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Association Between Pharmacological Treatment of Attention-Deficit/Hyperactivity Disorder and Long-term Unemployment Among Working-Age Individuals in Sweden

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Abstract

IMPORTANCE Adults with attention-deficit/hyperactivity disorder (ADHD) are at greater risk for unemployment. Pharmacological treatment is effective in reducing the core symptoms of ADHD, but whether it helps to reduce the unemployment rate among adult patients remains unclear.

OBJECTIVE To investigate the association between use of ADHD medication and long-term unemployment in working-age adults with ADHD.

DESIGN, SETTING, AND PARTICIPANTS Data for this population-based cohort study were extracted from Swedish national registers. Among 25 358 individuals with ADHD born from 1958 to 1978, 12 875 middle-aged adults among the workforce were included. The longitudinal cohort was followed up from January 1, 2008, to December 31, 2013. Data were analyzed from March 1, 2020, through May 31, 2021.

EXPOSURES Use of medication for ADHD during the previous 2 years was the main exposure, as both categorical and continuous variables.

MAIN OUTCOMES AND MEASURES Yearly accumulated unemployed days were derived from the Public Employment Service, and long-term unemployment was defined as 90 or more days of unemployment per year. Overall and sex-specific relative risks (RRs) with 95% CIs were estimated using generalized estimating equations.

RESULTS Among 12 875 individuals with ADHD (5343 women [41.50%] and 7532 men [58.50%]; mean [SD] age, 37.9 [5.6] years), the use of ADHD medications during the previous 2 years was associated with a 10% lower risk of long-term unemployment in the following year (adjusted RR, 0.90 [95% CI, 0.87-0.95]). An association between use of ADHD medications and long-term unemployment was found among women (RR, 0.82 [95% CI, 0.76-0.89]) but not men (RR, 0.96 [95% CI, 0.91-1.01]). Longer treatment duration was associated with a lower risk of subsequent long-term unemployment among women (RR for use of 1-6 months, 0.86 [95% CI, 0.78-0.95]; RR for use of 18-24 months, 0.72 [95% CI, 0.58-0.90]; $P < .001$ for trend). Within-individual comparisons showed that the long-term unemployment rate was lower during periods of ADHD medication treatment compared with nontreatment periods (RR, 0.89; 95% CI, 0.85-0.94).

CONCLUSIONS AND RELEVANCE The findings of this cohort study suggest that the use of ADHD medication is associated with a lower risk of subsequent long-term unemployment for middle-aged women. These findings should be considered together with the existing knowledge of risks and benefits of ADHD medication when developing treatment plans for working-age adults.

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Key Points

Question Is pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD) associated with a lower unemployment rate among working-age adults?

Findings In this cohort study of 12 875 middle-aged adults with ADHD, the use of ADHD medications was associated with a 10% lower risk of long-term unemployment.

Meaning These findings suggest that pharmacological treatment is associated with lower risk of long-term unemployment in individuals with ADHD.

+ Supplemental content

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders, characterized by inattention and hyperactivity with or without impulsivity. Attention-deficit/hyperactivity disorder affects approximately 5.0% of children and adolescents and approximately 2.5% of adults worldwide.[1-3] Adults with ADHD have occupational impairments such as poor work performance, less job stability, financial problems,[4,5] and increased risk for unemployment.[6-8] However, less is known about the extent to which pharmacological treatment for ADHD is associated with reductions in unemployment rates.[9,10] This is a critical limitation, because long-term unemployment is associated with economic difficulties, worse mental and physical health, and higher mortality rates.[11-13]

