Descriptive title: Injury among children and young people with and without attention deficit-hyperactivity disorder in the community: the risk of fractures, thermal injuries and poisonings

Short title: ADHD and injury

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Contributors' Statement:

Vibhore Prasad: Dr Prasad conceived the idea for the study, conducted the data management, analysis and interpretation, drafted the initial manuscript, and approved the final manuscript as submitted.

Denise Kendrick: Professor Kendrick conceived the idea for the study, provided clinical input and interpretation throughout the project, critically reviewed and approved the final manuscript as submitted.

Kapil Sayal: Professor Sayal made contributions to the design of the study, provided clinical input and interpretation throughout the project, critically reviewed and approved the final draft of the manuscript.

Joe West: Professor West conceived the idea for the study, guided the data management and analysis, provided clinical input and interpretation throughout the project, critically reviewed and approved the final draft of the manuscript.

Abstract

Background: Injuries commonly cause morbidity and mortality in children and young people (CYP). Attention deficit-hyperactivity disorder (ADHD) is the commonest neurobehavioural disorder in CYP and is associated with increased injury risk. However, large, population-based estimates of the risk of specific injuries are lacking. We aimed to provide estimates of the risk of fractures, thermal injuries and poisonings in CYP with and without ADHD.

Methods: In this population-based cohort study we used primary and secondary care medical records from England from the Clinical Practice Research Datalink (CPRD). There were 15,126 CYP with ADHD frequency-matched to 263,724 without, aged 3-17 years at diagnosis. The risk of: (i) fractures (ii) thermal injuries, and (iii) poisonings in CYP with ADHD was compared to those without.

Results: The absolute rate of injury per thousand person years at risk in CYP with vs. without ADHD was: fracture 28.9 (95%CI 27.5 to 30.3) vs. 18.7 (95%CI 18.5 to 19.0); long bone fracture 17.7 (95%CI 16.7 to 18.8) vs. 11.8 (95%CI 11.6 to 12.0); thermal injuries 4.4 (95%CI 3.9 to 4.9) vs. 2.2 (95%CI 2.1 to 2.3); poisonings 6.3 (95%CI 5.7 to 6.9) vs. 1.9 (95%CI 1.9 to 2.0). Adjusting for age, sex, geographical region, deprivation and calendar year, CYP with ADHD had: 25% increase in risk of fracture, (hazard ratio, HR=1.25 (95% CI 1.19 to 1.31)); 21% increase in risk of long bone fracture, (HR=1.21 (95% CI 1.13 to 1.28)); double the risk of thermal injury (HR=2.00 (95% CI 1.76 to 2.27) and almost four times the risk of poisoning (HR=3.72 (95% CI 3.32 to 4.17).

Conclusions: CYP with ADHD are at greater risk of fracture, thermal injury and poisoning compared to those without. Paediatricians and healthcare professionals should provide injury prevention advice at diagnosis and reviews.

Introduction

Attention deficit-hyperactivity disorder (ADHD) is the commonest neurobehavioural disorder in children and young people (CYP) (NICE, 2018). CYP with ADHD have developmentally inappropriate levels of hyperactivity, impulsivity and inattention with evidence of pervasive impairment in multiple settings (e.g. school and home) (NICE, 2018). The community prevalence of ADHD is 5% (Sayal, Prasad, Daley, Ford, & Coghill, 2018).

Worldwide and in the UK, injuries are a leading cause of morbidity and mortality in CYP (World Health Organisation, 2005). Unintentional injuries are an important public health problem with, for example an incidence of 2,000 medically attended injuries per 10,000 person years (Finkelstein, Corso, & Miller, 2006) and a total lifetime cost of $130 billion in 2000 (Finkelstein et al., 2006). The epidemiology of injury varies by age as children develop and mature (MacInnes & Stone, 2008) and boys are more likely than girls to sustain injuries, especially as teenagers (Mytton, Towner, Brussoni, & Gray, 2009). Fractures are common in CYP with an incidence in the UK of 181 per 10,000 person years (Baker, Tata, Kendrick, & Orton, 2016). Thermal injuries are also common, with incidence of 36 per 10,000 person years (Baker et al., 2016). Unintentional poisonings are a significant cause of deaths and hospital admissions worldwide (World Health Organisation, 2008), with an incidence of 42 per 10,000 person years (Baker et al., 2016) and a total lifetime cost of $583 million (Finkelstein et al., 2006).

Most estimates of injury risk in CYP with ADHD compared to CYP without (Chen & Goedken, 2014; Kang, Lin, & Chung, 2013; Man et al., 2014; Marcus, Wan, & Olfson, 2008; Merrill, Lyon, Baker, & Gren, 2009; Tai, Gau, & Gau, 2013; van den Ban et al., 2014) are for all injury types combined, rather than by specific injury types. CYP with ADHD appear to be at approximately twice the risk of all injuries compared to CYP without (Brehaut, Miller,

Raina, & McGrail, 2003; Kang et al., 2013; Merrill et al., 2009; Tai et al., 2013). There is a dearth of published studies quantifying the absolute and relative risk of common specific injury types in CYP with ADHD compared to CYP without. This limits the injury prevention advice that can be provided for CYP and their parents/caregivers. This study investigates the risk of three common injuries (fracture, thermal injury and poisoning) in CYP with ADHD.

