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ADHD medication and unintentional injuries in children and adolescents

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Abstract

Objective: Our objective was to determine whether ADHD medication is associated with a decreased risk of unintentional injuries in children and adolescents in the United States across sexes, age groups and injury types.

Methods: We used de-identified inpatient, outpatient, and filled prescription claims data from the Truven Health MarketScan® Research Databases. Individuals were followed from January 1, 2005, date of first ADHD diagnosis or medication prescription, or age 6, whichever occurred last, until December 31, 2014, first healthcare insurance disenrollment, or the first year at which their age was recorded as 19, whichever occurred first. A person was considered on ADHD medication during a given month if a prescription was filled in that month. The outcome was defined as emergency department visits for injuries, including traumatic brain injuries, with unintentional causes. Odds of having the outcome were compared between medicated and un-medicated months at the population-level and in within-individual analyses using logistic regression.

Results: Among 1 968 146 individuals diagnosed with ADHD or receiving ADHD medication, 87 154 had at least one event. At the population-level, medication use was associated a lower risk of injuries, both in boys (OR= 0.85; 95% CI: 0.84–0.86) and girls (OR=0.87; 95% CI: 0.85–0.89). Similar results were obtained from within-individual analysis among male (OR= 0.72; 95% CI: 0.70–0.74) and female (OR= 0.72; 95% CI: 0.69–0.75) children, and among male (OR= 0.64; 95% CI: 0.60–0.67) and female (OR= 0.65; 95% CI: 0.60–0.71) adolescents. Similar results were found for traumatic brain injuries.

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Conclusion: ADHD medication use was associated with a reduction of different types of unintentional injuries in children and adolescents of both sexes.

LAY SUMMARY

We used de-identified insurance claims data from the Truven Health MarketScan® Commercial Claims and Encounters databases to study whether use of ADHD medication is associated with a decreased risk of unintentional injuries in children and adolescents in the United States. Use of ADHD medication was associated with a decreased risk of any unintentional injury in boys (Odds Ratio= 0.71, 95% Confidence Interval: 0.70–0.73) and girls (Odds Ratio=0.71, 95% Confidence Interval: 0.68–0.73). Similar associations were found for traumatic brain injuries and both in children and adolescents. The results suggest that ADHD medication use may have beneficial effects not only on core symptoms of ADHD, but also on other aspects of general health, such as prevention of physical injuries.

Keywords

Children; Adolescent; Attention Deficit Disorder with Hyperactivity/drug therapy; Attention Deficit Disorder with Hyperactivity/epidemiology; Central Nervous System Stimulants/therapeutic use

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder that affects about 3–5% of children worldwide.[1,2] ADHD is associated with several negative outcomes related to health and wellbeing,[3] including physical injuries.[4–6] Unintentional injuries, such as falls and road injuries, are the leading cause of morbidity and mortality among children in the United States.[7] Meta-analytical results suggest that ADHD is associated with a 40–50% increase in the risk of injuries in children and adolescents.[5,6] Pharmacological treatment for ADHD has been reported to be effective for core symptoms[8,9] and cognitive deficits[10] associated with ADHD. Hence it may be hypothesized that, by reducing distractibility, impulsivity and over-activity, ADHD medication may prevent unintentional injuries.

Although randomized controlled trials (RCTs) represent the gold standard approach to evaluate intervention efficacy, observational studies based on large and representative administrative databases, combined with designs and analytical techniques aimed at reducing confounding, may also contribute to the knowledge base around medication safety and effectiveness.[11] This is particularly true for studying rare-but-serious outcomes. One approach that is becoming increasingly used in observational studies evaluating concurrent effects of medication use is the within-individual design, which removes time-invariant confounding by comparing the risk of an outcome within the same individual under different treatment conditions.[12] A few recent observational studies have used within-individual designs to investigate if treatment with medications approved for the management of ADHD symptoms may influence the risk of injuries in children and adolescents.[4,13–16] Two recent meta-analyses of observational studies found support for a protective effect.[5,17] When focusing on studies that used within-individual comparisons, the pooled effect sizes pointed

