Vestergaard *et al. BMC Psychiatry* (2026) 26:191
https://doi.org/10.1186/s12888-026-07824-5

BMC Psychiatry

RESEARCH Open Access

Comorbidities and comedication among individuals in treatment for ADHD: a Danish nationwide study

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Abstract

Objectives To examine the prevalence of comorbidities and the use of psychiatric comedication among individuals in medical treatment for attention deficit hyperactivity disorder (ADHD), in comparison to a matched control group from the general population.

Methods This nationwide case-control study included 1,082,378 Danish individuals aged 7–64 of whom 98,398 had at least one prescription of ADHD medication during 2023. Data was collected over an observation period spanning from 2013 to 2023. Cases were matched to controls (1:10) from the general population on birth year and sex. Data were obtained and accessed through The Danish Health Data Authority. Associations were estimated using conditional logistic regression models.

Results Somatic and particularly psychiatric comorbidities were more common among individuals in ADHD treatment across all age groups. Among those in ADHD treatment 46.7% had at least one comorbidity compared to 23.3% in the control group. The use of psychiatric comedications (besides ADHD medication) was likewise more common among individuals in ADHD treatment (32.7%) compared to the controls (7.2%). The association estimates from conditional logistic regression revealed a higher likelihood of somatic and psychiatric comorbidities among those in ADHD treatment in all age groups. Females in ADHD treatment had 4.48–4.50 times higher odds of comorbidities compared to females not in ADHD treatment ($OR_{7-17\ years}$ = 4.48, 95% CI: 4.27–4.70; $OR_{18-29\ years}$ = 4.50, 95% CI: 4.37–4.64). Similar patterns were observed for males but with slightly lower ORs ($OR_{7-17\ years}$ = 2.35, 95% CI: 2.27–2.44; $OR_{18-29\ years}$ = 3.38, 95% CI: 3.28–3.50).

Conclusion This study reveals that both prevalence of somatic and psychiatric comorbidities and the use of psychiatric comedication are significantly higher among individuals in ADHD treatment. The highest occurrence is seemingly among females aged 7–17 year and 18–29 years. The coexistence of ADHD with other somatic and psychiatric conditions can constitute a more complex disease burden, necessitating enhanced disease management strategies to reduce complications and enhance quality of life. Longitudinal studies are needed to confirm the temporal association of these results.

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Keywords Attention deficit hyperactivity disorder (ADHD), ADHD medications, Comedication, Psychiatric medications, Polypharmacy, Somatic comorbidities, Psychiatric comorbidities

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopment disorder that originates in early childhood and continues to impact into adulthood [1]. In Denmark, it is estimated that 2.52% of the population have ADHD [1]. Specially for the 18-27-year-olds, the prevalence has been estimated to be 8.16% among men and 6.12% among women [1]. ADHD is diagnosed 1.5–2.5 times more in boys than girls, but this gap narrows by mid-adulthood due to differences in symptom presentation [2, 3].

Individuals with ADHD have difficulties in the brain's executive functions, affecting problem-solving, planning, and organizing daily activities [4, 5]. This often leads to significant learning and social challenges in children, while adolescents and adults may struggle with maintaining education and employment [4, 5]. In addition to personal and social challenges, previous studies have shown that ADHD imposes a substantial economic burden both for the individuals and for the society [6]. The most significant economic burden for adults arises from productivity and income losses, whereas for children, the primary cost categories include healthcare utilization and educational support [7].

Studies have shown that individuals with ADHD more often experience the coexistence of other psychiatric disorders and psychiatric comedication compared to the general population [8–11]. Additionally, a Nordic register-based study suggested that the use of psychotropic comedication increased with age and was more pronounced among females than males [9]. Particularly for younger individuals with ADHD studies have suggested a higher susceptibility to a range of somatic diseases, such as metabolic syndrome, disorders of chronic inflammation, and cardiovascular disorders [12–15]. The coexistence of ADHD with other somatic and psychiatric conditions together with the use of psychiatric comedication has been associated with an enhanced risk of severe illness compared to ADHD alone, and further an increased risk of hospital contacts, reduced quality of life, and mortality [16–19]. Furthermore the use of comedication among ADHD patients can complicate the management of ADHD and other comorbid conditions [8, 20]. Studies examining the co-occurrence of somatic comorbidities among individuals with ADHD are limited, so are Danish studies on psychiatric comedication.

Understanding the co-occurrence of comorbidities and the use of psychiatric comedication among individuals with ADHD is essential, since this coexistence can constitute a more complex disease burden necessitating enhanced disease management strategy to reduce complications and enhance the quality of life of these patients. Leveraging on the unique Danish health registries, the overall objective of this nationwide study was to examine the prevalence and patterns of the coexistence of selected somatic and psychiatric comorbidities as well as the use of psychiatric comedication among all Danish individuals 7–64 years of age in medical treatment for ADHD.