Randomized clinical trials have demonstrated that pharmacological treatments of ADHD are effective in reducing the core features of ADHD in adults, including difficulty concentrating, poor planning, lack of organization, self-regulation deficits, forgetfulness, and impulsivity.[14,15] These findings suggest that pharmacological treatments of ADHD may also have positive effects on occupational outcomes, but results from the few previously published studies on this topic are inconsistent. Two Norwegian studies[8,16] found that early treatment of ADHD showed beneficial influences on being in work in adulthood, but similar work productivity was reported between individuals with ADHD treated with atomoxetine and placebo in US.[17] However, self-reported pharmacological treatment of ADHD and occupational outcomes, the small sample size, retrospective and cross-sectional study designs, and lack of information on potential confounders indicate that the available evidence is inconclusive. Therefore, this large-scale population-based cohort study aimed to investigate the association between use of pharmacological treatment of ADHD and long-term unemployment in working-age adults with ADHD. Measured and unmeasured confounders (eg, genetic factors) were taken into consideration by using between- and within-individual designs.

Methods

This cohort study was approved by the Regional Ethical Review Board in Stockholm, Sweden. The requirement for informed consent was waived by the board because the data were pseudonymized from registers. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Sources and Study Cohort

Data were obtained from the following Swedish registries. The Total Population Register[18] contains information on all migrations since 1969. The National Patient Register[19] contains data on psychiatric care, with diagnoses based on the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*), from 1987. The Prescribed Drug Register[20] includes detailed information on drug identity (Anatomical Therapeutic Chemical [ATC] code), date of the prescription, and dosage of all registered prescriptions for the whole population in Sweden since July 1, 2005. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA)[21] covers information on annual measures of occupation since 1990. The Cause of Death Register[22] contains information on all registered deaths since 1961.

We identified 25 358 individuals with ADHD who were born between 1958 and 1978 and were aged 30 to 55 years during the study period (January 1, 2008, to December 31, 2013) as the study population. Attention-deficit/hyperactivity disorder was defined by diagnosis (*ICD-10* code F90) from the National Patient Register or prescription of medications for ADHD (methylphenidate [ATC code N06BA04], amphetamine [ATC code N06BA01], dexamphetamine [ATC code N06BA02], lisdexamfetamine [ATC code N06BA12], and atomoxetine [ATC code N06BA09]) from the Prescribed Drug Register. The specific age range of 30 to 55 years was used because, in Sweden,

people younger than 30 years might still be studying, and those older than 55 years might withdraw from the labor market.[23] We excluded those with severe intellectual disability (n = 532) and who died or emigrated before 30 years of age or before 2008 (n = 3208). To ascertain that all individuals were in the labor force and at risk of unemployment at baseline, we further excluded those without paid work (having annual work-related income <41 800 Sk or €4461 in 2008) (n = 1407), who had a disability pension (n = 8677), and who were on long-term sick leave (>183 days) (n = 2544) in 2008, yielding a study population of 12 875 individuals. We followed up participants from January 1, 2008, until death, emigration, or December 31, 2013, whichever came first.

Measures

Long-term Unemployment

Yearly accumulated unemployed days were obtained from administrative records reported by the Public Employment Service (registered in the LISA register).[21] The variable equals zero for those who have never been registered as unemployed in each year. Consistent with previous studies,[24-26] long-term unemployment was defined as having 90 or more days of unemployment in a calendar year.

Pharmacological Treatment of ADHD During the Previous 2 Years

Pharmacological treatment of ADHD during the previous 2 years was used as the main exposure of the present study. The 2-year limit for defining exposure was chosen to examine the accumulative effects of long-term use of ADHD medications. The Prescribed Drug Register provides information on the date of dispensation from a pharmacy, drug identity according to ATC code, package size, number of packages dispensed, and free-text treatment instructions from the prescriber. We used a validated natural language–processing algorithm to estimate the duration of ADHD medication from free-text prescription in the Prescribed Drug Register.[27] We assessed the exposure as (1) treated status (ie, whether or not the individual was treated with ADHD medications during the previous 2 years) and (2) duration of treatment. Using 6 months as the time interval, we further classified the group with pharmacologically treated ADHD at 4 levels: treated for less than 6 months, 6 to less than 12 months, 12 to less than 18 months, and 18 to 24 months. We then use days on which medication was used as a continuous variable to test for a linear association between use of ADHD medications and risk of long-term unemployment, for which we used 90 days (3 months) as 1 unit.

