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Association of Psychiatric Comorbidity With the Risk of Premature Death Among Children and Adults With Attention-Deficit/Hyperactivity Disorder

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IMPORTANCE A previous register-based study reported elevated all-cause mortality in attention-deficit/hyperactivity disorder (ADHD), but cause-specific risks and the potential associations of psychiatric comorbidities remain unknown.

OBJECTIVES To investigate the all-cause and cause-specific mortality risks in ADHD and to explore the potential role of psychiatric comorbidities.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study used Swedish national registers to identify 2 675 615 individuals born in Sweden from January 1, 1983, through December 31, 2009, as the study population, among whom 86 670 individuals (3.2%) received a diagnosis of ADHD during follow-up. Follow-up was completed December 31, 2013, and data were analyzed from October 2018 through March 2019.

EXPOSURES Attention-deficit/hyperactivity disorder identified by first clinical diagnosis or first prescription of ADHD medications as recorded in Swedish registers. Clinical diagnosis of psychiatric comorbidity was available in the National Patient Register.

MAIN OUTCOMES AND MEASURES All-cause and cause-specific mortalities and hazard ratios (HRs) using Cox proportional hazards regression models.

RESULTS In the overall cohort of 2 675 615 individuals, 1 374 790 (51.4%) were male (57 919 with an ADHD diagnosis) and 1 300 825 (48.6%) were female (28 751 with an ADHD diagnosis). Mean (SD) age at study entry was 6.4 (5.6) years. During follow-up, 424 individuals with ADHD and 6231 without ADHD died, resulting in mortality rates of 11.57 and 2.16 per 10 000 person-years, respectively. The association was stronger in adulthood (HR, 4.64; 95% CI, 4.11-5.25) compared with childhood (HR, 1.41; 95% CI, 0.97-2.04) and increased substantially with the number of psychiatric comorbidities with ADHD (HR for individuals with only ADHD, 1.41 [95% CI, 1.01-1.97]; HR for those with ≥4 comorbidities, 25.22 [95% CI, 19.60-32.46]). In adulthood, when adjusting for early-onset psychiatric comorbidity, the association between ADHD and risk of death due to natural causes was attenuated substantially and was no longer statistically significant (HR, 1.32; 95% CI, 0.94-1.85). When adjusting for later-onset psychiatric disorders, the association was attenuated to statistical nonsignificance for death due to suicide (HR, 1.13; 95% CI, 0.88-1.45) but remained statistically significant for death caused by unintentional injury (HR, 2.14; 95% CI, 1.71-2.68) or other external causes (HR, 1.75; 95% CI, 1.23-2.48).

CONCLUSIONS AND RELEVANCE Psychiatric comorbidity appears to play an important role in all-cause and cause-specific mortality risks in ADHD. In adulthood, early-onset psychiatric comorbidity contributed primarily to the association with death due to natural causes, whereas later-onset psychiatric comorbidity mainly influenced death due to unnatural causes, including suicide and unintentional injury. These findings suggest that health care professionals should closely monitor specific psychiatric comorbidities in individuals with ADHD to identify high-risk groups for prevention efforts.

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting approximately 5% of children and adolescents and 2.5% of adults worldwide.[1] Individuals with ADHD show impairments in psychosocial functioning.[2-4] Several large observational studies have reported that ADHD is associated with factors that increase the risk for premature death, such as conduct disorder,[5,6] substance use disorders (SUD),[7-9] and incidence of unintentional injuries[10,11] and suicidal behaviors,[12-15] but little is known about how ADHD is directly associated with premature death and the potential role of psychiatric comorbidities.

A Danish register-based study[16] found a 2-fold increased risk of all-cause mortality in ADHD, with unintentional injury as the leading cause of death. The association was stronger when ADHD was diagnosed in adulthood than in childhood, and the mortality rates were higher among individuals with co-occurring conduct disorder, oppositional defiant disorder, and/or SUD. One important limitation in the Danish study was the lack of statistical power to clarify cause-specific mortality risks associated with ADHD, especially death due to unintentional injuries and suicide. Furthermore, the study did not explore in detail the role of psychiatric comorbidity, such as early-onset disorders that include autism spectrum disorders[17] and intellectual disability (ID),[18] as well as psychiatric disorders with a later age at onset, including mood and personality disorders[19-21] and eating disorders.[22,23] Improved understanding of the potential contributions by psychiatric comorbidity for associations between ADHD and premature death could substantially facilitate surveillance, intervention, and prevention efforts. In the present cohort study based on the Swedish national registers, we investigated associations between ADHD and all-cause as well as cause-specific mortality risks and explored the potential effects of number and type of psychiatric comorbidities (ie, early-onset vs later-onset comorbid psychiatric disorders).

