**ADHD pharmacotherapy and mortality in individuals with attention-deficit/hyperactivity disorder: a target trial emulation study**

Lin Li1, PhD, Nanbo Zhu1,MSc, Le Zhang1, PhD, Ralf Kuja-Halkola1, PhD, Brian M. D’Onofrio1,2, PhD, Isabell Brikell1,3, PhD, Paul Lichtenstein1, PhD, Samuele Cortese4-6, MD, PhD, Henrik Larsson7, PhD, Zheng Chang1, PhD

1*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden* 2*Department of Psychological and Brain Sciences, Indiana University, Bloomington, USA 3Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway* 4*Centre for Innovation in Mental Health - School of Psychology, Faculty of Environmental and Life Sciences, and Clinical and Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK* 5*Hassenfeld Children’s Hospital at NYU Langone, New York University Child Study Center, New York City, NY, USA*

6 *Solent NHS Trust, Southampton, UK 7School of medical sciences, Örebro University, Örebro, Sweden*

\*Correspondence to:

Zheng Chang, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, Stockholm 17177, Sweden. E-mail: zheng.chang@ki.se. Phone: +46-(0)8-524 824 12

Lin Li, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, Stockholm 17177, Sweden. E-mail: lin.li@ki.se;

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**Key points**

**Question:** Is initiation of ADHD medication associated with a reduced mortality risk in individuals with ADHD?

**Findings:** In this observational target trial emulation analysis that included 148,578 individuals diagnosed with ADHD in Sweden, initiation of prescribed ADHD medication was significantly associated with lower all-cause (hazard ratio [HR], 0.79) and unnatural-cause (HR, 0.75) mortality, while the association with natural-cause mortality was not significant (HR, 0.86).

**Meaning:** Among individuals diagnosed with ADHD, ADHD medication initiation was significantly associated with lower mortality, in particular for unnatural causes.

**Abstract:**

**Importance:** Attention-deficit/hyperactivity disorder (ADHD) is associated with increased risks of adverse health outcomes including premature death, but it is unclear whether ADHD pharmacotherapy influences the mortality risk.

**Objective:** To investigate whether initiation of ADHD pharmacotherapy was associated with reduced risk of mortality in individuals with ADHD.

**Design, Setting and Participants:** In a nationwide cohort study applying the target trial emulation framework, we identified individuals aged 6-64 years with an incident diagnosis for ADHD between 2007-2018 and no ADHD medication dispensation prior to diagnosis. Individuals were followed from ADHD diagnosis until death, emigration, two years after ADHD diagnosis, or December 31st, 2020, whichever came first. Data were analyzed between January, 2023 and July, 2023.

**Exposures:** ADHD medication initiation was defined as dispensing of ADHD medication within three months of ADHD diagnosis.

**Main Outcomes and Measures:** We assessed all-cause mortality within two-year after ADHD diagnosis, as well as natural-cause (e.g., physical conditions) and unnatural-cause (e.g., unintentional injuries, suicide, and accidental poisonings) mortality. We further assessed the age- and sex-specific associations.

**Results:** Of 148,578 individuals with ADHD (61,356 [41.3%] females), 84,204 (56.7%) initiated ADHD medication. The median age at diagnosis was 17.4 (interquartile range, 11.6-29.1) years. The two-year mortality risk was lower in the initiation group (39.1/10,000) than the non-initiation group (48.1/10,000), with risk difference of -8.9/10,000 (95% CI= -17.3 to -0.6). ADHD medication initiation was associated with statistically significant lower rate of all-cause (HR=0.79, 95% CI=0.70-0.88) and unnatural-cause mortality (two-year mortality risk 25.9/10 000 vs 33.3/10,000; risk difference=-7.4/10 000, 95%CI=-14.2 to -0.5; HR=0.75, 95% CI=0.66-0.86), but not for natural-cause mortality (two-year mortality risk=13.1/10,000 vs 14.7/10,000; risk difference=-1.6/10,000; 95%CI=-6.4 to 3.2; HR=0.86, 95% CI=0.71-1.05). Results were similar in children/youths and adults. Females with ADHD had lower mortality risk for both natural (5.9/10,000) and unnatural causes (9.3/10,000) than males (8.5/10,000 for natural-cause and 20.2/10,000 for unnatural-cause), and ADHD medication initiation was only associated with lower rate of natural-cause mortality in females (HR=0.64, 95% CI=0.45-0.90; risk difference=-4.4/10,000, 95% CI=-10.8 to 1.9).

**Conclusions and Relevance:** Among individuals diagnosed with ADHD, ADHD medication initiation was significantly associated with lower mortality, particularly for death due to unnatural-causes.**Introduction**

Attention-deficit/hyperactivity disorder (ADHD) was the most prevalent neurodevelopmental condition, affecting 5.9% of youths and 2.5% of adults worldwide, according to the 2021 World Federation of ADHD International Consensus Statement.1 In the United States, the prevalence of ADHD is estimated to be 9.8% among children and adolescents2 and 4.4% among adults.3 The disorder was associated with a broad range of psychiatric and physical comorbidities, as well as adverse functional outcomes.4-7 Further, individuals with ADHD had a two-fold increased risk of premature death compared with those without the disorder, mainly due to unnatural causes.8