Covariates

We identified age at baseline, sex, and country of birth (Sweden, another Nordic country [including Denmark, Finland, Norway, or Iceland], and others) from the Total Population Register; highest educational level attained (elementary [≤9 years], high school [10-12 years], and postgraduate education [>12 years]) from the LISA register; crime records (length of incarceration) from the National Crime Register; and psychiatric comorbidities (anxiety disorders, autism spectrum disorders, bipolar disorders, conduct disorders, depressive disorders, personality disorders, schizophrenia spectrum disorders, and substance use disorders) from the National Patient Register. The *ICD-10* codes are provided in eTable 1 in the Supplement.

Statistical Analysis

Data were analyzed from March 1, 2020, through May 31, 2021. Between-individual design was applied in the main analysis for the association between use of ADHD medications and long-term unemployment. Generalized estimating equations (GEE) with a log link were used to calculate the relative risks (RRs) and 95% CIs, with adjusting for age, sex, country of birth, highest educational level attained, and psychiatric disorders. Generalized estimating equations account for the interdependence between repeated within-individual measurements by assigning them a correlation structure. Sex-specific analyses were then conducted. We further examined the dose-response association between duration of use of ADHD medications and the risk of long-term unemployment

by using multivariate-adjusted restricted cubic spline function in the GEE model, with knots selected at 60, 180, 360, and 540 days of medication use.

Previous research has demonstrated that many individuals start, discontinue, and restart treatment with ADHD medication over time, although many individuals with ADHD may need longer-term and continued pharmacotherapy.[28] The within-individual variation of medication and unemployment status during the follow-up period is presented in eTable 2 in the Supplement. In the within-individual design, the unemployment status during years of medication use was compared with years of medication nonuse in the same individual during the follow-up period. We tested the association between use of ADHD medications and long-term unemployment using a conditional GEE model, with each individual as a separate cluster. Because each individual serves as their own control in this design, implicit adjustments were made for all the time-invariant confounders, including sex, genetic background, and severity of ADHD symptoms. We therefore only included age as a covariate in the conditional GEE model.

We also performed a series of subgroup and sensitivity analyses to test the robustness of the results. First, we stratified the analyses by age at baseline (30-40 vs 41-50 years),[29] educational attainment (≤9 vs >9 years),[6] and number of psychiatric comorbidities (0 vs ≥1),[30,31] because they are important factors associated with occupational outcomes among individuals with ADHD. Second, we examined whether incarceration influenced our findings. In the LISA register, all other forms of activities were contrasted with unemployment, including being employed and being out of the labor force.[32] In addition to disability and study activities, being in prison could also be registered as 0 days of unemployment, given the well-established association between ADHD and criminal behavior.[33] Therefore, we repeated the analyses by excluding those who were sentenced for more than 2 years during the study period. Third, we restricted the analyses among more recent years to test whether the results were sensitive to calendar year, given the increased trend of ADHD prescriptions over time worldwide.[34,35] Finally, we reran the analyses with use of ADHD medications in the most recent 3 years as exposure to test whether the results were robust when including the concurrent use of ADHD medications.

Data management was performed using SAS, version 9.4 (SAS Institute Inc), and data analyses were performed using R, version 4.0.5 (R Foundation for Statistical Computing). The package drgee was used for GEE analyses.[36] Two-sided $P < .05$ indicated statistical significance.

