD, which must have been made using recognized diagnostic criteria, such as the DSM or ICD classifications, or the use of prescription medication for the treatment of ADHD in the population. For example, a study that identified participants by relying on a survey to classify children as hyperactive without standard diagnosis of ADHD would be excluded. On the other hand, a study that used the prescription of methylphenidate to indicate the presence of ADHD would be included. This latter decision was made because medications used to treat ADHD are not typically used off-label in children or adolescents for other purposes; therefore, an underlying diagnosis of ADHD is likely present if children or adolescents are being prescribed methylphenidate [11].

The third inclusion criterion concerned the type of study and study methodology. To be included in the meta-analysis, the study must have provided a sample of patients with ADHD followed (prospectively or retrospectively) over a period of five or more years with a subset that have experienced bone fractures. The patients with ADHD could not be part of a specific population, such as Medicaid patients or have fractures sustained exclusively as a result of physical abuse. However, the population was not restricted to any geographic location or setting (for example, inpatient or outpatient records were acceptable).

The fourth inclusion criterion was the article type. To be considered in the review, articles had to be published

in peer-reviewed journals as full-text manuscripts. Conference abstracts and commentaries were excluded from the review. Finally, the fifth inclusion criterion was that the study population was a unique population that had not been covered by any other article in the review. Studies that examined the same dataset or group of patients through various articles were only included once in the meta-analysis. Additionally, it should be noted, that this review was on bone fractures in human subjects only; therefore, studies conducted exclusively on animal models or human dental fractures were excluded.

Study selection

The resulting articles from the electronic search were entered into Mendeley (version 1.19.2) where duplicates were removed. Then articles were assessed based on their abstracts to exclude entries that did not meet the inclusion criteria. Subsequently, full-text articles were retrieved for the remaining entries and examined by two independent reviewers (H.S. and S.M.) to evaluate inclusion into the systematic review and meta-analysis.

Data extraction

A data extraction form was created to extract key elements of the study, including findings that could be used to calculate fracture prevalence among subjects with ADHD. Data extraction included the following: (1) author, (2) year, (3) country, (4) study setting, (5) study design, (6) duration, (7) sample size of ADHD group, (8) sample size of control group, if applicable, (9) age range, (10) ADHD diagnosis method, (11) fracture identification method, and (12) fracture locations, if specified.

Quality assessment

Two independent reviewers (H.S. and S.M.) conducted quality assessment of the studies that were included in the meta-analysis using the Joanna Briggs Institute (JBI) critical appraisal tool for prevalence studies [12]. The checklist includes nine questions that are marked as “yes,” “no,” “unclear,” or “not applicable.” The authors of this meta-analysis agreed to translate the checklist into a point system by assigning one point for any question marked “yes,” no points to questions marked “no” or “unclear,” and not to count any questions marked as “not applicable” in the final calculation.

Data analysis

Meta-analysis was completed using a Microsoft Excel tool developed by Neyeloff, Fuchs, and Moreira [13]. The sample size of each study was the number of patients diagnosed with ADHD. The number of events was the number of fractures experienced within each study's ADHD group. The prevalence of fractures among this population was the calculated effect size. Neyeloff,

Fuchs, and Moreira [13] warn that combining prevalence rates cannot be called “effects” because there is not an intervention causing an effect. Rather, they state that this rate should be named “single group summary” and refer to it simply as “outcome,” which they abbreviate as “es, effect size.” For the purpose of simplicity, this meta-analysis will refer to the outcome (prevalence of fractures) as es.

The authors decided to use a random effects model to calculate the es of the meta-analysis for several reasons. A random effects model allows for the assumption that factors other than error or chance exist within and between studies. It also allows for the assumption that the studies used are a random sample of a hypothetical population of studies. Additionally, a random effects approach allows for generalizations to be made beyond the studies included in the meta-analysis [14]. JBI encourages the use of a random effects model that is presented with a 95% confidence interval (CI) for prevalence meta-analyses [14].

The level of heterogeneity or “variation in true effect sizes underlying the different studies” [15, p. 1158] included in the meta-analysis was assessed using the I^2 measure. Higgins, Thompson, Deeks, and Altman [16] recommend the use of I^2 as a measure of consistency between studies, especially when a meta-analysis consists of a small number of studies. I^2 is total variation (in percentage) across studies due to heterogeneity and not due to chance [14]. Heterogeneity is expected in meta-analysis [15] especially when it comes to studies in medicine [17].

