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Review article

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

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ABSTRACT

A systematic review with meta-analyses was performed to: 1) quantify the association between ADHD and risk of unintentional physical injuries in children/adolescents ("risk analysis"); 2) assess the effect of ADHD medications on this risk ("medication analysis"). We searched 114 databases through June 2017. For the *risk analysis*, studies reporting sex-controlled odds ratios (ORs) or hazard ratios (HRs) estimating the association between ADHD and injuries were combined. Pooled ORs (28 studies, 4,055,620 individuals without and 350,938 with ADHD) and HRs (4 studies, 901,891 individuals without and 20,363 with ADHD) were 1.53 (95% CI = 1.40,1.67) and 1.39 (95% CI = 1.06,1.83), respectively. For the *medication analysis,* we meta-analysed studies that avoided the confounding-by-indication bias [four studies with a self-controlled methodology and another comparing risk over time and groups (a "difference in differences" methodology)]. The pooled effect size was 0.879 (95% CI = 0.838,0.922) (13,254 individuals with ADHD). ADHD is significantly associated with an increased risk of unintentional injuries and ADHD medications have a protective effect, at least in the short term, as indicated by self-controlled studies.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD), characterized by a persistent, age inappropriate, and impairing pattern of inattention and/or hyperactivity-impulsivity (American Psychiatric Association, 2013), is the most commonly diagnosed neurodevelopmental disorder. Its worldwide prevalence is estimated to be about 5% in school-age children (Polanczyk et al., 2014). Hyperkinetic Disorder (HKD), as defined in the International Classification of Diseases, 10th Edition (ICD-10) (World Health Organization, 2016), is a narrower diagnostic category, requiring both symptoms of inattention and hyperactivity/impulsivity, similarly to the combined presentation of ADHD as per the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5). ADHD is more frequent in males than in females, with male-to-female ratios of 3:1 in population-based samples and even higher (from 6:1 to 9:1) in clinical samples, probably due to referral bias (Gaub and Carlson, 1997). ADHD is often comorbid with other disorders, such as oppositional defiant disorder (ODD), conduct disorder (CD), and anxiety disorders (Faraone, 2015). Available treatments for ADHD include pharmacological and non-pharmacological interventions. Due to its core symptoms and associated conditions, ADHD imposes huge burdens on affected individuals, families (Beining, 2014; Kvist et al., 2013) and society (Doshi et al., 2012; Holden et al., 2013; Le et al., 2014).

A factor that may contribute to the societal costs of ADHD is its possible association with an increased risk of unintentional physical

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injuries (UPIs), which in turn may be among the causes of increased mortality in ADHD (Dalsgaard et al., 2015b). Indeed, core ADHD symptoms (i.e., inattention, hyperactivity and impulsivity), as well as characteristics related to comorbid disorders (e.g., aggressiveness associated with ODD/CD) may increase the risk of UPIs. However, despite a number of studies (e.g., (Bonander et al., 2016; Dalsgaard et al., 2015a; Lange et al., 2016)) reporting a significantly increased risk of UPIs in individuals compared to those without ADHD, available findings are quite mixed (e.g. (Dudani et al., 2010; Sciberras et al., 2016)). Some of the most recent studies have found statistically significant effect sizes with odds ratios (ORs) below 2. For example, a study following over 700,000 Danish children estimated the OR of suffering an injury at age 12 in ADHD compared to controls as 1.3 (95% Confidence Interval, CI = 1.23, 1.37) (Dalsgaard et al., 2015a), whereas a German study surveying over 350,000 participants found an OR of 1.55 (95% CI = 1.49, 1.71) (Lange et al., 2016). In contrast, a population-based survey from Canada including over 1.5 million individuals did not find a relation between ADHD an injuries when comorbidity was accounted for (OR = 0.75, 95% CI = 0.53, 1.06) (Dudani et al., 2010), and another recent population-based survey across Europe with over 4,000 participants found similar results (OR = 0.91, 95% CI = 0.56, 1.48) (Keyes et al., 2014). Moreover, some case-control studies have reported much higher and statistically significant odds ratios (Ghanizadeh, 2008; Shilon et al., 2012). Summarizing, the exact extent to which ADHD in children and adolescents is associated with an increased risk of UPIs, even after controlling for comorbid conditions, is still unclear.

Perhaps even more importantly, meta-analytic evidence on possible beneficial or harmful effects of ADHD medications on the risk of UPIs is lacking. To the best of our knowledge, no randomized controlled trials have aimed to assess the effects of ADHD medications and the risk of injuries, possibly due to the relatively low incidence of injuries. Hence, studies using observational data can offer useful information on the association, provided appropriate methodologies are applied. Whilst case-control studies aimed at addressing the effect of ADHD medication on risk of UPIs are hampered by the "confound by indication" bias (pharmacological treatment is more common in children with severe compared to mild forms of ADHD), self-controlled case series (SCCS) studies or other methodologies that take into account individual differences have a suitable design to explore this issue.