Results

Sociodemographic characteristics for the study population are presented in **Table 1**. The cohort consisted of 12 875 individuals (5343 women [41.50%] and 7532 men [58.50%]) with ADHD, and the mean (SD) age at baseline was 37.9 (5.6) years. Most participants were born in Sweden (11 443 [88.88%]) and had more than 9 years of education (10 253 of 12 629 with data available [81.19%]). A total of 8928 individuals (69.34%) had at least 1 diagnosis of comorbid psychiatric disorders. The most prevalent comorbidities of ADHD were depressive disorder (5186 [40.28%]), anxiety disorder (4541 [35.27%]), and substance use disorder (3704 [28.77%]). The mean length of medication use was 49 days per year (range, 0-366 days). During the follow-up period, 4024 individuals with ADHD among the 12 860 with medication data available (31.29%; 1690 of 5339 [31.65%] for women and 2334 of 7521 [31.03%] for men) never used ADHD medication. Among those who were treated with ADHD medications (8836 of 12 860 [68.71%]), only 416 (3.23%; 156 of 5339 [2.92%] for women and 260 of 7521 [3.46%] for men) had persistent medication use during the follow-up period. We further found that 4998 of 12 865 individuals with data available (38.85%; 1907 of 5341 [35.70%] for women and 3091 of 7524 [41.08%] for men) were recorded as having at least 1 long-term unemployment event (range, 0-6) across the study period, whereas 38 (0.30%; 8 of 5341 [0.15%] for women and 30 of 7524 [0.40%] for men) were registered as having long-term unemployment (>90 days) in each of those years.

In between-individual analysis (**Table 2**), we found use of ADHD medications during the previous 2 years was associated with a 10% lower risk of subsequent long-term unemployment (RR, 0.90 [95% CI, 0.87-0.95]) after adjusting for age, sex, birth country, highest educational level attained, and psychiatric comorbidities. An association between use of ADHD medication and long-term unemployment was found in women with ADHD (RR, 0.82; 95% CI, 0.76-0.89) but not in men with ADHD (RR, 0.96; 95% CI, 0.91-1.01; $P < .001$ for sex differences). When considering duration of treatment as a categorical variable, longer duration of ADHD medication use during the previous 2 years was associated with lower risk of long-term unemployment among women (RR for 1-6 months, 0.86 [95% CI, 0.78-0.95]; RR for 18-24 months, 0.72 [95% CI, 0.58-0.90]; $P < .001$ for trend). The associations remained in men, although the estimates appeared to be weaker, and statistically significant associations were only found among those who were prescribed ADHD medications for 6 to 12 months (RR, 0.90 [95% CI, 0.83-0.97]). Multivariable-adjusted restricted cubic spline analyses suggested a significant linear relationship between ADHD medication use during the previous 2 years and long-term unemployment (**Figure**) in women, which indicated that every additional unit of

