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Serious transport accidents in adults with ADHD, and the effect of medication: A population based study

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Abstract

Importance—Studies have shown that Attention-deficit/hyperactivity disorder (ADHD) is associated with transport accidents, but the magnitude of the association remains unclear. Importantly, it is also unclear whether ADHD medication reduces this risk.

Objective—First, to estimate the association between ADHD and the risk of serious transport accidents. Second, to explore the extent to which ADHD medication influences this risk among ADHD patients.

Design, Setting, and Participants—17,408 patients with a diagnosis of ADHD were followed from 2006 to 2009 for serious transport accidents in Swedish national registers. The association between ADHD and accidents was estimated with Cox regression. To study the effect of ADHD medication, we used stratified Cox regression to compare the risk of accidents during medication period with the risk during non-medication period within the same patients.

Main Outcome and Measure—Serious transport accident, identified as admission to an emergency hospital care or death due to transport accident.

Results—Compared with individuals without ADHD, male ADHD patients (adjusted hazard ratio [HR] =1.47, 95% confidence interval [CI] 1.32–1.63) and female ADHD patients (HR=1.45, 95% CI 1.24–1.71) had increased risk of serious transport accidents. In male ADHD patients, ADHD medication was associated with a 58% risk reduction (HR=0.42, 95% CI 0.23–0.75), but there was no significant association in female patients. Estimates of the population attributable fractions suggested that 41% – 49% of the accidents in male patients with ADHD could have been avoided if they had been on treatment the entire follow-up.

Conclusions and Relevance—ADHD is associated with an increased risk of serious transport accidents, and this risk seems to be possibly reduced by ADHD medication, at least among male ADHD patients. This should lead to increased awareness of the association between serious transport accidents and ADHD medication among clinicians and patients.

Transport accidents are a major public health problem. According to the World Health Organization (WHO) report, approximately 1.3 million individuals are killed each year by traffic accidents, and 50 million are injured or disabled.¹ Transport accidents are also associated with substantial economic burden, accounting for about 2% of the gross national product of the entire global economy.¹

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Inattention and distractibility is one of the most common reasons for transport accidents.² An emerging literature has documented an association between ADHD and transport accidents (e.g., collision and trauma).^{3–7} The association is driven by the core symptoms of ADHD (inattention, hyperactivity, and impulsivity), as well as by problems that frequently co-occur with ADHD, such as excessive risk taking, poor control of aggression, and substance use.^{3,8} However, small sample sizes, lack of females in the studies, absence of objective measures, inadequate controls, and referral bias^{3,6} raise uncertainty about the magnitude of the association.

Randomized controlled trials (RCTs) suggest that ADHD medication has beneficial short-term effects on the core symptoms of ADHD,^{9–12} but there are no population-based studies on the association between ADHD medication and transport accidents. A few studies have explored if ADHD medication improves driving ability in virtual reality driving simulators.^{3,5,6,13} The extent to which these effects generalize to real-world situations remains uncertain, however, and most available studies were industry-sponsored.⁶ Because decisions regarding the prescription of ADHD medication need to consider the effect sizes of the benefits and risks of medication at the population level,^{14,15} a population-based prospective study with measures of transport accidents in real life (such as injuries and deaths) is needed.

In this longitudinal study, we used data from population-based registers in Sweden to assess two research questions. First we estimated the magnitude of the association between ADHD and serious transport accidents (injuries and deaths). Second, we explored the extent to which ADHD medication influences this risk among patients with ADHD.

Methods

Setting

We used data from several longitudinal population-based registers in Sweden, which were linked using unique personal identification numbers.¹⁶ We identified all individuals born from 1960 to 1988 with at least one diagnosis of ADHD (ICD-10 code: F90) in the Patient Register since 2001 (N= 17,408). These patients were followed from 1/1/2006 to 12/31/2009 (48 months) for any serious transport accident via the Patient Register and Cause of Death Registers. The Prescribed Drug Register was used to obtain information on all prescribed medications since July 2005.¹⁷ Information regarding socio-demographic variables, crime records, and migrations was obtained from the Integrated Database for Labour Market Research (LISA), the Crime Register, and the Migration Register, respectively. A non-ADHD general population sample, matched 1 to 10 on age, sex, and residential area at the time of the diagnosis was extracted from the Total Population Register. The study was approved by the Ethics committee at Karolinska Institutet.