Pharmacological treatment, including stimulant and non-stimulant medications, is recommended for both children and adults diagnosed with ADHD, alongside non-pharmacological treatment.9 Randomized controlled trials have demonstrated that ADHD medications are effective in reducing core ADHD symptoms. Pharmaco-epidemiological studies have also shown a reduction in short-term risks of negative outcomes, such as injuries, traffic accidents, criminality and substance use disorders, which would be expected to decrease the mortality rate.10 However, there are concerns regarding the cardiovascular safety of ADHD medications, especially following long-term use, which could increase the mortality rate.11

To date, three studies have examined the association between ADHD medication use and mortality with mixed results.12-14 These studies had important limitations, including small number of deaths,12,13 indication bias (e.g. starting methylphenidate in depressed or debilitated patients in their latest phase of life),14 no consideration of time-varying exposure,12-14 and absence of a control group.13 Importantly, no study has rigorously examined the association in adults with ADHD, which is a critical knowledge gap, given the increasing number of diagnoses and prescriptions in adults.1,15 Adults with ADHD have a higher prevalence of somatic comorbidities, including cardiovascular diseases 16,17 and other physical conditions,5 compared to children and youths. Therefore, there is a need for population-based studies with long-term follow-up to investigate the risk of premature death associated with ADHD medication use across the lifespan.

Using the Swedish national registers, we investigated whether initiation of ADHD medication was associated with the mortality rate in children/youths and adults with ADHD, using the target trial emulation approach to avoid key biases in pharmaco-epidemiological studies.18

**Methods**

This study was approved by the Swedish Ethical Review Authority (reference number 2020-06540). Informed consent is not required for pseudo-anonymized register-based research according to the Swedish law.

**Study cohort**

Data were obtained by linking multiple Swedish registries using the unique personal identification number assigned to every individual registered in Sweden, including XXX (details in the eMethods). We identified all individuals aged 6-64 years and residing in Sweden with a diagnosis of ADHD (ICD-10: F90) between January 1st, 2007 and December 31st, 2018. In Sweden, individuals showing signs and symptoms of ADHD undergo a comprehensive neuropsychiatric evaluation before an official diagnosis is made in specialist care. To obtain a cohort naïve to ADHD medication before cohort entry, we only included individuals without any ADHD prescription for at least 18 months before the ADHD diagnosis (Figure 1). We followed the cohort from ADHD diagnosis (baseline) until death, emigration, two years after baseline or December 31st, 2020, whichever came first. In a sensitivity analysis, we extended the maximum follow-up to five years. In this cohort, we emulated a hypothetical target trial18 to evaluate the effect of ADHD medication initiation on the risk of all-cause and cause-specific mortality. Table 1 (details in eMethods) summarizes the protocol of the target trial.

**Measurements**

***Exposure***

We identified all six medications licensed for ADHD treatment in Sweden (Methylphenidate, Amphetamine, Dexamphetamine, Lisdexamfetamine, Atomoxetine and Guanfacine) during the study period (eTable 1). The exposure was initiation of ADHD medication, defined as dispensation of any ADHD medication within three months (90 days) of diagnosis (i.e. grace period).19

***Outcomes***

The main outcomes were all-cause and cause-specific mortality during a two-year follow-up period. Specific causes of death were categorized into natural (e.g., physical conditions; ICD-10 codes: A00-R99, U07) and unnatural causes (e.g. suicide, accidental injuries, and accidental poisoning; ICD-10 codes: S00-T98, V01-Y98) according to the underlying cause of death.20 We also examined specific unnatural causes including suicide, accidental injuries, and accidental poisoning (eTable 2). Accidental poisoning involves unintentional exposure to harmful substances, while suicide entails deliberate self-harm with the intent to end one's life. In sensitivity analysis and subgroup analysis, the five-year mortality, sex- and age-specific associations were also assessed.

**Covariates**

Baseline covariates included age at ADHD diagnosis, calendar year of baseline (2007-2018), sex (male, female), birth country (Sweden, countries other than Sweden), highest education level (primary or lower secondary, upper secondary, post-secondary or postgraduate, unknown; parents' highest education level for those younger than 25 years), diagnosis of mental disorders (i.e., anxiety disorder, autism spectrum disorder, bipolar disorder, conduct disorder, depressive disorder, eating disorder, intellectual disability, personality disorder, schizophrenia, alcohol use disorder, tobacco use disorder and drug use disorder), physical diseases (i.e. cardiovascular disease, epilepsy, type 2 diabetes, hyperlipidaemia), suicide attempt and external injures or trauma (eTable 3), dispensation of other psychotropic medications (ATC codes: antipsychotics [N05A], anxiolytics, hypnotics, and sedatives [N05B, N05C], antidepressants [N06A], antiepileptic drugs [N03A], anti-addiction drugs [N07B], and opioid [N02A]), number of outpatient visits (0, 1-4, 5-9, 10+) for psychiatric and non-psychiatric reasons, and number of hospitalizations (0, 1-2, 3-4, 5+) for psychiatric and non-psychiatric reasons. Time-varying covariates included the abovementioned diagnoses, dispensations, any outpatient visit for psychiatric and non-psychiatric reason, and any hospitalization for psychiatric and non-psychiatric reason in the previous month.