Table 1. Sociodemographic and Clinical Characteristics of Study Patients

Characteristic	Patient population[a]		
	Total (N = 12 875)	Women (n = 5343)	Men (n = 7532)
Age at baseline, mean (SD), y	37.88 (5.60)	37.71 (5.52)	38.00 (5.66)
Country of birth			
Sweden	11 443/12 875 (88.88)	4758/5343 (89.05)	6685/7532 (88.75)
Denmark, Finland, Norway, or Iceland	335/12 875 (2.60)	141/5343 (2.64)	194/7532 (2.57)
Other	1097/12 875 (8.52)	444/5343 (8.31)	653/7532 (8.67)
Highest educational level attained			
0-9 y	2376/12 629 (18.81)	772/5273 (14.64)	1604/7356 (21.81)
10-12 y	6550/12 629 (51.86)	2540/5273 (48.17)	4010/7356 (54.51)
Postgraduate	3703/12 629 (29.32)	1961/5273 (37.19)	1742/7356 (23.68)
Psychiatric comorbidities			
Conduct disorder	80/12 875 (0.62)	18/5343 (0.34)	62/7532 (0.82)
Autism spectrum disorder	983/12 875 (7.63)	377/5343 (7.05)	606/7532 (8.05)
Substance use disorder	3704/12 875 (28.77)	1102/5343 (20.63)	2602/7532 (34.55)
Depressive disorder	5186/12 875 (40.28)	2405/5343 (45.01)	2781/7532 (36.92)
Bipolar disorder	1460/12 875 (11.34)	751/5343 (14.05)	709/7532 (9.41)
Anxiety disorder	4541/12 875 (35.27)	2053/5343 (38.42)	2488/7532 (33.03)
Schizophrenia	67/12 875 (0.52)	13/5343 (0.24)	54/7532 (0.72)
Personality disorder	1485/12 875 (11.53)	691/5343 (12.93)	794/7532 (10.54)
Any of above	8928/12 875 (69.34)	3753/5343 (70.24)	5175/7532 (68.71)
No. of psychiatric comorbidities			
0	3947/12 875 (30.66)	1590/5343 (29.76)	2357/7532 (31.29)
1	3715/12 875 (28.85)	1524/5343 (28.52)	2191/7532 (29.09)
2	2811/12 875 (21.83)	1204/5343 (22.53)	1607/7532 (21.33)
≥3	2402/12 875 (18.66)	1025/5343 (19.18)	1377/7532 (18.28)
Treated status during the follow-up period			
No medication	4024/12 860 (31.29)	1690/5339 (31.65)	2334/7521 (31.03)
Medication use	8420/12 860 (65.47)	3493/5339 (65.42)	4927/7521 (65.51)
Persistent medication use	416/12 860 (3.23)	156/5339 (2.92)	260/7521 (3.46)
Long-term unemployment during the follow-up period			
Never	7867/12 865 (61.15)	3434/5341 (64.30)	4433/7524 (58.92)
At least once long-term unemployment	4960/12 865 (38.55)	1899/5341 (35.55)	3061/7524 (40.68)
Persistent long-term unemployment	38/12 865 (0.30)	8/5341 (0.15)	30/7524 (0.40)

[a] Unless otherwise indicated, data are expressed as number/total number (%) of patients. Owing to missing data, denominators may not equal totals in column headings.

treatment duration (90 days) reduced the risk of long-term unemployment by 4% (Table 2). Consistent associations were found in the within-individual analysis (**Table 3**), and similar association patterns by sex were also observed (RR for the whole population, 0.89 [95% CI, 0.85-0.94]; RR for women, 0.84 [95% CI, 0.77-0.91]; and RR for men, 0.92 [95% CI, 0.87-0.99]).

Table 2. Associations Between ADHD Medication Use and Long-term Unemployment Status

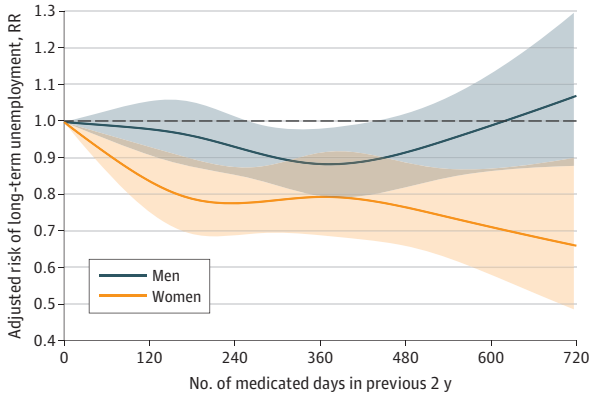
	Between-patient design, RR (95%CI)		
Use of ADHD medication status	Total[a]	Women[b]	Men[b]
Treated			
No	1 [Reference]	1 [Reference]	1 [Reference]
Yes	0.90 (0.87-0.95)	0.82 (0.76-0.89)	0.96 (0.91-1.01)
Duration of treatment, mo			
0	1 [Reference]	1 [Reference]	1 [Reference]
<6	0.95 (0.90-0.99)	0.86 (0.78-0.95)	0.99 (0.93-1.06)
6 to <12	0.86 (0.81-0.92)	0.80 (0.71-0.89)	0.90 (0.83-0.97)
12 to <18	0.91 (0.80-0.99)	0.78 (0.65-0.94)	0.98 (0.87-1.10)
18 to 24	0.90 (0.80-1.00)	0.72 (0.58-0.90)	0.99 (0.87-1.13)
P value for trend	<.001	<.001	.77
Days of medication use as continuous variable	0.98 (0.97-1.00)	0.96 (0.94-0.99)	1.00 (0.98-1.02)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; RR, relative risk.