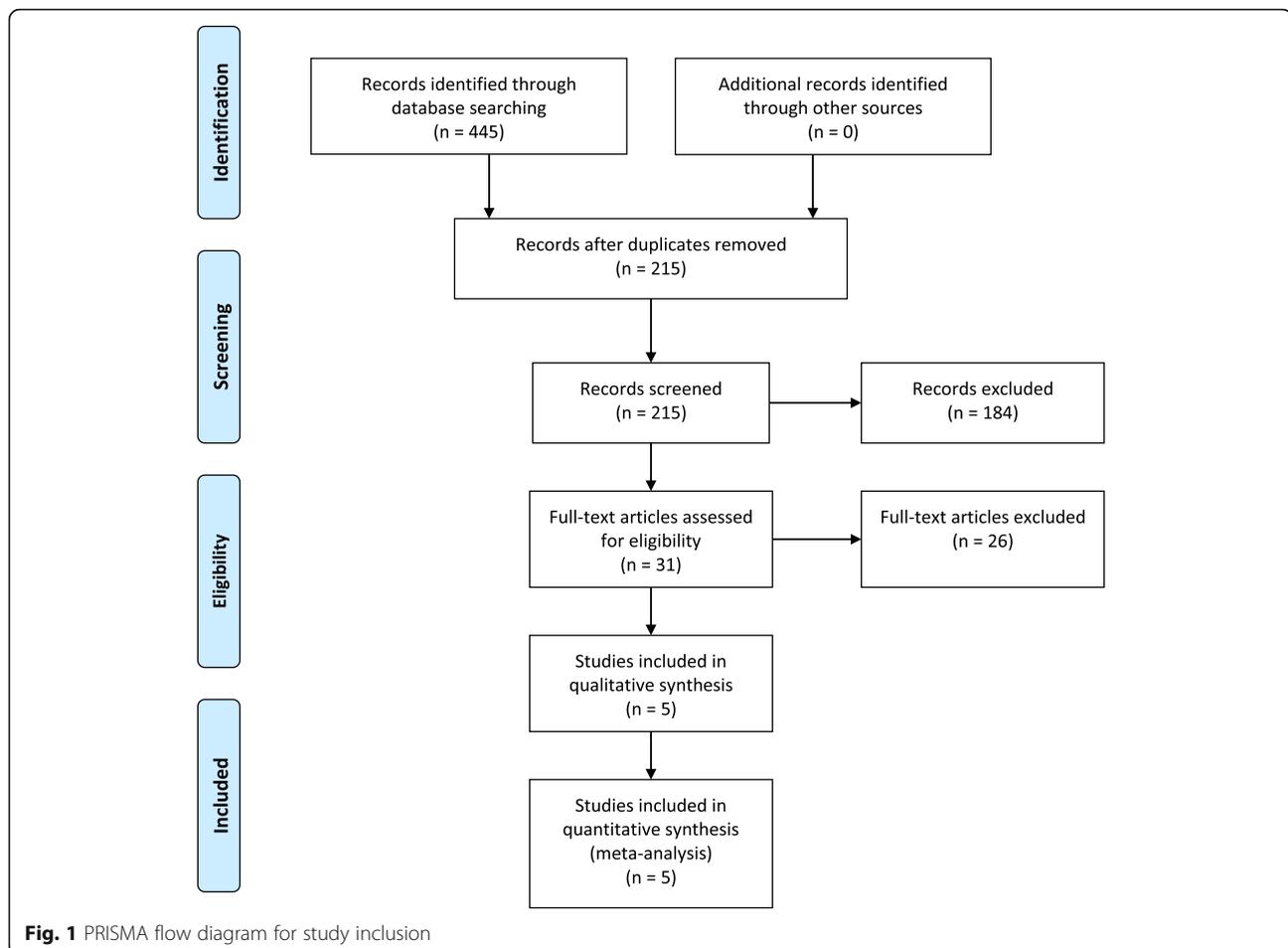
Results

Search results

The initial database search resulted in 445 articles (Fig. 1). Of these articles, 230 were found to be duplicates and removed. The remaining 215 articles were reviewed for inclusion based on their abstracts, from which 184 articles were excluded. Then, the remaining 31 records were retrieved for analysis of the full text, of which five met the inclusion criteria and were included in the systematic review and meta-analysis.