Key Points

Question Is attention-deficit/hyperactivity disorder (ADHD) associated with premature death, and what is the role of psychiatric comorbidity?

Findings This cohort study of Swedish register data of 86 670 individuals with ADHD found that ADHD was associated with elevated risk of premature death, and psychiatric comorbidity played an important role for the all-cause and cause-specific associations in adults. Early-onset psychiatric comorbidity was mainly associated with the risk of natural deaths whereas later-onset psychiatric comorbidity was mainly associated with death due to unnatural causes, including suicide and unintentional injury.

Meaning These findings suggest that health care professionals should closely monitor specific psychiatric comorbidities in individuals with ADHD to identify high-risk groups and implement prevention efforts.

Methods

Data Sources and Study Cohort

The study was approved by the Regional Ethics Committee in Stockholm, Sweden. According to Swedish law, informed consent is not required because this is a register-based study using anonymized data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

We linked several Swedish national registers using unique personal identification numbers. The Medical Birth Register includes information of births in Sweden since 1973. The National Patient Register (NPR) contains information of all inpatient discharges since 1987 and specialist outpatient care since 2001, with diagnoses coded according to the Swedish version of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) from 1997. The Prescribed Drug Register has complete coverage of prescriptions in Sweden since July 2005, coded according to the Anatomical Therapeutic Chemical (ATC) classification system. The longitudinal integration database for health insurance and labor market studies (LISA) keeps census information, including employment and highest completed educational level, since 1990. The Cause of Death Register initiated in 1952 provides information on dates and causes of all deaths in Sweden. Furthermore, the Multi-Generation Register covering people born after 1932 in Sweden was used to identify parents of cohort members, and the Migration Register was linked to account for all emigrations from Sweden.

The study cohort, identified from the Medical Birth Register, included all individuals born in Sweden from January 1, 1983, through December 31, 2009, who were alive and residing in Sweden on their 1-year birthday or January 1, 2001 (from when outpatient data was available), whichever came later, and followed up until death, emigration from Sweden, or December 31, 2013 (whichever came first), with the oldest cohort member censored at 31 years of age.

Measures

Exposures and Outcomes

The main exposure was ADHD identified by first diagnosis (*ICD-10* code F90) from NPR or the first prescription of ADHD medications (methylphenidate hydrochloride [ATC code N06BA04], amphetamine [ATC code N06BA01], dextroamphetamine sulfate [ATC code N06BA02], and atomoxetine hydrochloride [ATC code N06BA09]) from the Prescribed Drug Register during follow-up. The main outcome was all-cause mortality after 1 year of age. Cause-specific mortality was used as a secondary outcome. Specific causes of death consisted of natural causes, including somatic diseases and medical conditions (*ICD-10* codes A00-R99), and unnatural causes, including unintentional injuries (*ICD-10* codes V00-X59), suicide (*ICD-10* codes X60-X84 and Y87.0), and other external causes (*ICD-10* codes S00-T98 and X85-Y98, excluding Y87.0).

Covariates

We selected covariates according to previous literature on ADHD and mortality risks.[1,5,16] Birth-related covariates included birth weight (<2000, 2000-3999, or ≥4000 g), year of birth, and maternal age at birth (analyzed as 1-year interval),

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which were extracted from the Medical Birth Register. Highest parental educational level (primary and lower secondary, upper secondary, postsecondary, or postgraduate) and most recent parental employment status (employed or unemployed) during follow-up were extracted from LISA.

We identified the clinical diagnoses based on *ICD-10* codes in NPR for psychiatric comorbidities and categorized them into the following 2 groups based on the mean age at diagnosis in our cohort: (1) early-onset disorders, consisting of autism spectrum disorders, ID, and conduct disorders, including oppositional defiant disorder; and (2) later-onset disorders, consisting of eating disorders, SUD, depressive disorders, bipolar disorders, anxiety disorders, schizophrenia spectrum disorders, and personality disorders (*ICD-10* codes and age at diagnosis are shown in eTable 1 in the Supplement).