Measures

The exposure (or risk factor) for the first research question was ADHD. The exposure for the second research question was ADHD medication, which was identified according to the Anatomical Therapeutic Chemical codes in the Prescribed Drug Register. Both stimulant (N06BA04, N06BA01, N06BA02) and non-stimulant (N06BA09) medications are used in Sweden for ADHD treatment.¹⁸ In accordance with previous studies,^{18–20} an individual was defined as under medication during the interval between two dispensed prescriptions (picked up by the individuals themselves, family members, or health care staff) of ADHD medication, unless the prescription occurred more than 6 months apart. An individual was defined as off medication during intervals of 6 months or more without any prescription.

The main outcome for both research questions was serious transport accident, which was identified as admission to an emergency hospital care or death due to transport related trauma (ICD-10 code: V01–V99)⁷ through the Patient Register and Cause of Death Register.

Several potential confounding factors were measured. Five socio-demographic factors (civil, employment, and education status, living in one of the three large cities in Sweden, disposable family income in 2006) were retrieved from the LISA database. Information on previous psychiatric diagnosis (other than ADHD), other common psychotropic medications, and criminal convictions were obtained from the Patient Register, Prescribed Drug Register, and Crime Register, respectively.

Statistical analyses

To explore the association between ADHD and serious transport accidents, we first compared the rate of accidents between individuals with and without ADHD using Cox regression. Second, we included measured covariates into the model to control for confounding.

To investigate the association between ADHD medication and accidents among ADHD patients, we first used ordinary between-individual Cox regression, with robust standard errors accounting for the correlations between periods within the same individual. Next, within-individual analyses were performed using stratified Cox regression with each individual entering as a separate stratum.²¹ That is, each patient served as his or her own control, and the rate of accidents during ADHD medication was compared to the same individual while untreated. Current ADHD medication, age, previous history of ADHD medication and transport accidents were included as time-varying covariates. As such, the within-individual hazard ratio is adjusted for confounding by all unmeasured covariates that are constant within each individual during the follow-up (e.g. genetic predisposition and early environments), and by all measured time-varying covariates. A more detailed description of this method can be found in a recent study of ADHD medication and criminality.²⁰

To assess the public health impact of ADHD medication on serious transport accidents we used population attributable fraction (PAF). PAF was originally proposed for cross-sectional data,²² but extensions are available for cohort studies.²³ In the absence of unmeasured confounding, this PAF measures the proportion of accidents that would be eliminated if the whole cohort of ADHD patients would be medicated during the follow-up. Details regarding the estimation and interpretation of PAF can be found in eMethods.

Due to the gender difference of ADHD²⁴ and transport accidents²⁵, all analyses were conducted for males and females separately. Since young males are the single most risky demographic group,²⁶ separate analyses were also conducted in young and middle-aged adults.

Sensitivity analyses

To examine the robustness of our findings, we analyzed the association between ADHD medication and serious transport accidents with different definitions of the cohort, exposure, and outcome.

First, we analyzed a cohort of individuals that received at least one prescription for ADHD medication during follow-up (identified from the Prescribed Drug Register), but not necessarily had a registered ADHD diagnosis, which avoids potential bias due to the fact that some counties have historically been less consistent in reporting outpatient data to the Patient Register (the Prescribed Drug Register has complete coverage).¹⁷ Second, to explore

if the association between ADHD medication and accidents was explained by drug abuse or criminality, individuals with any drug abuse diagnosis or crime conviction during the follow-up were excluded from the analysis. Third, we performed sensitivity analysis with selective serotonin reuptake inhibitor (SSRI) treatment as exposure (instead of ADHD medication). This analysis enabled us to compare the general effects of being prescribed medication with the specific effects of ADHD medication. Fourth, to explore whether the association depends on the type of ADHD medication (stimulants vs. non-stimulants), we performed sensitivity analysis on individuals that only received stimulant medications. Fifth, because the health registers lack information about whether the patient was a driver or passenger in an accident, we performed a sensitivity analysis restricted to motorcycle rider injuries (assuming that most patients were drivers). Finally, it is possible that the association between medication and transport accidents was due to life changes accompanied with medication status changes. We addressed this potential confounding by comparing the differences in risk of accidents between two consecutive periods (a period without ADHD medication compared to a period with ADHD medication) for patients with different patterns of medication changes.²⁰

Results

The study included 10,528 men and 6,880 women with ADHD aged 18–46 years old in 2006 (See Table 1 for descriptive data at baseline and during follow-up). Among men diagnosed with ADHD, 57.5% had been prescribed ADHD medication, and 6.5% had at least one serious transport accident during follow-up. The corresponding numbers in the matched general population controls were 0.3% and 2.6%, respectively. Among women with ADHD, 65.3% had been prescribed ADHD medication, and 3.9% had at least one serious transport accident during follow-up, compared to 0.2% and 1.8% among controls.