Excluded studies

As mentioned above, 184 articles were excluded after an examination of their abstracts. Common reasons for exclusion at this point were articles that exclusively examined dental fractures in the ADHD population, the effects of brain injury on the development of ADHD, non-human models, the effects of ADHD medication on fractures, and fractures as a result of abuse. It was also possible to exclude, based on abstracts, several studies that did not meet the age inclusion requirements.



The next stage of study exclusion was based on a full-text appraisal of the remaining 31 articles (completed by H.S. and S.M.). Of these, 26 articles were excluded based on not meeting the inclusion criteria of age ($n = 4$), ADHD diagnosis ($n = 8$), study type ($n = 10$), article type ($n = 3$), and being a population examined by another study that was already included ($n = 3$). Two of these articles were excluded for two reasons each (Table 1).

Characteristics of included studies

Two authors (H.S. and S.M.) assessed the quality of the five included studies and disagreements were discussed until consensus was reached. The characteristics of the included studies are given in Table 2. Three of the studies [9, 43, 44] contained a control group of children and adolescents who were not diagnosed with ADHD. Four of the studies [9, 43–45] indicated the percentage of ADHD patients who were male (between 76.5 and 81.6%). Three of the studies [43, 45, 46] provided data on the anatomic location of fractures experienced by ADHD patients.

Outcomes

The summary es of the meta-analysis revealed a fracture prevalence of 4.83 %, with a 95 % CI between 3.07 and 6.58 (Table 3). The I^2 score revealed a heterogeneity level of 66.63 %, a level that may be referred to as moderate-to-high [16]. The forest plot displaying the included studies and summary prevalence is given in Fig. 2.

Two other outcomes were calculated using the available data from the included studies: fracture locations (Table 4) and fold-increase in fracture prevalence among the ADHD population (Table 5). It was determined, from the three studies that provided information on the locations of fractures, that the distribution of fractures among children and adolescents with ADHD is 69.62 % in the upper limbs, 22.85 % in the lower limbs, and 7.53 % in other skeletal regions (Table 4). Three of the studies in the meta-analysis included a control group design; therefore, by combining data solely from these studies, it was determined that there exists a 2.55-fold increase in the prevalence of fractures among children and adolescents with ADHD compared to those without ADHD (Table 5).

Table. 1 Summary of excluded articles, with reasons

Article	Exclusion Criteria					Explanation
	Age	ADHD Diagnosis	Article Type	Study Type	Repeat Population	
Ayaz, 2015 [18]				x		Point-in-time data
Barkley, 2001 [8]			x			Commentary
Cairney, 2014 [19]			x			Commentary
Chen, 2017 [20]					x	Same population as Chou, 2014
Duramaz, 2018 [21]		x				Tool used assessed impulsive behavior (not ADHD diagnosis)
Erdogan, 2014 [22]				x		All patients have fractures (case-control)
Guo, 2016 [23]					x	Same population as Chou, 2014
Guy, 2016 [24]				x		Assessed Medicaid patients only
Hellgren, 1993 [25]		x				Mixed patient population (cannot isolate ADHD)
Hurtig, 2016 [26]		x				Assessed hyperactivity and symptoms consistent with ADHD (not ADHD diagnosis)
Lu, 2017 [27]		x				ADHD diagnosed only as a comorbid condition with Tourette Syndrome
Merrill, 2009 [28]	x					Population 0–65 years
Ozer, 2010 [29]				x		All patients have fractures (case-control)
Pastor, 2006 [30]				x		Point-in-time data
Perry, 2016 [31]	x					Population 0–40 years
Prasad, 2018 [32]				x		Point-in-time data
Rowe, 2004 [33]				x		Point-in-time data
Schermann, 2019 [34]	x					Population of military recruits
Schermann, 2018 [35]	x					Population of military recruits
Siwani, 2014 [36]				x		All patients have fractures (case-control)
Tai, 2013 [37]		x			x	All hyperkinetic disorders are included; Same population as Chou, 2014
Uslu, 2008 [38]		x				Tool used assessed impulsive behavior (not ADHD diagnosis)
Uslu, 2007 [39]		x				Tool used assessed impulsive behavior (not ADHD diagnosis)
van den Ban, 2011 [40]			x			Conference abstract (full study included in meta-analysis)
Wassenberg, 2004 [41]				x		Does not indicate fractures in ADHD patients
Yang, 2016 [42]		x		x		Excluded children previously diagnosed with ADHD; Assessed ADHD risk in those with fractures

Discussion

ADHD is a significant neurodevelopment disorder with a prevalence of 5 % among children and adolescents [4]. Bone fractures account for 25 % of accidents and injuries among children and adolescents [5]. Considering the hallmark characteristics of inattention, hyperactivity, and impulsivity in ADHD [1], it is critical to examine the prevalence of bone fractures in this population.

