

## Original Investigation

# Serious Transport Accidents in Adults With Attention-Deficit/Hyperactivity Disorder and the Effect of Medication

## A Population-Based Study

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**IMPORTANCE** Studies have shown that attention-deficit/hyperactivity disorder (ADHD) is associated with transport accidents, but the magnitude of the association remains unclear. Most important, it is also unclear whether ADHD medication reduces this risk.

**OBJECTIVES** To estimate the association between ADHD and the risk of serious transport accidents and to explore the extent to which ADHD medication influences this risk among patients with ADHD.

**DESIGN, SETTING, AND PARTICIPANTS** In total, 17 408 patients with a diagnosis of ADHD were observed from January 1, 2006, through December 31, 2009, for serious transport accidents documented in Swedish national registers. The association between ADHD and accidents was estimated with Cox proportional hazards regression. To study the effect of ADHD medication, we used stratified Cox regression to compare the risk of accidents during the medication period with the risk during the nonmedication period within the same patients.

**MAIN OUTCOMES AND MEASURES** Serious transport accident, identified as an emergency hospital visit or death due to transport accident.

**RESULTS** Compared with individuals without ADHD, male patients with ADHD (adjusted hazard ratio, 1.47; 95% CI, 1.32-1.63) and female patients with ADHD (1.45; 1.24-1.71) had an increased risk of serious transport accidents. In male patients with ADHD, medication was associated with a 58% risk reduction (hazard ratio, 0.42; 95% CI, 0.23-0.75), but there was no statistically significant association in female patients. Estimates of the population-attributable fractions suggested that 41% to 49% of the accidents in male patients with ADHD could have been avoided if they had been receiving treatment during the entire follow-up.

**CONCLUSIONS AND RELEVANCE** Attention-deficit/hyperactivity disorder 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 patients. This should lead to increased awareness among clinicians and patients of the association between serious transport accidents and ADHD medication.

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

Inattention and distractibility are the most common reasons for transport accidents.<sup>2</sup> An emerging literature has documented an association between attention-deficit/hyperactivity disorder (ADHD) and transport accidents (eg, collision and trauma).<sup>3-7</sup> 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.<sup>3,8</sup> However, small sample sizes, lack of female participants in the studies, absence of objective measures, inadequate controls, and referral bias<sup>3,6</sup> raise uncertainty about the magnitude of the association.

Randomized clinical trials suggest that ADHD medication has beneficial short-term effects on the core symptoms of ADHD,<sup>9-12</sup> but to our knowledge, there are no population-based studies on the association between ADHD medication and transport accidents. A few studies have explored whether ADHD medication improves driving ability in virtual reality driving simulators.<sup>3,5,6,13</sup> The extent to which these effects generalize to real-world situations remains uncertain, however, and most available studies have been industry sponsored.<sup>6</sup> 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,<sup>14,15</sup> 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 2 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.<sup>16</sup> We identified all individuals born from 1960 through 1988 with at least 1 diagnosis of ADHD (code F90 in the *International Classification of Diseases, Tenth Revision*) in the Patient Register since 2001 (N = 17 408). These patients were observed from January 1, 2006, through December 31, 2009 (48 months), for any serious transport accident via the Patient Register and Cause of Death Register. The Prescribed Drug Register was used to obtain information on all prescribed medications since July 2005.<sup>17</sup> Information regarding sociodemographic variables, crime records, and migrations was obtained from the Inte-

grated Database for Labour Market Research, 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 (codes N06BA04, N06BA01, and N06BA02) and nonstimulant (code N06BA09) medications are used in Sweden for ADHD treatment.<sup>18</sup> In accordance with previous studies,<sup>18-20</sup> an individual was defined as on medication during the interval between 2 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 an emergency hospital visit or death due to transport-related trauma (codes V01-V99 in the *International Classification of Diseases, Tenth Revision*)<sup>7</sup> through the Patient Register and Cause of Death Register.