Methods

Study population

We conducted a cohort study using linked primary and secondary care medical records of CYP from the Clinical Practice Research Datalink (CPRD); a primary care database containing records of approximately 12 million people (66 million person years of follow-up) from 625 General Practitioner (GP) practices, and representing 8% of the United Kingdom (UK) population (CPRD, 2013) of which around half from England have linked hospital medical records from the Hospital Episodes Statistics (HES) database (Health and Social Care Information Centre, 2013). The CPRD is subjected to rigorous data quality checks (e.g. ensuring a minimum of 95% of patient encounter events are recorded, validation checks and audits) and a systematic review (Herrett, Thomas, Schoonen, Smeeth, & Hall, 2010) demonstrated the high validity of diagnoses in the CPRD, with a median of 89% of cases confirmed by GP record request, algorithm and manual review (Herrett et al., 2010). The CPRD contains information on GP consultations, coded using Read codes, and drug prescriptions (de Lusignan, 2005). HES data include hospital diagnosis codes from overnight hospital stays, coded using International Classification of Disease version 10 (ICD10) (World Health Organization, 2011), and procedure codes from operations, coded using the Office of Population Censuses and Surveys version 4 (OPCS4) (Health & Social Care Information Centre, 2013). Read codes are designed for use in primary care and use a system similar to ICD codes (de Lusignan, 2005). Although the link between CPRD and HES practices was based on individual GP practices consenting to the link (CPRD, 2013), the CPRD-HES-linked population used for this study is similar to the overall CPRD and UK population in terms of age, sex and geographical region (Crooks, 2013; Herrett et al., 2015). Lists of Read and drug codes for ADHD were drawn up by three clinical academic doctors (VP, DK and KS). Using the Read and drug codes, the medical records of all CYP with ADHD between 1st

January 1998 to 31st December 2012 were extracted from the June 2013 version of the CPRD (CPRD, 2013).

Definition of ADHD

CYP aged 3 to 17 years during the study period of 1998-2012, with at least one diagnosis code or at least one drug code for ADHD in the CPRD, were included in the population of CYP with ADHD. A lower age limit of 3 years was chosen because, according to the National Institute of Clinical Excellence (NICE), a diagnosis of ADHD is appropriate only from 3 years (NICE, 2018). An upper age limit of 17 years was chosen because, firstly, this is the age around which CYP are transferred to adult services (Hall et al., 2013; McCarthy et al., 2009; Wong et al., 2009). Secondly, there are limited services to diagnose and treat ADHD in adults, potentially resulting in people with ADHD not having a diagnosis or prescription in their medical records (Hall et al., 2013; McCarthy et al., 2009; Wong et al., 2009). CYP with ADHD were frequency-matched by age band with all CYP who did not have ADHD eligible for inclusion in the analysis. This resulted in thirteen to eighteen CYP without ADHD for every CYP with ADHD by age band. For example, in the analysis for fractures, this resulted in the following numbers of CYP without ADHD per CYP with: age 3 to 4, 16 CYP; age 5 to 9, 17 CYP, age 10 to 14, 18 CYP, age 15 to 17, 13 CYP. . The lists of Read code descriptions and drug codes used are available from the authors on request. The date of the earliest Read or drug code was taken as the date of diagnosis of ADHD.

As ADHD is a neuro-developmental condition that does not have a sudden onset of symptoms we did not exclude CYP with a diagnosis of ADHD made before registration with the practice (NICE, 2018). Using a computer algorithm, we randomly assigned a date of 'pseudodiagnosis' for CYP without ADHD that could be any date starting from three months after they registered with the practice and up to the date they left the practice. Age for CYP

with(out) ADHD was described in terms of the age of individuals at (pseudo)diagnosis. CYP diagnosed before registration were classified by age at registration.

Definition of outcome

The outcome was the first injury to occur after (pseudo)diagnosis of ADHD. We chose to focus on fractures, thermal injuries and poisonings as these are common causes of morbidity and health resource use. Each injury type was identified using a list of: Read codes, for the injuries recorded in the CPRD; and ICD10 or OPCS4 codes, for the injuries recorded in the HES (code lists available on request). The Read codes were drawn up by VP and an academic public health consultant (EO). The ICD10 and OPCS4 code lists were drawn up by two clinical academic doctors (VP and RB). RB categorised the code list for fractures into long bone and non-long bone groups. We included both mechanisms of injury (e.g. accidents caused by fire and flames) and anatomic sites of injury (e.g. burn of lower limbs) to maximise ascertainment of injuries. The outcome of interest was the first injury to be recorded after (pseudo)diagnosis. A separate analysis was conducted using the same study population for each injury type, i.e. fractures, thermal injuries, poisonings.

Follow-up

CYP were followed from the latest date of: (pseudo)diagnosis of ADHD, three months after registration with the practice; 1st January 1998 (the first full year that the link between CPRD and HES was established). Based on previous work it is known that injuries occurring prior to registering with the practice can be incorrectly recorded as new injuries in the first three months of registration (Lewis, Bilker, Weinstein, & Strom, 2005). Therefore, the first three months of registration were excluded from follow-up. The last date of follow-up in the study was taken as the earliest of the date when the: CYP left the practice; practice stopped contributing data to the CPRD; CYP died; CYP turned 25 years old; first had an injury; or

30th March 2012 (the last date that GP-hospital-linked medical records were available to download). We also explored the relationship between ADHD and long bone fractures as indicators of severe injury (Cryer, Jarvis, Edwards, & Langley, 1999; Cryer, Langley, Stephenson, Jarvis, & Edwards, 2002).

Confounders

Age, sex, geographical region of the practice, socioeconomic status and calendar year at study entry were chosen as *a priori* confounders. We used the Index of Multiple Deprivation (IMD) 2010 (UK Department for Communities and Local Government, 2011), of the CYP's home postcode as a proxy of socioeconomic status. The IMD score combines indices from seven domains: income; employment; health and disability; education, skills and training, barriers to housing and services, living environment; crime (UK Department for Communities and Local Government, 2011). IMD scores were categorised into national (English) quintiles. Using Read (and drug) codes, we identified several comorbid conditions that may confound the relationship between ADHD and injury. These included epilepsy (Bakken et al., 2012; Cohen et al., 2013; Suren et al., 2013), behaviour disorder (including oppositional defiant disorder, antisocial behaviour and behaviour disorder), learning disability and cerebral palsy (Kadesjo & Gillberg, 2001). Therefore, we sought evidence for the comorbid conditions in the GP medical records for all CYP in the study using a pre-defined Read code list (and drug code list, in the case of epilepsy) drawn up by VP. At least one diagnosis code (in the case of epilepsy, at least one drug code or one diagnosis code) on the record was taken as evidence that the CYP had the condition.

