Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Data sources

Data were obtained by linking multiple Swedish registries using the unique personal identification number assigned to every individual registered in Sweden. The Total Population Register[1] includes all individuals in Sweden born since 1932, who were alive in 1963 and later. It also contains information on all migrations in or out of Sweden since 1969. The National Patient Register[2] includes data on inpatient care since 1973 and outpatient care since 2001, with diagnosis of diseases recorded by the Swedish version of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) since 1997. The Prescribed Drug Register[3] includes detailed information on all dispensed drugs in Sweden, coded according to the Anatomical Therapeutic Chemical (ATC) classification, since July 1st 2005. The Cause of Death Register[4] contains information on all registered deaths since 1961, including underlying and contributing causes of death. The Longitudinal Integration Database for Health Insurance and Labor Studies[5] covers the entire Swedish population aged 16 or older since 1990. The Multi-Generation Register[6] provides family information for all residents in Sweden since 1932.

Specifying the protocol of the target trial

Eligibility Criteria

We included all individuals aged 6-64 years residing in Sweden who were newly diagnosed with ADHD (ICD-10 code: F90) between January 1st, 2007 and December 31st, 2018. To identify new users of ADHD medication, we required a washout period without any prior dispensation of ADHD medication for at least 18 months before the index ADHD diagnosis.

Treatment Strategies

In our hypothetical target trial, we compared two treatment strategies: initiation of ADHD medication remained on the prescribed drug versus no initiation of ADHD medication. The treatment strategies needed to be implemented within a prespecified period (i.e., the grace period) after baseline.

Follow-up period

The start of follow-up (i.e., baseline or time zero) for each individual was the date of the index ADHD diagnosis. The end of follow-up was death, emigration, 24 months after follow-up, or December 31st, 2020, whichever came first. In a sensitivity analysis, we extended the maximum follow-up to 60 months.

Outcomes

The main outcomes were all-cause and cause-specific mortality. Specific causes of death were categorized into either natural or unnatural cause according to the underlying cause of death. Among the unnatural causes, we further examined three primary categories, including suicide, accidental injuries, and accidental poisoning. When examining cause-specific mortality, death due to the other causes was a competing event which was treated as censoring time points.

Causal Contrasts

The causal contrast of interest was the effect of sustained treatment with ADHD medication (as defined in the protocol), that is, the effect that would have been observed if all individuals had adhered to the treatment strategies during the entire follow-up. In a sensitivity analysis, we also estimated the effect of initiation of ADHD medication within the grace period, irrespective of treatment non-adherence after the grace period, which only required adherence to the treatment strategies during the grace period.

The cloning, censoring, and weighting approach

Here we describe in detail our implementation of the cloning, censoring, and weighting approach[7] to compare the strategies “initiating ADHD medication within three months after diagnosis and remaining on treatment” versus “not initiating ADHD medication during the follow-up” in patients with ADHD.

1. Cloning step

The first step consists of cloning each eligible individual into two identical copies, each of whom is assigned to one treatment strategy at baseline. The expanded dataset is twice as large compared with the original dataset. Since each individual occurs in both strategies, no baseline confounding is present. This step ensures the alignment of eligibility, start of follow-up, and treatment assignment, thereby preventing immortal time bias.

2. Censoring step

Then copies are artificially censored if and when they deviate from their assigned treatment strategy, which ensures that the copies follow their assigned strategy. Initiation of ADHD medication on the same day as the ADHD diagnosis was labeled as "initiating treatment on day 1". At monthly (30-day) intervals, we assessed whether copies adhered to their assigned treatment strategy. Copies assigned to the initiation arm would be censored at the third month if they did not have any dispensation of ADHD medication before/on day 90, or would be censored at the month when they discontinued ADHD medication treatment or switched to another ADHD medication after the grace period. Copies assigned to the non-initiation arm would be censored at the corresponding month when they had a dispensation of ADHD medication during the follow-up. Each individual’s treatment strategy was completely determined at the end of the grace period, so at most only one copy from each individual still contributes person-time to the analysis by the end of the grace period.

3. Weighting step

The artificial censoring is likely to be informative and therefore introduces selection bias, which needs to be adjusted for using inverse probability weighting. Informally, uncensored copies receive a weight equal to the inverse of the probability of remaining uncensored, conditional on their history of treatment and covariates. Intuitively, copies who are censored transfer their weights in the analysis to those who remain uncensored. This creates a hypothetical population in which censoring is independent of measured covariates.