Gaining insight into the magnitude of the association between ADHD and risk of UPIs in children and adolescents, as well as on a possible beneficial or harmful effect of ADHD medications, is highly relevant from a clinical and public health standpoint. In particular, meta-analytic evidence of a significant association between ADHD and increased risk of injuries and of a protective role of ADHD pharmacotherapy could inform the debate regarding the discontinuation of medication during week-ends or school holidays (Ibrahim and Donyai, 2015). Furthermore, findings of a protective effect of medication would contribute to the current, controversial scientific debate around the actual benefits and risks of ADHD medications (Banaschewski et al., 2016).

Of note, a recent meta-analysis by Amiri et al. (Amiri et al., 2017) pooled 35 studies published until 2014 and found a pooled odds ratio in children of 1.96 (95% CI = 1.6, 2.4), indicating that ADHD is significantly associated with a risk of injury. However, several methodological sound studies have been published in the past three years, which could not be included in this previous meta-analysis, and some other important (for example, the above mentioned Canadian survey by (Dudani et al., 2010) were not included. Additionally, the Amiri et al. study did not control for gender effects, which are a crucial confounder due to the association of both risk of UPIs and ADHD to male gender (Gaub and Carlson, 1997; Peden et al., 2008). Finally, and importantly, the meta-analysis by Amiri et al. was not aimed to assess the impact of ADHD medications on the risk of UPIs.

The present meta-analysis extends in important ways the meta-analysis by Amiri et al. including studies in children and adolescents published until June 2017, controlling for gender and, importantly, exploring the effects of ADHD medication by pooling self-controlled studies. We hypothesized that: 1) the prevalence of UPIs would be higher in children/adolescents with compared to those without ADHD; 2) the risk of UPIs would be significantly lower when children/adolescents with ADHD are treated with ADHD-approved medications for the disorder compared to when they are not treated pharmacologically.

2. Methods

Methods were developed according to the MOOSE (Stroup et al., 2000) and PRISMA (Liberati et al., 2009) recommendations. The protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO, ID = CRD42017064967) and was published in (Ruiz-Goikoetxea et al., 2017).

2.1. Data sources and searches

We searched PubMed, Scopus, Web of Science and a large number of other databases from inception to June 2017, with no date/language restrictions. We also scanned references of retrieved pertinent papers to find additional studies. See additional details, including search syntax, in Methods S1 and S2 (Supplementary material).

2.2. Study selection

2.2.1. Study type

We pooled data from published or unpublished studies that contrasted the risk of having suffered an UPI in children and/or adolescents with ADHD and in typically developing individuals (for the "*Risk analysis*"), and in individuals with ADHD while taking and not taking medication (for the "*Medication analysis*"). We also included studies comparing medicated and non- medicated children/adolescents with ADHD for a qualitative review. We included any type of empirical study regardless of the design, the temporality (i.e., prospective, retrospective or cross-sectional) or setting (clinical or epidemiological). Because both ADHD (Gaub and Carlson, 1997) and the risk of injury (Peden et al., 2008) are more common in males than in females, to avoid an important bias, we only included studies that controlled for sex differences between individuals with and without ADHD, either by sample selection or statistically.

2.2.2. Population

ADHD: children and/or adolescents (< 18 years) with: 1) a categorical diagnosis of DSM-5 (American Psychiatric Association, 2013) (or previous editions) ADHD or with HKD as per the ICD (World Health Organization, 2016); or 2) use of a symptom threshold on a validated ADHD rating scale; or 3) a positive answer to questions like: "Did your doctor ever tell you that you have ADHD?"; 4) a medical record diagnosis of ADHD; or 5) being prescribed ADHD medication(s). We excluded studies including only pre-schoolers (since the methods for the assessment of ADHD in this population are still matter of discussion, (e.g.: (Fiks et al., 2016)) as well as those using the diagnosis of "Deficits in attention, motor control, and perception" (DAMP (Gillberg, 2003)), or equivalent constructs (Magallon et al., 2015). Comparisons: Participants without ADHD (defined as above).

2.2.3. Intervention/exposure

For the meta-analysis of risk, we considered ADHD as exposure. As for the medication analysis, we considered the impact of the most commonly used ADHD drugs worldwide, namely methylphenidate, amphetamine derivatives and atomoxetine.