Statistical analysis

We described categorical variables using frequencies and proportions. The age bands chosen were: 3-4; 5-9; 10-14; 15-17 years. We estimated crude absolute rates for the first injury after

diagnosis for CYP with and without ADHD, with 95% confidence intervals (95% CIs). We estimated hazard ratios (HRs) for each injury type for CYP with ADHD compared to those without, using a Cox regression model. We adjusted hazard ratios for *a priori* confounders (age, sex, geographical region, area-level deprivation and calendar year at study entry). We then adjusted for each comorbid condition (learning disability, epilepsy, cerebral palsy) in turn. However, after an inspection of Read codes for behaviour disorder in CYP with ADHD compared to CYP without, we noted a peak of behaviour disorder codes around the date of diagnosis in CYP with ADHD. We did not see a similar peak of behaviour disorder codes for CYP without ADHD. This implied that GPs may use Read codes for behaviour disorder prior to a CYP being given a definitive diagnosis of ADHD by a specialist. Therefore we did not adjust for behaviour disorder because adjustment for behaviour disorder could effectively adjust estimates for ADHD itself. For other confounders, when adjustment for a comorbid condition led to a change of >10% in the adjusted HR the confounder was retained in the model and the remaining comorbid conditions were assessed for inclusion in the model as described (Maldonado & Greenland, 1993).

We explored interactions between ADHD and age, sex and area-level deprivation by adding interaction terms to the models with a $p<0.05$ taken as statistically significant. Models were checked by inspection of plots of the logarithm of cumulative hazard against time, Schoenfeld residuals against time and a statistical test for non-proportional hazards. We undertook sensitivity analyses assessing the effect on our findings through varying the definition of ADHD as: (i) at least two drug codes and at least two diagnosis codes; (ii) at least two diagnosis codes and less than two drug codes; (iii) at least two drug codes and less than two diagnosis codes; (iv) one drug code or one diagnosis code/one drug code and one diagnosis code.

Statistical analysis was performed using Stata® version 12MP (StataCorp, College Station, Texas, USA).

Ethics

Approval was obtained from the CPRD's independent scientific advisory committee (ISAC). CPRD data are anonymised and further ethical approval was not required.

Results

Table 1 shows the characteristics of the study population. In the analysis of fractures, there were 15,126 with and 263,724 CYP without ADHD. All data were complete apart from 1% of CYP with missing data on deprivation.

Table 2 shows risk of injury in CYP with ADHD compared to those without. In the analysis for fractures CYP were followed for a median (interquartile range) of 2.9 (1.2 to 5.8) years in CYP with vs. 2.4 (0.9 to 5.4) years without ADHD. The injury rate was highest for any fractures, followed by poisonings and thermal injuries.

After adjusting for age, sex, geographical region, deprivation and calendar year at study entry, CYP with ADHD had an almost four times greater risk of poisoning compared to those without (adjusted HR=3.72 (95% CI 3.32 to 4.17)), double the risk of thermal injury (adjusted HR=2.00 (95% CI 1.76 to 2.27)) and a 25% increase in risk of fracture (adjusted HR=1.25 (1.19 to 1.31)). Restricting analyses to long bone fractures had little effect on hazard ratio estimates (adjusted HR=1.21 (95% CI 1.13 to 1.28)). Adjusting estimates for learning disability, epilepsy and cerebral palsy had little impact on estimates of risk.

We explored whether the increased risk of injury in CYP with ADHD varied by age, sex and deprivation (Supplementary Tables 1 to 3). There was little difference in the estimated HRs comparing CYP with ADHD to those without, by age, sex or deprivation for each injury type.

Tests for non-proportional hazards for CYP with ADHD compared to CYP without suggested that the hazards were proportional. Table 3 shows sensitivity analyses in which the definition of ADHD was varied which indicates that defining ADHD using at least 2 diagnosis codes and less than 2 drug codes resulted in higher hazard ratios for fractures (HR 1.36 (95%CI 1.16 to 1.59)), thermal injuries (HR 2.86 (95%CI 2.04 to 4.01)) and poisonings (HR 4.05

(95%CI 2.92 to 5.63)) than in the main analysis. However, confidence intervals overlapped with those from the main analysis.

Discussion

CYP with ADHD are at greater risk of fractures, thermal injuries and poisonings compared to CYP without ADHD. Specifically, in CYP with ADHD, the risk of: fracture is 25% greater; thermal injury is two times greater; and poisoning is nearly four times greater, compared to CYP without ADHD.

The strengths of our study include that, to our knowledge, this is the first study to explore associations between ADHD and fractures, thermal injuries and poisonings in CYP using primary and secondary care data. As we used the primary care and linked hospital admissions records we based our estimates of risk of injuries recorded in both primary and secondary care settings. Misdiagnosis of ADHD is unlikely because ADHD is diagnosed by specialists in line with NICE guidelines (NICE, 2018; Sayal et al., 2018). Misclassification of ADHD could have occurred but our sensitivity analyses using varying definitions of ADHD made little difference to the estimated risks of injuries, suggesting any misclassification is likely to have minimal impact on our findings. Misclassification of the injuries could have occurred if an injury was not recorded in primary care and linked hospital records or an injury that had not occurred was incorrectly coded as occurring. However, we found similar hazard ratios for all fractures and for long bone fractures, which we expected to have high levels of recording (Van Staa, Abenhaim, Cooper, Zhang, & Leufkens, 2000). We included mechanisms of injury (e.g. accidents caused by fire and flames), anatomic sites of injury (e.g. burn of lower limbs), hospital diagnosis codes and operative procedure codes to maximise ascertainment of injuries. Although there is a potential risk of ascertainment bias, whereby CYP with ADHD who may have higher GP consultation rates have more opportunities to report injuries than people without ADHD, our findings of similar hazard ratios for all fractures and for long bone fractures would suggest this was not occurring. We have no reason to suspect that misclassification is more likely to occur or more likely to be differential for poisonings or