Statistical Analysis

Data were analyzed from October 2018 through March 2019. Data management was conducted in SAS, version 9.4 (SAS Institute, Inc), and analyses were completed using Stata, version 14.2 (StataCorp). Descriptive comparisons were performed using 2-sided χ^2 tests. Mortality rates (presented per 10 000 person-years) were calculated across the groupings of ADHD status and covariates. Cox proportional hazards regression models were used to calculate hazard ratios (HRs), and the cluster robust sandwich estimator was used to adjust the 95% CIs. The underlying time scale in the Cox proportional hazards regression model was attained age (range, 1-31 years). Attention-deficit/hyperactivity disorder and comorbid psychiatric disorders were time-varying variables.

ADHD and Risk of Premature Death

We first estimated the association between ADHD and all-cause or cause-specific mortality risks without considering psychiatric comorbidity by using 2 models. In addition to underlying attained age, model 1 adjusted for sex and year of birth, and model 2 further adjusted for birth weight, maternal age at birth, highest parental educational level, and parental employment status. While investigating all-cause mortality risks, we modeled the interaction between ADHD and different age bands (1-17 years as childhood and 18-31 years as adulthood) to test whether the associations differed in strength for children and adults. We also examined potential association of age at first ADHD diagnosis with all-cause mortality. When investigating cause-specific HRs, death causes were treated as independent outcomes. Owing to few deaths in childhood, we did not test the interaction between ADHD and age bands for specific death-cause categories.

Psychiatric Comorbidity With ADHD and Risk of Premature Death

We restricted the analyses of psychiatric comorbidity to individuals who survived until adulthood (18 years or older), because several of the psychiatric disorders were diagnosed during early adulthood (eTable 1 in the Supplement) and few deaths occurred in childhood. First, we investigated the all-cause mortality risks stratified on number of comorbid psychiatric disorders (0, 1, 2, 3, or ≥4) using model 1 and model 2 comparing individuals with and without ADHD. Second, among individuals with ADHD, we compared all-cause mortality risks between cases with and without each specific comorbidity. Third, we explored the role of early-onset and later-onset psychiatric comorbidity for all-cause as well as cause-specific mortality risks by comparing individuals with and without ADHD. Two additional models were used. Model 3 adjusted for early-onset psychiatric comorbidity. Model 4 further adjusted for later-onset psychiatric comorbidity. Finally, we explored how specific psychiatric comorbidities were associated with mortality risks due to natural causes, suicide, and unintentional injury in the ADHD group, using models 1 and 2.

Sensitivity Analyses

To test the robustness of the ADHD definition, we reran the analyses investigating age-specific associations between ADHD and all-cause mortality, restricting these to the first ADHD diagnosis recorded during follow-up (ie, not including information on ADHD medication for the identification). When investigating all-cause mortality risks in groups with only ADHD and various numbers of psychiatric comorbidities, we identified prescriptions for the following psychotropic medications for a broader definition of psychiatric comorbidity apart from clinical diagnosis: antipsychotics (ATC code N05A); anxiolytics, hypnotics, and sedatives (ATC code N05B or N05C); antidepressants (ATC code N06A); antiepileptic drugs (ATC code N03A); drugs used in addictive disorders (ATC code N07B); and opioid pain medications (ATC code N02A). We also stratified the analysis by sex when adjusting for early-onset and later-onset disorders in adulthood, to test whether the results were stable across the sexes, because male and female patients with ADHD may present with different patterns of psychiatric comorbidity.[24]

Results

Cohort Description and Overall Mortality

We followed up 2 675 615 individuals in the cohort (1 374 790 [51.4%] male and 1 300 825 [48.6%] female), with a mean (SD) age at study entry of 6.4 (5.6) years and a mean (SD) follow-up of 11.1 (3.1) years with a total 29 237 993 person-years at risk. In the cohort, 86 670 individuals (3.2%; 57 919 male and 28 751 female) were diagnosed with ADHD (**Table 1**), among whom 12 246 (14.1%) were only identified by medication use records from the Prescribed Drug Register. The mean (SD) age at ADHD diagnosis was 14.3 (5.7 years (13.5 [5.5] years for male and 16.0 [5.6] for female individuals). Significantly higher incidences of all comorbid psychiatric disorders were present in the ADHD group compared with the non-ADHD group (eg, 11 518 [13.3%] diagnosed with substance use disorder in the ADHD group vs 68 187 [2.5%] in the non-ADHD group). Diagnosis of psychiatric disorders in male and female individuals is shown in eTable 2 in the Supplement.