Men with ADHD showed significantly higher rates of accidents than those without ADHD (Table 2); the unadjusted hazard ratio (HR) was 2.45 (95% confidence interval [CI]: 2.27–2.65). The association was attenuated but remained significant when controlling for socio-demographic factors, previous psychiatric diagnosis, other psychotropic medications, and criminal convictions (HR=1.47, 95% CI: 1.32–1.63). Similar results were observed in young men and middle-aged men (eTable 1). We found similar results for females (Adjusted HR=1.45, 95% CI: 1.24–1.71).

To explore the association between ADHD medication and serious transport accidents, all subsequent analyses were based on ADHD patients. Comparing the accident rate during medication and non-medication periods in males showed that ADHD medication decreased the accident rate by 29% (HR= 0.71, 95% CI: 0.57–0.89, Table 2). The association was not statistically significant in females (HR=0.92, 95% CI: 0.78–1.23).

Since patients receiving medication might be different from the non-medicated patients, a within-individual analysis comparing the risk between medication and non-medication period is a more informative test of the association. For men, the stratified Cox Regression, a within-individual comparison, showed that medication decreased the accident rate by 58% in males (HR=0.42, 95% CI: 0.23–0.75, Table 3), illustrating that even within an individual (i.e., after controlling for all confounders that are constant during follow-up and measured time-varying covariates), ADHD medication was associated with a significant reduction of accidents. The associations were similar in young men and middle-aged men with ADHD (eTable 2). Again, we did not observe significant association among females.

We estimated the population attributable fractions of serious transport accidents due to non-treatment (Table 4). Among male ADHD patients, 20% of the total person-years across the

4-year follow-up were medication periods and 80% were non-medication periods (i.e., exposure rate). Based on this exposure rate, 49% of the accidents might be explained by non-medication, under certain assumptions (see eMethods, e.g., no unmeasured confounding). It should be noted that ADHD prescription rates have increased substantially in Sweden¹⁸ and elsewhere.^{27,28} At the end of follow-up, 37% of male ADHD patients were treated with ADHD medications. With this exposure rates, 41% of the accidents were attributable to non-medication.

Sensitivity analyses

Because of the absence of significant associations in females, all sensitivity analyses of the association between ADHD medication and serious transport accidents were performed in males only. We observed similar within-individual result when the cohort was identified from the Prescribed Drug Register (HR=0.38; Table 5), suggesting our result was robust to selection criteria. We also observed similar results when excluding individuals with drug abuse or crime during the follow-up, although the estimate did not reach statistical significance because of the smaller sample size. In contrast to the reductions in risks when analyzing ADHD medication, there was no statistically significant association when we investigated the association between SSRI medication and accidents (HR=1.39, 95% CI: 0.62–3.14), suggesting the associations with ADHD medication were not due to the proclivity to take or discontinue medications in general. When analyzing stimulant medication only, we found a similar reduction in the rate of accidents (HR=0.31). When restricting the outcome to motorcycle rider injuries, a strong rate reduction was observed (HR=0.10). Finally, the risk of accidents increased when ADHD patients moved from medication periods to non-medication periods and decreased when moving from non-medication periods to medication periods (eTable 3).

Discussion

The present study found that ADHD patients were at increased risk for serious transport accidents and that in males patients, ADHD medication was associated with reduced rates of accidents, even when using within-individual analyses.

We found that individuals with ADHD had 42% – 47% increased rate of serious transport accidents compared with individuals without ADHD, in both men and women. The magnitude of the association is similar to results from a population-based case-control study in North American.⁷ Studies have suggested that visual inattentiveness and impulsiveness are the largest contributions to the risk of transport accidents in ADHD patients.⁶ Although the stability of ADHD from childhood to adulthood is increasingly recognized,²⁴ ADHD is still commonly underdiagnosed in adults.^{11,29} Our results provide further evidence that the adverse effect of ADHD extend beyond the early years of driving.