thermal injuries than for fractures. Although we adjusted for key confounders, it is possible that some residual confounding remains, e.g., due to parent-related factors (e.g. parents' educational level, parental mental health problems or parental ADHD (Russell, Ford, Rosenberg, & Kelly, 2014)), which would not have been possible to measure using the CRPD. In addition, not adjusting for behavioural disorders means that there may be some residual confounding for CYP with ADHD and comorbid behaviour disorders (such as conduct disorder or oppositional defiant disorder). As 1% of CYP had missing data on deprivation, we treated CYP with missing data as a separate group. The risk of injuries stratified by deprivation (shown in supplementary tables) indicates that the confidence intervals for this 'missing data' group were wide (e.g. fractures: HR 1.37 (95%CI 0.84 to 2.25); thermal injuries: HR 3.00 (95%CI 0.85 to 10.66); poisonings: 6.06 (95%CI 2.18 to 16.85). As only 1% of CYP had missing data on deprivation, is unlikely that alternative methods of imputing missing data would have altered our overall estimates of injury risk.

Previous studies indicate that the risk of all injuries combined in CYP with ADHD is approximately one and a half to two times greater than in CYP without (Kang et al., 2013; Merrill et al., 2009; Spinks, Nagle, Macpherson, Bain, & McClure, 2008; Tai et al., 2013). However, most studies do not explore the risk of injuries in CYP with ADHD by specific injury types and no previous studies have explored the risk of fractures, thermal injuries and poisonings in CYP with ADHD compared to CYP without, which limits the specific injury prevention advice that may be given to CYP and their carers. Compared to previous studies that estimate the risk of injuries in CYP with ADHD compared to CYP without, the overall estimates of risk in this study are similar to published estimates. There is some evidence that medication for ADHD may lower injury risk, as a self-controlled case series study using a large primary care database (The Health Improvement Network (THIN)) found a lower risk of injuries during periods of medication for ADHD than in periods without medication

(Raman et al., 2013). However, these findings related to all injuries combined and the generalisability of these findings to specific injury types is not known. Our study identified CYP with ADHD using diagnosis codes and prescriptions. Internationally, there is considerable variation in clinical rates of recognition, diagnosis and drug treatment of ADHD (Sayal et al., 2018). Therefore these estimates of injury risk may vary depending on under or over-recognition of ADHD in different healthcare systems. However, the overall findings of the risk of three specific injury types for CYP with ADHD are likely to be generalisable to countries with health care systems, ADHD medication prescribing rates and ADHD identification rates that are similar to those in England.

Conclusion

CYP with ADHD will have frequent interactions with paediatricians, GPs and pharmacists but current guidance, such as NICE and American Academy of Pediatrics guidance, does not specifically address injury counselling for CYP with ADHD. Our findings highlight the need for this. The increased risk of injury should be communicated to CYP and their carers at diagnosis, medication reviews, follow-up visits and age-appropriate injury prevention guidance should be given during visits to the paediatricians, GPs, nurses and contacts with the pharmacist (Gardner, 2007).

Key messages

1. Injuries commonly cause morbidity and mortality in children and young people (CYP).

2. Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder and is associated with an increased risk of all injury types.

3. There is a lack of large, population-based studies estimating risk of specific common injury types associated with ADHD.

4. This cohort study used primary care and hospital records of 15,737 CYP with ADHD and 291,894 without. CYP with ADHD had a 25% increase in risk of fracture; double the risk of thermal injury and almost four times the risk of poisoning.

5. At diagnosis and reviews, paediatricians and healthcare professionals should provide information on the risks and advice about the prevention of fractures, thermal injury and poisonings associated with ADHD.

References

Baker, R., Tata, L. J., Kendrick, D., & Orton, E. (2016). Identification of incident poisoning, fracture and burn events using linked primary care, secondary care and mortality data from England: implications for research and surveillance. *Injury Prevention, 22*(1), 59-67. doi:10.1136/injuryprev-2015-041561

Bakken, I. J., Aase, H., Chin, R., Gunnes, N., Lie, K. K., Magnus, P., . . . Stoltenberg, C. (2012). Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. *Pediatrics, 130*(1), e152-158. doi:http://dx.doi.org/10.1542/peds.2011-3217

Brehaut, J. C., Miller, A., Raina, P., & McGrail, K. M. (2003). Childhood Behavior Disorders and Injuries Among Children and Youth: A Population-Based Study. *Pediatrics, 111*(2), 262-269. doi:10.1542/peds.111.2.262

Chen, Z., & Goedken, A. (2014). Attention-deficit/hyperactivity disorder medications and injuries among children. *Journal of the American Pharmacists Association, 54 (2)*, e181. doi:http://dx.doi.org/10.1331/JAPhA.2014.14511

Cohen, R., Senecky, Y., Shuper, A., Inbar, D., Chodick, G., Shalev, V., & Raz, R. (2013). Prevalence of epilepsy and attention-deficit hyperactivity (ADHD) disorder: A population-based study. *Journal of Child Neurology, 28*(1), 120-123. doi:http://dx.doi.org/10.1177/0883073812440327

CPRD. (2013). The Clinical Practice Research Datalink (CPRD). Available at: http://www.cprd.com/intro.asp (Accessed 13 February 2013).

