Title:

Effectiveness of pharmacological treatment for attention deficit/hyperactivity disorder on physical injuries: A systematic review and meta-analysis of observational studies

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Abstract (212 words)

BACKGROUND: Patients with attention-deficit/hyperactivity disorder (ADHD) are more prone to physical injuries, including motor vehicle accidents, fractures and brain injuries Several observational studies have been published investigating the association between the use of pharmacological treatment for ADHD and the incidence of physical injuries among patients with ADHD; however, the findings are not concordant.

OBJECTIVE: This study is a systematic review and meta-analysis of the existing literature and estimates the overall association between the use of ADHD medications and physical injury. Injury is defined as medically attended physical injuries in the form of hospitalisations, emergency department visits or general practitioners visits.

METHODS: PubMed, EMBASE, PsycINFO, CINAHL and the Cochrane Review databases were searched for relevant studies published up to May 2017 related to ADHD medication and risk of injuries. Observational study with any study design, all age group (children and adults) and all ADHD medications (stimulant and non-stimulants) were included. Studies relevant to the association between ADHD medication exposure and risk of injuries in ADHD patients were extracted and compiled for meta-analysis. Both within-individual and between-individual analysis were conducted.

RESULTS: 2001 citations were identified and ten observational studies were included. Three self-controlled case series and two self-controlled cohorts were eligible for meta-analysis of within-individual studies. Five cohort studies were included in meta-analysis of between-individual studies. The adjusted rate ratio of the within-individual methods was 0.76 (95%CI 0.61 to 0.93) and 0.88; 95% CI, 0.85-0.92 for between-individual studies.

CONCLUSION: The findings of this meta-analysis support a reduced risk of injuries among ADHD patients who were treated with ADHD medications.

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Key points:

- Patients with ADHD are prone to sustaining injuries that require medical attention.
- Pharmacological treatment can reduce ADHD symptoms and may reduce injury risk.
- Use of medication was associated with lower rates of medically attended physical injuries in the form of hospitalisations, emergency department visits or visits to general practitioners.
- Similar protective association was found in both genders.
- Potential treatment benefit was greater for elder adolescents and adults.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by hyperactivity, impulsivity, and cognitive dysfunction [1, 2]. ADHD often causes major negative impact in one's daily life and generally patients with ADHD are more prone to injuries including motor vehicle accidents, fractures and brain injuries [3]. Risk of injury to children and adolescents with ADHD might be mediated by several factors, such as impairment of motor functions, developmental coordination disorders or other core symptoms [4]. Indeed, core ADHD symptoms such as impulsivity, inhibitory deficits as well as inattention to surroundings may be the major factors to accidents. Pharmacological treatments such as methylphenidate, dexamphetamine, or atomoxetine are effective in the treatment for ADHD symptoms [1]. Stimulant medication use was hypothesised to decrease injury risk by reducing ADHD symptoms such as inattention or impulsivity [5, 6]. Indeed, a large number of the studies based on artificial laboratory simulations have shown that ADHD treatment reduces "errors and accidents" [7]. Some published studies have reported the association between ADHD medications and lower risk of injuries in ADHD [5, 6] while other did not report the same findings [8, 9]. The impact of ADHD medications in the prevention of physical injury still remains uncertain. In view of the above issues, we undertook a systematic review and meta-analysis of published studies to evaluate the effectiveness of ADHD medications in reducing injuries in the real-life setting.

2. Method

A systematic literature search was conducted using the search terms listed in Appendix A. PubMed, EMBASE, PsycINFO, CINAHL and the Cochrane Review databases were searched up to 15th May 2017. Only English studies were included. Titles and abstracts were screened and full texts of relevant articles were retrieved for further review to identify relevant studies. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for guidelines to ensure clear and comprehensive reporting.

2.1 Inclusion and exclusion criteria

Inclusion:

A. Analytical observational studies using cohort, case control, self-controlled case series or case crossover study design.