Medications that alleviate ADHD symptoms might be expected to translate into safer driving behavior and subsequently reduce the risk of accidents.³⁰ Similar to a study on criminality,²⁰ and experimental and clinical studies on stimulant medication effects on driving^{3,5,13,31} the results presented here clearly suggest that ADHD medication was associated with reduced rates of serious transport accidents. Compared with non-medication periods, the transport accidents rate during medication periods significantly decreased by 58% in males, and similar effect was found in young and middle-aged men. Our estimates of population attributable fractions suggest that, under certain assumptions, 41% – 49% of the accidents in male patients with ADHD could have been avoided if they had been medicated the entire follow-up. It is important to note, however, that PAF estimates will be lower in countries with higher prescription rates than Sweden^{26,27} and that the beneficial effects of

ADHD medication needs to be weighed against potential adverse effect, including side effects and potential over-prescription.

This is the first population-based study of ADHD medication and serious transport accidents. Population-based register data have several strengths compared to clinical studies. The sample size is substantial and representative for the population, therefore avoiding referral bias, selective participation, and other threats to validity and generalizability. ADHD diagnoses are made by specialized psychiatrists in Sweden,³² and blind to outcomes. ADHD medication is recorded when a prescription is filled, and free from recall bias. Nevertheless, observational studies are always liable to selection effects.³³ The biggest threat is that some patients might receive medication because they are different (usually more symptoms or with comorbid conditions). Unlike RCTs, observational studies like ours cannot account for all possible confounders that select individuals to treatment. Our main attempt to control for this was within-individual analyses, which adjust for all potential confounders that are constant during the follow-up (genetic predisposition and early environment). However, unmeasured confounders and mediators that varied during follow-up (engagement with services that provide prescriptions, cyclic nature of the disorder itself, substance use, or crime) can never be fully ruled out in this research design. To address this issue, we first analyzed accidents rates among patients who had discontinued SSRI instead of ADHD medication, where no association was found. Second, we analyzed the association in a subgroup of patients without any substance abuse or crime during follow-up, and the within-individual estimate did not change substantially. Third, we compared the differences in risk of accidents between two consecutive periods when patients changed their medication status, and the association remained regardless of the order of change in medication status. Although these analyses are consistent with a causal hypothesis, they are only suggestive. Thus, future RCTs or observational studies with medication dosage information are obviously needed.

The findings should also be considered in the context of other limitations. First, we measured ADHD medication using dispensed prescriptions, and our study might be affected by poor medication adherence. This is similar to RCTs and our effect estimate can be compared to an intention to treat analysis. We used a 6-months cutoff between prescriptions to define “off medication”, which is an empirical cutoff based on previous research.^{18–20} To explore the potential influence of exposure misclassification, we re-analyzed the data with a 3-months cutoff and found similar result (eTable 4). If some individuals did not take medication as prescribed, this would reduce the effect estimates; hence, our findings are probably conservative estimates of the actual effects of medication on accidents. Second, because of small numbers we were not able to explore the specific effect of non-stimulant medication or compare different types of medication. However, the magnitude of the associations was similar when considering all medication and stimulant medication only. Third, we used emergency hospital visits or deaths due to transport accidents as our primary outcome, which is a serious outcome. In addition, we have no information on who was responsible for an accident, so an alternative interpretation might be that ADHD may impair one’s ability to avoid accidents initiated by others. Regardless of the culpability of the accident, injuries and deaths due to transport accidents are important public health concern. Future research will need to explore whether the findings generalize to less severe outcomes of transport accidents. Fourth, we found no statistically significant evidence that medication was associated with serious transport accidents in female ADHD patients. The between-individual estimate showed small protective effect of medication. In contrast, the within-individual estimate suggested that medication increased the risk of accidents. However, these results were most likely chance findings as indicated by the wide confidence intervals. Finally, the findings are based on Swedish population data, and generalizations across cultures/countries should be made with caution. Although the ADHD prevalence and the

overall rates of traffic fatality and disability are lower in Sweden compared to other developed countries,^{1,24} the magnitude of risk among ADHD patients was similar to other studies.⁷

In conclusion, we found that ADHD was associated with increased risk of serious transport accidents and that ADHD medication was associated with a reduced rate of accidents among male adult ADHD patients. WHO predicts that traffic injuries will become the fifth leading cause of death by 2030.¹ The findings call attention to a prevalent, preventable and costly cause of mortality and morbidity. The association between ADHD and serious transport accidents does not by itself justify withholding a driver's license; nevertheless our findings suggested that a large number of injuries and death due to traffic accidents associated with ADHD was conferred to periods when patients were off medication. Clinicians should consider informing patients about the increased risk for transport accidents associated with ADHD,³⁴ as well as possible benefits of ADHD medication. This would provide opportunities not only to reduce morbidity and mortality for ADHD patients, but also contribute the public safety in transport.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Sample characteristics at baseline and rate of ADHD medication and serious transport accidents during follow-up.