To estimate the inverse probability weights, we fitted a pooled logistic regression model for each treatment arm separately,[7,8] allowing for potential interactions between covariates and treatment. The probability of remaining uncensored was modelled as a function of independent variables including a time indicator (natural cubic splines) and potential time-fixed and time-varying confounders. Time-fixed confounders included age (continuous), calendar year (2007-2018; each year as a category), sex (male, female), birth country (Sweden, countries other than Sweden), highest education level (primary or lower secondary, upper secondary, post-secondary or postgraduate, unknown; using parents' highest education level for those younger than 25 years), number of outpatient visits (0, 1-4, 5-9, 10+) for psychiatric and non-psychiatric reasons, number of hospitalizations (0, 1-2, 3-4, 5+) for psychiatric and non-psychiatric reasons, diagnosis of psychiatric disorders (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 (cardiovascular disease, epilepsy, type 2 diabetes, and hyperlipidaemia), suicide attempt, external injures or trauma, and dispensation of other psychotropic medications (antipsychotics, anxiolytics, hypnotics, and sedatives, antidepressants, antiepileptic drugs, anti-addiction drugs, and opioid). Time-varying confounders included the abovementioned diagnoses, dispensations, any outpatient visit for psychiatric and non-psychiatric reasons, and any hospitalization for psychiatric and non-psychiatric reasons in the previous month. The regression coefficients from these models are shown in eTable 4.

Next, we used the probabilities estimated by these models to construct the inverse probability of censoring weights. Weights were set to 1 during the first two months for copies in the initiation arm, as their probability of being uncensored is, by definition, 1. For each study participant, the weight at month *m* was calculated by 1 divided by the product of the predicted monthly probabilities of remaining uncensored until month $t \leqslant m$ given uncensored at month *t*. We truncated the weights at the 99.5th percentile to avoid undue influence of extreme weights. To evaluate whether the weighting step achieved a good covariate balance between arms, we calculated the standardized mean difference (SMD) for all covariates at the end of the grace period (3 months post-baseline). A variable with an SMD <0.1 is usually considered balanced. The weights showed good ability to remove imbalance at the end of the grace period, except for any outpatient visit for psychiatry in the previous month (see Table 2 in the main text).

4. Primary analysis

We fitted an inverse probability weighted discrete-time hazard model using pooled logistic regression. In this model, the outcome of interest was regressed on the treatment arm and time. Because the outcome of the models is rare at all times, the odds ratio from this model approximates the hazard ratio.[8,9] To estimate the cumulative incidence of mortality, we used the regression-then-marginalization approach.[10] First, we fitted a weighted outcome regression using a pooled logistic regression model, with treatment arm, time, and treatment-time interactions as independent variables. Second, we estimated the standardized (marginal) survival at month *m* for the initiation group (and also for non-initiation group), by multiplying the predicted conditional probabilities of surviving to month $t \leq m$ given survival through *t-1* for each study participant, and then averaging the estimate across all participants. Cumulative incidence of mortality was computed as 1 minus the standardized survival. From the cumulative incidence curve, we also obtained the absolute risks and corresponding risk differences for initiators versus non-initiators. For all the estimates, 95% confidence intervals (CIs) were computed using non-parametric bootstrap with 500 copies.

Case-crossover analysis

A case-crossover analysis[11] was employed as an approach to triangulate the evidence, which has a different study design and underlying assumptions. The aim of this analysis was to mitigate potential unmeasured confounding, in which only cases who died were included and served as their own controls. This method has been commonly used in observational studies to assess the association between transient exposures (e.g. medication use) and an acute event, typically an adverse health outcome.[11] As this method involves the comparison of the exposure status of individuals at the time of the event (case period) with their exposure status at other times (control periods) within the same individual, all time-invariant unmeasured confounding within each person were automatically controlled for (self-matching).