The overall mortality rate during follow-up was 2.28 per 10 000 person-years (eTable 3 in the Supplement), because 6655 cohort members (0.3%) died. Mortality rates were much higher in individuals diagnosed with psychiatric disorders

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Table 1. Characteristics of Individuals With and Without ADHD[a]

Characteristic	Participants, No. (%)[b]		
	Overall (N = 2 675 615)	ADHD Group (n = 86 670)	Non-ADHD Group (n = 2 588 945)
Sex			
Male	1 374 790 (51.4)	57 919 (66.8)	1 316 871 (50.9)
Female	1 300 825 (48.6)	28 751 (33.2)	1 272 074 (49.1)
Year of birth[c]			
1983-1992	1 031 701 (38.6)	30 563 (35.3)	1 001 138 (38.7)
1993-2002	931 442 (34.8)	46 462 (53.6)	884 980 (34.2)
2003-2009	712 472 (26.6)	9645 (11.1)	702 827 (27.1)
Birth weight, g			
<2500	109 358 (4.1)	5303 (6.1)	104 055 (4.0)
2500-3999	2 058 794 (76.9)	64 883 (74.9)	1 993 911 (77.0)
≥4000	507 463 (19.0)	16 484 (19.0)	490 979 (19.0)
Maternal age at birth, y[c]			
<20	61 000 (2.3)	4311 (5.0)	56 689 (2.2)
20-29	1 402 730 (52.4)	50 390 (58.1)	1 352 340 (52.2)
30-39	1 146 787 (42.9)	30 163 (34.8)	1 116 624 (43.1)
≥40	65 098 (2.4)	1806 (2.1)	63 292 (2.4)
Parental educational level			
Primary and lower secondary	85 744 (3.2)	4061 (4.7)	81 683 (3.2)
Upper secondary	1 085 759 (40.6)	44 287 (51.1)	1 041 472 (40.2)
Postsecondary	1 269 195 (47.4)	29 582 (34.1)	1 239 613 (47.9)
Postgraduate	234 917 (8.8)	8740 (10.1)	226 177 (8.7)
Parental employment status			
Employed	2 528 192 (94.5)	78 082 (90.1)	2 450 110 (94.6)
Not employed	147 423 (5.5)	8588 (9.9)	138 835 (5.4)
Psychiatric comorbidity[d]			
Autism spectrum disorder	34 968 (1.3)	15 755 (18.2)	19 213 (0.7)
Intellectual disorder	20 894 (0.8)	6015 (6.9)	14 879 (0.6)
Conduct disorder	8983 (0.3)	5900 (6.8)	3083 (0.1)
Eating disorder	19 996 (0.7)	1857 (2.1)	18 139 (0.7)
Substance use disorder	68 187 (2.5)	11 518 (13.3)	56 669 (2.2)
Depression	80 591 (3.0)	16 113 (18.6)	64 478 (2.5)
Bipolar disorder	10 315 (0.4)	3244 (3.7)	7071 (0.3)
Anxiety disorder	82 911 (3.1)	16 369 (18.9)	66 542 (2.6)
Schizophrenia	6937 (0.3)	1576 (1.8)	5361 (0.2)
Personality disorder	13 637 (0.5)	3914 (4.5)	9723 (0.4)
No. of psychiatric comorbidities			
0	2 456 891 (91.8)	41 432 (47.8)	2 415 459 (93.3)
1	145 661 (5.4)	23 826 (27.5)	121 835 (4.7)
2	50 279 (1.9)	11 903 (13.7)	38 376 (1.5)
3	18 722 (0.7)	5447 (6.3)	13 275 (0.5)
≥4	4062 (0.2)	4062 (4.7)	0

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

[a] All variables were statistically different between ADHD and non-ADHD groups, with $P < .001$ by 2-sided χ^2 test.

[b] Percentages have been rounded and may not total 100.

[c] Analyzed as 1-year intervals in Cox proportional hazards regression models.

[d] Indicates psychiatric disorders other than ADHD.

(range, 9.52 to 45.09 per 10 000 person-years) and higher in adulthood than in childhood (4.36 vs 1.26 per 10 000 person-years).