Method

Study population

In this study, we assembled a nationwide Danish cohort of individuals in medical treatment for ADHD during 2023. These were identified by having at least one redeemed prescription of ADHD medications in 2023 registered in the Danish National Prescription Register [21]. We excluded individuals who had a diagnosis of narcolepsy (ICD-10 code: G49) as some ADHD medications are used to treat both ADHD and narcolepsy. We matched cases on birth year and sex with a randomly selected 1:10 control group from the general population not in medical treatment for ADHD. The control group was defined solely by the absence of ADHD medication treatment in 2023, enabling a comparison between individuals in treatment for ADHD and those not registered with a treatment for ADHD. This resulted in a study population of 1,082,378 individuals between 7 and 64 years of age who were alive and residing in Denmark in 2023 (Fig. 1). The study population was subsequently divided into the following age groups: 7–17, 18–29, 30–49, and 50–64 years.

Data were obtained, processed, and stored at The Danish Health Data Authority. Linkage between the registers was possible through the unique personal identification number assigned to all persons with permanent residence in Denmark [22].

ADHD

Medical treatment for ADHD includes the following stimulants: dexamfetamine (ATC code: N06BA02), methylphenidate (ATC code: N06BA04), lisdexamfetamine (ATC code: N06BA12), and two non-stimulants: Guanfacine (ATC code: C02AC02) and atomoxetine (ATC code: N06BA09).

Treatment duration was calculated as the time between the first and last prescription redemption and operationalized into four groups: One prescription, ≤ 6 months, 6–12 months, and > 12 months. Treatment discontinuation was defined as more than 6 months between redemptions [8, 23–25]. We identified all treatment

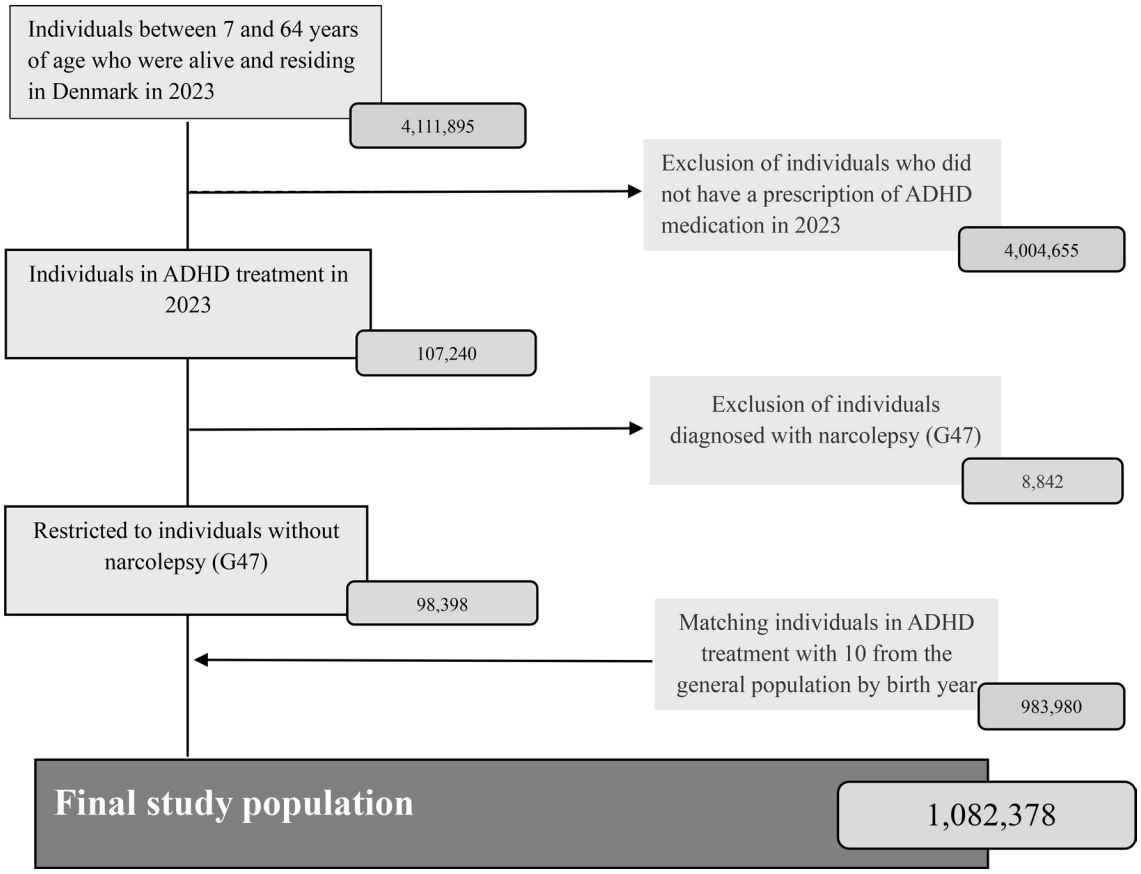

Fig. 1 Flow chart of the eligible study population aged 7–64 in ADHD treatment in 2023

periods overlapping into 2023. If a patient had multiple treatment periods, only the longest period overlapping into 2023 was included in the analysis.