towards a reduction in the rate of injuries by 12–14% during medicated periods compared with un-medicated periods.[5,17] However, not all the studies have consistently reported a significant risk reduction.[15] One point that remains unclear is whether the association between ADHD medication and injuries may depend on age. One study reported very similar estimates across age groups,[13] while other studies reported different associations in different age groups.[14,16] Understanding the consequences of ADHD across childhood and adolescence has important implications for clinical practice, as many patients stop using their medication during adolescence.[18] Another important factor is the type of the injury. For example, one study found an association between medication use and traumatic brain injuries (TBI) but did not find a significant association with any type of injury, although the point estimates indicated a risk reduction.[13] This may suggest that different types of injuries may not be associated with medication in the same way, an aspect that deserves further investigation, because of the public health relevance and implications for clinical practice when weighting the risks and benefits of ADHD medication. In addition, it is not clear whether the results from previous studies in European and Asian countries, where ADHD medication prevalence estimates are around 2%,[19] will generalize to other settings, such as the United States, where the prevalence of diagnosed ADHD and ADHD medication use are higher.[19,20]

In this study, we estimated the concurrent association between ADHD medication use and unintentional injuries (that is, excluding intentional self-harm) in a sample of commercially-insured children and adolescents in the United States. In addition, capitalizing on the availability of data from a large health-care database, we explored if the association was consistent across sex and age and for TBI, given that the available evidence on these aspects is still inconclusive.

METHODS

Study sample

We used data from the Truven Health MarketScan® Commercial Claims and Encounters databases of de-identified inpatient, outpatient, and filled prescription claims.[21] As confirmed with the University of Chicago institutional review board, the analysis of MarketScan Databases is exempt because records are de-identified, and informed consent is not required.

We identified all individuals with an ADHD diagnosis (codes 314 in the International Classification of Diseases, Ninth Edition [ICD-9]) or an ADHD medication prescription between January 1, 2005 and December 31, 2014. The first inpatient or outpatient diagnosis or filled prescription was defined as the index date. Individuals included in the study were followed from the index date or age 6, whichever occurred later, until their first disenrollment, December 31, 2014 or the first year at which their age was recorded as 19, whichever occurred first. Disenrollment was defined as zero days of medical or drug insurance coverage in a given month. A non-ADHD control group (no ADHD diagnosis or medication, as defined above), matched 1:1 on sex, calendar year, age at first enrollment, and length of enrollment, was also selected from MarketScan Databases enrollees. More details are available elsewhere.[22,23]

Exposure

We identified data ADHD medication using national drug codes for the following generic names: amphetamine salt combination, atomoxetine hydrochloride, dexmethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, methamphetamine hydrochloride, methylphenidate, and methylphenidate hydrochloride, consistent with other studies.[22–23] We required prescription claims to have valid fill dates and day supply (180 days or less). A person was considered to be receiving medication during a given month if a prescription was filled in that month or if there was a carryover from a prior month.

Outcome

To identify unintentional injuries we defined the outcome events as Emergency Department (ED) visits for injuries (ICD-9 codes: 800–929; 950) with an unintentional cause (ICD-9 codes: E001-E869; E880-E928). In addition, we identified TBI as ED visits for unintentional causes (ICD-9 codes: 800, 801, 803, 804; 850–854; 950.1–950.3; 959.01). We focused on ED visits rather than any hospital visit in order to identify acute events.

We allowed unintentional injuries to occur multiple times during the follow-up. To avoid reverse causation, if a new prescription was filled in a month when an event occurred, the medication was considered used only if the prescription was filled before the date of the event. In a small number of instances (n = 2441; less than 0.01% of the included months) patients began new prescriptions and experienced the event in the same month. In these cases, we considered patients as unmedicated if the event occurred before or on the same date as the first prescription fill.