2.2.4. Outcomes

We considered studies reporting data on unintentional injuries defined according to the S00-T98 codes of the ICD-10 (World Health

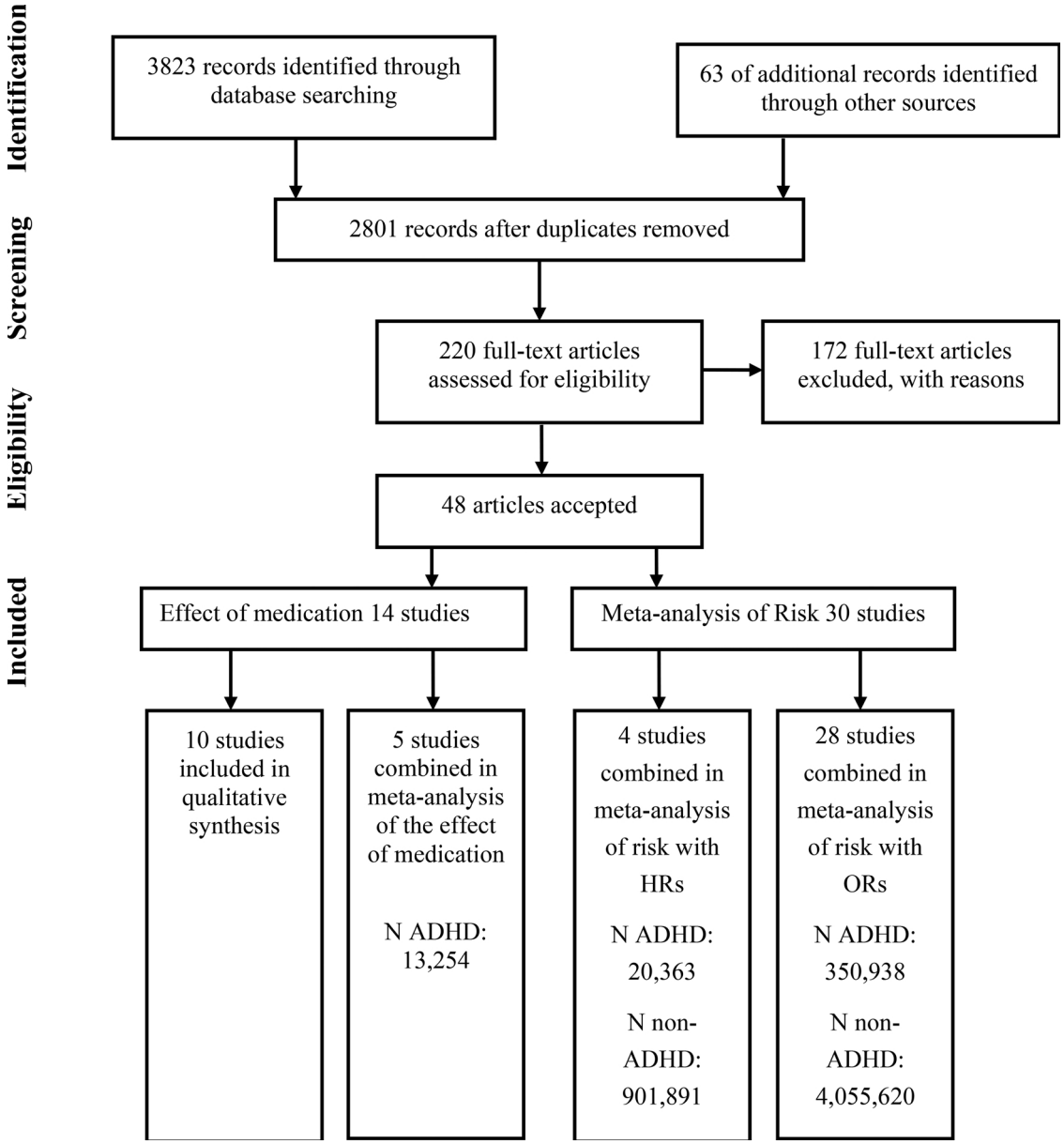

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses Flow Diagram.
Legend: flow diagram of the record identification and study selection. The total amount of studies is not the exact sum of in the number of studies included in the final row of boxes, as some articles were included in more than one subanalysis. Similarly, articles with linked data were aggregated into single studies (see Results S1 in Supplementary Material).

Organization, 2016), as reported in medical registries, recorded in medical histories, or self-reported. We did not consider traumatic brain injury (TBI) or concussion as an outcome as they may introduce bias, since TBI can increase attentional and impulsivity problems, as well as the risk of an ADHD diagnosis (Adeyemo et al., 2014). In this regard, the relationship between TBI and ADHD is likely bidirectional and complex. Whereas ADHD could increase the risk of future TBIs, brain injury is likely related to an increase in the risk of ADHD diagnosis. We assumed that this complex relationship would not be easy to disentangle in the included studies and hence, including studies focusing on TBI could bias our final estimation of differential risk.

We also excluded studies focusing on intoxications or self-inflicted injuries (e.g., self-mutilations), which were beyond the scope of this study.

