

Time after time: failure to identify and support females with ADHD – a Swedish population register study

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Background: Attention deficit hyperactivity disorder (ADHD) is associated with risk taking and negative health-related outcomes across the lifespan. Due to delay in referral and diagnostics, young females with ADHD may not be identified, nor appropriately supported by adequate interventions. **Methods:** A total of 85,330 individuals with ADHD, all of whom were residents in Stockholm County between January 01, 2011, and December 31, 2021, were included as participants in this population-based, cross-sectional cohort study. Population controls ($n = 426,626$) were matched by age, sex, and socioeconomic status (SES). Data was obtained from Regional Healthcare Data Warehouse of Region Stockholm (VAL) in Stockholm County. Exposure was ADHD-index, defined as the first record of either ICD-10 F90 diagnosis and/or ATC-code for stimulant or non-stimulant ADHD-medication during the study period. Primary outcome was age at ADHD-index. Secondary outcome measures were psychiatric comorbidity, pharmacological treatment, and health care utilization, prior to and after ADHD-index. **Results:** Females were older at ADHD-index (23.5 years, SD 13.8) compared to males (19.6 years, SD 13.9, 95% CI of difference 3.74–4.11). Overall, females with ADHD showed higher rates of psychiatric comorbidity, pharmacological treatment, and health care utilization, compared to males with ADHD and female controls. **Conclusions:** Females with ADHD receive diagnosis and treatment for ADHD approximately 4 years later than males. They have a higher burden of comorbid psychiatric conditions and health care utilization, compared to males with ADHD and female controls, both prior to and after ADHD-index. To prevent long-term adverse consequences for females with ADHD, methods, and tools for early diagnosis and treatments that mitigate personal suffering and societal burden are warranted. **Keywords:** Attention deficit hyperactivity disorder; sex; comorbidity; diagnosis; girls; women.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder characterized by impairing symptoms of hyperactivity, impulsivity, and inattention (Faraone et al., 2015; Thapar & Cooper, 2016). The worldwide prevalence of childhood and adolescent ADHD is estimated to be approximately 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Sex differences in the prevalence of ADHD have been reported to range between 3 and 16 males for every diagnosed females (Novik et al., 2006), with decreasing rate differences in adulthood (Cortese, Faraone, Bernardi, Wang, & Blanco, 2016). As ADHD is currently considered a lifelong condition, this indicates that many girls and young women with ADHD likely remain unidentified and untreated during important and formative years, despite reporting symptoms associated with ADHD to parents, teachers, and health care

professionals (Elkins, Malone, Keyes, Iacono, & McGue, 2011; Klefsjo, Kantzer, Gillberg, & Billstedt, 2021; Kopp, Kelly, & Gillberg, 2010).

ADHD is associated with a plethora of adverse health outcomes, such as externalizing and risk-taking behaviors (Pollak, Dekkers, Shoham, & Huizenga, 2019) including sexual risk-taking and victimization (Barkley, Fischer, Smallish, & Fletcher, 2006; Flory, Molina, Pelham Jr., Gnagy, & Smith, 2006; Owens & Hinshaw, 2019), emotional and social impairment (Ros & Graziano, 2018), accidental injuries, suicide, and premature death (Dalsgaard, Ostergaard, Leckman, Mortensen, & Pedersen, 2015; Ruiz-Goikoetxea et al., 2018; Sun et al., 2019), substance use disorders (SUD) (Lee, Humphreys, Flory, Liu, & Glass, 2011), criminality and delinquency (Beaudry, Yu, Langstrom, & Fazel, 2021; Young, Heptinstall, Sonuga-Barke, Chadwick, & Taylor, 2005), and academic underachievement (Korrel, Mueller, Silk, Anderson, & Sciberras, 2017). Thus, ADHD is associated with significantly reduced estimated life expectancy irrespective of sex (Barkley & Fischer, 2018). Pharmacological treatment with stimulant medication is part

Conflict of interest statement: See Acknowledgements for full disclosures.

of the multimodal treatment recommended for ADHD and may ameliorate adverse outcomes (Faraoe et al., 2021). Consequently, early detection, diagnosis, and treatment are important to reduce the risk of serious distress, morbidity, mortality, and impairments in life.

Klefsjo et al. (2021) recently reported results from a small clinical trial in which they found that females are older than males when they receive their ADHD diagnosis. In addition, females made more visits to child- and adolescent psychiatry before they were diagnosed, were prescribed pharmacotherapy for conditions other than ADHD more often, and received more individual psychotherapy than same-aged males. Previous research suggests that misdiagnosis or late diagnosis in females may be due to display of fewer externalizing or 'disruptive' symptoms, or because they primarily present with symptoms of comorbidity (Fratice et al., 2022; Young et al., 2020). Thus, to ensure equal access to detection, diagnostic assessment, and treatment for females and males it is pertinent to explore if, and to what extent, there is a diagnostic delay in females compared to males. In addition, to properly detect and consequently mitigate the negative consequences associated with ADHD, it is important to explore and display sex-specific factors such as comorbidity, pharmacological treatment, and health care utilization patterns before, at, and following diagnosis.