Statistical Analysis

ADHD and the risk of injuries—To examine the association between ADHD and unintentional injuries, we compared the odds of having at least one event between ADHD patients and matched controls. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were estimated using conditional logistic regression. The same model was used to analyze the association between ADHD and unintentional TBI.

ADHD medication use and the risk of injuries—To explore the concurrent association between ADHD medication use and ED visits for unintentional injuries, we created a monthly person-time data set and performed two sets of analyses using logistic regression. First, we compared the odds of having an event between medicated and un-medicated months at the population-level , adjusting for time-varying covariates (age, calendar year, and time since the last accidental injury event), with robust standard errors accounting for the correlation among months within individual. We converted the ORs into Risk Ratios (RRs) and calculated the adjusted rate difference as $I_0 \times (RR_a - 1)$, where I_0 is the unadjusted event rate in the unexposed periods and RR_a is the adjusted RR.[24]

Second, we compared the odds of having the event between medicated and un-medicated months at the individual level (within-individual analysis). That is, each individual served as his or her own control. ORs were estimated using conditional logistic regression. This model controlled for all unmeasured confounding factors that were constant within the individual

during the follow-up (for example, genetic make-up and early environmental exposures).[25] In addition, we adjusted for time since the last accidental injury event. These two sets of analyses were also applied to estimate the association between ADHD medication use and unintentional TBI. Assuming that the estimate from within-individual analysis could be generalized to the full sample, we estimated the rate difference between medicated and un-medicated months.

We obtained separate estimates for boys and girls. Furthermore, we examined the associations between ADHD medication use and unintentional injuries in two separate age groups: individuals aged 6–15 years and individuals aged 16–19 years, consistent with a previous study.[14]

Sensitivity Analysis

To examine the robustness of the within-individual associations between ADHD medication use and ED visits for both unintentional injuries and unintentional TBI, we performed sensitivity analyses using different definitions of the cohort, exposure, and outcome. The first analysis examined the association in a cohort with incident diagnoses of ADHD (i.e., patients who were newly diagnosed with ADHD and had no prescription of ADHD medication for at least one year), in order to evaluate the association among patients who were new to ADHD treatment. The second analysis censored individuals after the first event in the incident diagnosis cohort (i.e., the one used for the first sensitivity analysis) to exclude possible bias due to reverse causation (i.e., the prescription of ADHD medication was influenced by an unintentional injury). The third analysis excluded the last month before disenrollment because the coverage for the last month might be incomplete. The fourth and fifth analyses examined the association among people with index dates 2005–2008 and 2009–2014 respectively, as average severity of treated patients might have changed over time. The sixth analysis extended the medicated periods by one month so that the definition of un-medicated months following treatment discontinuation was more conservative. In the seventh analysis we excluded prescriptions with less than 10 day of supply (about 1% of total prescriptions) so that we excluded short medication periods. The eighth analysis examined the associations with only stimulant medications as the exposure (i.e., excluding atomoxetine) to explore whether the association depended on the type of ADHD medication (i.e., stimulant vs non-stimulant). The ninth and tenth analyses excluded patients who received other psychotropic medication and psychotherapy, respectively, in order to test whether the observed associations were explained by other concomitant treatments. The eleventh analysis used selective serotonin reuptake inhibitors (SSRIs) as the main exposure to evaluate if the observed association was specific to ADHD medication or similar pattern could be observed with other psychotropic medications. In this analysis the exposure to SSRIs was defined and modelled in the same way as ADHD medication in the main analysis.

All analyses were performed using statistical software (SAS, version 9.4; SAS Institute Inc).

RESULTS

We identified 1 968 146 individuals with a diagnosis of ADHD or a prescription for ADHD medication during the follow-up time. The main characteristics of the study cohort are presented in Table 1. Over 60% of the sample were boys and the median age at the start of the follow-up was 11 for boys and 12 for girls. The proportion of individuals with at least one event was slightly higher in boys (4.8%) than in girls (3.6%).