2.3. Identification and selection of studies

The process included two stages: 1) Two investigators independently and blindly screened retrieved titles and abstracts of all non-duplicated papers and excluded those clearly not pertinent. A final list was agreed with discrepancies resolved by consensus between the two authors. 2) The full-text versions of the articles passing stage 1 were assessed for eligibility following the same process. Data from multiple reports of the same study were linked together. If required, we contacted the corresponding author to inquire on study eligibility.

2.4. Data extraction

Two investigators independently and blindly performed extraction of data relevant to the present meta-analysis. Study quality and bias, including confounding, were assessed using the Newcastle-Ottawa Scale (NOS) (Wells et al., n.d.) (for items included in this scale, see Methods S3 in supplementary material), as recommended by the Cochrane collaboration (Higgins and Green, 2011). Discrepancies were resolved by consensus. Additional details on outcome selection and data extraction are reported in Methods S4 (Supplementary Material).

2.5. Data synthesis

ORs/HRs expressing the association between ADHD and UPIs in children and adolescents were extracted from articles or calculated from available data. Whenever an article fulfilled all other inclusion criteria, but did not report enough data to calculate ORs, authors were contacted.

For the meta-analysis of risk, we calculated a population-average effect size through the combination of the most general and better statistically controlled outcome per study. If there were more than one possible outcome fulfilling these criteria, they were all included in the analysis. To deal with the non-independence of outcomes, we used Robust Variance Estimation (RVE) (Hedges et al., 2010). We carried a similar analysis with Hazard Ratios (HRs) obtained from Cox models.

For the analysis on the effect of medications, we 1) qualitatively reviewed studies comparing groups of medicated and unmedicated individuals; 2) statistically pooled effect sizes obtained from studies taking a within subject approach. First, we combined the incident rate ratio (IRR) obtained from self-controlled studies. Then, these were pooled with the results from others studies that were deemed eligible (i.e., that controlled for individual characteristics) but used different statistical metrics. Studies on the effect of medications were combined using a fixed-effect model (Borenstein et al., 2010). We expected the final model to include only a small number of studies and estimation of random-effects models with few studies has been shown to be unreliable (Guolo and Varin, 2017). However, random-effects models were carried out in a sensitivity analysis.

We used Q-Cochran's and the I^2 index (Higgins et al., 2003) to evaluate heterogeneity between studies and the Begg's adjusted rank correlation and Egger's test to formally assess the presence of "small-sample" bias. To test the robustness of the findings, we conducted multiple sensitivity analyses (Methods S5). Finally, we performed meta-regression analyses considering as dependent variables the NOS rating or age, and comparing effect sizes between sexes. We also compared the effect sizes of outcomes in which the effect of comorbidity with ODD and CD had been controlled to those in which it had not been controlled. Analyses were carried out in STATA v13 and R v3.2.2. Forest plots were created using the DistillerSR Forest Plot Generator from Evidence Partners. Additional details are reported in Methods S5.

3. Results

Fig. 1 shows the PRISMA flowchart. Studies not included in the meta-analysis after assessment of the full text are listed, with reasons for exclusion, in Table S1.We retained 30 studies for the risk analysis (described in Results S1 and Table S2-S6 in Supplementary Material) (Bijur et al., 1988; Bonander et al., 2016; Brehaut et al., 2003; Bruce et al., 2007; Chou et al., 2014; Christoffel et al., 1996; Constant et al., 2014; Dalsgaard et al., 2015a; Dudani et al., 2010; Fleming et al., 2017; Ghanizadeh, 2008; Guo et al., 2016; Hire, 2016; Hurtig et al., 2016; Jensen et al., 1988; Kang et al., 2013; Keyes et al., 2014; Lalloo et al., 2003; Lam et al., 2006; Lange et al., 2016; Leibson et al., 2001; Maxson et al., 2009; Odoi et al., 2002; Pastor and Reuben, 2006; Prasad, 2016; Rowe et al., 2004; Sciberras et al., 2016; Shilon et al., 2012; Silva et al., 2014; Spinks et al., 2008; Swensen et al., 2004; Tai et al., 2013; Xiang et al., 2005). As for the medication analysis, we found ten studies that did not control for individual characteristics. They are qualitatively summarized in Table S7, with results from individual studies being very variable. Additionally, we found five studies that controlled for individual participant characteristics (Dalsgaard et al., 2015a; Man et al., 2015; Mikolajczyk et al., 2015; Raman et al., 2013; van den Ban et al., 2014) (Table 1). A report by Dalsgaard is included in the qualitative analysis (Dalsgaard et al., 2014), whereas another report from the same authors using the same database is included in the statistical pooling (Dalsgaard et al., 2015a), reason why only 14 studies are counted in Fig. 1. Overall, we included 350,938 children or adolescents with ADHD in the risk meta-analysis based on ORs; 20,363 in the risk meta-analysis based on HRs; 13,254 in the medication meta-analysis and at least 10-fold more individuals without ADHD (4,055,620 for OR and 901,891 for HR).