**Statistical analyses**

The two treatment strategies considered in our main analysis were “initiating ADHD medication within three months after diagnosis and remaining on the prescribed medication” versus “not initiating ADHD medication during the follow-up”. We focused on the effect of sustained treatment with ADHD medication because deviations from the initially assigned treatment strategies were common. We implemented a three-step approach comprising cloning, censoring, and inverse-probability weighting (see eMethods for details)18,21 to compare the mortality rate between the two treatment strategies. First, in the cloning step, we created a dataset with two copies of each eligible individual and assigned each of the replicates to one of the treatment strategies at the start of follow-up. Second, in the censoring step, we assessed whether replicates adhered to their assigned treatment strategy at monthly intervals. For example, participants assigned to the initiation arm were censored at the third month if they did not receive any dispensation of ADHD medication during the grace period, or were censored at the month when they discontinued ADHD medication treatment or switched to another ADHD medication after the grace period. In contrast, participants assigned to the non-initiation arm were censored at the month when they redeemed an ADHD medication dispensation. Finally, in the weighting step, each individual received time-varying inverse probability weights of remaining uncensored at each month,22 to adjust for potential selection bias induced by this artificial censoring. To estimate the weights, we fitted a pooled logistic regression model for each treatment arm separately, including an indicator for time (with cubic splines) and the abovementioned time-fixed and time-varying covariates. Model coefficients for remaining uncensored in each treatment group are shown in eTable 4.

To evaluate whether the weighting step achieved a good covariate balance between arms, we calculated the standardized mean differences (SMDs) for all confounders at the end of the grace period. We fitted an inverse probability weighted discrete-time hazard model using pooled logistic regression.23 In this model, the outcome was regressed on treatment and time, providing an approximation of the hazard ratio (HR). To estimate the mortality risk at each month, we conducted an outcome regression with treatment, time, and treatment-time interaction as independent variables. We used a nonparametric bootstrap with 500 samples to compute the 95% confidence intervals (CIs). To estimate cause-specific hazard ratios we treated the competing event as a censoring event, rather than fitting competing risks models (see eMethods).

We further performed stratified analyses by age (children and youths [6-24 years], adults [≥25 years]) and by sex. Additionally, we extended the follow-up period from two years to five years to examine longer-term associations.

To test the robustness of our findings, we introduced four sensitivity analyses. First, we used a two-week interval to more precisely model the time-varying censoring weights. Second, we compared two less restricted treatment strategies, “initiating ADHD medication within three months after diagnosis” versus “not initiating ADHD medication during the grace period”, irrespective of switches between treatment strategies after the grace period. Third, we emulated a head-to-head trial comparing the effectiveness of stimulants with non-stimulants on all-cause mortality. Finally, we conducted a case-crossover analysis24 to address unmeasured confounding using a different design based on other assumptions than the main analysis. All individuals who died during the follow-up were included in this analysis, and the exposure status at the time of the death (case period) was compared with the exposure status at other times before death (control periods) within individual, with adjustment for time-varying covariates (see eMethods). This method controls for all time-invariant confounders within individual (even unmeasured, e.g. genetic factors) by design since each case serves as its own control.

Our study was reported in line with the REporting of studies Conducted using Observational Routinely collected health Data - pharmacoepidemiological research (RECORD-PE) guidelines.25 Data management was performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). Statistical analyses were conducted with R, version 4.0.5 (R Foundation for Statistical Computing). A two-sided P value <0.05 was considered statistically significant.

**Results**

We identified 148,578 eligible individuals with incident ADHD diagnosis (61,356 [41.3%] females; 87,222 [58.7%] males) (Figure 1). The median age at baseline was 17.4 (interquartile range, 11.6-29.1) years (Table 2). A total of 632 individuals died during the two-year follow-up and 1,402 died during the five-year follow-up. The primary causes of death are listed in eTable 2, with more than half deaths due to unnatural causes (66.7%).

Within three months following ADHD diagnosis, 84,204 (56.7%) individuals initiated, and 64,296 (43.3%) did not initiate ADHD medication treatment. The remaining 78 individuals who died or emigrated during the grace period contributed to both treatment arms to avoid immortal-time bias. The characteristics in each treatment arm at the end of the grace period before and after weighting are shown in Table 2. The inverse probability weighting showed a balance of the covariates (SMD <0.1),26 except for any outpatient visit for psychiatric reason (SMD=0.28), which was further adjusted in the outcome regression models.

The crude two-year mortality rate was lower among those who initiated ADHD medication (17.3/10,000) compared to those who did not initiate medication (31.8/10,000). The weighted cumulative incidence curve of all-cause mortality was shown in eFigure 1. During the two-year follow-up period, we found ADHD medication initiation was associated with statistically significant lower rate of all-cause (weighted two-year mortality risk=39.1/10,000 vs 48.1/10,000; risk difference=-8.9/10,000, 95%CI=-17.3 to -0.6; HR=0.79, 95% CI=0.70-0.88) and unnatural-cause mortality (two-year mortality risk 25.9/10,000 vs 33.3/10,000; risk difference=-7.4/10,000, 95%CI=-14.2 to -0.5; HR=0.75, 95% CI=0.66-0.86), but not for natural-cause mortality (two-year mortality risk=13.1/10,000 vs 14.7/10,000; risk difference=-1.6/10 000, 95%CI=-6.4 to 3.2; HR=0.86, 95% CI=0.71-1.05) (Figure 2). In our analyses of specific unnatural causes of death, we observed a significant lower risk, following ADHD medication initiation, in death due to accidental poisoning (two-year mortality risk=6.0/10,000 vs 12.1/10,000; risk difference=-6.0/10,000, 95%CI=-9.8 to -2.3; HR=0.47; 95% CI=0.36-0.60).