[a] Adjusted for age, sex, birth country, highest educational level attained, and psychiatric comorbidities.

[b] Adjusted for age, birth country, highest educational level attained, and psychiatric comorbidities.

Figure. Association of the Use of Medication for Attention-Deficit/Hyperactivity Disorder (ADHD) and Risk of Long-term Unemployment



Relative risks (RRs) for long-term unemployment by days of medication use during the previous 2 years using restricted cubic spline and adjusted for age, birth country, highest educational level attained, and psychiatric comorbidities were adjusted. Knots were set at 60, 180, 360, and 540 days of medication use. The dashed line indicates that there is no association between the use of medications and long-term unemployment (RR = 1.00). Shaded areas indicate 95% CIs.

Table 3. Associations Between Use of ADHD Medication and Long-term Unemployment Status Using Within-Patient Design

	Within-patient design, RR (95%CI)[a]		
Use of ADHD medication status	Total	Women	Men
Treated			
No	1 [Reference]	1 [Reference]	1 [Reference]
Yes	0.89 (0.85-0.94)	0.84 (0.77-0.91)	0.92 (0.87-0.99)
Duration of treatment, mo			
0	1 [Reference]	1 [Reference]	1 [Reference]
<6	0.93 (0.87-0.98)	0.87 (0.78-0.96)	0.96 (0.89-1.03)
6 to <12	0.84 (0.79-0.91)	0.80 (0.71-0.91)	0.87 (0.80-0.95)
12 to <18	0.90 (0.81-1.00)	0.85 (0.71-1.03)	0.93 (0.82-1.06)
18 to 24	0.90 (0.80-1.02)	0.80 (0.63-1.01)	0.95 (0.82-1.10)
P value for trend	<.001	<.001	.03
Days of medication use as continuous variable	0.97 (0.96-0.99)	0.96 (0.94-0.98)	0.98 (0.96-1.00)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; RR, relative risk.

[a] Adjusted for age.

Subgroup and Sensitivity Analyses

Table 4 presents results from the subgroup and sensitivity analyses. First, when stratifying the analyses by age at baseline, all associations presented generally similar patterns to those noted in the main analysis, but the protective association of using ADHD medication during the previous 2 years with long-term unemployment was slightly stronger among younger adults (RR, 0.89; 95% CI, 0.85-0.95) than older adults (RR, 0.93; 95% CI, 0.86-0.99). Second, the associations were stronger among those with more than 9 years of education (RR, 0.88; 95% CI, 0.84-0.93). Among those with less than 9 years of education (2376 of 12 629 [18.81%]), all associations were attenuated toward null. Third, when stratifying the analyses by presence or absence of psychiatric comorbidities, similar protective association patterns remained in both groups. Fourth, during the study period, a total of 3206 individuals (24.90%; 2528 men [33.56%] and 678 women [12.69%]) had at least 1 crime

Table 4. Associations Between ADHD Medication Use and Long-term Unemployment Status by Number of Psychiatric Comorbidities