The OR meta-analysis of risk using the most general and controlled outcomes included 56 outcomes from 28 articles. It indicated a significantly higher risk of injuries in ADHD compared to children or adolescents without ADHD (OR = 1.53, 95% CI = 1.40, 1.67; Fig. S4). Heterogeneity of studies was significant (X^2 = 106.55, df = 27, p = < 0.001, I^2 = 74.7%). Risk of small sample bias was not significant (Egger t = 0.81, p = 0.424; Begg Z = 0.57, p = 0.580). Results were robust to all sensitivity manipulations (Results S2). Regarding risk of bias, a metaregression including the NOS scores as a regressor showed no significant effects (Beta Coefficient-*B*- = −0.018, 95% CI = −0.114, 0.078, p = 0.674). None of the other metaregression analyses carried out to investigate the effect of variables of clinical interest such as age (*B* = −0.001, 95% CI = −0.069, 0.068, p = 0.984) or sex (*B* = 0.071, 95% CI = −0.061, 0.204, p = 0.205) were statistically significant. The comparison of the average effect sizes in studies controlling for ODD against studies that did not control for these variables was not statistically significant (*B* = 0.32, CI = −0.152, 0.794, p = 0.119).

Similarly to the meta-analysis of ORs, the meta-analysis of HRs showed a significantly increased risk of injuries in children and adolescents with ADHD (OR = 1.39, 95% CI = 1.06, 1.83, Fig. S5). Heterogeneity of studies was significant (X^2 = 13.36, df = 3, p = 0.004, I^2 = 77.5%). Risk of small sample bias was not significant (Egger t = 0.08, p = 0.940; Begg Z = 0.68, p = 0.497).

Four of the studies on the effect of medications used a self-controlled methodology (Man et al., 2015; Mikolajczyk et al., 2015; Raman et al., 2013; van den Ban et al., 2014). Their sample sizes ranged between 328 and 4934 ADHD children and adolescents who had been injured and had been taking medication at some point of the exposure time (total sample: 8679 individuals with ADHD). Three of the samples were from Europe and the remaining from Taiwan. Methylphenidate was the most frequent drug among children and adolescents with ADHD. The fixed-effects combination of the self-controlled studies showed a significant protective effect of the medication (0.898, 95% CI = 0.851, 0.948). Of note, heterogeneity of studies was not significant (X^2 = 4.46, df = 3, p = 0.215, I^2=32.8%). Risk of small sample bias was not significant either (Egger t = −2.30, p = 0.148, Begg Z = −1.36, p = 0.174). The study by Dalsgaard et al. (Dalsgaard et al., 2015a) used a different statistical measure comparing the risk over time and groups (a "difference in differences" methodology) in which each individual acts as their own control and adjustments for time trends are carried out with a control group. The authors followed a cohort of 710,120 Danish children (4557 of which had ADHD), and found that medication reduced the prevalence of injuries between age five and 12 by up to 45.5% (95% CI = 18.1%, 69.0%). Additionally, the authors provided an OR derived from comparing the medicated and unmedicated groups in an adjusted linear mixed model. The fixed-effects combination of the self-controlled studies and the OR provided by this latter study yielded a pooled effect size of 0.879 (95% CI = 0.838, 0.922; Fig. 2). Heterogeneity (X^2 = 7.10, df = 4, p = 0.130, I^2=43.8%) and risk of small sample bias (Egger t = −1.90, p = 0.153, Begg Z = −0.98, p = 0.327) were non-significant. Further statistical details on all analyses are provided in Results S2 and Figs. S1 to S4 (Supplementary Material). Supplementary analyses also included random-effects models of the effect of medication which showed very similar results to those of the main analysis.

4. Discussion

We carried out a systematic review/meta-analysis of published and unpublished data to 1) quantify the risk of UPIs in children/adolescents with ADHD and 2) assess the effect of ADHD medication, pooling

Table 1
Details of studies included in the medication analysis.

Name	Country	Risk Measure	N Medicated	N Not-medicated	Type of medication (%)	Age	Type of injury
Daalsgard	Denmark	DID	1457	3100	98.2%MPH	NR (5–10)	Any
Man	China	IRR	4934	–	100% MPH	6.9 (6–19)	Any
Mikolajczyk	Germany	IRR	2128	–	92% MPH, 8% Atomoxetine;	NR (3–17)	Leading to hospitalization
Raman	UK	IRR	328	–	MPH 76.8% Long-acting MPH 21.7% Dexamphetamine 1.5%	9.7 (1–18)	Any
van den Ban	The Netherlands	IRR	1289	–	MPH and atomoxetine. Percentages are not reported	NR (1–18)	Leading to hospitalization

Country: Country where data were collected; Medicated: percentage of medicated ADHD individuals; Age: the age at injury, reported as mean or median age at injury (range). MPH: Metylphenidate. NR Not reported. IRR: Incident Risk ratio. DID: risk difference in differences.

estimates from studies with an adequate design, i.e., self- controlled case series comparing the rates of injuries in the same individuals when individuals were medicated compared to when they were not or other highly controlled methodologies. We found that ADHD was significantly associated with an increased risk of injuries in children/adolescents and that its pharmacological treatment had a protective effect.