The meta-analysis revealed that the prevalence of fractures among children and adolescents diagnosed with ADHD is 4.83 % (95 % CI: 3.07 to 6.58). A subset of the studies included in the meta-analysis also determined a 2.55-fold increase in the prevalence of fractures among this group when compared to a control group. Another subset of studies discovered the distribution of fractures among the population with ADHD to be in the upper

Table 2 Characteristics of included studies

Study, Year	Country	Study Setting	Study Design	Duration	Sample Size		Age Range	Sex (of ADHD cohort)	Identification Method		Outcomes Reported	Fracture Types Reported
					ADHD Group	Control Group			ADHD	Fracture		
Brehaut, 2003[9]	Canada	British Columbia (BC) Linked Health Dataset (BCLHD) and the BC Triplicate Prescription Program	Cohort (retrospective)	7 years	16,806	1,010,067	0–19 years	81.6 %	Methylphenidate prescription	ICD-9-CM	Fractures; Open wounds; Poisoning/toxic effect; Intracranial; Concussion; Burns	Overall
Chou, 2014[43]	Taiwan	Longitudinal Health Insurance Database (LHID)	Cohort (retrospective)	11 years	3,640	14,560	0–18 years	79.0 %	ICD-9-CM	ICD-10	Fractures	Skull, neck, ribs, and spine; Upper limb; Lower limb
Jacob, 2017[45]	Germany	Disease Analyzer database (IMS Health)	Nested case-control	6 years	27,880		6–17 years	76.5 %	ICD-10	ICD-10	Fractures	Forearm; Wrist and hand; Shoulder and upper arm; Foot and toe (except ankle); Lower leg (including ankle); Skull and face; Other
Raman, 2013[46]	United Kingdom	The Health Improvement Network (THIN)	Self-controlled case series	15.5 years	4,234		1–18 years		Read clinical classification system identification AND methylphenidate or dexamphetamine prescription	Read clinical classification system identification	Fractures; Intracranial; Traumatic complications; Sprains and strains; Superficial injury; Contusion; Open wound; Poisoning; Crushing injury; Foreign body in orifice; Burns; Other	Upper limb; Lower limb; Skull
van den Ban, 2013[44]	Netherlands	PHARMO record linkage system (RLS)	Cohort (retrospective)	11 years	1,289	7,332	0–18 years	79.8 %	Methylphenidate and atomoxetine prescription	Methylphenidate and atomoxetine prescription	Injuries or poisoning; Fractures; Intracranial; Open wounds	Overall

Table. 3 Fracture prevalence outcomes, with 95 % CI

Study	Fractures (among ADHD)	Sample Size (ADHD)	Prevalence	CI lower	CI upper
Brehaut, 2003	723	16,806	4.30 %	3.99 %	4.62 %
Chou, 2014	389	3,640	10.69 %	9.62 %	11.75 %
Jacob, 2017	1,447	27,880	5.19 %	4.92 %	5.46 %
Raman, 2013	80	4,234	1.89 %	1.48 %	2.30 %
van den Ban, 2013	30	1,289	2.33 %	1.49 %	3.16 %
Summary			4.83 %	3.07 %	6.58 %

limb (69.62 %), lower limb (22.85 %), and other anatomic regions (7.53 %).

There is an array of possible reasons for injuries and fractures in children with ADHD that may be attributed to the characteristic symptoms of the disorder. For example, parents report that impulsive children do not think before they act, can show poor judgment, and seek immediate gratification [47]. Another study found that while children with ADHD were able to identify hazards, they anticipate less severe consequences to their behaviors [48]. Pastor and Reuben [30] determined that although children with ADHD experience more injuries, their modes of injury are similar to children without ADHD. Therefore, characteristics of ADHD may make these children more prone to experiencing injuries and fractures even when they are in similar settings and situations to their counterparts without ADHD.