In subgroup analyses (Figure 3), we found ADHD medication initiation was significantly associated with lower rate of all-cause and unnatural-cause mortality in children/youths (6-24 years old), adults (25 years and above), and in males. Females with ADHD had lower mortality risk for both natural (5.9/10 000) and unnatural causes (9.3/10 000) than males (8.5/10 000 for natural-cause, and 20.2/10 000 for unnatural-cause), and ADHD medication initiation was only associated with lower rate of natural-cause mortality in females (two-year mortality risk 8.5/10,000 vs 12.9/10,000; risk difference=-4.4/10 000, 95%CI=-10.8 to 1.9; HR=0.64, 95%CI=0.45-0.90). When extending the follow-up to five years, the associations attenuated for all outcomes but remained statistically significant for unnatural-cause mortality (five-year mortality risk=66.5.0/10,000 vs 70.5/10,000; risk difference=-4.0/10,000, 95%CI=-17.2 to 9.2; HR=0.89; 95% CI=0.81-0.97) (eTable 5).

In sensitivity analysis, we found similar results when using two weeks as time interval (eTable 6) and ignoring switches between treatment strategies after the grace period (eTable 7). Although most ADHD medication initiators (91.9%) started with stimulants, initiation of stimulants versus non-stimulants showed no significant difference in terms of all-cause mortality rate (eTable 8). In the case-crossover analysis, ADHD medication use was associated with significantly lower risk of all-cause mortality (OR=0.70, 95% CI=0.57-0.88) and unnatural-cause mortality (OR=0.66, 95% CI=0.51-0.85), but not with the risk of natural-cause mortality (OR=0.81, 95%CI=0.53-1.24) (eTable 9).

**Discussion**

In this population-based study of 148,578 individuals with ADHD, we found that initiation of ADHD medication, compared to non-initiation, was significantly associated with lower mortality at two years after diagnosis, especially for unnatural-cause mortality. To our knowledge, this study is the first emulated trial using real-world data in ADHD research. Additional strengths are the long follow-up time, validated measures on exposure and outcome in a nationwide sample, and a broad age range that enabled us to explore the association in both children and adults.

ADHD medication may reduce the risk of unnatural-cause mortality by alleviating the core symptoms of ADHD (in particular impulsivity and inattention) and its psychiatric comorbidities, leading to improved impulse control and decision-making, ultimately reducing the occurrence of fatal events, in particular those due to accidental poisoning. Previous studies have reported improvements in comorbid psychiatric symptoms when ADHD is effectively treated.27 For instance, early and optimal treatment of ADHD may alter the trajectory of psychiatric morbidity by preventing the onset of comorbidities such as mood, anxiety, or substance use disorders.28,29 There is also evidence showing protective effects of ADHD medications on risk of accidents, substance abuse, and criminality,10 which in turn could lead to lower rates of unnatural deaths. We did not observe any statistically significant association between the use of ADHD medication and death by suicide, although the magnitude of the association (HR=0.88, 95%CI=0.74-1.04) is in line with some previous pharmacoepidemiology studies examining the relationship between ADHD medication and suicide-related outcomes.10 Previous research suggests that stimulant medication may reduce the risk of suicidal behavior in individuals with ADHD via both the direct improvement of ADHD symptoms and indirect reduction of risks associated with conditions like depression or substance use disorder.30,31 However, to what extent these findings extend to death by suicide requires further studies with larger sample size.

In contrast to the extensive literature on psychiatric and behavioral outcomes associated with ADHD medication, the impact of ADHD medication on physical comorbidities is less well understood. There is evidence that stimulants contribute to lower rates of smoking in adults, which could improve overall health.32 Additionally, methylphenidate is associated with improvement in lifestyle, self-regulation and enhancement of executive function,33 which could contribute to the reduction of natural mortality risks associated with ADHD. However, there are also concerns regarding the cardiovascular safety of stimulants.11 Our results were reassuring that ADHD medication was not associated with increased risk of natural-cause mortality, and if anything, a reduced risk of natural-cause mortality in females. Nevertheless, future studies with larger sample sizes are warranted to confirm the relationship between ADHD medication use and natural-cause morbidity and mortality.

When considering sex-stratified associations, the initiation of ADHD medication was associated with a lower risk of all-cause and unnatural-cause mortality in males. In females, the only observed statistically significant association was between initiation of ADHD medication and natural-cause mortality. Notably, females had a higher median age at baseline in our study, suggesting delayed ADHD diagnosis compared to males, and previous studies have also reported distinct patterns of psychiatric and physical comorbidities (e.g., females with ADHD have higher rates of depression, sleep disorder, atrial fibrillation, and asthma than males).5,34 Nevertheless, it is important to consider the difference in sample size and lower mortality rates in females when interpreting the results. Collectively, these findings underscore the need for further exploration of any sex-difference in the relationship between ADHD treatment and mortality to inform targeted interventions aimed at optimizing outcomes for both males and females with ADHD.

It is important to note that this study focused on children to middle-age adults (6-64 years at baseline), and during the follow-up period, the absolute incidence of all-cause and cause-specific mortality was relatively small in magnitude. Consequently, the interpretation of these findings should be made with caution, considering the limited number of events observed within our study population. Nevertheless, ADHD is associated with a two-fold increased risk of premature death,8 which is as high as the risk for type 2 diabetes.35 As premature mortality is a major public health issue, the appropriate use of ADHD medications may contribute to decrease this burden.