As for the meta-analysis of risk, we pooled studies presenting odds ratios (ORs) as well as those including hazard ratios (HRs). ORs were the most commonly reported outcomes: their combination yielded a significant pooled OR of 1.53 with very small, and hence precise, confidence intervals (95% CI = 1.40, 1.67). We note that, since it is not infrequent for children to have more than one injury over time, follow-up periods could have influenced results. However, it is important to highlight that the meta-analysis of HR obtained from Cox models, in which we were able to include outcomes from large databases that are time-independent, provided similar results (HR = 1.39, 95% CI = 1.06, 1.83). Moreover, results were similar when we pooled results from studies with less (OR = 1.50, 95% CI = 1.36, 1.67) or more than a year of follow-up (OR = 1.54, 95% CI = 1.30, 1.84). It is also relevant that our results were robust to all sensitivity analyses, indicating that the type of OR (adjusted or unadjusted), the method used to diagnose ADHD, the definition of injury and the period during which the study was conducted did not significantly affect the results. Likewise, our meta-regression analysis showed that the study quality did not significantly influence the results. Additionally, our meta-regression analyses did not provide evidence for a significant effect of age, gender or comorbidity. However, these results should be taken with caution given the number of studies the analyses relied on, and warrant future studies.

Our study addresses some limitations of a previous meta-analysis on the risk of injuries in children ADHD by Amiri et al. (Amiri et al., 2017). These authors obtained both a more variable and higher estimation of UPIs in children with ADHD (pooled OR = 1.96, 95% CI = 1.6, 2.4). This may be accounted for by the fact that, compared to our meta-analysis, they included studies that did not control for gender, which is an important confounder. Moreover, differently from what we did, Amiri et al. (Amiri et al., 2017) combined different effect measures (ORs, HRs and rates) within the same analysis, included studies on pre-schoolers and also accepted studies that did not use a dichotomous threshold for clinical scales. All these factors likely contributed to the variability of their results. Additionally, the fact that we used a wider search strategy over multiple databases and included a larger time period led us to include several cohort and other high-quality studies not present in their study. These studies summed at least 3,700,000 children and adolescents without ADHD and 329,000 with ADHD, and give further confidence on our estimation compared to the previous one. Finally, it is also of note that the methods of the present meta-analysis were pre-registered in an official website for systematic review protocols (PROSPERO), providing a more transparent analysis.

We also note that we did not include studies focusing on traumatic brain injuries (TBI), due to the concern that they might introduce heterogeneity. Indeed, a meta-analysis (Adeyemo et al., 2014) on the risk of TBI in children with ADHD found even greater ORs (2.1), which would further prove that the nature of the relation between ADHD and physical injuries other than TBI is different from that between ADHD and TBI. It is sensible to hypothesize that ADHD could lead to higher rates of TBIs and TBIs may lead to higher rates of ADHD diagnoses. Adeyemo et al. (Adeyemo et al., 2014) found specific support for ADHD subsequent to TBI, but could not find evidence for asignificant association between ADHD and subsequent TBIs. However, in this previous meta-analysis, the authors could only locate two studies using a prospective design, a key reason for the exclusion of TBI studies here. Whereas our work does not directly address the question on the