Comorbidities and psychiatric comedications

Information on somatic and psychiatric comorbidities was identified from the Danish National Patient Registry in the period from 2013 to 2023 [26]. A priori, we selected 19 comorbidities based on the literature and that further coincided with the National Health Profile 2021 [27]. These consisted of Asthma, Chronic Lung Diseases, Rheumatoid Arthritis, Osteoarthritis, Osteoporosis, Herniated Disc and Other Back Problems, Diabetes, Allergy, Hypertension, Angina Pectoris, Acute Myocardial Infarction, Neoplasms, Stroke, Migraine, Cataract, Tinnitus, Schizophrenia and Related Disorders, Affective Disorders, Anxiety and Stress-Related Disorders (Supplementary file 1). Somatic and psychiatric comorbidities were operationalized separately in different ways; individually, as a binary variable (yes/no) indicating the coexistence of minimum one comorbidity, as a categorical variable indicating the number of comorbidities (1, 2, 3–4, 5+), and finally as the mean number of comorbidities among those with comorbidities.

In a sensitivity analysis, we further estimated the mean number of comorbidities among all study participants, and the proportion of individuals with comorbidities (yes/no) stratified by age and sex.

Information on the use of psychiatric comedications was obtained from the National Prescription Registry [21]. Psychiatric medication (besides ADHD medication) was included if prescribed in 2023. The included medications consisted of: Antipsychotic drugs, antidepressive drugs, sedative drugs, and sleeping drugs (Supplementary file 2). The operationalization was performed in line with comorbidities. For both comorbidities and psychiatric comedication, these may occur either before or after the redemption of ADHD medication. As this is a cross-sectional case-control study, no conclusions regarding temporality can be drawn from this.

Statistical analysis

Descriptive statistics were used to summarize the distribution of sex and age in the study population, ADHD treatment duration, and the number of ADHD medications. We used the Chi-squared test and t-test to assess heterogeneity between the groups. Conditional logistic regression analysis was applied to estimate the odds ratio

(OR) and 95% confidence intervals (95% CI) for the association between ADHD treatment and the coexistence of comorbidities. We adjusted for place of residence. Due to the assumption that the impact of ADHD treatment on comorbidities may differ across both sex and age, we explored these differences by evaluating first-order interaction for both sex and ADHD treatment, and between age and ADHD treatment. Since the tests indicated interaction for both sex (P = < 0.0001*) and age (P = < 0.0001*), we stratified the models by age and sex.

We conducted several sensitivity analyses to assess the robustness of our findings under varying conditions. In a sensitivity analyses, we age-stratified the prevalence of comorbidities among males and females. Secondly, we estimated the mean number of comorbidities and psychiatric comedication for the entire study population including individuals with and without comorbidities/psychiatric comedication. Lastly, we conducted a sensitivity analysis restricting the population to individuals registered in hospital with an ADHD diagnosis since 1995 (ICD-10: F90) to reflect if more severe cases affected our findings.

All statistical procedures were performed using R (RCore Team, 2022), and RStudio (Rstudio Team, 2022).

Results

We identified 98,398 Danish individuals aged 7 to 64 who had redeemed at least one prescription of ADHD medication in 2023 (Fig. 1) Overall, most individuals in ADHD treatment were between 18 and 49 years of age. ADHD treatment was more common among males (65%) among individuals aged 7–17 years old (Table 1). However, with increasing age, the sex difference reversed slightly, with more females (53.3%) than males (46.7%) in ADHD treatment in the older age groups aged 50–64. For all age groups, we found that most individuals were treated with only one ADHD medication in 2023, and the majority had been in ADHD treatment for more than 12 months. For the latter, the proportion of individuals who had been treated for 12 months or longer increased with increasing age.

Somatic and psychiatric comorbidities

The prevalence of somatic and psychiatric comorbidities was higher among individuals in ADHD treatment compared to the controls. The prevalence increased with age, except for schizophrenia, affective disorders, allergies, anxiety, and asthma (Table 2, supplementary file 3).

Individuals in ADHD treatment were overrepresented in all numbers of comorbidity categories (1, 2, 3–4, and 5 + comorbidities) compared to the control group. We found that 46.7% of individuals in ADHD treatment had at least one comorbidity, whereas this percentage was only 23.3% among controls. Among individuals with