In the current study, only the 1,402 cases who died were included and served as their own controls. For each individual, their exposure status to ADHD medication on the date of their death was compared with that on 12 control dates, each corresponding to reference dates spread across the 12 months prior to their death. We additionally adjusted for time varying covariates including diagnosis of major psychiatric diseases (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 other drug use disorder); major physical disease (i.e., cardiovascular disease, epilepsy, type 2 diabetes, and dyslipidemia); suicide attempt and external injures/trauma; 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 any outpatient visits for psychiatric and non-psychiatric reasons; number of any hospitalizations for psychiatric and non-psychiatric reasons. Odds ratios and 95% CIs were estimated using conditional logistic regression analysis, with each individual serving as a separate stratum.

By examining the outcomes separately in our case-crossover analysis, we looked at distinct events (e.g. natural death and unnatural death) separately in each analysis. This approach allowed us to examine each

outcome independently. The self-matching in the case-crossover design helps address the limitation in cohort studies that individuals censored for competing risks may differ in their exposure and outcome risk from those remaining in the cohort. In contrast, the control periods in self-matching are derived from the same cases.[12]

The key assumptions in case-crossover analysis include[11,13]:

1) Temporal Association: The exposure must be transient and associated with the outcome within a short timeframe. Our investigation focused on the effect of ADHD medication, known for its typically immediate effect; and 2) Independence of Control Period Selection: The selection of control periods should be independent of the exposure history. In our study, we adhered to this assumption by choosing 12 control dates, each corresponding to reference dates spread across the 12 months preceding the occurrence of death for each case. This deliberate selection process helped ensure that control periods were independent of prior exposure status, thereby supporting the validity of our use of this approach.

Estimating cause-specific hazard ratio

When estimating cause-specific hazard ratios, we treated the competing event of other death as a censoring event. Using a competing risk analysis, such as the Fine-Gray model, would estimate subdistribution hazard ratios. However, using this model to account for competing risks would likely increase confounding rather than remove it when the aim is to estimate the direct (causal) effect of exposure on outcome. This is because when the subdistribution hazard ratio is estimated it does so by relating covariates (e.g., the exposure) to the cumulative probability of the event of interest while accounting for the cumulative probability of the competing events and the association between these competing events and covariates. And this is accomplished by not censoring individuals when they experience a competing event (e.g., die from “event B”), i.e., they are not removed from the “event A” risk set (the set of individuals at risk for event A). This becomes “unnatural” since an individual that dies from event B cannot be at risk of experiencing event A in the future. However, keeping individuals who experience the competing event in the risk set is necessary to get an unbiased estimate of the cumulative incidence. The cumulative incidence is useful for, e.g., prediction-related research questions. However, using the Fine-Gray model for analyzing the causal effects of covariates on an outcome in the presence of competing risks is likely to confound them; an exposure that increases risk for event A will decrease risk for event B, simply because event A will eliminate the possibility of event B, regardless whether the exposure also is directly causing event B or not. Hence, the Fine-Gray model will be problematic for answering the causal research question of if the exposure directly causes the outcome, such as we aim to answer in our study.

In our study, the Fine-Gray model would estimate the subdistribution hazard ratio of “natural death” (i.e., the event of interest) in the presence of death by suicide (i.e., a competing risk), and vice versa. However, the effect estimate for ADHD medication on “natural death” could be driven (entirely or partly) by the effects of ADHD medication on death by suicide. This would mean that, even in the complete absence of any direct effect of ADHD medication on “natural death”, the Fine-Gray model would estimate an increased subdistribution hazard ratio if ADHD medication users were more likely to die from “natural death” simply as a result of being less likely to die from other causes (that is, if ADHD medication was associated with lower rates of suicide). Thus, the Fine-Gray model could lead to the inference that initiation of ADHD medication is a risk factor for “natural death”, without acknowledging that it is so only by altering the rates of suicide death. i.e., based on such results the resulting recommendation with regard to "natural death" would be to not initiate ADHD medication, even though no group of individuals who had initiated ADHD medication had an increased rate of "natural death" at any given time-point. These inferences are not compatible with our causal research question. We therefore believe that it is not useful to apply the Fine-Gray model.

eTable 1. Anatomical Therapeutic Chemical (ATC) codes for ADHD medication from the Prescribed Drug Register

ADHD Medications	ATC codes
Methylphenidate	N06BA04
Amphetamine	N06BA01
Dexamphetamine	N06BA02
Lisdexamfetamine	N06BA12
Atomoxetine	N06BA09
Guanfacine	C02AC02

eTable 2. The number and proportion of causes of death during a 5-year follow-up period