***Limitations***

Several limitations should be considered. First, due to the observational nature, our results cannot conclusively establish causal effects of ADHD medication treatment on mortality risk as unmeasured confounders, such as lifestyle factors, could contribute to the associations. It is also crucial to recognize that the treatment for ADHD involves more than just taking medication; it often includes various aspects of care, including social engagement and support. These non-medication components may also affect the treatment outcomes. Therefore, the observed lower mortality may not be entirely accounted for by the medication per se. Second, given the potential for type 1 error resulting from multiple comparisons regarding cause-specific mortality and subgroup analyses, findings from these analyses should be interpreted as exploratory in nature, rather than as definitive conclusions. Third, we cannot rule out exposure misclassification, as some individuals may not have consistently adhered to their prescribed medication, leading to potential underestimation of the true effects. Fourth, we cannot rule out misclassification of death due to suicide and accidental poisoning as sometimes the intent may not be definitely determined.

# **Conclusions**

In this target trial emulation study using national register data, we found that, among individuals diagnosed with ADHD, ADHD medication initiation was associated with significantly lower mortality, in particular for death due to unnatural causes.

**Disclosures:**

SC declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD. HL reports receiving grants from Shire Pharmaceuticals; personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire/Takeda Pharmaceuticals and Evolan Pharma AB, all outside the submitted work.

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**Role of the funder**

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Access to data and data analysis**

Dr. Li had full access to all the data in the study. Dr. Li takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Data sharing statement**

The data supporting the findings of this study are available from Statistics Sweden and The Swedish National Board of Health and Welfare; however, due to ethical permissions and restrictions, these data are not publicly available.

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# **TABLES AND FIGURES**

**Figure 1.** Flowchart of the cohort selection.

**Figure 2.** Association between ADHD medication initiation and two-year mortality among individuals with ADHD

*IR, Incidence rate, per 10,000 person-years; 2-year absolute risk and 2-year risk difference: per 10,000 individuals. Natural cause mortality included death from somatic diseases and medical conditions (ICD-10 codes: A00-R99, U07) and unnatural cause mortality included suicide, accidental injuries, and accidental poisoning; ICD-10 codes: S00-T98, V01-Y98)*

**Figure 3.** Association between ADHD medication initiation and two-year mortality among individuals with ADHD stratified by age and sex.

*IR, Incidence rate, per 10,000 person-years; 2-year absolute risk and 2-year risk difference: per 10,000 individuals. Natural cause mortality included death from somatic diseases and medical conditions (ICD-10 codes: A00-R99, U07) and unnatural cause mortality included suicide, accidental injuries, and accidental poisoning; ICD-10 codes: S00-T98, V01-Y98)*

**Table 1.** Protocol and emulation of a target trial evaluating the effects of initiating versus not initiating ADHD medication on mortality in individuals with ADHD

|  |  |  |
| --- | --- | --- |
| Protocol component | Target trial | Emulation using observational data |
| Eligibility criteria | * Individuals (6-64 years) with new clinical diagnosis of ADHD between January 2007 and December 2018
* No prior dispensation of ADHD medication
 | Same as target trial |
| Treatment strategies | 1. Initiate ADHD medication within 3 months after diagnosis and remain on the prescribed medication
2. Not initiate ADHD medication during the follow-up
 | Same as target trial |
| Assignment procedures | Eligible individuals are randomly assigned to either strategy at baseline and are aware of the assigned strategy. | Randomization is assumedconditional on baseline covariates |
| Follow-up period | Follow-up starts at treatment assignment and ends at death, loss to follow-up (emigration), or administrative end of follow-up (December 31, 2020 or two years after baseline), whichever occurs first. | Same as target trial |
| Outcomes  | All-cause and cause-specific mortality within two years after baseline | Same as target trial |
| Causal contrasts of interest | Effect of adhering to the treatment strategies (as defined in the protocol) during follow-up  | Same as target trial |
| Analysis plan | Effect estimates are calculated from an inverse probability weighted pooled logistic regression model, with censoring at deviation from the protocol and adjustment for baseline and post-baseline covariates. | The analyses are conducted in an expanded dataset that included clones of each eligible individual. |

Table 2 Characteristics of the study cohort at baseline and at the end of 3-month grace period (before and after weighting)