Table 1 Patterns of ADHD medication prescriptions among ADHD patients

Characteristics	ADHD drug users				Control group			
	Children (7–17 years)	Young adults (18–29 years)	Middle-aged-adults (30–49 years)	Older adults (50–64 years)	Children (7–17 years)	Young adults (18–29 years)	Middle-aged-adults (30–49 years)	Older adults (50–64 years)
Total	22,797	34,538	32,874	8,189	227,916	345,446	328,743	81,875
Sex (%)								
Females	7,973 (35.0%)	18,479 (53.5%)	16,738 (50.9%)	4,365 (53.3%)	79,724 (35.0%)	184,818 (53.5%)	167,368 (50.9%)	43,640 (53.3%)
Males	14,824 (65.0%)	16,059 (46.5%)	16,136 (49.1%)	3,824 (46.7%)	148,192 (65.0%)	160,628 (46.5%)	161,375 (49.1%)	38,235 (46.7%)
Number of different ADHD medications (%)								
1	17,872 (78.4%)	27,700 (80.2%)	26,149 (79.5%)	6,796 (83.0%)	-	-	-	-
2	4,017 (17.6%)	5,617 (16.3%)	5,428 (16.5%)	1,149 (14.0%)	-	-	-	-
3+	908 (4.0%)	1,221 (3.5%)	1,297 (3.9%)	244 (3.0%)	-	-	-	-
Duration of ADHD medication (%)								
Single prescription[a]	624 (2.7%)	1,156 (3.3%)	666 (2.0%)	97 (1.2%)	-	-	-	-
Short term (≤ 6 months)	3,493 (15.3%)	4,928 (14.3%)	3,137 (9.5%)	393 (4.8%)	-	-	-	-
Medium-term (6–12 months)	3,668 (16.1%)	5,475 (15.9%)	3,685 (11.2%)	532 (6.5%)	-	-	-	-
Long-term (> 12 months)	15,012 (65.9%)	22,979 (66.5%)	25,386 (77.2%)	7,167 (87.5%)	-	-	-	-

[a] Single prescription here entails single dispensed prescriptions of any ADHD medication. Switching between different types of ADHD medications is not captured by this number

comorbidities, those in ADHD treatment had a significantly higher mean of 1.59 comorbidities, whereas those in the control group had a mean of 1.40 comorbidities. In contrast, the mean number of comorbidities (Supplementary file 6) in the entire study population was 0.74 for individuals in ADHD treatment compared to 0.33 for controls.

Psychiatric comedications

Individuals in ADHD treatment had a higher use of other psychiatric medications compared to the control group (Table 3). Specifically, we observed that 32.7% of those in ADHD treatment also used other psychiatric drugs compared to just 7.2% in the control group. Additionally, among individuals with psychiatric comedication, those in ADHD treatment had a significantly higher mean of 1.31 psychiatric medications, whereas the control group had a mean of 1.21 psychiatric comedications. In contrast, the mean number of comedications (Supplementary file 7) in the entire study population was 0.43 for individuals in ADHD treatment compared to 0.09 for those in the control group.

Association between medical treatment for ADHD and comorbidities

Individuals in ADHD treatment had higher odds of comorbidities across all age groups compared to the control group with particularly increased odds among females (Fig. 2). Females in the younger age groups had a 4.48–4.50 times higher likelihood of comorbidities than the control group ($OR_{7-17\ years}$ = 4.48, 95% CI: 4.27–4.70; $OR_{18-29\ years}$ = 4.50, 95% CI: 4.37–4.64). The same patterns were observed for men with slightly lower association estimates. Females aged 50–64 had 3.16 times higher likelihood of comorbidities compared to the control group (95% CI: 2.97–3.37), while males in the same age range had 2.90 times higher likelihood (95% CI: 2.72–3.09). Supplementary files 4 and 5 present age-stratified comorbidity prevalence, showing an increase in prevalence with age in both males and females, with consistently higher rates in ADHD treatment groups. Moreover, the prevalence of comorbidities was higher among women than men in both the ADHD treatment groups and control groups. This difference was particularly pronounced in the 18–29 age group, where 54.4% of women receiving ADHD medication had at least one comorbidity compared to 38.7% of men in the same age group (Supplementary files 4 and 5). We also found stronger associations when restricting the population to individuals with both treatment and ADHD diagnosis in 2023 (Supplementary file 9).

Discussion

This nationwide Danish study of more than 1 million individuals provides a comprehensive overview of comorbidities and psychiatric comedication patterns among individuals in ADHD treatment. We demonstrated that more males than females were treated with ADHD medications among children. However, the gap changes by young adulthood, where most individuals in ADHD treatment were females. Psychiatric comedication was likewise more common among individuals in ADHD treatment. Our results demonstrated that the likelihood of comorbidities was increased for individuals in ADHD treatment, especially among females aged 7–17 and 18–29 years, compared to the control group.

Our results complement previous literature showing that being in ADHD treatment is associated with a higher risk of comorbidities, such as anxiety, sleeping disorders, depression, and psychotic disorders [8–10, 12–14, 28]. We found an increased prevalence of comorbidities among both children and adults in ADHD treatment. This aligns with research demonstrating that children with ADHD have significantly higher rates of anxiety (18% vs. 2%) and depression (14% vs. 1%) compared to the general population [29], and adults with ADHD had a higher prevalence of psychiatric comorbidities including anxiety, depression, bipolar disorder, personality disorders, schizophrenia, and substance use disorder when compared to the general population [30, 31]. While substantial evidence links ADHD to psychiatric comorbidities, fewer studies have examined its association with specific somatic conditions [12–14]. Surprisingly, we found significant differences in the prevalence of all somatic diseases between the two groups with a higher prevalence among individuals in ADHD treatment. A previous study has identified associations between ADHD and various somatic conditions including asthma, migraine, diabetes, hypertension, myocardial infarction, allergies, and rheumatoid arthritis, which is consistent with the findings of our study [15].