Crooks, C. (2013). *Epidemiology of upper gastrointestinal bleeding studying its causes and outcomes using case control studies and surivival analyses.* Ph. D. Thesis. The University of Nottingham,

Cryer, P. C., Jarvis, S. N., Edwards, P., & Langley, J. D. (1999). How can we reliably measure the occurrence of non-fatal injury? *International Journal for Consumer and Product Safety, 6*(4), 183-191. doi:10.1076/icsp.6.4.183.7527

Cryer, P. C., Langley, J. D., Stephenson, S. C., Jarvis, S. N., & Edwards, P. (2002). Measure for measure: the quest for valid indicators of non-fatal injury incidence. *Public Health, 116*(5), 257-262.

de Lusignan, S. (2005). Codes, classifications, terminologies and nomenclatures: definition, development and application in practice. *Informatics in primary care, 13*(1), 65-70.

Finkelstein, E. A., Corso, P. S., & Miller, T. R. (2006). *The incidence and economic burden of injuries in the United States*: Oxford University Press.

Gardner, H. G. (2007). Office-Based Counseling for Unintentional Injury Prevention. *Pediatrics, 119*(1), 202-206. doi:10.1542/peds.2006-2899

Hall, C. L., Newell, K., Taylor, J., Sayal, K., Swift, K. D., & Hollis, C. (2013). 'Mind the gap'--mapping services for young people with ADHD transitioning from child to adult mental health services. *BMC psychiatry, 13*, 186. doi:http://dx.doi.org/10.1186/1471-244X-13-186

Health & Social Care Information Centre. (2013). The Health and Social Care Information Centre (HSIC). Available at: http://systems.hscic.gov.uk/data/clinicalcoding/codingstandards/opcs4/opcs-4.6/opcs-4-5 (Accessed 15 November 2013).

Health and Social Care Information Centre. (2013). Hospital Episodes Statistics Admitted Patient Care - England 2011-12. Available at: http://www.hscic.gov.uk/searchcatalogue?productid=13264&q=title%3a%22Hospital+Episode+Statistics%2c+Admitted+patient+care+-+England%22&sort=Relevance&size=10&page=1#top (Accessed 19 January 2015).

Herrett, E., Gallagher, A. M., Bhaskaran, K., Forbes, H., Mathur, R., van Staa, T., & Smeeth, L. (2015). Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International Journal of Epidemiology, 44*(3), 827-836. doi:10.1093/ije/dyv098

Herrett, E., Thomas, S. L., Schoonen, W. M., Smeeth, L., & Hall, A. J. (2010). Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *British Journal of Clinical Pharmacology, 69*(1), 4-14. doi:10.1111/j.1365-2125.2009.03537.x

Kadesjo, B., & Gillberg, C. (2001). The comorbidity of ADHD in the general population of Swedish school-age children. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 42*(4), 487-492.

Kang, J.-H., Lin, H.-C., & Chung, S.-D. (2013). Attention-deficit/hyperactivity disorder increased the risk of injury: a population-based follow-up study. *Acta Paediatrica, 102*(6), 640-643. doi:http://dx.doi.org/10.1111/apa.12213

Lewis, J. D., Bilker, W. B., Weinstein, R. B., & Strom, B. L. (2005). The relationship between time since registration and measured incidence rates in the General Practice Research Database. *Pharmacoepidemiology and Drug Safety, 14*(7), 443-451.

MacInnes, K., & Stone, D. H. (2008). Stages of development and injury: an epidemiological survey of young children presenting to an emergency department. *BMC Public Health, 8*, 120.

Maldonado, G., & Greenland, S. (1993). Simulation Study of Confounder-Selection Strategies. *American Journal of Epidemiology, 138*(11), 923-936.

Man, K. K. C., Chan, E. W., Douglas, I., Ip, P., Wong, W. H. S., Coghill, D., & Wong, I. C. K. (2014). Attention-deficit/hyperactivity disorder (ADHD) pharmacological treatment and its effect on accident and emergency admission due to injury: A self-controlled case-series study. *Pharmacoepidemiology and Drug Safety, 23*, 317. doi:http://dx.doi.org/10.1002/pds.3701

Marcus, S. C., Wan, G. J., & Olfson, M. (2008). Injury among Stimulant-treated Youth with ADHD. *Journal of Attention Disorders, 12*(1), 64-69.

McCarthy, S., Asherson, P., Coghill, D., Hollis, C., Murray, M., Potts, L., . . . Williams, T. (2009). Attention-deficit hyperactivity disorder: treatment discontinuation in adolescents and young adults. *The British Journal of Psychiatry, 194*(3), 273-277.

Merrill, R. M., Lyon, J. L., Baker, R. K., & Gren, L. H. (2009). Attention deficit hyperactivity disorder and increased risk of injury. *Adv Med Sci, 54*(1), 20-26. doi:8814402U1K615156 [pii]

10.2478/v10039-009-0022-7 [doi]

Mytton, J., Towner, E., Brussoni, M., & Gray, S. (2009). Unintentional injuries in school-aged children and adolescents: lessons from a systematic review of cohort studies. *Injury Prevention, 15*(2), 111-124.

NICE. (2018). *Attention deficit hyperactivity disorder: diagnosis and management (NG87)*. London: National Institute for Health and Care Excellence.

Raman, S. R., Marshall, S. W., Haynes, K., Gaynes, B. N., Naftel, A. J., & Stürmer, T. (2013). Stimulant treatment and injury among children with attention deficit hyperactivity disorder: an application of the self-controlled case series study design. *Injury Prevention, 19*(3), 164-170. doi:10.1136/injuryprev-2012-040483

Russell, G., Ford, T., Rosenberg, R., & Kelly, S. (2014). The association of attention deficit hyperactivity disorder with socioeconomic disadvantage: alternative explanations and evidence. *Journal of Child Psychology & Psychiatry & Allied Disciplines, 55*(5), 436-445. doi:http://dx.doi.org/10.1111/jcpp.12170

Sayal, K., Prasad, V., Daley, D., Ford, T., & Coghill, D. (2018). ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry, 5*(2), 175-186. doi:10.1016/S2215-0366(17)30167-0

Spinks, A. B., Nagle, C., Macpherson, A. K., Bain, C., & McClure, R. J. (2008). Host Factors and Childhood Injury: The Influence of Hyperactivity and Aggression. *Journal of Developmental & Behavioral Pediatrics, 29*(2), 117-123 110.1097/DBP.1090b1013e318163c318163b318160.