	RR (95%CI)		
Variable	Whole population[a]	Women[b]	Men[b]
Subgroups analyses			
Baseline age			
30-40 y			
Treated vs untreated	0.89 (0.85-0.95)	0.81 (0.74-0.89)	0.95 (0.89-1.01)
Days of medication use as continuous variable	0.99 (0.97-1.01)	0.97 (0.94-1.00)	0.97 (0.89-1.06)
41-50 y			
Treated vs untreated	0.93 (0.86-0.99)	0.84 (0.74-0.89)	0.97 (0.87-1.08)
Days of medication use as continuous variable	0.98 (0.96-1.01)	0.96 (0.92-1.01)	0.99 (0.97-1.03)
Educational attainment			
≤9 y			
Treated vs untreated	0.88 (0.84-0.93)	0.82 (0.75-0.89)	0.92 (0.87-0.98)
Days of medication use as continuous variable	0.98 (0.97-1.00)	0.97 (0.94-0.99)	0.99 (0.97-1.02)
>9 y			
Treated vs untreated	1.00 (0.92-1.10)	0.84 (0.70-0.10)	1.06 (0.96-1.18)
Days of medication use as continuous variable	1.00 (0.97-1.03)	0.98 (0.91-1.02)	1.01 (0.98-1.05)
Psychiatric comorbidities			
None			
Treated vs untreated	0.91 (0.83-1.00)	0.98 (0.92-1.04)	0.91 (0.81-1.02)
Days of medication use as continuous variable	0.97 (0.95-1.00)	0.92 (0.91-1.01)	0.98 (0.94-1.01)
≥1			
Treated vs untreated	0.91 (0.87-0.96)	0.80 (0.73-0.87)	0.92 (0.78-1.07)
Days of medication use as continuous variable	0.99 (0.98-1.01)	0.98 (0.95-1.00)	1.01 (0.99-1.03)
Sensitivity analyses			
Criminal records			
<2 y			
Treated vs untreated	0.90 (0.86-0.94)	0.82 (0.76-0.89)	0.95 (0.89-1.00)
Days of medication use as continuous variable	0.99 (0.97-1.00)	0.97(0.94-0.99)	0.97 (0.94-0.99)
More recent years (2011-2013)			
Treated vs untreated	0.93 (0.89-0.98)	0.84 (0.77-0.92)	0.99 (0.98-1.06)
Days of medication use as continuous variable	0.99 (0.97-1.00)	0.96(0.94-0.99)	0.99 (0.97-1.01)
Medication use in recent 3 years			
Treated vs untreated	0.95 (0.91-0.98)	0.89 (0.83-0.96)	0.98 (0.93-1.03)
Days of medication use as continuous variable	0.98 (0.97-0.99)	0.98 (0.98-0.99)	0.99 (0.98-1.00)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; RR, relative risk.

[a] Adjusted for age, sex, birth country, highest educational level attained, and psychiatric comorbidities.

[b] Adjusted for age, birth country, highest educational level attained, and psychiatric comorbidities.

record during the study period. Similar patterns of associations were observed after excluding those with a total sentence duration for longer than 2 years (624 [4.85%]). Fifth, when we limited the analyses to more recent years or use of ADHD medication in the most recent 3 years as exposure, the estimates were slightly attenuated but generally consistent with main analyses. All these associations were robust when use of ADHD medication was a continuous variable.

Discussion

To our knowledge, this is the largest population-based longitudinal study to assess the association of pharmacological treatment of ADHD with subsequent long-term unemployment among middle-aged adults. We found that among individuals with ADHD, the use of ADHD medications during the previous 2 years was associated with a decreased risk of subsequent long-term unemployment, especially in women. Longer duration of treatment with ADHD medication was associated with lower risk of long-term unemployment among women.