In line with this, a systematic review found links between ADHD and somatic conditions like migraine, asthma, and allergy [32], aligning with our findings of higher prevalence among individuals in ADHD treatment. However, they found no association with rheumatoid arthritis, which we observed, and they reported a negative/no association between diabetes and ADHD [32], which contrasts with the prevalence distribution in our study where the prevalence is higher among individuals in ADHD treatment. Differences in findings between this study and the systematic review may be related to differences in definitions of exposure, smaller sample sizes, and the fact that the presence of diabetes and rheumatoid arthritis are self-reported in two of the referenced studies. Several mechanisms have been proposed to

Table 2 Prevalence of Somatic and Psychiatric Comorbidities among ADHD drug users Compared with the Control Group

Type of disorders [a]	ADHD drug users *n* (%)[b]	Control group *n* (%)[b]	*P*-value [c]
Asthma			<0.0001
Children (7-17 years)	1,497 (6.6)	10,991 (4.8)	
Young adults (18-29 years)	1,500 (4.3)	9,637 (2.8)	
Middle-aged adults (30-49 years)	1,410 (4.3)	7,675 (2.3)	
Older adults (50-64 years)	394 (4.8)	2,365 (2.9)	
Chronic lung diseases			<0.0001
Children (7-17 years)	269 (1.2)	1,907 (0.8)	
Young adults (18-29 years)	137 (0.4)	1,007 (0.3)	
Middle-aged adults (30-49 years)	422 (1.3)	1,680 (0.5)	
Older adults (50-64 years)	341 (4.2)	1,438 (1.8)	
Rheumatoid arthritis			<0.0001
Children (7-17 years)	202 (0.9)	1,772 (0.8)	
Young adults (18-29 years)	248 (0.7)	1,596 (0.5)	
Middle-aged adults (30-49 years)	662 (2.0)	4,459 (1.4)	
Older adults (50-64 years)	300 (3.7)	2,291 (2.8)	
Herniated disc and other back problems			<0.0001
Children (7-17 years)	602 (2.6)	4,812 (2.1)	
Young adults (18-29 years)	2,192 (6.3)	15,587 (4.5)	
Middle-aged adults (30-49 years)	4,401 (13.4)	28,179 (8.6)	
Older adults (50-64 years)	1,655 (20.2)	10,933 (13.4)	
Diabetes			<0.0001
Children (7-17 years)	102 (0.4)	1,017 (0.4)	
Young adults (18-29 years)	290 (0.8)	2,250 (0.7)	
Middle-aged adults (30-49 years)	616 (1.9)	3,966 (1.2)	
Older adults (50-64 years)	314 (3.8)	2,574 (3.1)	
Allergy			<0.0001
Children (7-17 years)	819 (3.6)	7,648 (3.4)	
Young adults (18-29 years)	1,013 (2.9)	8,484 (2.5)	
Middle-aged adults (30-49 years)	946 (2.9)	7,080 (2.2)	
Older adults (50-64 years)	172 (2.1)	1,465 (1.8)	
Hypertension			<0.0001
Children (7-17 years)	81 (0.4)	195 (0.1)	
Young adults (18-29 years)	211 (0.6)	841 (0.2)	
Middle-aged adults (30-49 years)	722 (2.2)	4,479 (1.4)	
Older adults (50-64 years)	646 (7.9)	5,066 (6.2)	
Migraine			<0.0001
Children (7-17 years)	370 (1.6)	2,778 (1.2)	
Young adults (18-29 years)	1,002 (2.9)	7,125 (2.1)	
Middle-aged adults (30-49 years)	1,233 (3.8)	8,128 (2.5)	
Older adults (50-64 years)	326 (4.0)	1,873 (2.3)	
Tinnitus			<0.0001
Children (7-17 years)	32 (0.1)	205 (0.1)	
Young adults (18-29 years)	106 (0.3)	521 (0.2)	
Middle-aged adults (30-49 years)	195 (0.6)	1,376 (0.4)	
Older adults (50-64 years)	138 (1.7)	919 (1.1)	
Schizophrenia and related disorders			<0.0001
Children (7-17 years)	387 (1.7)	683 (0.3)	
Young adults (18-29 years)	1,815 (5.3)	6,256 (1.8)	
Middle-aged adults (30-49 years)	1,419 (4.3)	5,220 (1.6)	
Older adults (50-64 years)	225 (2.7)	898 (1.1)	
Affective disorders			<0.0001
Children (7-17 years)	729 (3.2)	1,381 (0.6)	
Young adults (18-29 years)	6,124 (17.7)	15,180 (4.4)	
Middle-aged adults (30-49 years)	6,102 (18.6)	12,826 (3.9)	
Older adults (50-64 years)	1,454 (17.8)	2,532 (3.1)	
Anxiety and stress-related disorders			<0.0001

