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Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Attention-deficit hyperactivity disorder (ADHD) has been related to increased rates of unintentional injuries. However, the magnitude of the effect and to which extent variables such as sex, age or comorbidity can influence this relationship is unknown. Additionally, and importantly, it is unclear if, and to which degree, ADHD medications can decrease the number of unintentional injuries. Due to the amount of economic and social resources invested in the treatment of injuries, filling these gaps in the literature is highly relevant from a public health standpoint. Here, we present a protocol for a systematic review and meta-analysis to estimate the relationship between ADHD and unintentional injuries and assess the impact of pharmacological treatment for ADHD

Methods and analysis We will combine results from 114 bibliographic databases for studies relating ADHD and risk of injuries. Bibliographic searches and data extraction will be carried out independently by two researchers. The studies' risk of bias will be assessed using the Newcastle-Ottawa Scale. Articles reporting ORs or HRs of suffering an injury in ADHD compared with controls (or enough data to calculate them) will be combined using Robust Variance Estimation, a method that permits to include multiple non-independent outcomes in the analysis. All analyses will be carried out in Stata. Age, sex and comorbid conduct disorders will be considered as potential causes of variance and their effect analysed through meta-regression and subgroup analysis. Sensitivity analyses will exclude articles with longer follow-ups, non-stringent definitions of ADHD or controls and statistically uncontrolled/controlled outcomes. Studies implementing a self-controlled case series methodology to investigate if ADHD drugs reduce the risk of injuries will be combined with a generalised linear mixed model using the Poisson distribution and a log link function.

Registration details PROSPERO—Prospective Register of Systematic Reviews (CRD42017064967)

Strengths and limitations of this study

► Search and data extraction conducted independently by two authors in three major databases (PubMed, Scopus, Web of Science) and a results aggregator searching simultaneously in 113 databases, without time or language limitations.

► Analytical plan including two different meta-analyses aimed at answering two different but related questions: risk of injuries in attention-deficit hyperactivity disorder (ADHD) and possible protective role of ADHD drugs for this risk.

► Clinical importance of answering whether ADHD medications have a significant influence on the risk of injuries.

► Usage of Robust Variance Estimation: a recent statistical methodology that permits the combination of non-independent outcomes.

► It is expected that the scope of this review will be limited by the number of studies reporting the relationship between medication for ADHD and risk of injuries.

INTRODUCTION

Unintentional injuries in childhood

According to WHO, injury can be defined as, 'The physical damage that results when a human body is suddenly subjected to energy in amounts that exceed the threshold of physiological tolerance or else the result of a lack of one or more vital elements, such as oxygen'.[1] Therefore, unintentional injuries in children and young people (CYP) include traffic injuries, drowning, poisoning, falls or any other traumatic injury and burns.

Childhood unintentional injury is a major cause of death and disability among children and adolescents: over 500 000 children die worldwide every year from unintentional injuries and many more are left with permanent

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disabilities.[1] Injuries are especially relevant in childhood compared with adulthood. Developmental factors make CYP more prone to unintentional injuries compared with adults. Additionally, their anatomical fragility, smaller size and brain immaturity lead to more serious injuries and sequelae.[2] Injury risk varies by sex, with a higher risk in males. It also varies with age. According to the WHO 2008 report on child injury prevention,[1] in high-income countries children under 1 year and over 15 years have greater risks of death from unintentional injuries (28 and 23.9 death rates per 100 000, respectively). Socioeconomic deprivation is an additional factor associated with the probability of unintentional injury. Rates (per 100 000) of estimated mortality due to unintentional injuries in CYP in high-income countries were 12.2 as opposed to 41.7 in low-income and middle-income countries in this same report by WHO.[1]

Moreover, CYP from families from low socioeconomic areas have a higher incidence of unintentional injuries compared with those less deprived,[1] for example, a study found that across England rates of serious injury in children as pedestrians were higher in the most deprived areas than in the least deprived (rate ratio (RR) 4.1; 95% CI 2.8 to 6.0 domestic product).[3] As a result of the higher incidence of unintentional injuries in more economically deprived CYP, there is a contribution to ongoing inequalities between children within nations and comparing children from different nations.