Limitations

The authors have identified several limitations to this meta-analysis including its heterogeneity and the causes

of this heterogeneity. Heterogeneity may be clinical, methodological, or statistical. Clinical heterogeneity may stem from differences in the characteristics of the populations in the study [14]. As was previously discussed, different diagnostic guidelines will identify varying subsets of children and adolescents as having ADHD. Therefore, since different methods of diagnosis were used among the studies, those identified with ADHD may have variable severities of the disorder, which may impact the prevalence of fractures.

Another source of clinical heterogeneity stems from whether medications were used to treat ADHD. In those studies where children and adolescents were identified through their diagnosis of ADHD and not the prescription of medications, it was not known if those experiencing fractures were using pharmacologic interventions for ADHD. It has been reported that the use of both stimulant and non-stimulant medications to treat ADHD is associated with a decrease in the number of bone fractures among patients with ADHD [31]. Another study revealed a 25 % decrease in the risk of fractures in those

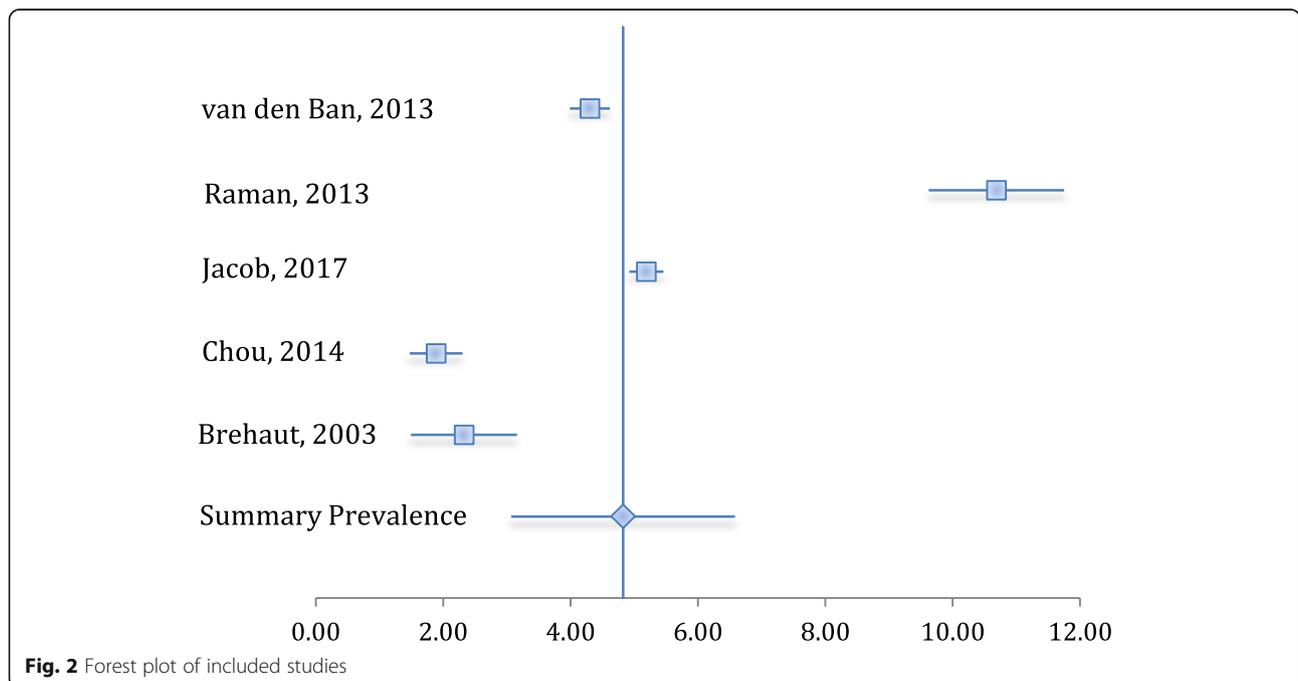


Fig. 2 Forest plot of included studies

Table. 4 Fracture locations among children and adolescents with ADHD

Study	Overall	Upper Limb		Lower Limb		Other	
		Number	Percent	Number	Percent	Number	Percent
Brehaut, 2003	723 ^a						
Chou, 2014	389	257	66.07 %	95	24.42 %	37	9.51 %
Jacob, 2017	1,447	1,026	70.90 %	320	22.10 %	101	7.00 %
Raman, 2013	80	51	63.75 %	23	28.75 %	6	7.50 %
van den Ban, 2013	30 ^a						
Summary	1,916	1,334	69.62 %	438	22.85 %	144	7.53 %

^adata not included in the summary numbers

who took methylphenidate for 180 days or longer [20]. Therefore, the prevalence of fractures between the studies may have been affected by the rate of pharmacological interventions.