Table 2 (continued)

Type of disorders [a]	ADHD drug users *n* (%)[b]	Control group *n* (%)[b]	*P*-value [c]
Children (7-17 years)	4,289 (18.8)	7,177 (3.1)	
Young adults (18-29 years)	9,930 (28.8)	28,062 (8.1)	
Middle-aged adults (30-49 years)	8,186 (24.9)	22,506 (6.8)	
Older adults (50-64 years)	1,654 (20.2)	4,216 (5.1)	
Chronic diseases			
No	52,407 (53.3)	754,921 (76.7)	<0.0001
Yes	45,991 (46.7)	229,059 (23.3)	
Number of chronic diseases			
1	27,146 (27.6)	161,697 (16.4)	<0.0001
2	13,019 (13.6)	49,803 (5.2)	
3-4	5,356 (5.4)	16,376 (1.7)	
5+	470 (0.5)	1,183 (0.1)	
The mean number of chronic conditions (SD)	1.59 (0.85)	1.40 (0.72)	<0.0001

[a]ICD-codes for each disease area are described in supplementary 1

[b]The percentage within each age interval is calculated based on the total number of individuals in each age interval in the study population for the control and ADHD groups, respectively

[c]The p-values for all disease areas are based on whether there is an overall difference in the prevalence of comorbidities between individuals receiving medication treatment for ADHD and the control group, and do not account for differences across age groups

Table 3 Prevalence of psychiatric comedications among ADHD drug users compared to the control group

Type of comedication [a]	ADHD drug users *n* (%)[b]	Control group *n* (%)[b]	*P*-value[c]
Antidepressive drugs			<0.0001
Children (7–17 years)	1,256 (5.5)	1,671 (0.7)	
Young adults (18–29 years)	8,502 (24.6)	18,084 (5.2)	
Middle-aged adults (30–49 years)	10,610 (32.3)	25,289 (7.7)	
Older adults (50–64 years)	3,347 (40.9)	7,867 (9.6)	
Antipsychotic drugs			<0.0001
Children (7–17 years)	633 (2.8)	694 (0.3)	
Young adults (18–29 years)	4,458 (12.9)	6,893 (2.0)	
Middle-aged adults (30–49 years)	5,543 (16.9)	7,905 (2.4)	
Older adults (50–64 years)	1,542 (18.8)	2,230 (2.7)	
Sedative drugs			<0.0001
Children (7–17 years)	193 (0.8)	659 (0.3)	
Young adults (18–29 years)	812 (2.4)	2,023 (0.6)	
Middle-aged adults (30–49 years)	1,631 (5.0)	3,236 (1.0)	
Older adults (50–64 years)	757 (9.2)	1,504 (1.8)	
Sleeping drugs			<0.0001
Children (7–17 years)	239 (1.0)	452 (0.2)	
Young adults (18–29 years)	1,007 (2.9)	2,740 (0.8)	
Middle-aged adults (30–49 years)	1,216 (3.7)	3,149 (1.0)	
Older adults (50–64 years)	369 (4.5)	980 (1.2)	
Psychiatric comedication			
No	66,207 (67.3)	913,503 (92.8)	<0.0001
Yes	32,191 (32.7)	70,477 (7.2)	
Number of psychiatric comedication			
1	23,768 (24.2)	57,526 (5.9)	<0.0001
2	7,031 (7.2)	11,116 (1.1)	
3	1,283 (1.3)	1,722 (0.2)	
4	109 (0.1)	113 (0.01)	
The mean number of psychiatric comedication (SD)	1.31 (0.56)	1.21 (0.48)	<0.0001

[a]ATC-codes for each medical area are described in supplementary 2

[b]The percentage within each age interval was calculated based on the total number of individuals in each age interval in the study population for the control and ADHD groups, respectively

[c]The p-values for all psychiatric comedications are based on whether there is an overall difference in the prevalence of psychiatric comedication between individuals receiving medication treatment for ADHD and the control group, and do not account for differences across age groups