Several potential confounding factors were measured. Five sociodemographic factors (civil, employment, and education status; living in 1 of 3 large cities in Sweden; and disposable family income in 2006) were retrieved from the Integrated Database for Labour Market Research. Information on previous psychiatric diagnoses (other than ADHD), other common psychotropic medications, and criminal convictions was obtained from the Patient Register, Prescribed Drug Register, and Crime Register, respectively.

### Statistical Analysis

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 proportional hazards regression. Second, we included measured covariates into the model to control for confounding.

To investigate the association between ADHD medication and accidents among patients with ADHD, we first used ordinary between-individual Cox proportional hazards regression, with robust standard errors accounting for the correlations between periods within the same individual. Next, within-individual analyses were performed using stratified Cox proportional hazards regression with each individual entering as a separate stratum.<sup>21</sup> That is, each patient served as his or her own control, and the rate of accidents during ADHD medication use was compared with the same individual while untreated. Current ADHD medication, age, history of ADHD medication, and transport accidents were included as time-varying covariates. As such, the within-individual hazard ratio is adjusted for confound-

ing by all unmeasured covariates that are constant within each individual during the follow-up (eg, 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.<sup>20</sup>

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

Because of the sex difference of patients with ADHD<sup>24</sup> and those involved in transport accidents,<sup>25</sup> all analyses were conducted for men and women separately. Since young males are the single most risky demographic group,<sup>26</sup> separate analyses were also conducted in young and middle-aged adults.

### Sensitivity Analysis

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 who received at least 1 prescription for ADHD medication during the follow-up (identified from the Prescribed Drug Register) but did not necessarily have a registered ADHD diagnosis, which avoids potential bias because some counties have historically been less consistent in reporting outpatient data to the Patient Register (the Prescribed Drug Register has complete coverage).<sup>17</sup> Second, to explore if the association between ADHD medication and accidents was explained by drug abuse or criminality, we excluded from the analysis individuals with any drug abuse diagnosis or crime conviction during the follow-up. Third, we performed sensitivity analysis with selective serotonin reuptake inhibitor 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 who received only 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 2 consecutive periods (without ADHD medication vs with ADHD medication) for patients with different patterns of medication changes.<sup>20</sup>

**Table 1. Sample Characteristics at Baseline and Rate of ADHD Medication and Serious Transport Accidents During Follow-up<sup>a</sup>**

Characteristic	Male	Female
No. at start of follow-up	10 528	6880
Received ADHD medication during follow-up	57.5	65.3
At least 1 serious transport accident during follow-up	6.5	3.9
Characteristics at baseline		
Age distribution, y		
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
Employed	29.2	29.8
In school	23.1	24.8
Living in metropolitan area	15.1	15.4
Median annual family income, hundred SEK (US \$)	1706 (260.02)	1782 (271.60)
Other psychotropic medications		
Prescribed antipsychotics	12.9	13.5
Prescribed hypnotics or 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

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

<sup>a</sup> Data are presented as percentages unless otherwise indicated.

## Results

The study included 10 528 men and 6880 women with ADHD aged 18 to 46 years 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 1 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 1 serious transport accident during follow-up compared with 0.2% and 1.8%, respectively, 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% CI, 2.27-2.65). The association was attenuated but remained significant when controlling for sociodemographic 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 and middle-aged men (eTable 1 in the Supplement). We found similar results for women (adjusted HR, 1.45; 95% CI, 1.24-1.71).

To explore the association between ADHD medication and serious transport accidents, we based all subsequent analyses on patients with ADHD. Comparing the accident rate during medication and nonmedication periods in men showed that ADHD medication decreased the accident rate by 29% (HR, 0.71; 95% CI, 0.57-0.89) (Table 3). The association was not statistically significant in women (HR, 0.92; 95% CI, 0.78-1.23).

Since patients receiving medication might be different from the nonmedicated patients, a within-individual analysis comparing the risk between medication and nonmedication periods is a more informative test of the association. For men, the stratified Cox proportional hazards regression, a within-individual comparison, showed that medication decreased the accident rate by 58% (HR, 0.42; 95% CI, 0.23-0.75) (Table 3), illustrating that even within an individual (ie, 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 and middle-aged men with ADHD (eTable 2 in the Supplement). Again, we did not observe a significant association among women.