Chapters	ICD-10 codes	N	%
Natural death	A00-R99, U07	467	33.3
I Certain infectious and parasitic diseases	A00-B99	16	3.4
II Neoplasms	C00-D48	124	26.6
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89	<10	-
IV Endocrine, nutritional and metabolic diseases	E00-E90	27	5.8
V Mental and behavioural disorders	F00-F99	21	4.5
VI Diseases of the nervous system	G00-G99	15	3.2
IX Diseases of the circulatory system	I00-I99	140	30.0
X Diseases of the respiratory system	J00-J99	31	6.6
XI Diseases of the digestive system	K00-K93	32	6.9
XIII Diseases of the musculoskeletal system and connective tissue	M00-M99	<10	-
XIV Diseases of the genitourinary system	N00-N99	<10	-
XV Pregnancy, childbirth and the puerperium	O00-O99	<10	-
XVII Congenital malformations, deformations and chromosomal abnormalities	Q00-Q99	<10	-
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	R00-R99	47	10.0
XXII Covid-19	U07.1	<10	-
Unnatural death	S00-T98, V01-Y98	935	66.7
Suicide	X60-X84, Y10-Y34	517	55.3
Accidental injures	V01-X39, X50-X59	76	8.1
Accidental poisoning by and exposure to noxious substances	X40-X49	311	33.3
Other external injures	All other ICD codes for unnatural death	31	3.3

eTable 3. International Classification of Diseases Tenth Revisions (ICD-10) codes from the Swedish National Patient Register

	ICD-10 codes
Psychiatric comorbidities	
Alcohol use disorder	F10
Tobacco use disorder	F17
Illicit drug use disorder	F11-F16, F18-F19
Schizophrenia	F20-F29
Bipolar disorder	F30-F31
Depressive disorder	F32-F33
Anxiety disorders	F40-F41
Eating disorders	F50
Personality disorders	F60, F69
Intellectual disability	F70-F79
Autism spectrum disorders	F84
Conduct disorder	F91
Other disease and behaviors	
Cardiovascular disease	I00-I70, I73.0, I74-I75
Type 2 diabetes	E11
Dyslipidemia	E78
Epilepsy	G40-G41
Suicide attempt	X60-X84, Y10-Y34
External injures	V00-X59, X92-Y99

eTable 4. Model coefficients for remaining uncensored in each treatment group

Variable	Initiation group		Non-initiation group	
	Coefficient	Standard error	Coefficient	Standard error
Intercept	0.474	0.026	1.501	0.028
Month	0.225	0.022	1.296	0.026
Month*	7.317	0.023	5.064	0.035
Month**	1.752	0.025	2.260	0.029
Baseline				
Age	-0.003	0.000	0.009	0.000
Sex Female	-0.046	0.007	-0.003	0.007
Calendar year 2008	0.084	0.026	-0.101	0.026
Calendar year 2009	0.194	0.025	-0.233	0.025
Calendar year 2010	0.258	0.024	-0.317	0.024
Calendar year 2011	0.282	0.024	-0.361	0.023
Calendar year 2012	0.230	0.023	-0.329	0.023
Calendar year 2013	0.201	0.023	-0.323	0.023
Calendar year 2014	0.141	0.023	-0.325	0.023
Calendar year 2015	0.085	0.023	-0.321	0.022
Calendar year 2016	-0.014	0.023	-0.293	0.022
Calendar year 2017	-0.042	0.022	-0.307	0.022
Calendar year 2018	-0.074	0.022	-0.373	0.022
Birth country Others	-0.089	0.013	0.133	0.013
Education Upper secondary	0.089	0.010	-0.105	0.010
Education Post-secondary or postgraduate	0.111	0.011	-0.140	0.011
Education Unknown	0.021	0.042	0.138	0.042
Anxiety disorders	-0.066	0.014	0.067	0.014
Autism spectrum disorder	-0.047	0.021	0.208	0.021
Bipolar disorder	0.065	0.024	0.013	0.023
Conduct disorder	0.106	0.029	-0.142	0.029
Depressive disorder	0.027	0.012	-0.070	0.012
Eating disorder	-0.006	0.026	0.022	0.026
Intellectual disability	-0.082	0.031	0.240	0.031
Personality disorders	-0.049	0.019	0.040	0.019
Schizophrenia	-0.073	0.031	0.222	0.032
Alcohol use disorder	-0.030	0.016	0.012	0.016