ADHD and the risk of injuries

ADHD was associated with an increased risk of having an unintentional injury in boys (OR=1.18, 95% CI: 1.17–1.20) and in girls (OR=1.36, 95% CI: 1.34–1.38) (Table2). Similar results were obtained for TBI, both in boys (OR=1.21, 95% CI: 1.18–1.24) and in girls (OR=1.49, 95% CI: 1.42–1.56) (Table2).

ADHD medication use and the risk of injuries

In the population-level analysis, ADHD medication use was associated a lower risk of having an ED visit for unintentional injuries (OR= 0.85, 95% CI: 0.84–0.86 for boys; OR= 0.87, 95% CI: 0.85–0.89 for girls) (Table 3). This corresponded to 37.90 (95% CI: 35.37–40.43) fewer events per 100 000 person-months in boys and 25.15 (95% CI: 21.28–29.02) fewer events per 100 000 person-months in girls. Similar results were obtained for TBI (OR= 0.85, 95% CI: 0.81–0.89 for boys; OR= 0.91, 95% CI: 0.84–0.98 for girls) (Table 3). This corresponded to 4.24 (95% CI: 3.11–5.38) fewer events per 100 000 person-months in boys and 1.87 (95% CI: 0.42–3.33) fewer events per 100 000 person-months in girls.

In the within-individual analysis, ADHD medication use was associated with a lower risk of having an ED visit for unintentional injuries, with equal effect sizes in boys (OR= 0.71, 95% CI: 0.70–0.73) and girls (OR=0.71, 95% CI: 0.68–0.73) (Table 3). This corresponded to 73.29 (95% CI: 68.24–75.82) fewer events per 100 000 person-months in boys and 56.11 (95% CI: 52.24–61.92) fewer events per 100 000 person-months in girls. Similar associations were estimated for TBI, both in boys (OR= 0.63, 95% CI: 0.59–0.67) and in girls (OR= 0.67, 95% CI: 0.60–0.75) (Table 3). This corresponded to 10.47 (95% CI: 9.34–11.60) fewer events per 100 000 person-months in boys and 6.87 (95% CI: 5.21–8.33) fewer events per 100 000 person-months in girls.

Age-stratified estimates showed that ADHD medication use was associated with a lower risk of having an ED visit for unintentional injuries in children and adolescents, both in boys (OR= 0.72, 95% CI: 0.70–0.74 for children; OR= 0.64, 95%CI: 0.60–0.67 for adolescents) and in girls (OR= 0.72, 95% CI: 0.69–0.75 for children; OR= 0.65, 95%CI: 0.60–0.71 for adolescents) (Table 4). Similar associations were observed for TBI (Table 4).

Sensitivity analyses

Similar results were observed in all the sensitivity analyses, indicating that the main results are robust across different definitions of the cohort, the exposure, and the outcome (Table 5). For example, similar estimates were found when the within-individual analysis was restricted to patients with no other psychotropic medication (OR= 0.67; 95% CI: 0.65–0.69

for boys; OR= 0.68; 95% CI: 0.65–0.72 for girls) or psychotherapy (OR= 0.68; 95% CI: 0.66–0.70 for boys; OR= 0.68; 95% CI: 0.65–0.72 for girls) (Table 5). In contrast, we did not observe a decreased risk of ED visits due to unintentional injuries with concurrent use of SSRIs (OR= 1.17; 95% CI: 1.12–1.23 for boys; OR= 1.09; 95% CI: 1.02–1.16 for girls), suggesting the protective association with ADHD medication was not due to the use of any psychotropic medication (Table 5).

DISCUSSION

To our knowledge, this is the first study that investigated the concurrent association between ADHD medication use and risk of ED visits for unintentional injuries in children and adolescents in the United States. The large sample size allowed us to obtain separate estimates across sexes, age groups and different types if injuries. Furthermore, we were able to specifically focus on unintentional injuries (i.e., excluding intentional self-harm). We found that use of ADHD medication was associated with a reduction of the risk of having an ED visit for unintentional injury, both at the population and at the individual level. The negative associations were present in boys and girls, children and adolescents, as well as for TBIs. The estimates were also robust to different definitions of the study sample, of the follow-up, of the exposure and of the outcome.