There is little evidence on the evidence of the economic costs of injuries as a proportion of gross domestic product globally. However, acute treatment costs of unintentional injuries sum €4000 million worldwide every year,[4] whereas the National Health Service in the UK calculated that the extra cost of healthcare of injured children compared with non-injured children was €45 million.[5] The injuries that occurred in the year 2000 in CYP under the age of 14 years from the USA will have an estimated lifetime cost from medical treatments of US$11 899 million and US$38 664 million from lost productivity.[6]

Importantly, an issue that makes unintentional injuries an even bigger healthcare priority is the fact that most of the times their consequences could be prevented or minimised with the proper educational, legal or environmental measures. In fact, injuries are the first preventable cause of death and disability.[5]

Attention-deficit hyperactivity disorder
Attention-deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder, with an estimated worldwide prevalence between 3% and 5% among children and adolescents, being three to four times more prevalent in males than females.[7–9] The most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), defines ADHD as a disorder characterised by a persistent pattern of hyperactivity/impulsivity and/or inattention, affecting both development and functioning. The symptoms need to be present in at least two settings and influence negatively academic,

occupational or social activities from childhood to adult life.[10]

The economic burden of ADHD is very high. Healthcare spending in patients with ADHD has been estimated to be between US$600 and US$2000 greater than for an individual without ADHD.[11 12] Importantly, a significant part of such increase in healthcare expenditure is a direct consequence of the higher likelihood of injuries in individuals with ADHD.[13] The relationship between ADHD and the risk of unintentional injuries has been widely studied.[14 15] However, available studies present with caveats and sample sizes and study methods have differed significantly across studies. Case-control studies are the most frequent in the literature, but, quite often, they assessed only one type of injuries such as dental,[16] fractures of specific body bones[17] or burns.[18] An important limitation of this type of studies is that they have typically relied on a small sample size, which hinders the statistical control of confounding factors that could be leading to a spurious correlation between ADHD and unintentional injuries. Nevertheless, studies tend to show a higher incidence of injuries in ADHD CYP. Longitudinal cohort studies have also been conducted on the relationship between ADHD and physical injuries. Although few in number, they included large sample sizes, hence permitting an increased statistical rigour. Estimates of the differences have varied greatly between studies. In a large sample, Rowe et al found an OR of 1.6 (95% CI 1.6 to 2.3) for a statistically significant increased risk of fractures in ADHD compared with controls, while others have found ORs over 3.[19–21]

Furthermore, comorbidity with oppositional defiant disorder (ODD) and conduct disorder (CD) has been related to an increased risk of unintentional injuries in some studies, so that it could be argued that both disorders, highly comorbid with ADHD, could play a major role in the relationship between ADHD and unintentional injuries. However, while a recent European study with a total sample of 4517 individuals found no differences between children with ADHD and controls (OR 0.91, 95% CI 0.56 to 1.48) when comorbidity and other variables were controlled for,[22] another study found a similar risk of injuries when ADHD with conduct problems were compared with controls than when ADHD without conduct problems were compared with controls (OR close to 1.5).[23] Another factor that could contribute to the differences in the risk estimation between studies could be an interaction between diagnosis and variables that influence the risk of injuries in the general population, namely age and sex.

Summarising, while there is evidence supporting a higher risk of injuries in ADHD CYP, the magnitude of the difference remains unclear. Additionally, to which extent variables such age and sex which could influence the possible association deserve further investigation.[24] Finally, the suggestion that comorbidity with ODD and CD[25] could lead to a higher risk of unintentional injuries needs to be more rigorously tested.

Unintentional injuries and ADHD medication

ADHD medications are effective for treating symptoms and improving academic achievement, at least in the short term.[26 27] There is evidence to suggest that the use of ADHD medication in children and adolescents could be associated with a reduced risk of drug abuse and criminality.[28–30] ADHD medication may also reduce the risk of unintentional injuries, but results are inconsistent across studies.[31–34]

Estimating and interpreting the effect of medication is not straightforward. For example, patients who receive medication could have more severe ADHD symptoms and, hence, they could have an increased risk of unintentional injuries.[35] Recent methodologically sound studies have taken advantage of the short half-life of stimulants and used it to compare the risk of accidents of individuals when taking the medication compared with themselves when not taking it. This statistical method is known as self-controlled case series and allows the control for all time time-invariant individual confounders (including sex, socioeconomic background and more importantly, severity of symptoms).[36] Importantly, the self-controlled case series methodology (SCCS from now on) requires that all study subjects have suffered at least one outcome (injury in our case) of interest. This, combined with the fact that unintentional injuries are not highly frequent, leads to the need of very large sample sizes to confidently estimate whether medication influences the risk of injuries. The first study using the self-controlled case series design in ADHD had a sample size of 328 individuals with ADHD who had suffered an injury and found a protective effect of medication only for male adolescents.[31] Similarly, Mikolajczyk et al found a protective effect only for the risk of traumatic brain injuries in a sample of 2128 injury cases among individuals with ADHD, whereas a more recent study with over 4000 patients concluded that medication decreases the risk of unintentional injuries.[37] Whereas the effect of medication on the risk of injury could theoretically only be rigorously assessed in randomised controlled trials, practical constraints associated with this design make them unsuitable to test the effect of a possible protective effect of medication on risk of injuries in the long term.