Variable	Initiation group		Non-initiation group	
	Coefficient	Standard error	Coefficient	Standard error
Tobacco use disorder	-0.078	0.058	0.158	0.059
Illicit drug use disorder	-0.062	0.016	0.040	0.016
Accidental injures	0.014	0.008	-0.041	0.008
Suicide attempt history	0.014	0.015	-0.038	0.015
Cardiovascular disease	-0.094	0.021	0.185	0.021
Type 2 diabetes	-0.062	0.044	0.077	0.044
Dyslipidemia	0.002	0.060	0.038	0.060
Epilepsy	-0.166	0.028	0.232	0.028
Antiepileptic drugs	-0.022	0.018	0.005	0.018
Anti-addiction drugs	0.091	0.019	-0.096	0.018
Antidepressants	0.016	0.012	-0.080	0.011
Anxiolytics, hypnotics, and sedatives	0.017	0.010	-0.079	0.010
Opioids	0.075	0.011	-0.126	0.010
Antipsychotics	0.006	0.015	-0.029	0.015
Number of outpatient visit for psychiatry 1-4	-0.054	0.010	0.060	0.010
Number of outpatient visit for psychiatry 5-9	-0.089	0.016	0.116	0.016
Number of outpatient visit for psychiatry 10+	-0.073	0.019	0.090	0.018
Number of hospitalizations for psychiatry 1-2	-0.057	0.014	0.084	0.014
Number of hospitalizations for psychiatry 3-4	-0.068	0.026	0.070	0.026
Number of hospitalizations for psychiatry 5+	-0.023	0.028	0.043	0.027
Number of outpatient visits for non-psychiatric reason 1-4	0.000	0.011	-0.027	0.011
Number of outpatient visits for non-psychiatric reason 5-9	-0.008	0.013	-0.023	0.013
Number of outpatient visits for non-psychiatric reason 10+	-0.051	0.015	-0.019	0.014
Number of hospitalizations for non-psychiatric reason 1-2	-0.023	0.008	0.016	0.008
Number of hospitalizations for non-psychiatric reason 3-4	-0.045	0.015	0.042	0.015

Variable	Initiation group		Non-initiation group	
	Coefficient	Standard error	Coefficient	Standard error
Number of hospitalizations for non-psychiatric reason 5+	-0.063	0.019	0.083	0.018
Time-varying				
Anxiety disorders	-0.277	0.036	0.451	0.033
Autism spectrum disorder	-0.194	0.026	0.534	0.022
Bipolar disorder	-0.346	0.042	0.537	0.039
Conduct disorder	-0.117	0.061	0.210	0.049
Depressive disorder	-0.350	0.026	0.365	0.023
Eating disorder	-0.227	0.076	0.424	0.071
Intellectual disability	-0.170	0.067	0.548	0.057
Personality disorders	-0.125	0.045	0.437	0.041
Schizophrenia	-0.400	0.085	0.650	0.091
Alcohol use disorder	-0.266	0.051	0.322	0.047
Tobacco use disorder	-0.314	0.275	0.349	0.262
Illicit drug use disorder	-0.378	0.038	0.440	0.034
Accidental injures	0.067	0.036	-0.186	0.034
Suicide attempt history	-0.049	0.082	-0.277	0.073
Cardiovascular disease	-0.401	0.077	0.003	0.080
Type 2 diabetes	-0.132	0.169	0.185	0.180
Dyslipidemia	0.362	0.289	-0.048	0.309
Epilepsy	-0.213	0.087	0.481	0.086
Antiepileptic drugs	-0.167	0.036	0.155	0.036
Anti-addiction drugs	0.247	0.066	-0.130	0.063
Antidepressants	-0.141	0.017	0.244	0.017
Anxiolytics, hypnotics, and sedatives	0.039	0.024	0.016	0.024
Opioids	-0.021	0.029	-0.035	0.029
Antipsychotics	-0.163	0.028	0.070	0.029
Any outpatient visit for psychiatry	0.480	0.011	-0.847	0.013
Any hospitalization for psychiatry	-0.170	0.041	0.171	0.031
Any outpatient visit for non-psychiatric reason	-0.106	0.018	0.191	0.016
Any hospitalization for non-psychiatric reason	-0.077	0.049	0.402	0.045

eTable 5. Association between ADHD medication initiation and five-year mortality among individuals with ADHD