B. Studies must report the association between ADHD medication use, stimulants and/or non-stimulants, and the risk of injuries. Injuries is defined as "medically attended

physical injuries in the form of hospitalisations, emergency department (ED) visits or general practitioner (GP).visits"

C. Studies on children, adolescents and/or adults.

Exclusion criteria:

A. Case reports

B. Animal studies.

2.2 Quality assessment

As recommended by the Cochrane Collaboration [10], the included studies were assessed for methodological quality using the Newcastle-Ottawa scale (NOS) [11]. Three authors (ML, EM and SL) independently reviewed and scored each study. Disagreements were resolved through discussions. A maximum of nine stars could be allocated for the following categories: selection, comparability and outcome. The total score was obtained by adding the number of stars in the sub-categories where a higher score indicated better quality.

2.3 Data extraction

Data from the included studies were extracted using a standardised data collection form. These included study duration and design, data source, outcome definition and effect size. Authors ML, EM, SL and WQ independently extracted data and completed the characteristics form that was subsequently cross-matched to ensure consistency and accuracy. Information for each study was extracted by two authors. Outcome parameters such as the adjusted incidence rate ratio (IRR), hazard ratio (HR), odd ratio (OR), rate ratio (RR) and the corresponding 95% confidence intervals (CI) were extracted and included in the meta-analysis if appropriate. Studies where such statistics could not be included in the meta-analysis were summarised in the narrative review. The primary outcome of interest was the risk of injuries following exposure to ADHD medications among patients with ADHD relative to patients or patient-time without medications. Any data on physical injuries such as open wounds, fractures, transport accidents and falls recorded from all points of care such as GP visits, hospitalisation and ED admissions were extracted for inclusion.

2.4 Statistical analysis

To estimate the association between the use of ADHD medications and incidence of injuries, the results of the included studies were combined using DerSimonian and Laird's random-effects model [12] to account for heterogeneity among studies. Analysis was performed

on the adjusted estimates from the studies. The pooled estimates with 95% CI were calculated.

As the studies included in the analysis were conducted in different settings, we examined the extent of heterogeneity among studies with the Cochran Q test [12], where a cut-off p-value of 0.1 was considered significant for heterogeneity. Higgin's I^2-statistic was reported for each figure to indicate the degree of heterogeneity [12]. All analyses were conducted using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3. Results

PubMed, EMBASE, PsycINFO, CINAHL and Cochrane review database were searched, up to May 2017, with 1343, 444, 92, 122, 0 records identified from each database respectively, yielding 2001 records in total and 1322 records after removing duplicates (Figure 1). Titles and abstracts were screened and full texts were retrieved for further assessment of 26 relevant records, of which 10 studies were found to be relevant. Six of the studies [6, 13-17] were conducted using nationwide databases, with two [15, 16] from the same nationwide claim database in Taiwan, three others [4, 18, 19] from insurance claim databases and one [5] from GP database, all with substantial numbers of patients. All studies evaluated physical injuries as the outcome, which was defined as medically attended injuries at any point of care, identified diagnoses for injury on database records, or through entries for trauma or transport-related injuries on medical records. Two studies [4, 13] limited the outcome to hospitalisations and three cohort studies [6, 14, 19] limited to ED visits from trauma- or transport-related injuries; while the remaining five incuded studies [5, 15-18] included attended injuries at all recorded points of care. All studies reported methylphenidate as a medication used in ADHD patients. ADHD medications studied were limited to methylphenidate only in two of the studies [6, 15], while one study [5] included stimulant medications only and the remaining seven studies [4, 13, 14, 16-19] included stimulant and non-stimulant medications. The characteristics and summary of results of the included studies are shown in Table 1, Figure 2a and 2b. The quality assessment of the included studies is shown in Table 2. Four cohort studies [13, 15, 16, 18] had six to seven out of nine stars from the NOS scale which are with adequate quality. As all cohort studies compared treated individuals to untreated individuals, they lost two stars from the "comparability" criteria. Other six studies [4-6, 14, 17, 19] had the full nine stars which were considered at high quality. Six out of the ten included studies [5, 6, 14, 16, 17, 19] reported significant association between injuries and ADHD medications use with a lower risk/incidence of injury in treated patients or treated periods. While the remaining four studies [4, 13, 15, 18] did not find a significant association, the results were favourable towards the use of medications being associated with lower risk of injuries.