| **Characteristics** | **Total cohorta** | **Before Weightingb** | **After Weightingb** |
| --- | --- | --- | --- |
| Initiation | Non-initiation | SMD | Initiation | Non-initiation | SMD |
| N | 148,578 | 84,161 | 64,296 |  | 148,221.8 | 158,223.7 |  |
| **Age at baseline (median, IQR)** | 17.4 [11.6, 29.1] | 16.4 [11.5, 27.8] | 19.1 [11.9, 30.6] | 0.14 | 16.6 [11.6, 28.2] | 17.8 [11.3, 28.5] | 0.02 |
| **Sex** |  |  |  | 0.01 |  |  | 0.01 |
|  Male | 87222 (58.7) | 49565 (58.9) | 37575 (58.4) |  | 86253.8 (58.2) | 93037.0 (58.8 |  |
|  Female | 61356 (41.3) | 34596 (41.1) | 26721 (41.6) |  | 61968.0 (41.8) | 65186.7 (41.2) |  |
| **Year of diagnosis** |  |  |  | 0.14 |  |  | 0.05 |
|  2007 | 4771 (3.2) | 2119 (2.5) | 2645 (4.1) |  | 4143.1 (2.8) | 5216.7 (3.3) |  |
|  2008 | 6500 (4.4) | 3080 (3.7) | 3414 (5.3) |  | 5797.7 (3.9) | 7064.6 (4.5) |  |
|  2009 | 7961 (5.4) | 4212 (5.0) | 3745 (5.8) |  | 7433.3 (5.0) | 8547.4 (5.4) |  |
|  2010 | 9842 (6.6) | 5516 (6.6) | 4315 (6.7) |  | 9511.2 (6.4) | 10611.3 (6.7) |  |
|  2011 | 11552 (7.8) | 6765 (8.0) | 4773 (7.4) |  | 11363.8 (7.7) | 12125.3 (7.7) |  |
|  2012 | 12709 (8.6) | 7279 (8.6) | 5415 (8.4) |  | 12502.5 (8.4) | 13510.3 (8.5) |  |
|  2013 | 13272 (8.9) | 7624 (9.1) | 5640 (8.8) |  | 13275.7 (9.0) | 14053.7 (8.9) |  |
|  2014 | 14463 (9.7) | 8382 (10.0) | 6066 (9.4) |  | 14764.2 (10.0) | 15184.6 (9.6) |  |
|  2015 | 15707 (10.6) | 9193 (10.9) | 6505 (10.1) |  | 16156.5 (10.9) | 16493.4 (10.4) |  |
|  2016 | 16508 (11.1) | 9337 (11.1) | 7159 (11.1) |  | 16827.3 (11.4) | 17785.3 (11.2) |  |
|  2017 | 17223 (11.6) | 9926 (11.8) | 7290 (11.3) |  | 17705.5 (11.9) | 18290.1 (11.6) |  |
|  2018 | 18070 (12.2) | 10728 (12.7) | 7329 (11.4) |  | 18741.0 (12.6) | 19340.9 (12.2) |  |
| **Birth country** |  |  |  | 0.05 |  |  | <0.01 |
|  Sweden | 136951(92.2) | 78101(92.8) | 58752(91.4) |  | 137051.8(92.5) | 146119.8(92.4) |  |
|  Otherc | 11627 (7.8) | 6060 (7.2) | 5544 (8.6) |  | 11170.0 (7.5) | 12103.9 (7.6) |  |
| **Education level at baselined** |  |  |  | 0.11 |  |  | 0.02 |
|  Primary or lower secondary  | 24783 (16.7) | 12753 (15.2) | 12010 (18.7) |  | 23697.5 (16.0) | 26401.1 (16.7) |  |
|  Upper secondary  | 75253 (50.6) | 42936 (51.0) | 32262 (50.2) |  | 75071.6 (50.6) | 79839.7 (50.5) |  |
|  Post-secondary or postgraduate | 47341 (31.9) | 27920 (33.2) | 19395 (30.2) |  | 48399.9 (32.7) | 50784.9 (32.1) |  |
|  Unknown | 1201 (0.8) | 552 (0.7) | 629 (1.0) |  | 1052.8 (0.7) | 1198.0 (0.8) |  |
| **Comorbidities at baseline** |  |  |  |  |
| Accidental injures | 85994 (57.9) | 48966 (58.2) | 36943 (57.5) | 0.01 | 86189.0 (58.1) | 91416.2 (57.8) | 0.01 |
| Depressive disorder | 28353 (19.1) | 15092 (17.9) | 13220 (20.6) | 0.07 | 27507.9 (18.6) | 30045.7 (19.0) | 0.01 |
| Other drug use disorder | 12906 (8.7) | 6207 (7.4) | 6651 (10.3) | 0.1 | 11907.2 (8.0) | 13602.0 (8.6) | 0.02 |
| Suicide attempt history | 12453 (8.4) | 6332 (7.5) | 6083 (9.5) | 0.07 | 11723.8 (7.9) | 13171.2 (8.3) | 0.02 |
| Alcohol use disorder | 12347 (8.3) | 6138 (7.3) | 6170 (9.6) | 0.08 | 11476.9 (7.7) | 12921.8 (8.2) | 0.02 |
| Anxiety disorders | 11940 (8.0) | 6028 (7.2) | 5896 (9.2) | 0.07 | 11300.2 (7.6) | 12473.3 (7.9) | 0.01 |
| Personality disorders | 7231 (4.9) | 3394 (4.0) | 3823 (5.9) | 0.09 | 6580.2 (4.4) | 7569.4 (4.8) | 0.02 |
| Bipolar disorder | 5137 (3.5) | 2546 (3.0) | 2582 (4.0) | 0.05 | 4710.8 (3.2) | 5372.9 (3.4) | 0.01 |
| Cardiovascular disease | 5000 (3.4) | 2232 (2.7) | 2752 (4.3) | 0.09 | 4317.9 (2.9) | 5284.2 (3.3) | 0.02 |