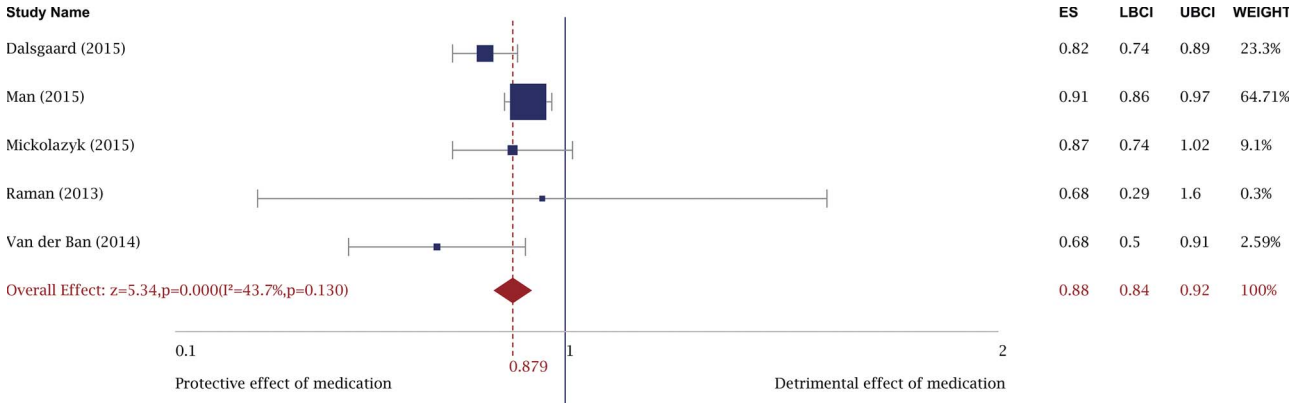

Fig. 2. Pooled effect size estimating the association between ADHD medication treatment and unintentional injuries in ADHD individuals.
Legend: 4 incident risk ratios and an odds ratio were combined. The area of each square is proportional to the weight that the individual study contributed to the meta-analysis. Weights are from a fixed-effects model. The diamond indicates the overall weighted mean effect across all studies.

relationship between ADHD and subsequent TBI, there is no a-priori reason to believe that this risk is different from the other types of injuries included. This specific issue could nevertheless be addressed in future work. As mentioned in the introduction, all the three core symptoms of ADHD (i.e., inattention, hyperactivity, and impulsivity), as well as clinical components often associated with ADHD, such as irritability and aggression, may increase the risk of injuries. Since studies included here did not present data according to the ADHD type/presentation (predominantly inattentive, predominantly impulsive or combined), we could not ascertain the individual contribution of each ADHD component, which should be explored in future studies.

Perhaps the most relevant and striking result was the protective effect of ADHD medication (mainly methylphenidate per prescription rates in the included studies). This relied on the combination of studies with a very powerful type of design, i.e., self-controlled case studies and difference in risk differences, which control for the "confounding by indication bias". It must be noted that the effect size included for the latter study was an OR that did not directly control for intra-individual characteristics. However, the fact that the protection estimated through the difference in difference model was greater than that obtained from the linear mixed model from which the OR was derived indicates that the pooled estimation when including all the articles, is, if anything, a conservative one.

Although one may think that our finding should be taken with caution since it derives from 5 studies only, we note that this analysis included 13,254 children/adolescents with ADHD. Additionally, while the results of the risk meta-analysis were characterized by a high heterogeneity (likely accounted for by the variability that we addressed with the sensitivity and meta-regression analyses), the meta-analysis on the effect of medication was associated with a low heterogeneity, increasing the confidence in the results. The effect size we found in relation to the protective effect of ADHD medications translates in an average of 10% reduction in the incidence of unintentional injuries. Whilst this figure may seem small, we deem our results relevant from a clinical and public health standpoint. Indeed due to the high prevalence of ADHD in children and adolescents, and the higher incidence of unintentional injuries in this population, even a small reduction of the risk would result in high potential social and economic benefits. Our results on the effect of the medication complement findings from a large body of evidence showing beneficial effects of ADHD medications not only in the short term, for ADHD core symptoms (Faraone and Buitelaar, 2010), but also for neuropsychological dysfunctions (Coghill et al., 2014) and for other very relevant outcomes, such as criminal acts both in adolescents (Dalsgaard et al., 2014) and adults with ADHD (Lichtenstein et al., 2012). Our findings are also important in the light of recent controversy about the evidence supporting the use of methylphenidate (Banaschewski et al., 2016).

Self-controlled case series are suited to estimate the short-term effects of medication as the issue they address is whether an individual is more prone to suffer an injury during the previous, recent, period when (s)he has not taken any ADHD drugs. Our meta-analysis of the four self-controlled case series shows that there is a short-term protective effect of medication. However, the study by Dalsgaard et al. (Dalsgaard et al., 2015a) investigated long-term differences in the risk of injuries, as individuals were included in the medicated group if they had received medication for as little time as six months. As already reported, this study showed a similar effect size to the self-controlled studies, and its inclusion in the meta-analysis did not change the estimation of the pooled effect-size. Future additional studies are needed to confirm the possible long-term protective effect of medication reported by Dalsgaard et al.

Overall, our results have relevant implications both from a research and clinical perspective. In terms of research, there has been for a long time a strong focus on the cognitive and academic impairments associated with ADHD. Indeed, many parents seek help only when there are academic failures or learning difficulties. More recently, there has been a growing interest on other very relevant aspects related to ADHD, such as somatic disorders (e.g, obesity (Cortese et al., 2016)) substance abuse (Groenman et al., 2017), sexual impulsivity −associated with higher rates of sexually transmitted diseases and un-planned pregnancy- (Ramos Olazagasti et al., 2013), legal problems and motor vehicle accidents (Barkley et al., 1990; Curry et al., 2017) and quality of life (Coghill et al., 2017). Our results add to this body of literature highlighting how UPIs are a significant aspect to consider.