	Male	Female
N at start of follow-up	10,528	6,880
% received ADHD medication during follow-up	57.5	65.3
% at least one serious transport accidents during follow-up	6.5	3.9
Characteristics at baseline		
Age distribution (%)		
18–25	47.3	40.4
26–35	29.0	30.9
36–46	23.7	28.7
Civil status (%)		
Unmarried	85.8	72.1
Married	7.9	15.0
Divorced	6.2	12.7
Widowed	0.1	0.2
In employment (%)	29.2	29.8
In School (%)	23.1	24.8
Living in metropolitan area (%)	15.1	15.4
Median family income (hundred SEK)	1,706	1,782
Other psychotropic medication (%)		
Prescribed antipsychotics	12.9	13.5
Prescribed hypnotics/anxiolytics	31.0	41.2
Prescribed antidepressants	33.1	48.6
Prescribed drugs used in addictive disorders	5.4	3.4
Psychiatric diagnosis (%)	58.0	62.1
Crime (%)	63.7	35.3

Table 2

Association between ADHD and serious transport accidents in Swedish adults.

Gender	ADHD	Person-years at risk	Number of accidents	Crude association		Adjusted association	
				Hazard Ratio	95% Confidence interval	Hazard Ratio	95% Confidence interval
Males	ADHD	41,793	897	2.45	2.27–2.65	1.47	1.32–1.63
	non-ADHD	415,662	3,217	1	-	1	-
Females	ADHD	27,399	330	2.10	1.86–2.38	1.45	1.24–1.71
	non-ADHD	271,866	1,417	1	-	1	-

Table 3
Rate of serious transport accident during medication periods compared to non-medication periods among Swedish adult ADHD patients.

Gender	Medication	Person-years at risk	Number of accidents	Between-individual		Within-individual	
				Hazard Ratio	95% Confidence interval	Hazard Ratio	95% Confidence interval
Males	medicated	8,377	144	0.71	0.57–0.89	0.42	0.23–0.75
	non-medicated	33,416	753	1	-	1	-
Females	medicated	6,195	67	0.92	0.78–1.23	2.35	0.83–6.64
	non-medicated	21,204	263	1	-	1	-

Table 4
Population attributable fraction (PAF) of serious transport accidents in male ADHD patients.

	P(E)	HR ₀	HR _a	PAF
The proportion of transport accidents attributable to off medication among ADHD patients	80% ^a	1.41 ^b	2.38 ^b	49%
	63% ^c	1.41	2.38	41%

Abbreviation: P(E): proportion of exposed in the population; HR₀=unadjusted Hazard ratio; HR_a=adjusted Hazard ratio. PAF was calculated as $\left\{1 + HR_0^{-1} \frac{1 - Pr(E)}{Pr(E)}\right\}^{-1} (1 - HR_a^{-1})$, see eMethods for details.

^a Among male ADHD patients, 80% were off medication on average during the follow-up.

^b for protective effect, reciprocals of HR₀ and HR_a were used to calculate the PAF of not being exposed to the protective factor (i.e., 1.41=1/0.71, and 2.38=1/0.42).

^c Among male ADHD patients, 63% were off medication at the end of follow-up.

Table 5

Sensitivity analyses of the within-individual effect of medication on serious transport accidents among Swedish adult men ADHD patients.

	Cohort	Exposure	Outcome	No. of patients	No. of accidents	Hazard ratio	95% Confidence Interval
1	Prescribed ADHD medication	Any ADHD medication	Any transport accidents	11,357	589	0.38	0.20–0.72
2	Excluding individuals with drug abuse or crime	Any ADHD medication	Any transport accidents	5,738	261	0.26	0.05–1.40
3	Full Cohort	SSRI	Any transport accidents	10,528	896	1.39	0.62–3.14
4	Stimulant only	Stimulant only	Any transport accidents	5,337	433	0.31	0.12–0.79
5	Full Cohort	Any ADHD medication	Motorcycle rider injury	10,528	269	0.10	0.01–0.81