Our findings strengthen and extend previous literature in 3 important ways. First, the longitudinal cohort study was from a large population-based sample of adults with ADHD in the middle of their working lives and used reliable measurements of both ADHD and unemployment. Second, this is the first population-based study, to our knowledge, to explore potential sex differences in response to pharmacological treatment of ADHD. We found that use of ADHD medications in women showed stronger negative associations with long-term unemployment than in men. These findings may be consistent with several clinical trials on ADHD medications reporting greater improvement in ADHD symptoms[37] and some functional outcomes (eg, social life and family functioning, well-being)[38,39] among women than in men. These findings are, nevertheless, inconsistent with findings from other clinical trials that have reported the reverse[40] or no sex differences[41] in response to these medications. However, based on the equivocal evidence, it is largely unknown whether there are true differences in the effectiveness of ADHD medications between men and women. Although differences in pharmacokinetics and pharmacodynamics across men and women[42,43] are well-established, our observed differences may be explained by other factors that differ between men and women, such as the unemployment rates, educational attainment, or symptom severity. Moreover, women with ADHD might be more likely to seek and adhere to nonpharmacological treatment than men.[44] These alternative explanations need to be explored in future research. Third, in observational studies, in which treatment allocation is not random, possible confounders may lead to biased estimates of the associations. Therefore, we performed within-individual analyses, subgroup analyses, and sensitivity analyses to control for unmeasured and measured confounders. We found robust results in these analyses, although the associations in some subgroups (eg, low educational attainment) were not statistically significant, probably owing to power issues. Other factors (eg, the developmental course of other comorbid conditions and the initial use of other psychotropic medications) could also explain the observed associations; therefore, our findings need to be replicated in studies from other settings and using other study designs.

Our results are consistent with the emerging evidence from systematic reviews of the available evidence from observation studies,[9,10,45] indicating that use of ADHD medication is associated with a lower risk of several functional problems (eg, academic performance, social function). Although our observed effect size may be viewed as small in magnitude, a reduction of 10% in the risk of long-term unemployment might translate into a substantial decrement of the economic burden at the societal level. Regardless, the small effect size suggested that other treatment programs, such as psychotherapy, are also needed to help individuals with ADHD in work-related settings.

Limitations

The present study has several limitations. First, the register-based data mainly capture more severe ADHD cases and individuals actively looking for work through the official employment agency in

Sweden. In addition, no data on ADHD symptoms and underlying reasons for unemployment are available in the national registers to further explain the mechanisms of the observed association. Also, given the specific economic, political, and cultural factors in Sweden, the findings may not generalize to other countries. Second, the current study focused on middle-aged adults, who usually have greater family responsibilities and financial strain than those in other age groups. Thus, the associations between ADHD medication use and long-term unemployment might be different among younger or older adults. However, an issue addressed during the previous studies is the misclassification caused by unemployed and economically inactive individuals (eg, studying, sick leave, or in prison)[25]; therefore, we strived to ensure that the study population only included those belonging to the workforce. As a consequence, we may have underestimated the associations if some of the sick leave or disability pension was caused by ADHD. Third, nonpharmacological interventions for adult ADHD (not in the registers) could also contribute to the effectiveness of pharmacological treatment on occupational outcomes; therefore, the generalizability of our results may be sensitive to the presence of nonpharmacological treatments. However, given that the results were robust across subgroup, sensitivity, and between- and within-individual analyses, the effect of nonpharmacological treatments might be limited. Further, the effectiveness of nonpharmacological treatments of adult ADHD for improving functional impairments was largely unclear according to a recent systematic review of randomized clinical trials[46]; therefore, this is an area that should be explored in future research. Fourth, owing to data constraints, we were not able to test the potential different effectiveness of stimulant and nonstimulant ADHD medications on long-term unemployment. Therefore, future comparative effectiveness studies are needed to explore the effect of different types of medications on occupational outcomes in adults.

Conclusions

In this population-based longitudinal cohort study of middle-aged adults with ADHD, we found an association between the use of ADHD medications and lower risk of subsequent long-term unemployment, especially in women. The potential beneficial associations of medication use with long-term unemployment should be carefully weighed against potential adverse effects of medication. Future research should further explore the effectiveness of stimulant and nonstimulant ADHD medications and replicate our findings in other settings.

ARTICLE INFORMATION

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SUPPLEMENT.

eTable 1. *International and Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) (1997-2013), Codes From the Swedish National Patient Register for All Comorbidities in the Study

eTable 2. Different Levels of Within-Individual Variation of Medication Use and Unemployment Days per Year During the Follow-up Period