Three of the studies [4-6] were self-controlled case series studies, reporting within-individual comparisons only [20]. The remaining seven studies [13-19] were cohort studies, one [17] with within-individual analysis only, four [13, 15, 16, 18] with between-individual analyses only and two [14, 19] with both between-individual and within-individual analyses. The within-individual analyses and between-individual analyses were included in separate meta-analyses. In each of the meta-analyses, the results were separated into subgroups of children and adults, as the safety and effectiveness of ADHD medications were less well studed in adults. The stratification of children and adults was according to definitions by investigators, with children defined as aged 18-21 or lower [4-6, 13, 15, 17] and adults defined as aged 18 or older [14, 16, 18, 19].

3.1 Meta-analysis of within-individual analyses

Three self-controlled case series (SCCS) and within-individual analysis of three cohort studies were included in the meta-analysis, comprising a total of 253,612 cases from databases in the United States, Sweden, Hong Kong, Germany, Denmark and the United Kingdom respectively [4-6, 14, 17, 19]. The study periods ranged from 1990 to 2014, with individual study spanning between 4 and 15 years (Table 1). The relative risk of injuries was significantly lower in the medicated periods (pooled RR=0.76; 95% CI, 0.61-0.93) (Figure 3). No significant difference was observed between different within-individual study designs (subgroup Q-statistics = 2.52, p=0.11, I^2 = 60.3%) (Figure 3). Lower risk of injuries was found (subgroup Q-statistics = 50.70, p < 0.01, I^2 = 98.0%) in the medicated periods in adults (pooled RR, 0.60; 95% CI, 0.57-0.63) than in children (pooled RR, 0.86; 95% CI, 0.79-0.93). A high heterogeneity was found across the studies (Q-statistics = 126.42, p <0.01, I^2 = 96%) (Figure 4). The heterogeneity may be the result of the difference in the outcome measures, the statistical analysis used and the ADHD medications included across the six studies.

3.2 Meta-analysis of between-individual analyses

The between-individual results from six cohort studies [13-16, 18, 19] were included in the meta-analysis, comprising 2,347,656 ADHD patients across the cohorts, among which 1,964,855 patients received medications. Two studies were from databases in the United States [18, 19], two from Taiwan [15, 16], and one each from Sweden [14] and Netherlands [13]. As Chien et al. [16] used the same database as Chen et al. [15], Chien et al's study [16] was not included in the main meta-analysis for between-individual analyses to avoid double-up of results; however it was substituted for Chen et al. [15] in the sensitivity analysis to assess the

impact on the overall results. The study periods ranged from 1996 to 2014, with individual studies spanning over 4 to 17 years (Table 1). The risk of injuries was significantly lower in the medicated individuals (pooled RR, 0.88; 95% CI, 0.85-0.92). A low heterogeneity was found between the studies (Q-statistics = 3.96, p = 0.41, I^2 = 0%) (Figure 5). Sensitivity analysis by subsituting Chen et al. with Chien et al. showed similar results (pooled RR, 0.86; 95% CI, 0.80-0.92). Similarly, low heterogeneity was observed (Q-statistics = 4.65, p = 0.33, I^2 = 14%) (Figure 6).

In the subgroup analysis, the risk of injuries were found to be significantly lower in the adults only (pooled RR, 0.86; 95% CI, 0.78-0.94) while no significant association was found in children (pooled RR, 0.93; 95% CI, 0.83-1.03) (Figure 7). However, no significant difference was found between the pooled estimates in children and adults (Q-statistics = 1.16, p = 0.28, I^2 = 13.9%).

4. Discussion

The results of all identified observational studies were largely favourable towards the use of medications being associated with reduction injuries as defined as "medically attended physical injuries in the form of hospitalisations, emergency department visits or general practitioners visits". Four out of the seven cohort studies [14, 16, 17, 19] and two out of three self-controlled case series studies [5, 6] showed significant association between injuries and ADHD medications use. While the remaining three cohort studies [13, 15, 18] and one self-controlled case series study [4] were unable to show the significant association, the nonsignificant finding may be due to insufficient statistical power.