The short-term and long-term effects of medication should be taken into account when weighting the clinical decision of prescribing drugs for ADHD. A possible protective effect of ADHD medications on unintentional injuries could be an additional key factor to be considered when assessing the possible benefits and harms of the pharmacological treatment for ADHD. Gaining insight into the effects of ADHD drugs on injuries may have important implications for the day-to-day clinical practice. For instance, a sizeable number of practitioners recommend stopping medication during school holiday periods. Assuming that ADHD drugs do have a protective effect on the occurrence of injuries, such practice should be discouraged, at least in individuals with ADHD at higher risk (eg, adolescents).

Due to the high prevalence of ADHD, and the fact that unintentional injuries represent a source of major impairment for society as a whole, decreasing the risk of injuries in ADHD should be a public health priority.

In view of the inconsistencies in the literature and the significance of this research, a systematic review and meta-analysis on the differential risk between individuals with and without ADHD and on the effect of medications will allow to provide meta-analytic support to address these important gaps in the literature. Results will directly inform clinical practice and healthcare planning.

We note that during the final stages of the preparation of this manuscript (and after our protocol had been registered in Prospective Register of Systematic Reviews (PROSPERO)), a systematic review and meta-analysis on the risk of injuries in ADHD was published by Amiri et al,[38] showing a significant association between ADHD and risk of injuries (pooled OR 2.04 (95% CI 1,59 to 2,63)). We deem that the present systematic review/meta-analysis expands and complements the work by Amiri et al in a number of ways. First, the bibliographic searches in Amiri et al were conducted for articles published between 2000 and 2014. Of note, in the last 3 years there has been a surge of high-quality articles relevant for our meta-analysis. Second, we aimed to control for gender effects, an important confounder. Third, and perhaps more importantly, we address a very relevant clinical and public health question, namely the effect of ADHD drugs on the risk of injuries. Finally, the fact that the current project is registered and follows reporting guidelines (including the publication of the protocol) should give further confidence in the precision of its results. For all these reasons, we believe that the current meta-analysis will help to advance our current understanding of ADHD and contribute to build the evidence for programmes aiming to prevent unintentional injuries in CYP.

HYPOTHESIS AND OBJECTIVES

The overarching aim of the study will be to assess the degree of association between ADHD and unintentional physical injuries and to estimate the impact of the pharmacological treatment of ADHD on the association.

Main review questions and hypothesis

1. Is the risk of unintentional physical injuries significantly higher in children and adolescents compared with those without ADHD?

   We hypothesise that children and adolescents with ADHD will have a significantly higher probability of suffering an unintentional injury compared with individuals without ADHD.

2. Do ADHD medications affect the risk of unintentional injuries in ADHD individuals?

   Our research hypothesis is that the pharmacological treatment of ADHD symptomatology significantly decreases the risk of unintentional injuries.

Additional review questions

Do age, gender and psychiatric comorbidities (ODD or CD) moderate differences in the risk of unintentional physical injuries in individuals with versus individuals without ADHD?

Our hypothesis is that comorbid behavioural disorders (ODD or CD) will increase the risk of unintentional injuries. However, we predict that the increased risk of injuries will still be significant after controlling for these comorbidities. Additionally, it has not been previously tested if there is an interaction between age or sex and diagnosis in relation to the risk of injuries and we do not have a priori hypotheses on the effect of this interaction.

METHODS

We will follow healthcare and epidemiology meta-analytic research guidelines, namely: 1) the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA,[39 40]), a 27-item checklist and associated information that includes aspects deemed essential for transparent reporting of a systematic review, and its counterpart for the reporting of protocols (PRISMA-P[41 42]) and 2) the Meta-Analysis of Observational Studies in Epidemiology,[43] a framework highlighting the specificities of meta-analysing population-based studies.

Eligibility criteria
Participants/population

The population to be studied will consist of children and adolescents with ADHD aged <18 years. The presence of ADHD will be defined operationally as one of the following:

1. A categorical diagnosis according to standardised criteria, either the DSM (III, III-R, IV, IV-TR or 5) or the diagnosis of hyperkinetic disorder as per International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) or previous versions.
2. A positive answer to the question: 'Have you ever been told that you have ADHD by a doctor?'
3. Being prescribed ADHD medication(s).
4. Being above a pre-established threshold in a validated psychometric scale for the screening of ADHD symptoms. This threshold can also be a percentile of the sample. Studies in which the severity of ADHD symptoms is related to injuries, but no explicit diagnostic threshold is used, will not be included.
5. ADHD-related codes in medical, healthcare or administrative registries.