The association of ADHD with higher risk of UPIs has also important clinical and preventive medicine implications. Children and adolescents with ADHD are an "at risk" population for injuries, and prevention is the best way to tackle this problem (Peden et al., 2008). Parents of children and adolescents with ADHD should have a stronger focus on child-proofing the home to avoid injuries and also educate their children in the use of protective equipment in sports, and more generally, to avoid unneeded risks.

From an economic perspective, arguably, medication management is not a low-cost intervention, as a continuous clinical follow up and a close monitoring of parameters such as weight, height, blood pressure, and pulse are recommended. However, the potential reduction of UPIs would save a lot of resources in direct costs, such as visits to the emergency room, hospital admissions, severe disability (physical or cognitive) or premature death; and also in indirect costs such as school absenteeism, parental stress and parental reduction of time at work (Maia et al., 2016).

Clinically, our finding on the reduction of risk of UPIs with medication highlights the importance of balancing risk and benefits when deciding to start, stop or continue medication. This should be considered during a balanced discussion over the pros and cons of medication therapy with parents so they can make an informed choice over therapeutic options that takes into account short and long-term outcomes. Moreover, medication discontinuation during the summer is a practice that is still frequent in many settings (Ibrahim and Donyai, 2015), as ADHD is sometimes identified only as a school performance problem. However, the risk of UPIs is especially high in this period of the year (Peden et al., 2008), and hence, our results are a further call for the reconsideration of this practice. At the very least, when the clinicians discuss the potential benefits on appetite, sleep, mood and other aspects when the medication is stopped, they should also address the risk of elevated injuries, in times when there is less structure and supervisions, such as summer vacation.

Our results should be evaluated in the light of study strengths and limitations. The former include the availability of a pre-registered protocol, limiting the possibility of reporting bias, the inclusion of unpublished data, and the focus, for the medication analysis, on studies with a very rigorous design suited to test medication effects, i.e., self-case control studies. As for all meta-analyses, limitations include: 1) bias on individual studies (although our meta-regression showed that study quality did not have a significant impact on the findings); 2) number of studies available for meta-regression analyses; 3) the impossibility of studying whether the protective effect varies between medications, if it is influenced by other variables, or if non-pharmacological interventions can also influence this risk. These limitations should be addressed with future studies and meta-analyses.

5. Conclusion

Our study provides meta-analytic evidence showing that children and adolescents with ADHD are at higher risk of injuries and that ADHD pharmacotherapy has a protective effect, at least in the short-term. These findings are highly relevant from a clinical and public health perspective.

Author's contributions

M. Ruiz-Goikoetxea and G. Arrondo contributed equally to this

work.

M. Ruiz-Goikoetxea and G. Arrondo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: M. Ruiz-Goikoetxea, S. Cortese and G. Arrondo.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: M. Ruiz-Goikoetxea, S.Cortese, C. Soutullo and G. Arrondo.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: M. Aznarez-Sanado and G. Arrondo.

Obtained funding: All authors.

Administrative, technical, or material support: C. Soutullo and G Arrondo.

Study Supervision: S. Cortese, S. Soutullo and G. Arrondo.

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Role of funder/Sponsor

The University of Navarra, provided database and bibliographic access, and licenses for proprietary programs (Mendeley institutional and STATA). The sponsor of this review was the Child and Adolescent Psychiatry Unit, Department of Psychiatry and Medical Psychology, University of Navarra Clinic, which has the final responsibility over the study

Data statement

All data used in the preparation of the systematic review and meta-analysis is available upon request.

Conflict of interest disclosures

S. Cortese has received grant/research support from the Solent National Health Service (NHS) Trust, UK. He has received honorarium and travel expenses from the Association for Child and Adolescent Mental Health (ACAMH). P. de Castro-Manglano has received research funds for his department from Caja Navarra Foundation and Shire and she has served as Consultant for the Alicia Koplowitz Foundation. C. Soutullo has received compensation for serving as consultant or speaker for, or him or the University of Navarra has received research support or royalties from the following companies or organizations: Alicia Koplowitz Foundation, DOYMA, Editorial Médica Panamericana, Eli Lilly, EUNETHYDIS (European Network on Hyperkinetic Disorder), EUNSA, Janssen, Lundbeck, Mayo Ediciones, Medice Group, NeuroTech Solutions Ltd, Rubió, Shire, Spanish Health Ministry Quality Plan (Clinical Practice Guidelines on TDAH and Clinical Practice Guidelines on Depression), TEVE, Universidad Internacional de La Rioja (UNIR) and Universidad Internacional Menéndez Pelayo. All other authors do not have any conflicts of interest to disclose (For full disclosure of COIs see Supplementary Appendix on Conflicts of Interest Disclosure)..

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2017.11.007.

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