ADHD and Risk of Premature Death

In total, 424 individuals with ADHD died during follow-up (all-cause mortality rate, 11.57 per 10 000 person-years) compared with 6231 deaths (2.16 per 10 000 person-years) in the non-ADHD group. Overall, ADHD was associated with a significantly increased risk of all-cause premature death (adjusted HR, 3.94; 95% CI, 3.51-4.43). The adjusted HR in adulthood (4.64; 95% CI, 4.11-5.25) was substantially higher than the HR in childhood (1.41; 95% CI, 0.97-2.04) (**Table 2**). The all-cause mortality risks significantly increased with the age at first ADHD diagnosis (HRs for ≤12 years, 1.50 [95% CI, 10.4-2.17]; 13-17 years, 2.69 [95% CI, 2.20-3.31]; ≥18 years, 10.34 [95% CI, 8.94-11.96]) (eTable 4 in the Supplement).

Individuals with ADHD primarily died due to unnatural causes (346 [81.6%]), with unintentional injury (152 [35.8%]) and suicide (133 [31.4%]) as the leading causes of death (eTable 5

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Table 2. Association Between ADHD and All-Cause Mortality in Childhood and Adulthood

Group[a]	No. of Deaths	Person-Years	Mortality Rate per 10 000 Person-Years	HR (95% CI)	
				Model 1[b]	Model 2[c]
Overall					
ADHD	424	366 332	11.57	4.44 (3.95-4.98)	3.94 (3.51-4.43)
Non-ADHD	6231	28 871 661	2.16	1 [Reference]	1 [Reference]
Childhood					
ADHD	40	194 048	2.06	1.58 (1.09-2.29)	1.41 (0.97-2.04)
Non-ADHD	2435	19 465 363	1.25	1 [Reference]	1 [Reference]
Adulthood					
ADHD	384	172 284	22.29	5.22 (4.62-5.90)	4.64 (4.11-5.25)
Non-ADHD	3796	9 406 298	4.04	1 [Reference]	1 [Reference]

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

[a] ADHD was treated as a time-varying exposure while calculating death counts and mortality rates per 10 000 person-years.

[b] Adjusted for sex and year of birth.

[c] Adjusted for model 1 covariates, birth weight, maternal age at birth, parental educational level, and parental employment status. No psychiatric comorbidities were adjusted for here.

Table 3. All-Cause Mortality Risks and Number of Comorbid Disorders With ADHD in Adults

Group	No. of Deaths	Person-Years	Mortality Rate per 10 000 Person-Years	HR (95% CI)	
				Model 1[a]	Model 2[b]
Overall	3821	16 206 949	2.36	NA	NA
ADHD only	39	102 989	3.79	1.56 (1.11-2.18)	1.41 (1.01-1.97)
ADHD plus 1 comorbidity[c]	73	57 575	12.68	4.21 (3.27-5.42)	3.71 (2.88-4.78)
ADHD plus 2 comorbidities	90	29 952	30.05	8.57 (6.73-10.92)	7.51 (5.89-9.57)
ADHD plus 3 comorbidities	73	14 146	51.60	15.69 (12.08-20.37)	13.52 (10.40-17.57)
ADHD plus ≥4 comorbidities	94	10 334	90.96	29.29 (22.77-37.66)	25.22 (19.60-32.46)
None of above	3452	15 991 953	2.16	1 [Reference]	1 [Reference]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio; NA, not applicable.

[a] Adjusted for sex and year of birth.

[b] Adjusted for model 1 covariates, birth weight, maternal age at birth, parental educational level, and parental employment status.

[c] Among autism spectrum disorder, intellectual disability, conduct disorder, eating disorder, substance use disorder, depression, bipolar disorder, schizophrenia, anxiety disorder, and personality disorder. ADHD and comorbid disorders were time-varying covariates when calculating death counts and mortality rates (per 10 000 person-years).

in the Supplement). Neoplasms (15 [3.5%]), diseases of the nervous system (12 [2.8%]), and circulatory system diseases (12 [2.8%]) accounted for the most deaths due to natural causes in the ADHD group. Compared with the non-ADHD group, the ADHD group had significantly higher risks of death due to natural (adjusted HR, 2.47; 95% CI, 1.66-4 3.68) and unnatural (adjusted HR, 6.48; 95% CI, 5.12-8.21) causes. Specifically among unnatural causes, ADHD was associated with an 8.63 (95% CI, 6.27-11.88) times higher risk of dying due to suicide and a 3.94 (95% CI, 2.49-6.25) times higher risk of dying due to unintentional injuries.