Operational definitions #1–3 have been designed to include articles identifying children with clinically known or recorded ADHD diagnoses. Operational definitions #4–5 have been chosen to include articles that evaluate ADHD in community studies or healthcare systems.

Studies will be included regardless of medication status (specific medications for ADHD or any other medication) or sex ratio. Comorbidities (psychiatric or other) in all or part of the study participants will not be exclusionary. Studies including only preschool children will not be eligible as diagnosis at this age range is controversial. Studies based on the diagnosis of deficits in attention, motor control and perception,[44] or equivalent constructs,[45] will not be included as the motor control problems required for their diagnosis and not needed in the case of ADHD diagnosis could be related to specific kinds of injuries or a different incidence of them, hence adding an extra source of variability.[46]

Intervention(s), exposure(s)

As the first part of this meta-analysis evaluates the risk of unintentional injuries in patients with ADHD compared with controls, no intervention will be assessed.

Regarding our second research question, we aim to evaluate the impact of any ADHD medication (ie, intervention) on the incidence of injuries and hence, we will be comparing only patient samples. ADHD medication intake will be defined as the medical advice for taking a drug containing dextroamphetamine, methylphenidate or atomoxetine as included in a medical registry, or the purchase of these compounds. To be included in this analysis, studies will have to compare the risk of injuries during periods with and without medication. Studies comparing the incidence of injuries in groups of medicated and unmedicated patients will be excluded since medication usage is related to confounding variables for our research question, such as symptoms severity.[35]

Unintentional injuries

The WHO definition of unintentional injuries will be followed to decide inclusion of articles. Hence, articles reporting injuries covered with the codes S00-T98 of the 19th chapter of the ICD-10[47] will be deemed eligible. An exception will be studies specifically on traumatic brain injury (TBI) or concussions. These will not be included in the systematic review as they may introduce bias, since traumatic brain injury can increase attentional and impulsivity problems, as well as the risk of an ADHD diagnosis.[48] Studies on intoxications will not be included either, as results would probably be influenced by the greater access of individuals with ADHD to medications and not the intrinsic characteristics of ADHD.[49]

We will include studies where injuries were documented in a medical setting, reported through medical registries, recorded in medical histories or self-reported. Articles in which the injuries were self-induced will be excluded. Examples of the latter type of injury include self-mutilation and fight-related injuries.

Studies in which individuals suffered an unintentional injury before being diagnosed will be included. Indeed, there is no reason to suspect a temporal relationship between injuries and diagnosis once TBI studies are omitted. Finally, studies reporting risk of injuries in general, that is, without discriminating between intentional or unintentional injury, will be included in the meta-analysis, as the majority of injuries in children or adolescents are expected to be unintentional in nature.

Controls

We will define controls as children and adolescents under the age of 18 without ADHD. Specifically, we will include as controls: 1) individuals recruited from samples thought to represent the general population that do not have any psychiatric or neurological disorder, 2) individuals thought to represent the general population that do not have ADHD but could have other psychiatric or neurological disorders or 3) individuals who were recruited specifically from other clinical populations other than ADHD that a priori were not judged by the study authors to be related to an increased risk unintentional injuries.

Types of studies to be included

We will pool the results from any published or unpublished study that contrasts unintentional injuries in children or adolescents with ADHD and in typically developing individuals (meta-analysis of risk), or alternatively in patients with ADHD while taking and not taking medication (meta-analysis on the effect of medications, which will compare time points with or without medication). Empirical papers that include statistical analyses (ie, typically not reviews, letters, commentaries and editorials) with any kind of design will be accepted (mainly cohort studies, case and controls and cross-sectional studies but also clinical trials). Any temporality of the design (ie, prospective, retrospective or cross-sectional) or setting (clinical or general population) will also be accepted.

It is well known that the risk of unintentional injuries is highly related to male gender. Similarly, ADHD diagnosis is fourfold more prevalent in males. Any outcome derived from a control and ADHD sample with a different proportion of sexes between them that is not statistically controlled will be doomed to show an spuriously high risk of injuries in the ADHD group due to this co-correlation. Therefore, we will only include studies that control for sex differences between individuals with ADHD and controls either by sample selection or statistically. It must be noted that the meta-analysis by Amiri *et al* did not take into account this confounder when selecting their outcomes and this could be yielding higher estimates of risk.[38]

When evaluating medication effects, only studies using a SCCS methodology will be included a priori.[31] Studies that controlled for individual differences between the medicated and unmedicated groups with different techniques than the SCCS will be judged on a case-by-case basis for inclusion in a secondary comparison aimed at evaluating the robustness of the main comparison in addition to SCCS studies. This could include randomised controlled trials, studies comparing a short period before and after starting medication usage or other designs not foreseen.