When the within-individual analysis results of three cohort studies [14, 17, 19] and three self-controlled case series studies [4-6] were pooled in the meta-analysis, reduction in injuries in patients was shown with the incidence significantly lowered by 24% (95% CI 7%-39%) during medication use as opposed to non-medicated periods, although a high heterogeneity was observed among the studies. The different statistics used in reporting the risk of injuries, including OR [17, 19], IRR [4-6] and HR [14], may contributed to the heterogeneity. The different outcome measures, with studies including injury treated at all points of care [5, 17], hospitalisations only [4] and ED visits only [6, 19] respectively, may have also contributed to the heterogeneity. The variation in the ADHD medications in the studies ranging from methylphenidate only [6] to both stimulant and non-stimulant medications included [4, 17, 19] could be another source of heterogeneity. While significant lower risk of injuries was found in both children and adults in the subgroup analysis, a greater effect was found in adults (40%, 95% CI 37%-43%) compared with children (14%, 95% CI 7%-21%) (Q-statistics = 50.70, p <

0. 01). The heterogeneity found in the subgroup analysis for children (Q-statistics = 5.84, p = 0.12, I^2 = 49%) and adults (Q-statistics = 0.05, p = 0.83, I^2 = 0%) were low to moderate. The difference in effect in children and adults could be a contributor to the heterogeneity found in the overall meta-analysis of all within-individual analyses. Given such high heterogeneity, the results need to be interpreted cautiously.

When the between-individual results of the five cohort studies [13-15, 18, 19] were pooled in the meta-analysis, risks of injuries in ADHD patients was also shown to be significantly lowered by 12% (95% CI 8%-15%) when medicated as compared to not medicated. Low heterogeneity was found across the studies (Q-statistics = 3.57, p = 0.47, I^2 = 0%). In the subgroup analysis, significant association was not found in children (pooled RR, 0.93; 95% CI, 0.84-1.10) while a 12% lower risk (pooled RR=0.86, 95% CI 0.78-0.94) was found in adults. However, the test for subgroup difference did not show significant difference in study results between children and adults (Q-statistics = 1.16, p = 0.28, I^2 = 13.9%). The nonsignificant result in children may be due to the insufficient power of the study design.

In two of the studies [5, 14], a lower risk was only found in treated males but not females. This may be due to the number of female cases identified being 33% to 85% fewer than that of male, resulting in insufficient statistical power to show significant finding.

Age-stratified analysis in two of the studies [6, 17] found that the benefit of injury reduction was greater in older adolescents, which is consistent with our finding from subgroup meta-analysis that the benefit of ADHD medications on injury reduction may be associated with age, with greater beneficial effect found in adults than in children.

Currently, injury prevention is not the indication of ADHD medications.. In this study, we found that the use of ADHD medication was associated with a significant lower risk of injury. This protective effect was clearly present not only in children and adolescents but also in adults which highlighted the importance of the medication on the well-being of ADHD patients. However, pharmacological treatment is part of the comprehensive treatment programme for ADHD, which incorporates psychosocial interventions as well. The initiation of drug treatment should accompany with careful clinical evaluation including an accurate diagnosis, clear impairment in function due to ADHD, and weighting the risks and benefits of the medication.

Randomised clinical trial (RCT) is recognised as the gold standard to evaluate efficacy of pharmacological interventions. However, it is also recognised that RCT is not an effective method to evaluate real-life outcomes due to relatively short duration of trial and relatively small sample size. On the other hand observational studies are more appropriate to evaluate outcomes in real-life practice. The major strength of observational studies using

clinical/adminstrative databases is the large sample size and long follow-up time. These provided a valuable basis to investigate the association of between ADHD treatment and some rare adverse outcomes such suicidal attempts, psychosis and mortality [21-23]. This meta-analysis identified ten large observational studies using clinical or administrative databases because these databases can provide information on injury-related medical encounter with large sample size and long-term follow-up . However, observational study is also prone to bias if confounding effects are not properly addressed. We conducted quality assessment on the included studies and all of them are with good quality. Six included studies [4-6, 14, 17, 19] with full stars in NOS scale applied within-individual study design. This could effectively remove time-invariant confounding effects to obtain an accurate estimate. On the other hand, the results from the four cohort studies (between-individual design) [13, 15, 16, 18] are similar to the pooled estimates of the within-individual design which showed robustness of the results. In addition, the evidence from observational studies reflected the real-world effectiveness of the treatment. This could provide direct clinical implications in actual practice. With reference to the results of this study, injury prevention should be considered as one of the benefits of ADHD medication in clinical practice.