This study extends previous findings from studies conducted in Europe[4,13,16] and Hong Kong[15] by showing that the injury risk reduction associated with concurrent ADHD medication use is consistent across sexes, age groups, injury type, and continents. Furthermore, while these studies did not differentiate between intentional and unintentional injury, we focused on unintentional injuries only, which represent a leading cause of disability and mortality in children and adolescents in the United States[7] and in Europe.[26]

Considering the burden of injuries in children and adolescents, this study has clear public health relevance. In particular, TBI has been associated with adverse outcomes in the educational and vocational domains,[27–29] and increased risk of hospitalization and premature mortality.[29] From a clinical perspective, the increasing evidence that ADHD medication seems to be associated with a reduction of severe outcomes, including injuries, but also criminality,[30] substance use disorder[23] and transport accidents,[22,31] may be an additional factor to consider when weighing benefits against risks of ADHD medications.

The study has some strengths and limitations that should be considered when interpreting the results. First, the use of data from a large sample of commercially-insured patients in the United States limits the generalization to other patient groups and to other countries. On the other hand, the large sample size also allowed us to explore the association between ADHD medication and injuries across age groups that may have different risk of injuries[32] and medication use pattern.[19,20,33] Second, only unintentional injuries that led to an ED visit were included in the study; less severe events, including unintentional injuries that did not require medical attention or that were treated in outpatient settings, were not captured by this study. Conversely, it is important to study severe events, including TBI, because of the public health impact.[27–29,34] Third, as a major methodological strength, the information on medication prescriptions was independent of the information on the outcome and free from

recall bias. However, these data did not include information on prescriptions that were not filled (non-adherence) or that were not claimed to the insurance provider. Fourth, because of the observational nature of the data, we were not able to account for all the possible confounders that select individuals into treatment. Some unmeasured factors that correlate with medication use (that is, time-varying confounders, which may lead to medication initiation or cessation) may also decrease or increase the risk of unintentional injuries. One factor that may correlate with ADHD medication use and with risk of injuries is psychotherapy or the use of other psychotropic medications. When we restricted the analysis to individuals with no psychotherapy or other psychotropic medication, we found similar protective estimates, suggesting that these interventions are not likely to explain the observed association. However, it is difficult to establish if the use of the within-individual design, measured time-varying covariates, and different sensitivity analyses ruled out all alternative explanations for the associations between ADHD medication and injuries. To further address the role of unmeasured confounding, we used concurrent use of SSRIs as the main exposure. The analysis found a positive association (i.e., SSRIs use was associated with a small increased risk of injuries). Of most importance to our study, the results for SSRIs showed a different pattern of results, which provides additional support for the specificity of the results for ADHD medication. Fifth, we were not able to check the indication of the medications and exclude individuals who may take ADHD medications for problems other than ADHD. However, in the first sensitivity analysis, where we examined the association in a cohort with recorded diagnoses of ADHD, we found similar results to those obtained in the full sample. Last, future research should investigate how the relative medication effect, assuming a causal effect of medication, translates into meaningfully reduction of rate of injuries and other health-adverse events compared to individuals without ADHD. Such information may help clinicians to plan for additional support via alternative (e.g., behavioral) interventions in the case that medication only cannot decrease the rate of health-adverse events to what expected in the general population.

In conclusion, use of ADHD medication is associated with a reduction of unintentional injuries in children and adolescents in the United States. This seems to be true in boys and girls of different age and for injury events of different severity. These results highlight how the use of ADHD medication may be associated with beneficial effects that go beyond reducing core symptoms of ADHD and extend to the prevention of health-adverse events, such as physical injuries, including TBI.