We will not limit the inclusion for papers to any specific language.

Information sources

Electronic searches will be performed separately in the following databases:

- ► PubMed (Medline Plus)
- ► Scopus
- ► Web of Science Core Collection

A similar search will be carried out in UNIKA (http://www.unav.edu/en/web/biblioteca), an institutional reference aggregator that uses the EBSCO discovery service (http://support.ebsco.com/help/index.php?lang=en&int=eds) to provide a combined list of references from both internal (library) and external (database vendors) sources. For a list with the 113 most important databases for medical research scoped through this service see the online supplementary file. We will perform searches in these databases from their inception to date without limiting the type of study, language or year. Additionally, the International Clinical Trials Registry Platform Search Portal and ClinicalTrial.gov will be checked to find ongoing or recently ended trials and, conversely, PROSPERO will be searched for ongoing or recently completed systematic reviews. Once the electronic search is completed, references from each pertinent paper will be checked in order to find out if there are any relevant studies which had been missed during the database searches.

Search strategy

The following search syntax will be used to find relevant terms in reference titles, abstracts or keywords (any field in the case of Medline-PubMed). Search terms and syntax will be adapted for each specific database: all the different searches can be found in the online supplementary file.

(ADHD OR adhd OR attention deficit disorder with hyperactivity OR syndrome hyperkinetic OR hyperkinetic syndrome OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR adhd attention deficit hyperactivity disorder OR adhd OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR attention deficit disorder hyperactivity OR attention deficit disorders hyperactivity OR child attention deficit disorder OR hyperkinetic syndromes OR syndromes hyperkinetic OR hyperkinetic syndrome childhood) AND ((fracture OR fractures OR traumatism OR traumatisms OR traumatology OR wound OR wounds OR drowning OR poisoning OR burning) OR ((trauma OR traumat* OR harm OR lesion OR lesions OR injury OR injuries) AND (emergency OR emergency visit OR emergency room OR hospital OR hospitaliz* OR er OR inpatient))).

The whole process of article selection will be presented in a diagram following the PRISMA guidelines.

OUTCOMES
Primary outcomes

Our primary outcome measure will be the OR of ADHD individuals suffering unintentional injuries that are evaluated at a medical setting (primary care doctor or any

other type of medical professional, emergency room or specialist care) compared with individuals without ADHD. The OR is the most common reported measure and the only one that can be obtained when comparing the number of individuals with ADHD in an injured sample to a non-injured group. The variable 'injuries' will have to be described dichotomously, that is, whether an individual has suffered an injury or not. If OR is not directly reported in the paper, but data to calculate it are, we will determine the OR for that particular study.

Since more than one injury can occur in one individual, the use of Cox Proportional Hazards Models is desirable since HR estimate the rate to injuries and are independent of the time of follow-up. Whereas this kind of studies is rare, we will additionally evaluate the average effect size of studies reporting HR outcomes.

In the case of the meta-analysis evaluating the efficacy of ADHD medication, the primary outcome will be the incident rate ratio (IRR) obtained from SCCS studies. The incident rate is a measure of event frequency during a period of time. It is defined as the count of events divided by the observed person-time. The IRR is a relative measure which consists of dividing the incident rates of two different conditions. We will specifically compare injury occurrence among subjects with ADHD when medicated to the periods without medication, taking into account the fact that the time on medication varies between subjects. The number of events (injuries) and the person-time at risk during the periods with and without medication will be needed for its calculation.

If effect measures other than OR, HR (from Cox models) or IRR are reported, and OR (or IRR for the medication case) cannot be calculated from the data in the studies, the authors will be contacted to gather relevant data.

Identification and selection of studies

Studies identified with electronic and manual searches will be listed with citation, titles and abstracts in Mendeley (Elsevier, New York) and duplicates will be excluded both using the function 'delete duplicates' of Mendeley and manually removing duplicates not discarded automatically. Members of the review team will be trained in software utilisation before starting the review.

Article screening against inclusion criteria will be carried out independently by two of the authors (MR and GA), who will try to reach consensus in case of discrepancies between them. A third author (SC) will arbitrate in the final decision whenever consensus is not reached.

There will be two stages in the articles selection process:

► The title and abstracts of all non-duplicated papers will be screened, and studies that clearly do not fulfil the inclusion criteria will be excluded from further analysis. If the two evaluators disagree in their ratings, articles will be moved forward to the next phase.

► All text of articles remaining from the previous screening will be downloaded. Eligibility will be judged following the same scheme than during the previous

phase: the same two authors will independently evaluate the studies for eligibility and seek comments from a third author in case of discrepancy.