This present large-scale epidemiological study aimed to explore the hypothesis that females are diagnosed at a higher age compared to males. The primary outcome was age at ADHD index. Secondary outcomes were differences in psychiatric comorbidity, pharmacological treatment, and health care utilization, between females and males with ADHD, and with population controls, before and after ADHD-index.

Methods

This population-based observational study comprised all patients with incident ADHD during the study period (January 1, 2011, to December 31, 2021) and matched population controls among Region Stockholm's 2.4 million inhabitants, accounting for approximately 24% of the entire Swedish population. The study was approved by the Swedish Ethical Review Authority (permit number 2021-02624).

Data sources

The data in this study is based on the VAL-registry, i.e., the Regional Healthcare Data Warehouse of Region Stockholm (VAL), including information on all individual contacts with health care in Stockholm County Council. In Sweden health care is almost exclusively publicly funded. Every individual residing in Sweden carries a unique Swedish personal identity number (PIN), which facilitates information linkage across registers (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekblom, 2009). The PIN identifies individuals according to born biological sex but can be changed after sex-affirmative

surgery. We understand that some individuals in our data may not identify as the sex they are designated. However, as we cannot control for this, we will use the word 'female' to identify individuals with a female PIN and 'males' to identify those with a male PIN. Data, expressed as ICD-10 diagnoses, for secondary care and inpatient care (i.e., hospitalizations) are available from 1987 and diagnoses from primary care are included from 2003. The drug dispensing data (based on The Anatomical Therapeutic Chemical (ATC) Classification system) is derived from the Swedish Prescribed Drug Register, with a population coverage of over 99% (Wettermark et al., 2007). The VAL include individuals who have received an ADHD-diagnosis from publicly funded psychiatry but not from private health care providers. They will however have a record of prescribed or dispensed ADHD-medication since this is covered by public reimbursement and thus included in the Prescribed Drug Register regardless of whether the diagnosis was made in private or publicly funded psychiatry. Information on prescription drugs dispensed in the ambulatory setting has been included since July 2010. In addition, VAL also contains demographic information on age, sex, migration status, and death.

Participants

All residents in Stockholm County between January 01, 2011, to December 31, 2021, were eligible for inclusion in the study. Patients were required to have been residents in the Stockholm Region for at least 12 months and be ≥ 3 years old prior to ADHD-index date (Figure 1). A total of 85,330 individuals ($n = 37,591$ females) with at least one record of ADHD diagnosis and/or stimulant or non-stimulant medication for ADHD between 2011 and 2021 were included (Figure 1). These individuals are hence forward defined as 'females with ADHD' and 'males with ADHD', respectively. Up to five population controls ($n = 426,626$) without a record of F90 diagnosis or ATC-code for stimulant or nonstimulant ADHD-medication during the study period, were matched (with replacement) by age, sex, and SES, to every individual with ADHD. The population controls were given the same index date as the individuals with ADHD they were matched to. SES was determined using Mosaic (Douglas & Szatkowski, 2013), an area-based classification system for estimating SES used in the VAL database. Over 100 variables measuring demographics, economy, urbanity, and type of dwelling are included in the mosaic classification, and collapsed into three categories: 'low', 'middle', and 'high' SES (Table 1).

Exposure

ADHD was defined as a recorded (primary and/or any) diagnosis of ADHD (ICD-10 code: F90 – Hyperkinetic disorders) between January 01, 2011, and December 31, 2021, and/or as filling a prescription of any of the following stimulant or non-stimulant medication for ADHD between July 01, 2011, and December 31, 2021: Amphetamine (N06BA01), Dexamphetamine (N06BA02), Methylphenidate (N06BA04), Atomoxetine (N06BA09), Lisdexamphetamine (N06BA12), and Guanfacine (C02AC02). ADHD is currently differentiated into three presentations: predominantly hyperactive-impulsive (F90.0A), combined (F90.0B), and predominantly inattentive (F90.0C) presentation (American Psychiatric Association, DSM-5 Task Force, 2013) (Table S1). Individuals may have a recorded diagnosis in more than one presentation. The diagnosis or the filling of the prescription was established as the ADHD-index date, whichever came first.

Primary outcome

The primary outcome was age at ADHD-index.