	Crude						Weighted									
	Initiation			Non-initiation			Initiation				Non-initiation				5-year risk difference	Hazard ratio (95% CI)
	Deaths	Person years	IR	Deaths	Person years	IR	Deaths	Person years	IR	5-year risk	Deaths	Person years	IR	5-year risk		
All-cause	380	212,692	17.9	494	161,722	30.5	1,549	723,585	21.4	107.2 (94.8, 121.3)	1,483	682,689	21.7	108.6 (98.3, 120.0)	-1.4 (-18.1, 15.3)	0.94 (0.88, 1.01)
Natural-cause	120	212,692	5.6	200	161,722	12.4	583	723,585	8.1	41.0 (33.0, 51.0)	512	682,689	7.5	38.3 (32.9, 44.7)	2.7 (-7.7, 13.1)	1.04 (0.92, 1.17)
Unnatural-cause	260	212,692	12.2	294	161,722	18.2	966	723,585	13.4	66.5 (57.4, 77.1)	971	682,689	14.2	70.5 (61.9, 80.3)	-4.0 (-17.2, 9.2)	0.89 (0.81, 0.97)
Suicide	150	212,692	7.1	150	161,722	9.3	544	723,585	7.5	37.1 (30.4, 45.2)	465	682,689	6.8	33.4 (28.0, 39.9)	3.7 (-5.6, 13.0)	1.04 (0.92, 1.18)
Accidental injures	23	212,692	1.1	23	161,722	1.4	64	723,585	0.9	4.4 (2.6, 7.4)	85	682,689	1.2	6.1 (3.9, 9.5)	-1.7 (-5.2, 1.9)	0.71 (0.51, 0.98)
Accidental poisoning	78	212,692	3.7	111	161,722	6.9	323	723,585	4.5	22.4 (17.3, 29.1)	386	682,689	5.6	28.4 (22.7, 35.3)	-5.9 (-14.3, 2.5)	0.74 (0.64, 0.86)

IR, Incidence rate, per 10,000 person-years; 5-year absolute risk and 5-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, accidental poisoning and other external injuries (ICD-10 codes: S00-T98, V01-Y98).

eTable 6. Association between ADHD medication initiation and two-year mortality among individuals with ADHD using a two-week interval

	Crude						Weighted									
	Initiation			Non-initiation			Initiation				Non-initiation				2-year risk difference	Hazard ratio (95% CI)
	Deaths	Person years	IR	Deaths	Person years	IR	Deaths	Person years	IR	2-year risk	Deaths	Person years	IR	2-year risk		
All-cause	231	133,201	17.3	292	91,912	31.8	613	317,227	19.3	38.6 (33.1, 45.0)	729	308,668	23.6	47.2 (41.6, 53.6)	-8.6 (-17.0, -0.2)	0.77 (0.69, 0.86)
Natural-cause	66	133,201	5.0	102	91,912	11.1	211	317,227	6.7	13.1 (9.9, 17.5)	228	308,668	7.4	14.6 (11.8, 18.1)	-1.5 (-6.4, 3.5)	0.86 (0.71, 1.04)
Unnatural-cause	165	133,201	12.4	190	91,912	20.7	401	317,227	12.6	25.4 (21.2, 30.3)	501	308,668	16.2	32.5 (27.9, 38.0)	-7.2 (-14.0, -0.4)	0.73 (0.64, 0.84)
Suicide	103	133,201	7.7	105	91,912	11.4	252	317,227	7.9	15.9 (12.7, 20.0)	268	308,668	8.7	17.4 (14.1, 21.5)	-1.5 (-6.7, 3.7)	0.86 (0.73, 1.03)
Accidental injures	19	133,201	1.4	11	91,912	1.2	39	317,227	1.2	2.5 (1.5, 4.1)	32	308,668	1.0	2.1 (1.1, 3.9)	0.4 (-1.4, 2.2)	1.25 (0.79, 2.01)
Accidental poisoning	38	133,201	2.9	68	91,912	7.4	97	317,227	3.1	6.1 (4.2, 8.8)	181	308,668	5.9	11.8 (9.1, 15.2)	-5.6 (-9.4, -1.9)	0.47 (0.36, 0.60)