Psychiatric Comorbidity With ADHD and Risk of Premature Death in Adults

First, when stratifying by the number of comorbid psychiatric conditions, the diagnosis of ADHD without comorbidity conferred a 40% higher risk of all-cause mortality (adjusted HR, 1.41; 95% CI, 1.01-1.97). The association increased substantially with the number of comorbidities in a dose-response pattern (adjusted HR for 1 comorbidity, 3.71 [95% CI, 2.88-4.78]; adjusted HR for ≥4 comorbidities, 25.22 [95% CI,19.60-32.46]), indicating a cumulative contribution of psychiatric comorbidity to premature death, including an independent contribution due to being diagnosed with ADHD (**Table 3**).

Second, most of the specific comorbid disorders except autism spectrum disorder (adjusted HR, 0.89; 95% CI, 0.64-1.25) and ID (adjusted HR, 0.36; 95% CI, 0.18-0.70) were associated with increased risk for all-cause mortality among individuals with ADHD (**Table 4**). The strongest association was found for SUD, with an adjusted HR of 8.01 (95% CI, 6.16-10.41), when compared with individuals with only ADHD.

Third, when adjusting for early-onset psychiatric comorbidity (model 3), the associations between ADHD and unnatural cause-specific mortality risks were partly attenuated, whereas death due to natural causes (HR, 1.32; 95% CI, 0.94-1.85) was no longer statistically associated with ADHD (**Table 5**). When adjusting for later-onset disorders (model 4), all associations were attenuated. The association became statistically nonsignificant for death due to suicide (HR, 1.13; 95% CI, 0.88-1.45) but remained statistically significant for death due to unintentional injury (HR, 2.14; 95% CI, 1.71-2.68) or other external causes (HR, 1.75; 95% CI, 1.23-2.48).

Finally, when analyzing specific psychiatric comorbidities among individuals with ADHD, associations were not significant for most of the early-onset disorders with cause-specific mortalities (eTable 6 in the Supplement). However, ADHD and comorbid ID presented a substantially lower risk of death due to unintentional injury (adjusted HR, 0.20; 95% CI, 0.05-0.80) compared with individuals with ADHD only. Among later-onset psychiatric comorbidities, SUD presented the strongest associations with death due to natural causes (adjusted HR, 3.23; 95% CI, 1.72-6.07), suicide (adjusted HR, 6.61; 95%

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Table 4. Psychiatric Comorbid Disorders and All-Cause Mortality Risks Among Adults With ADHD

Comorbidity[a]	Deaths, No. (%)	Mortality Rate per 10 000 Person-Years	HR (95% CI)	
			Model 1[b]	Model 2[c]
Overall	369 (100.0)	21.87	NA	NA
ADHD only	39 (10.6)	5.54	1 [Reference]	1 [Reference]
ADHD plus any	330 (89.4)	33.59	5.02 (3.51-7.18)	4.95 (3.47-7.08)
ADHD plus ASD	55 (14.9)	21.93	0.87 (0.62-1.23)	0.89 (0.64-1.25)
ADHD plus ID	13 (3.5)	9.91	0.37 (0.19-0.72)	0.36 (0.18-0.70)
ADHD plus CD/ODD	34 (9.2)	30.26	1.72 (1.16-2.56)	1.66 (1.11-2.47)
ADHD plus ED	14 (3.8)	29.51	2.50 (0.80-7.79)	2.49 (0.80-7.77)
ADHD plus SUD	256 (69.4)	79.41	8.07 (6.21-10.48)	8.01 (6.16-10.41)
ADHD plus depression	162 (43.9)	39.74	2.51 (1.98-3.19)	2.53 (1.99-3.21)
ADHD plus BD	45 (12.2)	55.99	2.87 (1.95-4.24)	2.86 (1.94-4.22)
ADHD plus anxiety disorder	191 (51.8)	51.10	3.85 (3.03-4.90)	3.83 (3.01-4.88)
ADHD plus SCZ	51 (13.8)	112.20	3.70 (2.62-5.22)	3.65 (2.58-5.14)
ADHD plus PD	99 (26.8)	89.40	4.48 (3.34-6.03)	4.45 (3.31-5.99)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CD, conduct disorder; ED, eating disorder; HR, hazard ratio; ID, intellectual disability; NA, not applicable; ODD, oppositional defiant disorder; PD, personality disorder; SCZ, schizophrenia disorder; SUD, substance use disorder.