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Table 1.

Characteristics of the study cohort

	Males		Females	
	N	**%**	**N**	**%**
Study cohort	1 333 048	-	635 098	-
At least one prescription of ADHD medication	1 105 675	82.9%	523 909	82.5%
At least one medication status switch	791 026	59.3%	378 060	59.5%
At least one event	64 346	4.8%	22 808	3.6%
	Median	IQR	Median	IQR
Age at start of follow-up	11	8–15	12	9–16
Follow-up months	17	9–35	15	8–32

Note: IQR= interquartile range ; N= number.

Table 2.

Association between ADHD and unintentional injuries

	N of individuals	N of individuals with at least one event	OR (95% CI)
All unintentional injuries			
Male			
ADHD patients	1 333 041	128 684	1.18 (1.17–1.20)
Controls	1 333 041	110 966	-
Female			
ADHD patients	635 094	51 164	1.36 (1.34–1.38)
Controls	635 094	38 745	-
Unintentional TBI			
Male			
ADHD patients	1 333 041	15 523	1.22 (1.19–1.25)
Controls	1 333 041	12 758	-
Female			
ADHD patients	635 094	5 654	1.52 (1.45–1.58)
Controls	635 094	3 747	-

Note: 95% CI= 95% confidence interval; OR= odds ratio; N= number; TBI= traumatic brain injury.

Table 3.

Association between ADHD medication use and unintentional injuries stratified by sex

	Person-months at risk	N of events	Population-level OR (95% CI)	Within-individual OR (95% CI)
All unintentional injuries				
Male				
Medicated	17 081 159	35 616	0.85 (0.84–0.86)	0.71 (0.70–0.73)
Un-medicated	15 924 449	40 320	-	-
Female				
Medicated	7 428 410	12 042	0.87 (0.85–0.89)	0.71 (0.68–0.73)
Un-medicated	7 340 475	14 223	-	-
Unintentional TBI				
Male				
Medicated	17 082 554	3 897	0.85 (0.81–0.89)	0.63 (0.59–0.67)
Un-medicated	15 923 054	4 507	-	-
Female				
Medicated	7 428 888	1 298	0.91 (0.84–0.98)	0.67 (0.60–0.75)
Un-medicated	7 339 997	1 529	-	-

Note: 95% CI= 95% confidence interval; OR= odds ratio; N= number; TBI= traumatic brain injury.

Table 4.

Association between ADHD medication use and unintentional injuries stratified by sex and age

	N of individuals	N of events	Within-individual OR (95% CI)
All unintentional injuries			
Male			
Age 6–15	1 061 164	64 559	0.72 (0.70–0.74)
Age 16–19	271 884	11 377	0.64 (0.60–0.67)
Female			
Age 6–15	451 573	20 862	0.72 (0.69–0.75)
Age 16–19	183 525	5 403	0.65 (0.60–0.71)
Unintentional TBI			
Male			
Age 6–15	1 061 164	7 182	0.64 (0.60–0.69)
Age 16–19	271 884	1 222	0.55 (0.47–0.66)
Female			
Age 6–15	451 573	2 073	0.69 (0.61–0.79)
Age 16–19	183 525	754	0.62 (0.50–0.78)

Note: 95% CI= 95% confidence interval; OR= odds ratio; N= number; TBI= traumatic brain injury.

Table 5.

Sensitivity analyses for the association between ADHD medication and unintentional injuries