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, accidental poisoning and other external injuries (ICD-10 codes: S00-T98, V01-Y98).

eTable 7. Association between ADHD medication initiation and two-year mortality among individuals with ADHD without accounting for deviations from the assigned treatment strategies after the grace period

	Crude						Weighted									
	Initiation			Non-initiation			Initiation				Non-initiation				2-year risk difference	Hazard ratio (95% CI)
	Deaths	Person years	IR	Deaths	Person years	IR	Deaths	Person years	IR	2-year risk	Deaths	Person years	IR	2-year risk		
All-cause	316	183,770	17.2	383	132,077	29.0	570	300,831	19.0	38.0 (33.7, 42.7)	698	299,117	23.3	46.4 (41.9, 51.4)	-8.4 (-15.0, -1.9)	0.82 (0.73, 0.91)
Natural-cause	89	183,770	4.8	127	132,077	9.6	175	300,831	5.8	11.7 (9.3, 14.5)	212	299,117	7.1	14.1 (11.8, 16.9)	-2.5 (-6.1, 1.2)	0.83 (0.68, 1.01)
Unnatural-cause	227	183,770	12.4	256	132,077	19.4	395	300,831	13.1	26.3 (22.9, 30.3)	485	299,117	16.2	32.3 (28.5, 36.7)	-6.0 (-11.5, -0.5)	0.81 (0.71, 0.93)
Suicide	144	183,770	7.8	138	132,077	10.4	248	300,831	8.2	16.5 (13.9, 19.7)	259	299,117	8.6	17.2 (14.5, 20.5)	-0.7 (-4.8, 3.4)	0.96 (0.81, 1.14)
Accidental injures	23	183,770	1.3	16	132,077	1.2	36	300,831	1.2	2.4 (1.5, 3.7)	36	299,117	1.2	2.3 (1.4, 3.9)	0.0 (-1.5, 1.6)	1.02 (0.64, 1.62)
Accidental poisoning	52	183,770	2.8	90	132,077	6.8	97	300,831	3.2	6.4 (4.8, 8.6)	166	299,117	5.5	11.1 (9.0, 13.7)	-4.6 (-7.6, -1.6)	0.58 (0.45, 0.75)

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, accidental poisoning and other external injuries (ICD-10 codes: S00-T98, V01-Y98).

eTable 8. Association between ADHD medication initiation and two-year all-cause mortality among individuals with ADHD, without excluding competing events by using the subdistribution function

	Initiation				Non-initiation					
	Deaths	Person years	IR/10,000 person-years	2-year risk	Deaths	Person years	IR/10,000 person-years	2-year risk	2-year risk difference	Hazard ratio (95% CI)
Natural-cause	203	310,362	6.6	11.0 (8.2, 14.8)	226	307,604	7.4	12.6 (10.1, 15.7)	-1.6 (-8.7, 3.8)	0.90 (0.63, 1.27)
Unnatural-cause	395	310,362	12.7	20.4 (17.0, 24.5)	505	307,604	16.4	28.5 (24.3, 33.3)	-8.0 (-20.6, -3.8)	0.78 (0.62, 0.99)

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, accidental poisoning and other external injuries (ICD-10 codes: S00-T98, V01-Y98).

eTable 9. Association of stimulants versus non-stimulants with two-year all-cause mortality among individuals with ADHD

	Stimulants				Non-stimulants				HR (95% CI)
	Deaths	Person years	Incidence rate	2-year risk	Deaths	Person years	Incidence rate	2-year risk	
All-cause mortality	172	116,078	14.8	29.1 (24.6, 34.5)	153	98,872	15.5	30.3 (19.0, 48.3)	0.96 (0.58, 1.58)