4.1 Strengths and limitations

We undertook a rigorous systematic review and meta-analysis which included all relevant literature to date. Reviewer selection bias was minimised by using a predefined search strategy for selection and data extraction being conducted by two independent authors. Differences in study designs, exclusion criteria, control groups, duration of follow-up, covariates included and analysis model can affect the accuracy of pooled estimates. We observed moderate to high heterogeneity in the pooled estimates. This may represent the difference in the analysis for each study, in particular which covariates were included and what analysis model was used; therefore some of the results should be interpreted with caution. However all studies were essentially measuring similar outcomes and there is no indication of large clinical heterogeneity to invalidate our meta-analysis and narrative reviews. More importantly the forest plots of the two analyses are consistent and make biological sense; thus, we believe it is appropriate to numerically summarize the results of some but not all studies in this systematic literature review. As the number of studies included in the meta-analysis is limited, a funnel plot was not performed as it would not reliably identify publication bias. In addition, the studies identified for meta-analysis are relatively recent (2009-2017) with similar results; therefore we cannot exclude the possibility of publication bias. As a result, the pooled estimates may be overestimated.

5. Conclusion

The results from this meta-analysis support that pharmacological treatment could lower the risk of injuries by an average of 13%. The benefit of ADHD medications in injury reduction may be associated with age, with greater benefit in older adolescents and adults. While the traditional consideration of ADHD management has been on improving academic performance, trauma prevention is another important aspect of care and should be further considered in the broader clinical assessment and management of ADHD when medications are prescribed.

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Table 1. Characteristics of included studies.

Study	Data source	Study period	Region	Study design[a]	Sample size[b]	Inclusion criteria	Exclusion criteria	Outcome definition	Statistical analysis	Effect size[c]
van den Ban et al. (2014) [13]	Dutch PHARMO record linkage system (RLS)	1998-2008	Netherlands	C	8621	Born in 1977 or later; all children and adolescents (<18 years), who started with ≥1 prescription for a drug approved for the treatment of ADHD[d]; at least 12 months of history in the PHARMO RLS prior to the index date		Hospital admissions for injuries or poisoning[e]	Incidence of injury in treated patients prior VS during use of ADHD medication[d]	IRR: 0.68 (95% CI 0.29-1.60)
Chen et al. (2017) [15]	Longitudinal Health Insurance Database (LHID), subset of National Health Insurance Research Database (NHIRD)	1996-2013	Taiwan	C	6201	<18 years old between 1996 and 2013; inpatient diagnosis or two outpatient diagnoses of ADHD during one year; prescribed with methylphenidate only	Born before 1996 or after 2005; fracture before ADHD diagnosis; missing residential data; ADHD diagnosis within one year prior to study period; prescribed with both methylphenidate and atomoxetine	Incidence of fracture[f], defined as ≥2 outpatient diagnoses in the same year or any inpatient diagnosis of fracture	Cox proportional hazard regressions of fracture in cohort with 0 VS 1-180 VS >180 days of methylphenidate treatment	Adjusted HR: 1-180 days: 1.18 (95% CI 0.98-1.43) >180 days: 0.77 (95% CI 0.63-0.94)
Chien et al.	LHID, subset of	2000-2010	Taiwan	C	655	≥3 outpatient	Diagnosed with	Incidence of	Cox proportional	Adjusted HR:

(2017) [16]	NHIRD					visits for ADHD within this one year; inpatient diagnosis of ADHD	injuries before 2000 or before the first visit for ADHD; diagnosed with ADHD before 2000; substance dependence or substance abuse diagnosis; aged <18; gender unknown	injury[g]	hazard regression of injury in treated VS untreated patients	Methylphenidate or atomoxetine: 0.774 (95% CI 0.487-0.895) Methylphenidate only: 0.668 (95% CI 0.487-0.895) Atomoxetine only: 0.692 (95% CI 0.206-2.225)
Merrill et al. (2009) [18]	Deseret Mutual Benefit Administrators (DMBA)	1998-2005	US	C	2186	≥2 visits with an ADHD diagnosis; a prescription of a drug used to treat ADHD[h]	Aged ≥65 years old	Incidence of injury[i]	Statistical analyses of injury in treated VS untreated patients	Adjusted RR: 0.89 (95% CI 0.75-1.05) Aged <20: 0.95 (95% CI 0.77-1.17) Aged ≥20: 0.87 (95% CI 0.65-1.17)
Chang et al. (2014) [14]	Swedish national registers	2006-2009	Sweden	C	17408 (211 with medications and injury)	Aged 18 years or older; ≥1 prescription for ADHD medication[j] but did not necessarily have a registered ADHD diagnosis	Individuals with any drug abuse diagnosis or crime conviction	Serious transport accident, which was identified as an emergency hospital visit or death due to transport-related trauma[k]	Between-individual and within-individual stratified Cox proportional hazard regressions of accident in treated patients during medicated VS nonmedicated	Adjusted HR: Between-individual In male: 0.71 (95% CI 0.57-0.89) In female: 0.92 (95% CI 0.78-1.23) Within-individual In male: 0.42