Suren, P., Bakken, I. J., Lie, K. K., Schjolberg, S., Aase, H., Reichborn-Kjennerud, T., . . . Stoltenberg, C. (2013). Differences across counties in the registered prevalence of autism, ADHD, epilepsy and cerebral palsy in Norway. *Tidsskrift for Den Norske Laegeforening, 133*(18), 1929-1934. doi:http://dx.doi.org/10.4045/tidsskr.13.0050

Tai, Y. M., Gau, S. S., & Gau, C. S. (2013). Injury-proneness of youth with attention-deficit hyperactivity disorder: a national clinical data analysis in Taiwan. *Res Dev Disabil, 34*(3), 1100-1108. doi:10.1016/j.ridd.2012.11.027

UK Department for Communities and Local Government. (2011). Indices of Deprivation 2010. Available at: https://www.gov.uk/government/publications/english-indices-of-deprivation-2010 (Accessed 16 March 2014).

van den Ban, E., Souverein, P., Meijer, W., van Engeland, H., Swaab, H., Egberts, T., & Heerdink, E. (2014). Association between ADHD drug use and injuries among children and adolescents. *European Child & Adolescent Psychiatry, 23*(2), 95-102. doi:http://dx.doi.org/10.1007/s00787-013-0432-8

Van Staa, T. P., Abenhaim, L., Cooper, C., Zhang, B., & Leufkens, H. G. M. (2000). The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. *Pharmacoepidemiology and Drug Safety, 9*(5), 359-366. doi:10.1002/1099-1557(200009/10)9:5<359::aid-pds507>3.0.co;2-e

Wong, I. C. K., Asherson, P., Bilbow, A., Clifford, S., Coghill, D., DeSoysa, R., . . . Taylor, E. (2009). Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY)--a pharmacoepidemiological and qualitative study. *Health Technology Assessment (Winchester, England), 13*(50), iii-iv, ix-xi, 1-120.

World Health Organisation. (2005). *Child and adolescent injury prevention: A global call to action*. Geneva: World Health Organisation.

World Health Organisation. (2008). *World Report on Child Injury Prevention*. Retrieved from Geneva:

World Health Organization. (2011). *International Statistical Classification of Diseases and Related Health Problems, ICD-10: Three Volume Set.* Geneva, Switzerland: World Health Organization.

Table 1 Characteristics of CYP with and without ADHD for analyses of fractures, thermal injuries and poisonings

Study cohort		Fractures		Thermal injuries		Poisonings	
Characteristic		**ADHD n=15,126 (%)**	**Non-ADHD n=263,724 (%)**	**ADHD n=15,260 (%)**	**Non-ADHD n=264,907 (%)**	**ADHD n= 15236 (%)**	**Non-ADHD n=264,927 (%)**
Age group at (pseudo)diagnosis of ADHD (years)	3-4	1,161 (7.7)	18,932 (7.2)	1,161 (7.6)	18,970 (7.2)	1,158 (7.6)	18,968 (7.2)
	5-9	7,747 (51.2)	135,533 (51.4)	7,795 (51.1)	136,059 (51.4)	7,798 (51.2)	136,091 (51.4)
	10-14	5,357 (35.4)	98,083 (37.2)	5,433 (35.6)	98,665 (37.3)	5,413 (35.5)	98,657 (37.2)
	15-17	861 (5.7)	11,176 (4.2)	871 (5.7)	11,213 (4.2)	867 (5.7)	11,211 (4.2)
Sex	Males	12,800 (84.6)	133,731 (50.7)	12,923 (84.7)	134,478 (50.8)	12,914 (84.8)	134,512 (50.8)
Geographical region	East Midlands	496 (3.3)	10,827 (4.1)	501 (3.3)	10,879 (4.1)	498 (3.3)	10,888 (4.1)
	East of England	2,157 (14.3)	32,200 (12.2)	2,183 (14.3)	32,328 (12.2)	2,181 (14.3)	32,334 (12.2)
	London	1,565 (10.4)	39,310 (14.9)	1,577 (10.3)	39,424 (14.9)	1,576 (10.3)	39,438 (14.9)
	North East	356 (2.4)	6,082 (2.3)	362 (2.4)	6,113 (2.3)	362 (2.4)	6,113 (2.3)
	North West	1,964 (13.0)	41,147 (15.6)	1,971 (12.9)	41,366 (15.6)	1,973 (13.0)	41,360 (15.6)
	South Central	2,171 (14.4)	33,540 (12.7)	2,193 (14.4)	33,693 (12.7)	2,185 (14.3)	33,667 (12.7)
	South East Coast	2,732 (18.1)	32,730 (12.4)	2,752 (18.0)	32,892 (12.4)	2,747 (18.0)	32,903 (12.4)
	South West	1,965 (13.0)	28,357 (10.8)	1,992 (13.1)	28,487 (10.8)	1,987 (13.0)	28,487 (10.8)
	West Midlands	1,291 (8.5)	27,663 (10.5)	1,299 (8.5)	27,794 (10.5)	1,297 (8.5)	27,806 (10.5)
	Yorkshire & Humber	429 (2.8)	11,868 (4.5)	430 (2.8)	11,931 (4.5)	430 (2.8)	11,931 (4.5)
Deprivation	Least deprived	2,563 (16.9)	62,126 (23.6)	2,593 (17.0)	62,424 (23.6)	2,585 (17.0)	62,341 (23.6)
	2nd least deprived	2,723 (18.0)	55,233 (20.9)	2,744 (18.0)	55,477 (20.9)	2,742 (18.0)	55,482 (20.9)
	Medium deprivation	2,760 (18.3)	47,932 (18.2)	2,777 (18.2)	48,181 (18.2)	2,778 (18.2)	48,173 (18.2)
	2nd most deprived	3,378 (22.3)	49,349 (18.7)	3,418 (22.4)	49,554 (18.7)	3,408 (22.4)	49,548 (18.7)
	Most deprived	3,522 (23.3)	46,928 (17.8)	3,550 (23.3)	47,111 (17.8)	3,544 (23.3)	47,132 (17.8)
	Missing data	180 (1.2)	2,156 (0.8)	178 (1.2)	2,160 (0.8)	179 (1.2)	2,161 (0.8)
Calendar year at study entry	1998-2001	3,187 (21.1)	55,623 (21.1)	3,205 (21.0)	55,819 (21.1)	3,205 (21.0)	55,829 (21.1)
	2002-2005	3,830 (25.3)	70,802 (26.9)	3,860 (25.3)	71,138 (26.9)	3,860 (25.3)	71,145 (26.9)
	2006-2009	5,188 (34.3)	83,236 (31.6)	5,250 (34.4)	83,635 (31.6)	5,237 (34.4)	83,631 (31.6)
	2010-2012	2,921 (19.3)	54,063 (20.5)	2,945 (19.3)	54,315 (20.5)	2,934 (19.3)	54,322 (20.5)
Behavior disorder		7,312 (48.3)	11,860 (4.5)	7,377 (48.3)	11,913 (4.5)	7,359 (48.3)	11,906 (4.5)
Learning disability		1,733 (11.5)	2,204 (0.8)	1,743 (11.4)	2,215 (0.8)	1,740 (11.4)	2,216 (0.84)
Epilepsy		814 (5.4)	3,179 (1.2)	817 (5.4)	3,193 (1.2)	814 (5.3)	3,195 (1.2)
Cerebral palsy		7 (0.05)	74 (0.03)	7 (0.05)	75 (0.03)	7 (0.05)	74 (0.03)