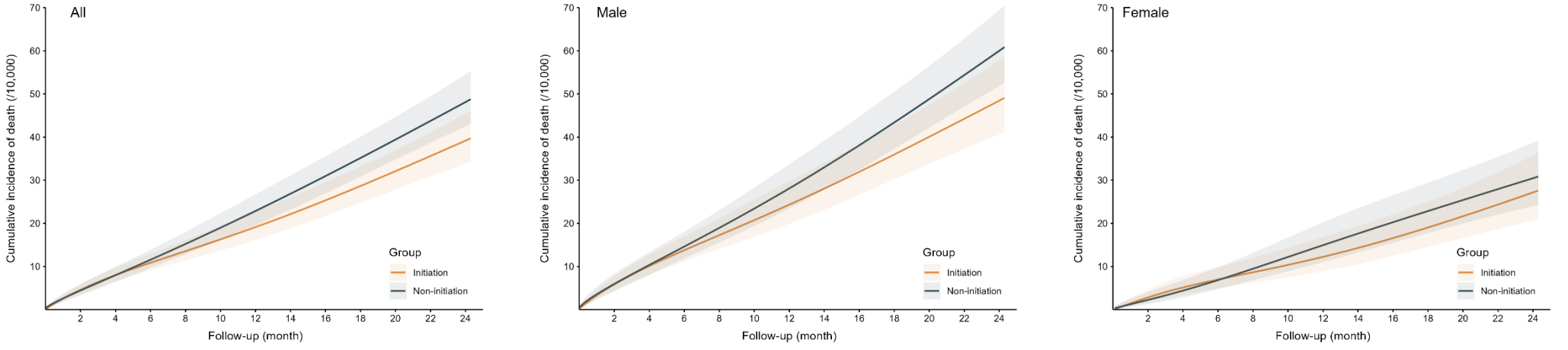
Incidence rate was reported per 10,000 person-years; 2-year risk was reported per 10,000 individuals.

eTable 10. Case-crossover analysis of the association between ADHD medication use and mortality

	No. of deaths	Crude odds ratio (95% CI)[*]	Adjusted odds ratio (95% CI)[#]
All-cause	1402	0.65 (0.53-0.81)	0.70 (0.57-0.88)
Natural-cause	467	0.74 (0.49-1.11)	0.81 (0.53-1.24)
Unnatural-cause	935	0.62 (0.48-0.80)	0.66 (0.51-0.85)

[*]In the crude model, all time-invariant confounders (e.g., sex, genetic makeup, and early life experiences) were automatically controlled by design.

[#]In the adjusted model, the following time-varying covariates were further adjusted for: diagnosis of major psychiatric diseases (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 other drug use disorder); major physical disease (i.e., cardiovascular disease, epilepsy, type 2 diabetes, and dyslipidemia); suicide attempt and external injures/trauma; 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]), any outpatient visit for psychiatric and non-psychiatric reasons; any hospitalization for psychiatric and non-psychiatric reasons.



	6 months	12 months	18 months	24 months
Initiation	10.9 (9.1, 12.9)	19.1 (16.2, 22.6)	28.7 (24.8, 33.1)	39.2 (33.8, 45.4)
Non-initiation	11.6 (9.6, 13.9)	22.9 (19.6, 26.7)	35.2 (30.9, 40.0)	48.1 (42.5, 54.5)
Risk difference	-0.7 (-3.5, 2.1)	-3.7 (-8.5, 1.1)	-6.5 (-12.6, -0.3)	-8.9 (-17.2, -0.6)

	6 months	12 months	18 months	24 months
Initiation	13.8 (11.2, 16.9)	24.3 (19.9, 29.7)	36.0 (30.2, 42.8)	48.4 (40.6, 57.7)
Non-initiation	14.6 (11.8, 18.0)	28.1 (23.4, 33.7)	43.4 (37.3, 50.5)	60.0 (51.9, 69.4)
Risk difference	-0.8 (-5.0, 3.3)	-3.8 (-10.8, 3.3)	-7.4 (-16.4, 1.6)	-11.5 (-23.7, 0.7)

	6 months	12 months	18 months	24 months
Initiation	7.0 (4.9, 9.9)	12.2 (8.9, 16.8)	19.1 (14.5, 25.0)	27.2 (20.7, 35.7)
Non-initiation	6.9 (4.8, 9.8)	14.9 (11.0, 20.2)	22.9 (17.8, 29.4)	30.5 (24.0, 38.7)
Risk difference	0.1 (-3.3, 3.6)	-2.7 (-8.6, 3.2)	-3.8 (-11.5, 3.9)	-3.3 (-13.7, 7.1)

eFigure 1. Cumulative incidence curves of all-cause mortality

Cumulative incidence of all-cause mortality was presented per 10,000.

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