| Autism spectrum disorder | 4765 (3.2) | 2279 (2.7) | 2484 (3.9) | 0.06 | 4314.4 (2.9) | 4720.2 (3.0) | <0.01 |
| Epilepsy | 3119 (2.1) | 1321 (1.6) | 1793 (2.8) | 0.08 | 2682.2 (1.8) | 3291.7 (2.1) | 0.02 |
| Eating disorder | 3053 (2.1) | 1622 (1.9) | 1430 (2.2) | 0.02 | 3009.1 (2.0) | 3172.2 (2.0) | <0.01 |
| Schizophrenia | 2401 (1.6) | 966 (1.1) | 1423 (2.2) | 0.08 | 1992.8 (1.3) | 2433.2 (1.5) | 0.02 |
| Conduct disorder | 2271 (1.5) | 1378 (1.6) | 892 (1.4) | 0.02 | 2358.0 (1.6) | 2377.0 (1.5) | 0.01 |
| Intellectual disability | 2268 (1.5) | 963 (1.1) | 1303 (2.0) | 0.07 | 1894.4 (1.3) | 2258.0 (1.4) | 0.01 |
| Type 2 diabetes | 1092 (0.7) | 453 (0.5) | 634 (1.0) | 0.05 | 874.9 (0.6) | 1165.6 (0.7) | 0.02 |
| Dyslipidemia | 570 (0.4) | 253 (0.3) | 315 (0.5) | 0.03 | 492.3 (0.3) | 619.6 (0.4) | 0.01 |
| Tobacco use disorder | 562 (0.4) | 243 (0.3) | 316 (0.5) | 0.03 | 479.1 (0.3) | 574.8 (0.4) | 0.01 |
| **Psychotropic medication use at baseline** |  |  |  |  |  |  |
| Antidepressants | 51568 (34.7) | 27689 (32.9) | 23810 (37.0) | 0.09 | 49970.7 (33.7) | 54534.2 (34.5) | 0.02 |
| Anxiolytics, hypnotics, and sedatives | 42503 (28.6) | 23152 (27.5) | 19291 (30.0) | 0.06 | 41487.2 (28.0) | 44986.8 (28.4) | 0.01 |
| Opioids e | 30541 (20.6) | 16909 (20.1) | 13583 (21.1) | 0.03 | 29664.1 (20.0) | 32284.7 (20.4) | 0.01 |
| Antipsychotics | 14915 (10.0) | 7454 (8.9) | 7420 (11.5) | 0.09 | 13840.8 (9.3) | 15529.5 (9.8) | 0.02 |
| Antiepileptic drugs | 10786 (7.3) | 5203 (6.2) | 5562 (8.7) | 0.09 | 9854.6 (6.6) | 11376.7 (7.2) | 0.02 |
| Anti-addiction drugs f | 7612 (5.1) | 3901 (4.6) | 3682 (5.7) | 0.05 | 7027.0 (4.7) | 8036.1 (5.1) | 0.02 |
| Number of prior outpatient visit for psychiatry (%) |  |  |  | 0.14 |  |  | 0.03 |
|  0 | 65697 (44.2) | 36280 (43.1) | 29384 (45.7) |  | 65253.9 (44.0) | 71316.0 (45.1) |  |
|  1-4 | 47624 (32.1) | 29139 (34.6) | 18448 (28.7) |  | 48998.7 (33.1) | 50201.7 (31.7) |  |
|  5-9 | 18185 (12.2) | 9937 (11.8) | 8231 (12.8) |  | 17739.5 (12.0) | 18949.4 (12.0) |  |
|  10+ | 17072 (11.5) | 8805 (10.5) | 8233 (12.8) |  | 16229.7 (10.9) | 17756.7 (11.2) |  |
| Number of prior hospitalizations for psychiatry (%) |  |  |  | 0.18 |  |  | 0.03 |
|  0 | 122280 (82.3) | 71764 (85.3) | 50471 (78.5) |  | 124265.3 (83.8) | 131025.9 (82.8) |  |
|  1-2 | 17072 (11.5) | 8294 (9.9) | 8742 (13.6) |  | 15846.7 (10.7) | 17676.5 (11.2) |  |
|  3-4 | 3946 (2.7) | 1815 (2.2) | 2112 (3.3) |  | 3516.3 (2.4) | 4101.9 (2.6) |  |
|  5+ | 5280 (3.6) | 2288 (2.7) | 2971 (4.6) |  | 4593.5 (3.1) | 5419.4 (3.4) |  |
| Number of prior outpatient visits for non-psychiatric reason |  |  |  | 0.05 |  |  | 0.01 |
|  0 | 25214 (17.0) | 14108 (16.8) | 11079 (17.2) |  | 24824.9 (16.7) | 26758.0 (16.9) |  |
|  1-4 | 65021 (43.8) | 37493 (44.5) | 27485 (42.7) |  | 65506.0 (44.2) | 69221.2 (43.7) |  |
|  5-9  | 31921 (21.5) | 18242 (21.7) | 13656 (21.2) |  | 31997.4 (21.6) | 34082.2 (21.5) |  |
|  10+ | 26422 (17.8) | 14318 (17.0) | 12076 (18.8) |  | 25893.5 (17.5) | 28162.3 (17.8) |  |
| Number of prior hospitalizations for non-psychiatric reason |  |  |  | 0.13 |  |  | 0.03 |
|  0 | 78959 (53.1) | 46359 (55.1) | 32563 (50.6) |  | 80454.5 (54.3) | 84263.3 (53.3) |  |
|  1-2 | 48693 (32.8) | 27438 (32.6) | 21213 (33.0) |  | 48472.2 (32.7) | 51725.0 (32.7) |  |
|  3-4 | 11737 (7.9) | 6136 (7.3) | 5583 (8.7) |  | 11182.5 (7.5) | 12496.3 (7.9) |  |
|  5+ | 9189 (6.2) | 4228 (5.0) | 4937 (7.7) |  | 8112.6 (5.5) | 9739.1 (6.2) |  |
| **Time varying covariates during the previous month** |  |  |  |  |  |  |