Methodological heterogeneity can arise from variations in study qualities or differences in study designs [14]. All of the studies included in this meta-analysis were found to be similar in quality, as discussed in the [quality assessment](#) section. Additionally, all study designs were composed of a retrospective method that used a national or regional database. However, the studies differed in their time periods, which may have led to methodological heterogeneity. Both the clinical and methodological heterogeneities may have given rise to the statistical heterogeneity observed in the meta-analysis.

Another shortcoming of the meta-analysis is having only aggregate numbers of fractures among patients with ADHD. It is not known if a patient experienced multiple fractures in one injury event, if a patient had a series of fractures over time, or if each patient had one fracture each to compose the overall fracture numbers. It was also not possible to stratify the prevalence findings by age subgroups or by gender.

Future implications

If studies become available, future meta-analyses should be completed on prospective study designs that can follow children and adolescents with ADHD over time to determine who experiences what types of fractures, from

what sources of injury, and at what age. The participants' usage of medication for the treatment of ADHD should also be tracked.

A thorough subgroup analysis is required in future research, especially by age and gender. The modes of injury and bone integrity for a young child may be very different than that of an adolescent. The ability to stratify bone fractures by age can inform measures aimed at preventing injuries that are most effectively aimed at specific age groups. Some studies that have assessed fractures by gender in children and adolescents with ADHD have determined a higher rate among girls than boys when compared to control groups of girls and boys without ADHD [49]. With the knowledge that such differences exist, future research needs to quantify this difference and qualify it in a way that can impact the lives of patients.

Conclusions

Bone fractures in children and adolescents are an important concern for public health because they have considerable influence on the activities and daily living of affected children [50]. With an ADHD prevalence of 5% among children and adolescents and a fracture prevalence of nearly 5% among this population, understanding bone fractures among children and adolescents with ADHD is of importance in improving health and healthcare delivery. This understanding is most critical to parents who care for and attempt to decrease the

Table. 5 Prevalence of fractures in ADHD group versus control group

Study	ADHD Group			Control Group			Fold Increase
	Sample Size	Fractures	Prevalence	Sample Size	Fractures	Prevalence	
Brehaut, 2003	16,806	723	4.30 %	1,010,067	20,025	1.98 %	2.17
Chou, 2014	3,640	389	10.69 %	14,560	1,188	8.16 %	1.31
Jacob, 2017	27,880 ^a	1,447 ^a	5.19 % ^a				
Raman, 2013	4,234 ^a	80 ^a	1.89 % ^a				
van den Ban, 2013	1,289	30	2.33 %	7,332	90	1.23 %	1.90
Summary	21,735	1,142	5.25 %	1,031,959	21,303	2.06 %	2.55

^adata not included in the summary numbers

occurrence of fractures in their children, practitioners who educate their patients in an attempt to prevent injury or who treat these children once they have experienced a fracture, and to policy makers whose obligation it is to create healthy and safe environments that promote the health of all children and adolescents.

Abbreviations

ADHD: Attention-deficit/hyperactivity disorder; es: Effect size; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; JBI: Joanna Briggs Institute; CI: Confidence interval

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Authors' contributions

HS conceived the systematic review and participated in the review design, development of the search strategy, screening of the articles, assessing study quality, data abstraction, data analysis, and manuscript drafting. SM participated in the review design, screening of the articles, assessing study quality, manuscript drafting and editing. JM participated in design of the study, development of the search strategy, assessing study quality, and manuscript drafting and editing. DW and RG participated in design of the review, and manuscript review and editing. All authors have read and approved the final manuscript.

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Availability of data and materials

This article is a systematic review and meta-analysis; therefore, all data is available through published studies as described in the article.

Declarations

Ethics approval and consent to participate

This article is a systematic review and meta-analysis; therefore, ethics approval was not required.

Consent for publication

Not applicable.

Competing interests

The authors do not have any conflicts of interests to declare.

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