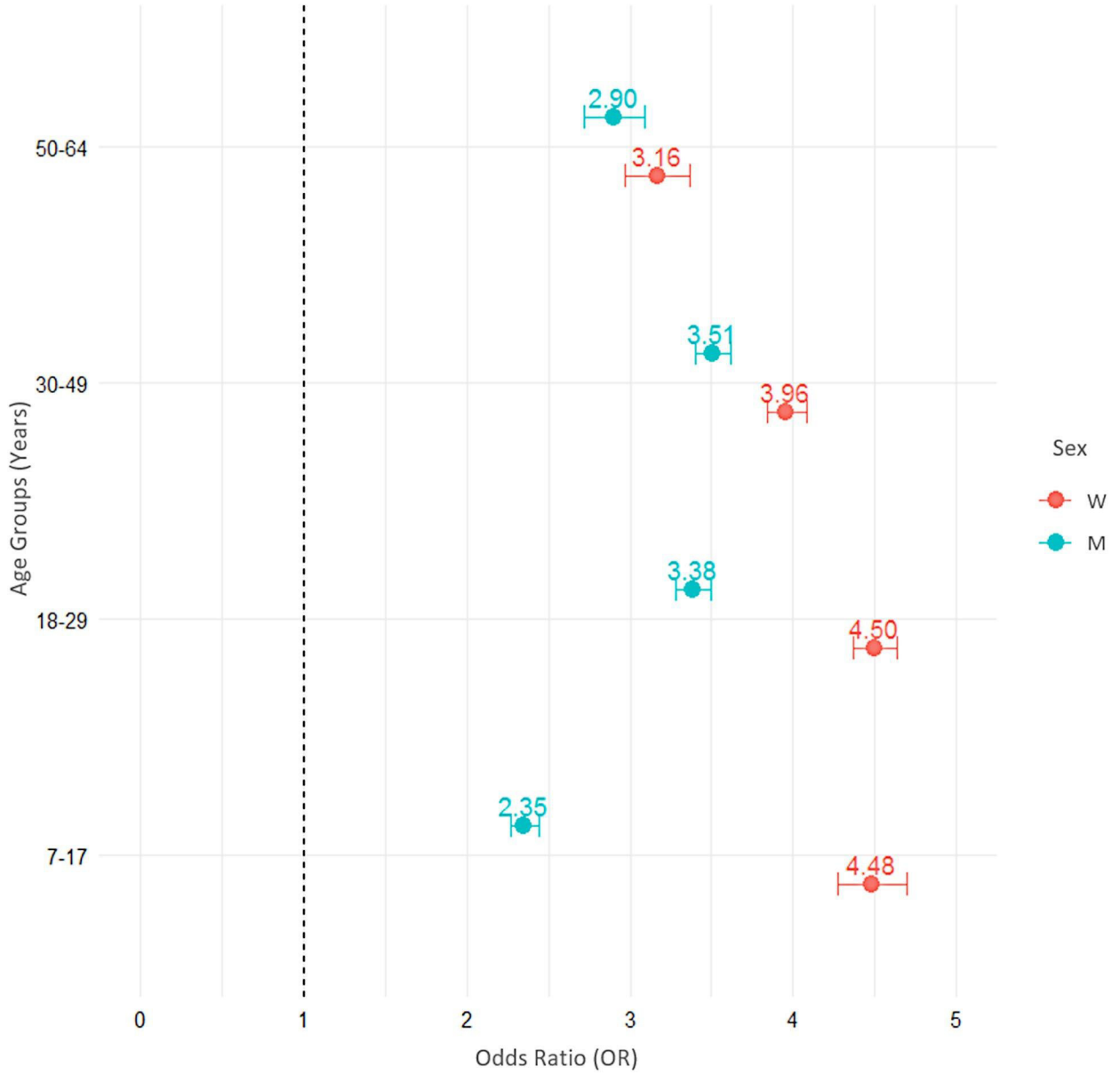

Fig. 2 Age- and sex-stratified conditional logistic regression model showing odds ratio (OR) for comorbidities adjusted for place of residence

explain the association between ADHD and somatic disorders. ADHD medication may influence the risk of some somatic disorders, with a study indicating a higher risk of cardiovascular diseases, such as hypertension, which is consistent with our findings of an increased prevalence of hypertension among individuals in ADHD treatment [33]. Another mechanism is that ADHD often co-occurs with psychiatric disorders such as depression [8–10] which in itself is associated with increased risk of somatic morbidity [34, 35], and may therefore act as a mediator or risk-enhancing factor. Finally, another hypothesis is that ADHD and somatic conditions share common genetic or neurobiological vulnerabilities [36].

The study findings align with previous literature showing that females are often diagnosed and treated later for ADHD, largely due to the dominance of inattentive symptoms [2, 37–39]. A systematic review suggested that females were less likely to be prescribed ADHD medications than men, although the difference is less pronounced in adults [2]. We found that females had a higher prevalence of comorbidities in all age groups. Previous studies have shown that anxiety, depression, bipolar, and personality disorders were more prevalent among females than men, while schizophrenia and substance use disorders were more common among men [31]. Further, a systematic review has highlighted that psychotropic

comedication is more pronounced among females [9]. For somatic comorbidities, the literature is limited, yet one study has evaluated the potential gender differences in somatic comorbidities among individuals with ADHD, and found that overall, the differences in ORs were small and no clear pattern could be identified [15].

Previous studies have demonstrated a strong association between polypharmacy and comorbidities [40]. The inherent link between comorbidities and comedication, underscores the relevance of examining both comorbidities and psychiatric comedications in our population within a Danish context. Our results, showing a higher proportion of psychiatric comedication among individuals in ADHD treatment, are consistent with previous studies suggesting a link between ADHD and increased risk of receiving psychiatric comedications [8–11]. A previous study suggested that individuals in ADHD treatment had a 15–21 higher likelihood of psychotropic medications compared to the general population [8]. Based on clinical assumptions, the proportion of young individuals receiving antipsychotic treatment is slightly elevated, which may be due to Tourette syndrome, as antipsychotics are commonly prescribed for this condition, and symptoms typically manifest during childhood or early adulthood [41]. Tourette syndrome is also frequently associated with ADHD, which may contribute to the increased antipsychotic use in this group [41]. From a public health perspective, it is important to be aware of the potential consequences of psychiatric comedication among ADHD patients due to possible drug interactions and their vulnerability to substance abuse [42, 43].