We estimated the PAF of serious transport accidents due to nontreatment (Table 4), calculated as

$$\left\{1 + HR_0^{-1} \frac{1 - Pr(E)}{Pr(E)}\right\}^{-1} (1 - HR_a^{-1})$$

See the eMethods section in the Supplement for details. Among male patients with ADHD, 20.0% of the total person-years across the 4-year follow-up were medication periods, and 80.0% were nonmedication periods (ie, exposure rate). Based on this exposure rate, 49% of the accidents might be explained by nonmedication under certain assumptions (see the eMethods section in the Supplement; eg, no unmeasured confounding). It should be noted that ADHD prescription rates have increased substantially in Sweden<sup>18</sup> and elsewhere.<sup>27,28</sup> At the end of follow-up, 37.2% of male patients with ADHD were treated with ADHD medications. With this exposure rate, 41% of the accidents were attributable to nonmedication.

Because of the absence of significant associations in women, all sensitivity analyses of the association between ADHD medication and serious transport accidents were performed in men only. We observed a similar within-individual result when the cohort was identified from the Prescribed Drug

Table 2. Association Between ADHD and Serious Transport Accidents in Swedish Adults

Characteristic	Person-years at Risk	No. of Accidents	HR (95% CI)	
			Crude Association	Adjusted Association
Men				
ADHD	41 793	897	2.45 (2.27-2.65)	1.47 (1.32-1.63)
Non-ADHD	415 662	3217	1 [Reference]	1 [Reference]
Women				
ADHD	27 399	330	2.10 (1.86-2.38)	1.45 (1.24-1.71)
Non-ADHD	271 866	1417	1 [Reference]	1 [Reference]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio.

Table 3. Rate of Serious Transport Accidents During Medication Periods Compared With Nonmedication Periods Among Swedish Adult Patients With ADHD

Characteristic	Person-years at Risk	No. of Accidents	HR (95% CI)	
			Between Individual	Within Individual
Men				
Medicated	8377	144	0.71 (0.57-0.89)	0.42 (0.23-0.75)
Nonmedicated	33 416	753	1 [Reference]	1 [Reference]
Women				
Medicated	6195	67	0.92 (0.78-1.23)	2.35 (0.83-6.64)
Nonmedicated	21 204	263	1 [Reference]	1 [Reference]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio.

Table 4. Population-Attributable Fraction of Serious Transport Accidents in Male Patients With ADHD

Characteristic	P(E), %	HR <sub>0</sub>	HR <sub>a</sub>	PAF, % <sup>a</sup>
Proportion of transport accidents attributable to being off medication among patients with ADHD	80.0 <sup>b</sup>	1.41 <sup>c</sup>	2.38 <sup>c</sup>	49
	62.8 <sup>d</sup>	1.41	2.38	41

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR<sub>0</sub>, unadjusted hazard ratio; HR<sub>a</sub>, adjusted hazard ratio; PAF, population-attributable fraction; P(E), proportion of exposed in the population.

<sup>a</sup> PAF was calculated as shown in the Results section. See also the eMethods section in the Supplement for details.

<sup>b</sup> Among male patients with ADHD, on average 80.0% were off medication

during the follow-up.

<sup>c</sup> For protective effect, reciprocals of HR<sub>0</sub> and HR<sub>a</sub> were used to calculate the PAF of not being exposed to the protective factor (ie, 1.41 = 1/0.71 and 2.38 = 1/0.42).

<sup>d</sup> Among male patients with ADHD, 62.8% 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 Male Patients With ADHD**

Cohort	Exposure	Outcome	No. of Patients	No. of Accidents	HR (95% CI)
Prescribed ADHD medication	Any ADHD medication	Any transport accidents	11 357	589	0.38 (0.20-0.72)
Excluding individuals with drug abuse or crime	Any ADHD medication	Any transport accidents	5738	261	0.26 (0.05-1.40)
Full cohort	SSRI	Any transport accidents	10 528	896	1.39 (0.62-3.14)
Stimulant only	Stimulant only	Any transport accidents	5337	433	0.31 (0.12-0.79)
Full cohort	Any ADHD medication	Motorcycle rider injury	10 528	269	0.10 (0.01-0.81)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio; SSRI, selective serotonin reuptake inhibitor.