	N of individuals	N of events	Within-individual OR (95% CI)
All unintentional injuries			
Male			
Incident diagnosis cohort	309 719	17 168	0.77 (0.74–0.81)
Incident diagnosis cohort and first event only	309 719	14 656	0.59 (0.56–0.63)
Cohort excluding the last month before disenrollment	1 293 717	73 364	0.72 (0.70–0.73)
Full cohort with index year in 2005–2008	336 132	22 012	0.76 (0.74–0.79)
Full cohort with index year in 2009–2014	996 916	53 834	0.70 (0.69–0.72)
Full cohort with one-month-extended medication periods	1 333 048	75 936	0.71 (0.70–0.73)
Full cohort without short prescriptions	1 234 590	60 374	0.84 (0.82–0.86)
Full cohort with stimulant medication as exposure only	1 333 048	75 936	0.72 (0.70–0.73)
With no other psychotropic medication	886 343	42 803	0.67 (0.65–0.69)
With no psychotherapy	911 081	44 067	0.68 (0.66–0.70)
Full cohort with SSRIs as exposure	1 333 048	75 936	1.17 (1.12–1.23)
Female			
Incident diagnosis cohort	162 727	6 562	0.79 (0.73–0.86)
Incident diagnosis cohort and first event only	162 727	5 680	0.59 (0.53–0.64)
Cohort excluding the last month before disenrollment	615 890	25 288	0.72 (0.69–0.75)
Full cohort with index year in 2005–2008	144 879	6 512	0.75 (0.70–0.81)
Full cohort with index year in 2009–2014	490 219	19 753	0.71 (0.68–0.74)
Full cohort with one-month-extended medication periods	635 098	26 265	0.71 (0.68–0.74)
Full cohort without short prescriptions	583 416	21 102	0.84 (0.81–0.87)
Full cohort with stimulant medication as exposure only	635 098	26 265	0.72 (0.69–0.74)
With no other psychotropic medication	383 010	12 444	0.68 (0.65–0.72)
With no psychotherapy	407 850	13 652	0.68 (0.65–0.72)
Full cohort with SSRIs as exposure	635 098	26 265	1.09 (1.02–1.16)
Unintentional TBI			
Male			
Incident diagnosis cohort	309 719	2 174	0.86 (0.75–0.98)
Incident diagnosis cohort and first event only	309 719	2 107	0.70 (0.61–0.81)
Cohort excluding the last month before disenrollment	1 290 747	8 042	0.63 (0.59–0.68)
Full cohort with index year in 2005–2008	336 132	1 477	0.58 (0.50–0.67)
Full cohort with index year in 2009–2014	996 916	6 927	0.65(0.61–0.70)
Full cohort with one-month-extended medication periods	1 333 048	8 404	0.61 (0.57–0.66)
Full cohort without short prescriptions	1 234 590	7 589	0.63 (0.59–0.67)
Full cohort with stimulant medication as exposure only	1 333 048	8 404	0.63 (0.59–0.67)
With no other psychotropic medication	886 343	4 746	0.61 (0.56–0.67)
With no psychotherapy	911 081	4 671	0.59 (0.54–0.64)
Full cohort with SSRIs as exposure	1 333 048	8 404	1.41 (1.23–1.61)

	N of individuals	N of events	Within-individual OR (95% CI)
Female			
Incident diagnosis cohort	162 727	736	0.79 (0.63–1.00)
Incident diagnosis cohort and first event only	162 727	719	0.68 (0.52–0.87)
Cohort excluding the last month before disenrollment	613 806	2 701	0.67 (0.60–0.75)
Full cohort with index year in 2005–2008	144 879	459	0.61 (0.47–0.79)
Full cohort with index year in 2009–2014	490 219	2 368	0.70 (0.62–0.79)
Full cohort with one-month-extended medication periods	635 098	2 827	0.67 (0.60–0.75)
Full cohort without short prescriptions	583 416	2 516	0.67 (0.60–0.75)
Full cohort with stimulant medication as exposure only	635 098	2 827	0.70 (0.62–0.78)
With no other psychotropic medication	383 010	1 225	0.72 (0.60–0.85)
With no psychotherapy	407 850	1 337	0.71 (0.61–0.84)
Full cohort with SSRIs as exposure	635 098	2 827	1.29 (1.08–1.54)

Note: 95% CI= 95% confidence interval; OR= odds ratio; N= number; SSRIs= selective serotonin reuptake inhibitors; TBI= traumatic brain injury.