[a] ADHD and comorbid disorders were time-varying exposures while calculating death counts and mortality rates (per 10 000 person-years).

[b] Adjusted for year of birth and sex.

[c] Adjusted for model 1 covariates, birth weight, maternal age at birth, parental educational level, and parental employment status.

Table 5. Early- and Later-Onset Psychiatric Comorbidity With ADHD and Risk of Premature Death in Adults

Cause of Death	ADHD Group		Non-ADHD		Adjustment, HR (95% CI)			
					Covariate		Comorbidity	
	No. of Deaths	Mortality Rate per 10 000 Person-Years[a]	No. of Deaths	Mortality Rate per 10 000 Person-Years[a]	Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
All	369	21.87	3452	3.69	5.65 (4.99-6.39)	5.00 (4.41-5.67)	3.87 (3.37-4.44)	1.48 (1.29-1.70)
Unnatural	311	18.44	2388	2.55	6.79 (5.92-7.78)	5.93 (5.17-6.81)	5.33 (4.59-6.20)	1.57 (1.35-1.83)
Unintentional injury	133	7.88	1105	1.18	6.80 (5.72-8.30)	5.89 (4.82-7.20)	5.85 (4.71-7.27)	2.14 (1.71-2.68)
Suicide	120	7.11	941	1.01	5.81 (4.61-7.32)	5.28 (4.18-6.66)	4.08 (3.15-5.29)	1.13 (0.88-1.45)
Other external	58	3.44	328	0.35	10.26 (7.44-14.13)	8.28 (5.99-11.45)	7.82 (5.51-11.10)	1.75 (1.23-2.48)
Natural	58	3.44	1052	1.13	2.93 (2.14-4.01)	2.68 (1.95-3.67)	1.32 (0.94-1.85)	1.01 (0.72-1.42)

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

[a] ADHD and comorbid disorders were time-varying exposures while calculating mortality rates (per 10 000 person-years).

[b] Adjusted for year of birth and sex.

[c] Adjusted for model 1 covariates, birth weight, maternal age at birth, parental educational level, and parental employment status.

[d] Adjusted for model 2 covariates and early-onset disorders including conduct disorders, autism spectrum disorder, and intellectual disability.

[e] Adjusted for model 3 covariates and later-onset disorders including substance use disorder, depressive disorder, bipolar disorder, anxiety disorder, schizophrenia, personality disorder, and eating disorders.

CI, 4.13-10.57), and unintentional injury (adjusted HR, 10.02; 95% CI, 6.49-15.49). Associations between most later-onset disorders other than SUD were stronger with death due to suicide than death due to unintentional injury or natural causes.

Sensitivity Analyses

When ADHD only was included from the NPR (eTable 7 in the Supplement), the all-cause mortality risks were similar to those of the main analysis, in which ADHD in adulthood (adjusted HR, 4.60; 95% CI, 4.04-5.24) showed a much stronger association than in childhood (adjusted HR, 1.33; 95% CI, 0.87-2.03). The estimates were generally consistent when using psychotropic medications to define numbers of psychiatric comorbidities (eTable 8 in the Supplement), although the association in the ADHD-only group declined to nonsignificance (adjusted HR, 0.92; 95% CI, 0.55-1.53), probably owing to power issue. Results for sex-stratified analysis adjusting for early- and later-onset disorders were generally similar without substantial difference across the sexes (eTable 9 in the Supplement).

Discussion

In a national register-based cohort study with more than 2.6 million individuals, we found that ADHD was associated with elevated all-cause and cause-specific mortality risks. The association was stronger in adulthood than in childhood, with increased risks when ADHD was diagnosed later. In adulthood, the all-cause mortality risk increased substantially with the number of psychiatric comorbidities with ADHD. Early-onset psychiatric comorbidity was associated with a substantial part of the mortality risks due to natural causes such as neoplasms. Later-onset psychiatric comorbidity, on

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the other hand, contributed substantially to the ADHD-associated mortality risks due to unnatural causes, such as suicide and unintentional injuries. Assessment of the risk and intervention focusing on different psychiatric comorbidities might help with not only improving general quality of life for individuals with ADHD[1] but also preventing premature deaths due to various causes.