As studies may sometimes be published as several reports, we will actively search for duplicate reporting of studies, taking into account as main indicators location of the study, authors and year. Whenever a study includes data from multiple reports, they will be linked in the data extraction sheet and data from the largest sample, when possible, will be used. In the case of prospective studies, only baseline data will be analysed. Corresponding authors of the original studies will be contacted to clarify article eligibility if necessary.

A list of excluded studies will be provided with reasons for exclusion. This list will include all articles that were preliminarily retained after stage 1 (selection from title and abstract) but finally excluded in stage 2.

Data extraction

All articles considered appropriate in the previous stage will be read and analysed by at least two independent authors (one will always be MR or GA), who will extract the key information and include it in a Microsoft Excel document, with a third author acting as an arbitrator when consensus on discrepancies is not reached (SC). This phase will be first piloted with a small number of articles. The Excel file will have as many drop-down lists as possible to maximise inter-rater reliability, and also space for notes. Moreover, it will also include in-cell messages with help texts. A training session will be provided for all researchers involved in data coding.

Data on publication and data extraction details will be inserted in an excel sheet as follows: first author, journal, year of publication, country(ies) where the study was conducted and a more specific location such as region or hospital when applicable, final checking of fulfilment of inclusion and exclusion criteria and date and author of data extraction.

The description of the study design will include type of study (cross-sectional, case-control, cohort or clinical trial); temporal sequence (prospective, retrospective or cross-sectional, duration of follow-up, participants enrolment (consecutive, non-consecutive); setting (clinical vs epidemiological population study) and year in which data acquisition for the study was carried out.

Regarding participant details, we will code sample size, age, gender distribution, ethnicity and sociodemographic status, characteristics of participants without ADHD (no ADHD, no ADHD or other conditions or comparisons with other diagnostic categories other than ADHD); psychiatric comorbidities of individuals with and without ADHD (type and prevalence); method to establish the diagnosis of ADHD (self-reported diagnosis, diagnosis recorded in medical files/registry, structured or semi-structured interview according to DSM or ICD, questionnaires, per medication usage or positive answer to the question: "Have you ever been told you have ADHD?"); medication status of individuals with and

without ADHD (type of medication and percentage of treated participants).

The primary outcome will be the OR (or HR) of suffering an unintentional injury in individuals with ADHD versus children and adolescents without ADHD. In relation to outcomes, data that will be coded include treatment setting (acute care hospitals, emergency facilities, general practice, medical specialist or other, including extended care facilities such as nursing homes, offices, schools and communities), method to document injuries (registry, acute treatment, through expert retrospective analysis or self-report), type of injury (traumatology, traffic injuries, drowning, poisoning, burns and chemical, other unintentional, self-induced, any kind of accidental injury or any kind of injury) and body location of the injuries.

To obtain ORs, any numeric data (raw number of accidents in each of the samples or ORs and their CIs) will be coded including both unadjusted analyses and analyses adjusted for covariates. In the latter case, covariates will also be included in the data extraction sheet. Finally, the reporting of any subgroup analysis or comparison of interest, the presence of other intervention groups and the main conclusions of the reports will also be annotated.

Whether the incidence of unintentional injuries differs between individuals with ADHD with medication and patients with ADHD without it will be assessed in a second meta-analysis. The data extraction sheet used for this second analysis will have the same variables and coding, but IRR instead of OR will be used.

We will extract information on multiple outcomes per article. Specifically, outcomes from different age or gender groups, multiple control groups, varying diagnosis techniques or statistical models will be valid. We will not include outcomes differentiating by injured body part. Each outcome or comparison will all be included in the spread sheet using a different line. A different comparison ID will be used in such case in combination with a report and study ID to link all related data.

Assessment of study quality and bias in included studies

The evaluation of study quality and possible bias will be individually performed by two researchers for each article. As there is no agreement about the best method to evaluate study quality in meta-analyses of observational studies, we will use an adapted version (included in the online supplementary file) of the Newcastle-Ottawa Scale,[50] which has been used in several previous meta-analyses[51 52] and is reviewed in the Cochrane Handbook. This scale evaluates the sample selection methods, the comparability among studied groups and the ascertainment of either the exposure (in case-control studies) or outcome of interest (for cohort studies) of non-randomised studies.

ANALYSIS PLAN

All analyses will be carried out in Stata, R and Matlab.