Strengths and limitations

This study was based on comprehensive, high-quality data from the Danish National Registries, enabling robust statistical analyses with large populations and accurate tracking of health outcomes [26, 44]. The high level of completeness in the Danish national registers ensures comprehensive coverage of all hospital-recorded diagnoses and all individuals receiving prescribed medications. Further, the large sample enhanced the robustness and generalizability of the estimates, making the findings more representative of the broader population and reducing the impact of random variation [44].

However, there are still limitations that should be considered when interpreting the findings. First, we only included diagnosis codes registered in secondary care, which may have led to an underestimation of the prevalence of some comorbidities, as diagnosis of certain conditions may be managed in primary care. Additionally, individuals in ADHD treatment may be more frequently diagnosed with certain diseases due to their higher frequency of hospital visits. This approach may result in misclassification, as comorbidities managed in primary care are not captured in the Danish registers, potentially leading to underestimation of the prevalence. However, primary care diagnosis is unavailable for research in a Danish setting.

Another limitation is the uncertainty regarding whether some ADHD medications were used off-label or for non-ADHD indications, as defining the treatment group based on medication redemptions may risk misclassifying treatment exposure by including individuals using these medications for other conditions. To address this, patients with a diagnosis code for narcolepsy were excluded, as certain ADHD medications including methylphenidate are approved for narcolepsy treatment [45]. A further limitation is that inclusion was defined by redemption of only one ADHD medication prescription, which may lead to misclassification, since the discontinuation rate is high in general among individuals receiving ADHD medication [46, 47]. The ADHD diagnosis code was not used to select study participants, as most ADHD diagnoses are given in the secondary sector, indicating that some individuals in primary care may lack a confirmed diagnosis. Moreover, hospital-diagnosed patients often have more severe and complex conditions, making diagnosis-based inclusion prone to selection bias. In line with this, a limitation is the inability to assess ADHD symptom severity directly as it may vary across the study population. Additionally, a sensitivity analysis using ADHD diagnosis codes was conducted, under the assumption that these represent the most severe cases, to refine the treatment group and evaluate the robustness of our findings.

We were able to include some demographic factors, but socioeconomic factors were not available in the data at hand. Previous studies have demonstrated an association between socioeconomic factors and ADHD, as well as between socioeconomic factors and comorbidities, with socioeconomic disadvantage being linked to ADHD and developing comorbidities [48, 49]. However, we adjusted for place of residence, taking geographical disparities into account which have enhanced the validity of the findings, however unmeasured confounding may be expected.

Conclusion

This study reveals that the co-occurrence of comorbidities, particularly psychiatric, and the use of psychiatric comedication are significantly higher among individuals in ADHD treatment in both children and adults and for both sexes compared to the control group. Yet, the highest occurrence for comorbidities is seemingly among females aged 7–17 year and 18–29 years. This highlights the substantial burden of comorbidities and psychiatric comedications faced by individuals in ADHD treatment. Further research is needed to understand the potential benefits and risks of comedication, as well as the possible

harms associated with a higher number of comorbidities, especially for somatic comorbidities, among individuals in ADHD treatment, given the current lack of evidence.

Abbreviations

ADHD	Attention deficit hyperactivity disorder
OR	Odds ratio
SD	Standard Deviation
95% CI	95% confidence interval
ATC-code	Anatomical Therapeutic Chemical code
ICD-10	International classification of diseases classification system 10

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-026-07824-5.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Acknowledgements
Not applicable.

Author contributions
MV drafted the manuscript, contributed to conceptualization of the study, study design, and method development, carried out data management and contributed to interpretation of study results. RFH contributed to method development, supervised the statistical analyses and data management, as well as interpretation of results, and critically revised the manuscript. PHT and AHB contributed to conceptualization of the study, interpretation of results, and critically revised the manuscript. ACFJ contributed to draft the manuscript, contributed to conceptualization of the study and study design, and method development, supervised the statistical analyses and interpretation of results, and critically revised the manuscript. All authors read and approved the final manuscript.

Funding
No funding.

Data availability
The datasets generated and/or analyzed in this study are not publicly available due to the rules that apply when working with microdata but are available for the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
According to Danish law and ethical guidelines, there is no need for an ethical approval of registry studies (cf. Section 14 [2] of the Danish Act on Committees) nor for obtaining consent from study participants (cf. Section 3 [10] of the Danish Act on Committees). Link to the Danish Act of Committees: https://www.retsinformation.dk/eli/lta/2011/593).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 26 June 2025 / Accepted: 13 January 2026
Published online: 04 February 2026

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