In line with the previous Danish register based study[16] and other studies,[25] we found that unnatural causes, including suicide and unintentional injuries, accounted for the most deaths among individuals with ADHD. The association between ADHD and the risk of dying due to suicide or unintentional injuries in adulthood was largely explained by later-onset psychiatric comorbidity. A survey of school-age children from Taiwan[26] reported that mood disorders and conduct disorders mediated about 20% and 8%, respectively, of the suicidality risk associated with ADHD, whereas our results suggested more pronounced associations in adulthood from later-onset psychiatric comorbidity, in particular SUD and mood disorders. Inattention and impulsivity in ADHD increase the proneness to risky behaviors and the risk of severe unintentional injuries,[25,27,28] suggesting a direct association of ADHD with death due to unintentional injuries. This theory was supported by our results with a 2-fold increased risk of death due to unintentional injuries after adjusting for psychiatric comorbidities, although the association was much stronger before the adjustment for later-onset psychiatric comorbidity.

The association between ADHD and risk of death due to natural causes in adulthood might be explained to a large extent by co-occurring early-onset disorders, including conduct disorder/oppositional defiant disorder, autism spectrum disorder, and ID. For example, individuals with ADHD and co-occurring ID had increased mortality risks compared with those with ADHD only, and most deaths in this group were due to natural causes. This finding is consistent with those of studies demonstrating that adults with mild to severe ID showed increased risk of premature death and mainly died due to somatic conditions other than external causes.[29,30] Intellectual disability-related poor self-care may increase the risk of preventable health conditions such as respiratory infections and digestive diseases.[29] Management of early-onset psychiatric comorbidities such as intellectual disability with ADHD needs to focus also on somatic conditions.

We analyzed the association of ADHD with and without specific psychiatric comorbidities with all-cause and cause-specific mortality risks in adulthood. Consistent with previous research,[16] comorbid conduct disorder and SUD further increased the all-cause mortality risks in ADHD. Substance use disorder was also associated with elevated risk of death due to suicide, unintentional injuries, and natural causes in individuals with ADHD. Common risk factors for suicide,[31] including depression, anxiety, and bipolar disorders, were consistently associated with significantly higher risk of suicide death in ADHD. On the other hand, individuals with ADHD and comorbid ID had a lower risk of death due to unintentional injuries compared with individuals with ADHD only, possibly owing to the fact that individuals with both disorders have lower possibility of experiencing severe traffic crashes because of difficulty obtaining a driving license. Such findings could guide clinical treatment and facilitate development of risk evaluation and prediction tools when different psychiatric comorbidities are identified with ADHD.

Limitations

The current study has several limitations. First, relying on clinical diagnosis and prescriptions to identify ADHD may lead to false-positive misclassification, although the results were stable when defining ADHD only from NPR diagnosis. Second, the mean age at ADHD diagnosis (14.3 years) was older than the recognized ADHD onset age defined by *DSM-5*.[32] Delayed diagnosis may result in misclassification from exposed to unexposed person-times, which may bias the association toward null. Third, the outpatient register, which contains a substantial proportion of psychiatric diagnosis records, was initiated in NPR from 2001. As a consequence, we may miss some diagnoses of early-onset disorders for people born earlier in our cohort. Fourth, restricting the analysis of psychiatric comorbidities to young adults does not allow investigating ADHD-associated unnatural deaths such as unintentional injuries in childhood. Future research should also expand the follow-up beyond early adulthood, which allows for longer exposure to later-onset disorders such as SUD, and when more deaths due to natural causes such as cardiovascular diseases can be observed. Furthermore, effects of ADHD medication should be analyzed because of documented potential benefits on ADHD symptoms and comorbid disorders.[1,10,11,33-38]

Conclusions

By using a longitudinal design based on national register data, our results suggest an elevated risk in ADHD for all-cause and cause-specific premature death, which may increase with the number of psychiatric comorbidities present. Among adults, early-onset psychiatric comorbidity contributed substantially to the premature mortality risks due to natural causes. On the other hand, later-onset psychiatric comorbidity, especially SUD, explained a substantial part of the risk for unnatural deaths, including all the risk of suicide deaths and most of the deaths due to unintentional injuries. These results suggest that overall health conditions and risk of psychiatric comorbidity should be evaluated clinically to identify high-risk groups among individuals with ADHD.

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