Meta-analysis of differences in risk between ADHD and controls

ORs will be calculated from the reported data if they cannot be directly extracted. OR and HR above 1 will indicate a higher risk of unintentional injuries in the ADHD population compared with the non-ADHD groups. All valid outcomes from articles will be included in a single database. These will include any unadjusted or adjusted OR or HR which would fulfil independently the inclusion criteria of our meta-analysis. Multiple valid outcomes within the same report are expected, often due to studies using different diagnosis strategies, reporting results in subgroups or including different valid treatment settings. This database will also encode other continuous or dichotomous (dummies) variables of interest for the meta-regression and subgroup analyses.

If an article reports two separates studies they will be considered independent, and conversely, if two articles report results on the same data or database they will be considered as multiple outcomes from the same study.

Heterogeneity and small sample bias

Q-Cochran's[53] and the I^2 index[54] will be used to evaluate heterogeneity between studies. Cochran's Q is calculated as the weighted sum of squared differences between individual study effects and the meta-analytic estimate. Weights are the same as in the meta-analysis (basically sample sizes), and hence, this measure is known to have low power when there are few and small studies. Conversely, the test has excessive power with many or big studies. The I^2 index is a newer, complementary measure that describes the percentage of total variation across studies that is due to heterogeneity, and it does not depend on the number of studies considered. The higher the I^2 value the higher the heterogeneity in the results, with values >50% indicating substantial heterogeneity.

Begg's adjusted rank correlation test[55] will be used to formally assess the presence of 'small-sample' bias (which encompasses publication bias); an approach that will be combined with the use of funnel plots for a qualitative visual analysis, and statistical testing of asymmetry.[56]

A single effect size will be used per study to calculate the degree of between-study heterogeneity and the risk of small-sample bias. The most general and statistically controlled outcome per study will be used. If there is more than one possible outcome fulfilling these criteria, it will be chosen at random from the available outcomes.

Dependency among outcomes

Effect sizes are assumed independent in standard meta-analytical procedures. A common way to deal with the non-independence of outcomes has been to compute a mean outcome and use the study-level combined measure in the meta-analysis,[57] but this approach leaves out potentially relevant information. A recent alternative is Robust Variance Estimation (RVE), a statistical technique that models the nested structure between outcomes of the same study.[58] RVE empirically estimates

the sampling variance in a way that is robust to misspecification of the weights and regarding the assumptions on distributions of the effect. Estimation of the meta-analytic parameters through RVE is adequate for dichotomous outcomes when enough studies are included.[59][60] Moreover, RVE has been shown to produce similarly unbiased results to other, more complex, methods of dealing with multiple outcomes and it is more efficient than averaging effects within studies.[61] A main advantage compared with other methods is that it does not require to have information on the covariance structure of the effect sizes, an information that is typically hard to acquire.

Whereas this method yields valid results regardless of the weights used, a strategy using approximate inverse-variance weights has been proposed for efficiency purposes: a random-effects model with variation of effect sizes between studies (τ^2) and equicorrelation (p) between same-study effect sizes (I^2) is assumed.[58] This strategy is efficient to estimate a mean model from outcomes which are typically correlated at the study level, but are usually independent between studies. We will use p=0.8, similarly to previous studies,[62] but these same studies and simulations by the RVE authors have shown little change with different values of p.[63] Moreover, a sensitivity analysis with varying levels of p can be carried out to check the influence of such decision.[58] RVE has been implemented in Stata and R and there are published guidelines for it.[64][65] This implementation includes an improved estimation for small samples.[66] We will use RVE for the inference of a mean effect size and meta-regression analyses. Regarding meta-regression, as df are obtained from the number of studies (instead of outcomes) and variables are likely to be correlated, it will be performed separately for each variable (bivariate regressions). RVE distinguishes between interstudy effects (variability due to factors that change at the study level but are maintained for different outcomes) and intrastudy effects (variability due to factors that change at the outcome level). An example of the former would be publication date, and an example of the latter would be sex in the case of those studies that report ORs separately for boys and girls. It must be noted however, that factor can vary both interstudies and intrastudies, for example, mean age also changes between studies.

Mean effect sizes

We will first calculate a population-average effect size (ORs and HRs separately) through the combination of the most general and better statistically controlled outcome per study. If there is more than one possible outcome fulfilling these criteria they will all be included in the analysis.

Initial sensitivity analyses for this average effect size will be: 1) to vary in 0.1 steps the p correlation parameter, 2) to compare articles with a follow-up of a year or less to articles with a longer follow-up (including variable follow-ups). Since an individual can have more than one injury along their life, but only dichotomous outcomes

are considered, different observation periods could modify differences between groups.

Additional sensitivity analyses will derive from the variety of designs accepted and the definitions of patients and controls. Data will be reanalysed excluding case-control studies (comparing injured vs non-injured individuals). Similarly, an analysis only using the most stringent definitions of ADHD (DSM, ICD, registry or clinical history) and controls (excluding studies with clinical control groups) will be carried out. Studies in which injuries are self-reported will be eliminated in another analysis. Risk of bias (number of stars in the Newcastle-Ottawa Scale) will be considered a continuous variable and its effect evaluated. A final analysis will compare the effect size of studies in which data were acquired before and after the year 2000.