									periods	(95% CI 0.23-0.75) In female: 2.35 (95% CI 0.83-6.64)
Chang et al. (2017) [19]	Truven Health Analytics MarketScan Commercial Claims and Encounters databases	2005-2014	US	C, with within-individual analysis	2319450	All patients with ADHD[l] 18 years or older between 2005-2014; prescription claims to have valid fill dates and days' supply(≤180days) ; emergency MVC (Motor Vehicle Crashes) claims	Recurring treatment visits; All person-months in the first 2 years of follow-up (for long-term association study of MVC events 2 years after prescription)	Emergency department visits for motor vehicle crash (MVC)	Conditional logistic regression of ED visits in treated VS untreated	Adjusted OR: <u>Population level</u> In male: 0.88 (95% CI 0.84-0.93) In female: 0.86 (95% CI 0.82-0.90) <u>Within-individual</u> In male: 0.62 (95% CI 0.56-0.67) In female: 0.58 (95% 0.53-0.62) In male 2 years after medication: 0.66 (95% CI 0.58-0.76) In female 2 years after medication: 0.73 (95% 0.64-0.84)
Dalsgaard et al. (2015) [17]	Danish national registers	1990-2010	Denmark	C	710120, Children with ADHD who	Born from 1990 to 1999; registered with ADHD; injuries after the age of	Diagnosed ADHD before age 5 years and after age 10 years	Prevalence of injuries and emergency ward visits[m]	Quasi-experimental, difference-in-difference (DID) analysis of injury	<u>Within-individual</u> Adjusted OR: Injury: 0.82 (95% CI

					received treatment (n=1457), children with ADHD without pharmacological treatment (n=3100)	10 years			and emergency ward visits in treated[n] patients before VS after treatment	0.74-0.89) Emergency ward visits: 0.86 (95% CI 0.79-0.93)
Man et al. (2015) [6]	Clinical Data Analysis & Reporting System (CDARS)	2001-2013	Hong Kong	SCCS	4934	Aged 6 to 19 years who received ≥1 prescription of methylphenidate with ≥1 trauma-related emergency department (ED) admission	≥1 atomoxetine prescription	Trauma-related ED admission[o]	Conditional Poisson regression of related admission in patients treated with methylphenidate during medicated VS nonmedicated periods	Adjusted IRR: 0.91 (95% CI 0.86-0.97)
Mikolajczyk et al. (2015) [4]	German Pharmaco-epidemiological Research Database	2004-2009	Germany	SCCS	1147	Aged 3 to 17 years with new diagnoses of ADHD in 2005 and 2006[p]	ADHD diagnosis prior to 2005, or drug treatment for ADHD in the 12months preceding 2005	Hospitalization from any injury or brain injury according to the injury mortality diagnosis matrix	SCCS analysis of hospitalization in treated patients during medicated VS nonmedicated periods	Adjusted IRR: 0.87 (95% CI 0.74-1.02)
Raman et al. (2013) [5]	The Health Improvement	01/01/1993-30/06/2008	UK	SCCS	328	Registered with a THIN practice;	All injury types were included	Incidence of injuries,	Conditional Poisson	Adjusted IRR: 0.68 (95% CI

Network (THIN) primary care database		events and diagnoses that occur >12 months after registration; aged 1–18 years old diagnosed as having ADHD[q] who experienced an incident medically-attended injury event; received ≥1 prescription for stimulant medication[r]	except for 'late effects of injury or poisoning events' and 'medical/ surgical procedures causing complications	defined as a record that described bodily harm with as 'injury and poisoning'[s] at any location of service (GP, emergency room or hospital)	regression of injury in treated patients during medicated VS nonmedicated periods	0.50-0.91)