Table 2 The risk of fractures, thermal injuries and poisonings in CYP with and without ADHD

Injury category	ADHD or non-ADHD	Events (n)	pyar	Rate (per 1000 pyar)	(95% CI)	Adjusted HR[a]	(95% CI)
Any fractures	ADHD	1,722	59,661	28.9	(27.5 -30.3)	1.25	(1.19 -1.31)
	Non-ADHD	17,245	920,248	18.7	(18.5 -19.0)	1	
Thermal injuries	ADHD	289	65,628	4.4	(3.9 -4.9)	2.00	(1.76 -2.27)
	Non-ADHD	2,128	979,330	2.2	(2.1 -2.3)	1	
Any poisonings	ADHD	412	65,592	6.3	(5.7 -6.9)	3.72	(3.32 -4.17)
	Non-ADHD	1,913	981,229	1.9	(1.9 -2.0)	1	
Injury sub-groups:							
Long bone fractures	ADHD	62,307	62,307	17.7	(16.7 -18.8)	1.21	(1.13 -1.28)
	Non-ADHD	11,115	943,375	11.8	(11.6 -12.0)	1	

pyar: Person years at risk

HR: Hazard ratio

[a]HRs were adjusted for for age, sex, geographical region, deprivation and calendar year at study entry

Table 3 The risk of fractures, thermal injuries and poisonings in CYP with and without ADHD by varying definitions of ADHD

Injury type	**ADHD definition**	**HR (95% CI)**	**Adjusted (95% CI) HR[a]**
Any fractures:			
	≥2 drug & ≥2 diagnosis codes	1.65 (1.51 -1.80)	1.30 (1.19 -1.42)
	≥2 diagnosis & <2 drug codes	1.66 (1.42 -1.95)	1.36 (1.16 -1.59)
	≥2 drug & <2diagnosis codes	1.51 (1.38 -1.65)	1.19 (1.09 -1.30)
	1 drug or 1 diagnosis, or 1 drug & 1 diagnosis code	1.47 (1.35 -1.60)	1.22 (1.12 -1.33)
Thermal injuries:			
	≥2 drug & ≥2 diagnosis codes	2.48 (2.02 -3.03)	2.48 (2.02 -3.04)
	≥2 diagnosis & <2 drug codes	2.90 (2.08 -4.06)	2.86 (2.04 -4.01)
	≥2 drug & <2diagnosis codes	1.95 (1.56 -2.43)	1.89 (1.51 -2.36)
	1 drug or 1 diagnosis, or 1 drug & 1 diagnosis code	1.55 (1.23 -1.95)	1.51 (1.19 -1.91)
Any poisonings:			
	≥2 drug & ≥2 diagnosis codes	3.04 (2.51 -3.67)	3.75 (3.08 -4.56)
	≥2 diagnosis & <2 drug codes	3.33 (2.40 -4.61)	4.05 (2.92 -5.63)
	≥2 drug & <2diagnosis codes	3.22 (2.68 -3.86)	3.36 (2.79 -4.06)
	1 drug or 1 diagnosis, or 1 drug & 1 diagnosis code	3.20 (2.69 -3.80)	3.91 (3.27 -4.67)
Injury sub-groups:			
Long bone fractures:			
	≥2 drug & ≥2 diagnosis codes	1.63 (1.46 -1.82)	1.27 (1.14 -1.42)
	≥2 diagnosis & <2 drug codes	1.79 (1.49 -2.17)	1.44 (1.19 -1.74)
	≥2 drug & <2diagnosis codes	1.43 (1.28 -1.60)	1.13 (1.01 -1.26)
	1 drug or 1 diagnosis, or 1 drug & 1 diagnosis code	1.42 (1.27 -1.58)	1.16 (1.04 -1.29)

pyar: Person years at risk (in years)