| Depressive disorder | 2475 (1.7) | 1908 (2.3) | 1547 (2.4) | 0.01 | 3506.1 (2.4) | 3483.8 (2.2) | 0.01 |
| Accidental injures | 2412 (1.6) | 1099 (1.3) | 929 (1.4) | 0.01 | 2014.0 (1.4) | 2115.8 (1.3) | <0.01 |
| Other drug use disorder | 1295 (0.9) | 745 (0.9) | 811 (1.3) | 0.04 | 1471.0 (1.0) | 1601.5 (1.0) | <0.01 |
| Anxiety disorders | 797 (0.5) | 910 (1.1) | 756 (1.2) | 0.01 | 1690.9 (1.1) | 1592.7 (1.0) | 0.01 |
| Autism spectrum disorder | 765 (0.5) | 2060 (2.4) | 1396 (2.2) | 0.02 | 3543.3 (2.4) | 2955.2 (1.9) | 0.04 |
| Alcohol use disorder | 730 (0.5) | 419 (0.5) | 417 (0.6) | 0.02 | 793.0 (0.5) | 813.6 (0.5) | <0.01 |
| Bipolar disorder | 708 (0.5) | 654 (0.8) | 692 (1.1) | 0.03 | 1279.2 (0.9) | 1413.2 (0.9) | <0.01 |
| Personality disorders | 617 (0.4) | 591 (0.7) | 541 (0.8) | 0.02 | 1133.2 (0.8) | 1089.1 (0.7) | 0.01 |
| Suicide attempt history | 570 (0.4) | 152 (0.2) | 160 (0.2) | 0.01 | 302.4 (0.2) | 306.1 (0.2) | <0.01 |
| Cardiovascular disease | 254 (0.2) | 105 (0.1) | 212 (0.3) | 0.04 | 210.1 (0.1) | 377.1 (0.2) | 0.02 |
| Eating disorder | 254 (0.2) | 170 (0.2) | 191 (0.3) | 0.02 | 315.2 (0.2) | 412.5 (0.3) | 0.01 |
| Conduct disorder | 248 (0.2) | 420 (0.5) | 167 (0.3) | 0.04 | 651.9 (0.4) | 417.6 (0.3) | 0.03 |
| Epilepsy | 234 (0.2) | 92 (0.1) | 182 (0.3) | 0.04 | 192.9 (0.1) | 321.4 (0.2) | 0.02 |
| Schizophrenia | 215 (0.1) | 93 (0.1) | 160 (0.2) | 0.03 | 197.7 (0.1) | 281.7 (0.2) | 0.01 |
| Intellectual disability | 188 (0.1) | 273 (0.3) | 218 (0.3) | <0.01 | 500.9 (0.3) | 404.8 (0.3) | 0.02 |
| Type 2 diabetes | 64 (0.0) | 18 (0.0) | 46 (0.1) | 0.02 | 40.2 (0.0) | 80.1 (0.1) | 0.01 |
| Tobacco use disorder | 16 (0.0) | 9 (0.0) | 17 (0.0) | 0.01 | 19.3 (0.0) | 36.9 (0.0) | 0.01 |
| Dyslipidemia | 14 (0.0) | 13 (0.0) | 14 (0.0) | <0.01 | 26.0 (0.0) | 32.8 (0.0) | <0.01 |
| Antidepressants | 6103 (4.1) | 4239 (5.0) | 3776 (5.9) | 0.04 | 7753.8 (5.2) | 8518.7 (5.4) | 0.01 |
| Anxiolytics, hypnotics, and sedatives | 3033 (2.0) | 2077 (2.5) | 1443 (2.2) | 0.01 | 3614.5 (2.4) | 3230.8 (2.0) | 0.03 |
| Opioids | 2441 (1.6) | 1182 (1.4) | 1119 (1.7) | 0.03 | 2150.1 (1.5) | 2489.0 (1.6) | 0.01 |
| Antipsychotics | 1829 (1.2) | 1309 (1.6) | 1280 (2.0) | 0.03 | 2478.1 (1.7) | 2612.9 (1.7) | <0.01 |
| Antiepileptic drugs | 1134 (0.8) | 689 (0.8) | 936 (1.5) | 0.06 | 1377.1 (0.9) | 1928.6 (1.2) | 0.03 |
| Anti-addiction drugs | 418 (0.3) | 265 (0.3) | 213 (0.3) | <0.01 | 493.2 (0.3) | 439.5 (0.3) | 0.01 |
| Any outpatient visit for psychiatry (%) | 145666 (98.0) | 23607 (28.0) | 9961 (15.5) | 0.31 | 38536.7 (26.0) | 23667.8 (15.0) | 0.28 |
| Any hospitalizations for psychiatry (%) | 5258 (3.5) | 665 (0.8) | 769 (1.2) | 0.04 | 1331.2 (0.9) | 1430.8 (0.9) | <0.01 |
| Any outpatient visit for non-psychiatric reason | 12428 (8.4) | 4236 (5.0) | 3574 (5.6) | 0.02 | 7702.1 (5.2) | 8040.5 (5.1) | 0.01 |
| Any hospitalizations for non-psychiatric reason | 2472 (1.7) | 479 (0.6) | 547 (0.9) | 0.03 | 930.0 (0.6) | 1090.5 (0.7) | 0.01 |

**a** Asseseed at baseline

**b** Asseseed at the end of the grace period when each individual’s treatment strategy was completely determined.

**c** Including all countiesother than Sweden, the information was extracted from Statistics Sweden.

**d** For those younger than 25 years, education level was replaced by parents’ highest education level.

e Refer to prescribed opioids in the Prescription Drug Register

f Including drugs used in nicotine dependence, drugs used in alcohol dependence, and drugs used in opioid dependence