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 criminal convictions 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 selective serotonin reuptake inhibitor 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 patients with ADHD moved from medication periods to nonmedication periods and decreased when moving from nonmedication periods to medication periods (eTable 3 in the Supplement).

## Discussion

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

We found that individuals with ADHD had a 45% to 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 America.<sup>7</sup> Studies have suggested that visual inattentiveness and impulsiveness are the largest contributions to the risk of transport accidents in patients with ADHD.<sup>6</sup> Although the stability of ADHD from childhood to adulthood is increasingly recognized,<sup>24</sup> ADHD is still commonly underdiagnosed in adults.<sup>11,29</sup> Our results provide further evidence that the adverse effects 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.<sup>30</sup> Similar to a study on criminality<sup>20</sup> and experimental and clinical studies on stimulant medication effects on driving,<sup>3,5,13,31</sup> the results presented here clearly suggest that ADHD medication was asso-

ciated with reduced rates of serious transport accidents. Compared with nonmedication periods, the transport accident rate during medication periods significantly decreased by 58% in men; a similar effect was found in young and middle-aged men. Our estimates of the PAF suggest that, under certain assumptions, 41% to 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 in Sweden<sup>26,27</sup> and that the beneficial effects of ADHD medication need to be weighed against potential adverse effects, including potential overprescription.

To our knowledge, this is the first population-based study of ADHD medication and serious transport accidents. Population-based register data have several strengths compared with 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. Diagnoses of ADHD are made by specialized psychiatrists in Sweden<sup>32</sup> and masked to outcomes. Medication for ADHD is recorded when a prescription is filled and free from recall bias. Nevertheless, observational studies are always liable to selection effects.<sup>33</sup> The biggest threat is that some patients might receive medication because they are different (usually more symptoms or with comorbid conditions). Unlike randomized clinical trials, observational studies such as 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 records) can never be fully ruled out in this research design. To address this issue, we first analyzed accident rates among patients who had discontinued selective serotonin reuptake inhibitors 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 records during follow-up, and the within-individual estimate did not change substantially. Third, we compared the differences in risk of accidents between 2 consecutive periods when patients changed their medication status, and the association re-

mained regardless of the order of change in medication status. Although these analyses are consistent with a causal hypothesis, they are only suggestive. Thus, future randomized clinical trials 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 randomized clinical trials, and our effect estimate can be compared with an intent-to-treat analysis. We used a 6-month cutoff between prescriptions to define “off medication,” which is an empirical cutoff based on previous research.<sup>18-20</sup> To explore the potential influence of exposure misclassification, we reanalyzed the data with a 3-month cutoff and found a similar result (eTable 4 in the Supplement). 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 nonstimulant 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 concerns. 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 patients with ADHD. The between-individual estimate showed a 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 and countries should be made with caution. Although the ADHD prevalence and the overall rates of traffic fatality and disability are lower in Sweden compared with other developed countries,<sup>1,24</sup> the magnitude of risk among patients with ADHD was similar to other studies.<sup>7</sup>

## Conclusions

We found that ADHD was associated with an increased risk of serious transport accidents and that ADHD medication use was associated with a reduced rate of accidents among male adult patients with ADHD. The World Health Organization predicts that traffic injuries will become the fifth leading cause of death by 2030.<sup>1</sup> 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 suggest that a large number of injuries and deaths due to traffic accidents associated with ADHD were conferred to periods when patients were off medication. Clinicians should consider informing patients about the increased risk for transport accidents associated with ADHD,<sup>34</sup> as well as possible benefits of ADHD medication. This would not only provide opportunities to reduce morbidity and mortality for patients with ADHD but also contribute to the public’s safety in transport.

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