HR: Hazard ratio comparing children with ADHD to children without ADHD

[a]HRs were adjusted for for age, sex, geographical region, deprivation and calendar year at study entry

Supplementary Table 1 The risk of fractures in CYP with and without ADHD by age, sex and deprivation

Characteristic		ADHD vs. non-ADHD HR (95% CI)	ADHD vs. non-ADHD Adjusted HR[$] (95% CI)	P-Value[+]
Injury type: Any fractures				
Age group at (pseudo)diagnosis of ADHD (years)	3-4	1.52 (1.28 -1.81)	1.37 (1.15 -1.63)	0.77
	5-9	1.38 (1.28 -1.48)	1.10 (1.02 -1.18)	
	10-14	1.83 (1.69 -1.98)	1.46 (1.35 -1.59)	
	15-17	1.49 (1.13 -1.97)	1.27 (0.96 -1.68)	
Sex	Males	1.24 (1.18 -1.31)	1.24 (1.18 -1.31)	0.67
	Females	1.26 (1.06 -1.50)	1.28 (1.07 -1.52)	
Deprivation	Least deprived	1.51 (1.34 -1.69)	1.23 (1.10 -1.38)	0.67
	2nd least deprived	1.52 (1.35 -1.71)	1.23 (1.09 -1.38)	
	Medium deprivation	1.51 (1.34 -1.70)	1.22 (1.08 -1.37)	
	2nd most deprived	1.68 (1.52 -1.86)	1.35 (1.22 -1.49)	
	Most deprived	1.49 (1.33 -1.66)	1.19 (1.07 -1.33)	
	Missing data	1.75 (1.07 -2.87)	1.37 (0.84 -2.25)	

HR: Hazard ratio

[+]Test for interaction comparing the estimate (adjusted for age, sex, geographical region, deprivation, calendar year of entry) with the adjusted estimate with an interaction term for age or sex or deprivation

[$]HRs were adjusted for age, sex, geographical region, deprivation and calendar year at study entry

Supplementary Table 2 The risk of thermal injuries in CYP with and without ADHD by age, sex and deprivation

Characteristic		ADHD vs. non-ADHD HR (95% CI)	ADHD vs. non-ADHD Adjusted HR[$] (95% CI)	P-Value[+]
Injury type: Thermal injuries				
Age group at (pseudo)diagnosis of ADHD (years)	3-4	2.75 (1.84 -4.11)	2.35 (1.58 -3.49)	0.83
	5-9	1.98 (1.65 -2.38)	1.91 (1.59 -2.30)	
	10-14	2.06 (1.69 -2.51)	2.03 (1.66 -2.48)	
	15-17	1.91 (1.11 -3.28)	2.03 (1.18 -3.50)	
Sex	Males	2.05 (1.78 -2.35)	1.96 (1.70 -2.26)	0.50
	Females	2.29 (1.70 -3.09)	2.20 (1.63 -2.97)	
Deprivation	Least deprived	2.23 (1.63 -3.03)	2.27 (1.66 -3.09)	0.52
	2nd least deprived	1.74 (1.27 -2.39)	1.78 (1.29 -2.44)	
	Medium deprivation	1.77 (1.31 -2.37)	1.77 (1.31 -2.38)	
	2nd most deprived	2.29 (1.80 -2.92)	2.35 (1.84 -3.00)	
	Most deprived	1.82 (1.42 -2.33)	1.85 (1.44 -2.38)	
	Missing data	3.05 (0.86 -10.81)	3.00 (0.85 -10.66)	

HR: Hazard ratio

[+]Test for interaction comparing the estimate (adjusted for age, sex, geographical region, deprivation, calendar year of entry) with the adjusted estimate with an interaction term for age or sex or deprivation

[$]HRs were adjusted for age, sex, geographical region, deprivation and calendar year at study entry

Supplementary Table 3 The risk of poisonings in CYP with and without ADHD by age, sex and deprivation

Characteristic		ADHD vs. non-ADHD HR (95% CI)	ADHD vs. non-ADHD Adjusted HR[$] (95% CI)	P-Value[+]
Injury type: Any poisonings				
Age group at (pseudo)diagnosis of ADHD (years)	3-4	4.27 (2.83 -6.44)	4.36 (2.92 -6.51)	0.37
	5-9	3.54 (2.99 -4.19)	4.07 (3.42 -4.84)	
	10-14	3.02 (2.57 -3.54)	3.37 (2.86 -3.97)	
	15-17	3.34 (2.24 -4.98)	3.80 (2.55 -5.67)	
Sex	Males	3.92 (3.43 -4.48)	3.62 (3.17 -4.14)	0.44
	Females	4.32 (3.51 -5.33)	4.00 (3.24 -4.93)	
Deprivation	Least deprived	2.62 (1.87 -3.66)	3.34 (2.39 -4.68)	0.29
	2nd least deprived	3.22 (2.41 -4.30)	4.05 (3.03 -5.41)	
	Medium deprivation	3.19 (2.53 -4.01)	3.92 (3.10 -4.95)	
	2nd most deprived	2.58 (2.10 -3.16)	3.13 (2.54 -3.86)	
	Most deprived	3.37 (2.73 -4.16)	4.27 (3.45 -5.29)	
	Missing data	4.05 (1.46 -11.26)	6.06 (2.18 -16.85)	

HR: Hazard ratio

[+]Test for interaction comparing the estimate (adjusted for age, sex, geographical region, deprivation, calendar year of entry) with the adjusted estimate with an interaction term for age or sex or deprivation

[$]HRs were adjusted for age, sex, geographical region, deprivation and calendar year at study entry