Two other population average models will be obtained by 1) computing a mean effect size only including unadjusted OR and 2) computing a mean effect size only including adjusted OR.

Effect sizes whose 95% CIs do not cover zero will be considered significant. All the effects described in this section are interstudy.

Subgroup analyses and meta-regression

We will also assess, if feasible, the moderating role of clinical and design variables at the intrastudy and interstudy levels. The former include gender, age, comorbidity (mainly ODD and CD), medication status and prevalence of ADHD, whereas the latter includes the setting of treatment. The data to be used in these analyses will include any outcome which would independently fulfil the inclusion criteria as long as they differ in something else than the statistical model used to obtain them: If there is more than one statistical model for the same data, the outcome derived from the model controlling for more covariates will be used. Percentage of medicated patients, age (ideally the mean or median of the whole group, otherwise midpoint in the interval of ages) and prevalence of ADHD (percentage of ADHD that a given diagnostic strategy yields in a cohort) will be included as continuous variables and their effect estimated through meta-regression. We will also explore the feasibility of conducting the following subgroup analyses: 1) male vs female participants, 2) three age groups (4–8, 9–13 and 14–17 years), 3) clinical setting (physician office visits, emergency department visit and hospitalisation). In all these cases, differences between groups will be statistically tested (p<0.05 will be considered significant). In the case of sex, intrastudy outcomes reported only in males will be compared with outcomes of studies in which ORs are reported for both boys and girls, and the same will be done for outcomes in females.

The evaluation of the effect of comorbidity is important in our meta-analysis, but such an effect is difficult to meta-analyse since studies handle it very differently. We are especially interested in disentangling the effect ODD and CD from that of ADHD. We will compare outcomes from studies in which the rate of ODD/CD is not controlled to

those in which the presence of ODD or CD is controlled in the patient sample by design (excluding subjects with ODD or CD) or statistically, and to those in which all patients have comorbidity with these disorders. If feasible, a similar analysis including any other comorbidities will be executed.

Sensitivity and meta-regression analyses will be carried out only for the combination of ORs, as we do not expect enough studies to carry out this kind of analyses for the combination of HRs.

Meta-analysis on the effect of medication

The second objective of the present project will be to assess the medication effect in the probability of non-intentional injuries occurrence. For this purpose, the chosen measure of association will be the IRR. Heterogeneity and presence of 'small-sample' bias will be evaluated as in the first meta-analysis.

A generalised linear mixed model using the Poisson distribution with the log link function will be implemented.[67] Specifically, since it is expected that a small number of studies will be included in this meta-analysis, a fixed effects Poisson regression model will be carried out. In this model, the dependent variable is set as the logarithm of the total number of counts, the logarithm of the person-time is included as an offset and the medication is included as an explanatory variable. Additionally, the model incorporates dummy variables as study-specific fixed effects, in order to preserve the within studies comparison of medicated versus non-medicated groups.

Sensitivity analyses will be performed based on the exclusion of studies which do not implement a self-controlled case series design.

PLANNED CONTRIBUTIONS TO THE META-ANALYSIS

The tasks regarding the systematic review and the meta-analysis will be as follows: MRG and GA will conduct searches, screen papers and retain those that fulfil inclusion criteria. SC will arbitrate discrepancies between these researchers regarding article inclusion. MRG GA, NA, SM, EL and PdCM will read the included papers and extract the data. MAS, GA, MRG and SC will carry out the statistical analysis. PdCM, SC and CS will provide expertise on issues related to child and adolescent psychiatry and results interpretation/implications. GA and MR will draft the article discussing the results and SC and CS will further edit it. All collaborators will approve the final article.

ETHICAL CONSIDERATIONS AND DISSEMINATION PLANS

No ethical issues are predicted. All the authors will declare if they have any competing conflict of interest. The results will be published in a peer-reviewed journal and presented at national and international conferences of psychiatry, psychology, paediatrics and traumatology.

REGISTRATION AND STATUS

Before data extraction completion, the protocol of this meta-analysis was registered in PROSPERO, an international register of protocols for health-related systematic reviews supported by the National Institute of Health Research (NIHR) and maintained by the University of York (UK). Registration date: 8 May 2017, protocol number CRD42017064967. Writing of the protocol and preliminary searches started by June 2016. Data piloting commenced in September 2016. Data extraction started in December 2016 an ended in August 2017. Data analysis is estimated to end by August 2017.

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