[a]C = cohort, SCC = self-controlled cohort, SCCS = self-controlled case-series

[b]Sample size of patients receiving medication in cohort study, sample size of patients receiving medications and having injury in SCCS

[c]IRR = incidence rate ratio, HR = hazard ratio, OR = odds ratio, RR = rate ratio

[d]Methylphenidate and atomoxetine

[e] International Classification of Diseases (ICD)-9 codes 800–995, excluding ICD-9 codes 905–909 (late effects of injuries, poisonings, toxic effects and other external causes) and specifically fractures (ICD9 800–829), intracranial injuries (ICD-9 850–854) and open wounds (ICD-9 870–897)

[f]ICD-9 codes 800-829

[g]ICD-9-CM codes 800–999, including fractures (ICD-9-CM 800–829), dislocations (ICD-9-CM 830–839), sprains and strains (ICD-9-CM 840–849), intracranial/ internal injuries (ICD-9-CM 850–869), open wounds (ICD-9-CM 870–899), injury to blood vessels (ICD-9-CM 900–904), superficial injuries/contusions (ICD-9-CM 910–924), crushing injuries (ICD-9-CM 925–929), foreign body entering through an orifice (ICD-9-CM 930–939), burns (ICD-9-CM 940–949), injury to nerves and spinal cord (ICD-9-CM 950–957), poisoning (ICD-9-CM 960–989), and any others

[h]Adderall, Concerta, Metadate, Methylin, Methylpheni, Pemoline, Ritalin, and Strattera

[i]ICD-9 codes 800-957

[j]Stimulant (methylphenidate N06BA04, amphetamine N06BA01, and dexamphetamine N06BA02) and nonstimulant (atomoxetine N06BA09) medications

[k]ICD-10 codes V01-V99

[l]Individual who received ADHD diagnosis or ADHD medication (amphetamine salt combination, atomoxetine hydrochloride, dexmethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, methamphetamine hydrochloride, methylphenidate, and methylphenidate hydrochloride)

[m]ICD-10-DCR codes S00-S99 or T08-T14, primary and secondary diagnoses

[n]Treated defined as treated with dexamphetamine (N06BA02), methylphenidate (N06BA04), or atomoxetine (N06BA09) for ≥6 months within a year before age 10

[o]Physicians identified trauma-related admission identified by a code in CDARS

[p]New diagnoses defined as ≥1 inpatient diagnosis of ADHD (ICD-10-GM code F90.0 or F90.1); ≥2 outpatient diagnoses of ADHD; ≥1 outpatient diagnosis of ADHD and ≥1 outpatient diagnosis with the unspecific ICD-10-GM code F90.9; ≥1 outpatient diagnosis of ADHD and ≥1 prescription of methylphenidate or atomoxetine within 365 days

[q]Coded as ADHD or hyperkinetic disorder

[r]Methylphenidate, dexamphetamine

[s]Fracture of upper limb; Intracranial injuries excluding skull fracture; Traumatic complications/unspecified injury; Sprains and strains; Superficial injury (abrasions, blisters, stings, bites); Contusion (bruise) and intact skin; Fracture of lower limb; Open wound head/neck/trunk; Poisoning (medicinal agent); Open wound of upper limb; Fracture of skull; Crushing injury; Foreign body in orifice; Burns; Dislocations and subluxations, open wound of lower limb, non-medicinal agent toxic effects

Table 2. Quality assessment of included studies using the Newcastle-Ottawa Scale.

Study	Study design	Selection	Comparability	Exposure/ outcome	Total
van den Ban et al. (2014) [13]	C	****		***	7
Chang et al. (2014) [14]	SCC	****	**	***	9
Chen et al. (2017) [15]	C	****		***	7
Chien et al. (2017) [16]	C	****		***	7
Dalsgaard et al. (2015) [17]	SCC	****	**	***	9
Man et al. (2015) [6]	SCCS	****	**	***	9
Merrill et al. (2009) [18]	C	***		***	6
Mikolajczyk et al. (2015) [4]	SCCS	****	**	***	9
Raman et al. (2013) [5]	SCCS	****	**	***	9
Chang et al. (2017) [19]	SCC	****	**	***	9

C = cohort, SCC = self-controlled cohort (only consider within-individual analysis), SCCS = self-controlled case series