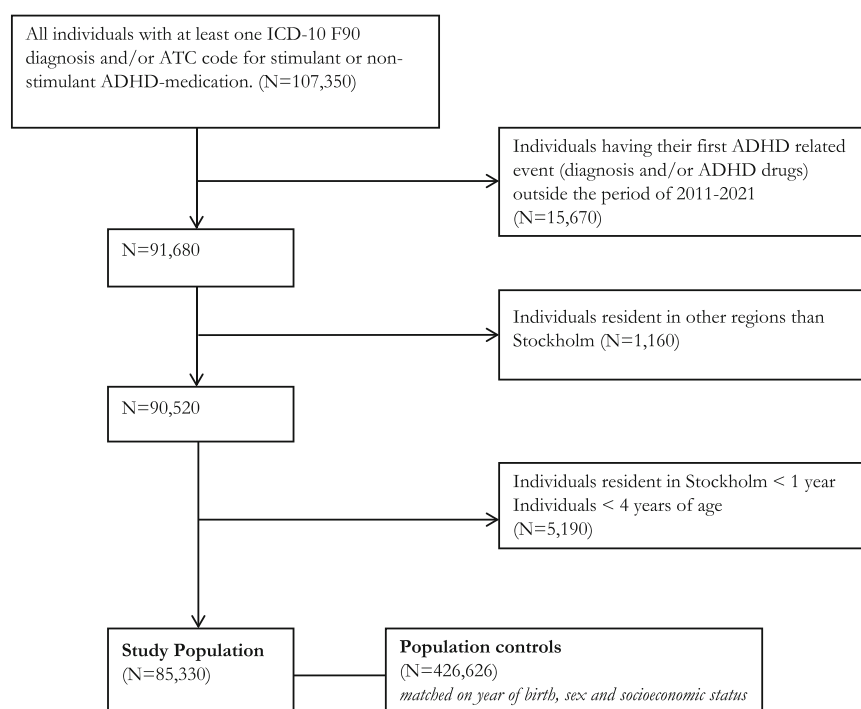


Figure 1 The derivation of the study population

Table 1 Age and socioeconomic status at first record of ICD10: F90 and/or ADHD-medication in the study population

	Females <i>N</i> = 37,591		Males <i>N</i> = 47,739		<i>p</i> -Value Females versus males (ADHD-group)
	With ADHD ¹ <i>N</i> = 37,591	Matched controls Without ADHD ² <i>N</i> = 187,946	With ADHD ¹ <i>N</i> = 47,739	Matched controls Without ADHD ² <i>N</i> = 238,680	
Age at index					
Mean (<i>SD</i>)	23.5 (13.8)	23.5 (13.8)	19.6 (13.9)	19.6 (13.9)	<.001 ³
Median (<i>IQR</i>)	19.0 (13.0–32.0)	19.0 (13.0–32.0)	14.0 (9.0–28.0)	14.0 (9.0–28.0)	<.001 ⁴
Socioeconomic status, <i>n</i> (%)					
High	9,196 (24.4)	45,978 (24.4)	11,863 (24.9)	59,310 (24.9)	.069 ⁵
Middle	12,505 (33.3)	62,522 (33.3)	16,377 (34.3)	81,882 (34.3)	
Low	13,271 (35.3)	66,354 (35.3)	16,730 (35.0)	83,647 (35.0)	
Missing	2,619 (7.0)	13,092 (7.0)	2,769 (5.8)	13,841 (5.8)	

¹Females and males with at least one record of ICD10: F90 and/or at least one record of an ADHD-medication (Amphetamine, Dexamphetamine, Methylphenidate, Atomoxetine, Lisdexamphetamine, Guanfacine) during the study period. Index date is the date of first record.

²Population controls matched to each individual with ADHD, who did not have any records of F90 diagnosis nor ADHD drugs during the study period. Up to five population controls, matched by age, sex, and socioeconomic status, were selected to each individual with ADHD. The population controls were given the same index date as the individuals with ADHD they were matched to.

³*p*-value for Welch two-sample *t*-test.

⁴*p*-value for Mann-Whitney *U* test.

⁵*p*-value for Pearson's Chi-square test. Individuals with missing values on socioeconomic status were excluded from analysis.

Secondary outcomes

Psychiatric comorbidity (Table 2) was expressed as 'ever had a record of the ICD-diagnosis prior to, or at the time of, ADHD-index' (Table 2). Self-harm (events of intentional self-harm (ICD-10: X60-X84) and/or event of undetermined intent (ICD-10: Y10-Y34)), was expressed as 'ever had a record of the ICD-diagnosis prior to, at, or after ADHD-index' (Tables S2A and S2B). Individuals may have a recorded diagnosis in more than one presentation. We classified pharmacological treatments into seven categories based on comorbidity associated with ADHD (Faraone et al., 2021), and calculated the annual proportion of individuals using these medications; analgesics (ATC-code N02), mood stabilizers (ATC-code N03)

psychoanaleptics (ATC-code N06), neuroleptics, sedatives, and hypnotics (ATC-code N05), pharmacological treatment for SUDs (ATC-codes N07) and pharmacological treatment for ADHD (ATC-codes N06 and C02AC02). For detailed information on drugs included in each category see Table 3. Psychological interventions (psychotherapy and psychoeducation) were defined by procedure codes (Table 3). The annual proportion of psychiatric and non-psychiatric health care utilization was expressed as at least one bed-day for inpatient health care (Figure 3A,B), and at least one visit for outpatient health care (Figure 4A,B). In- and outpatient health care utilization was measured at 5 and 2 years prior to, and at 2 and 5 years after ADHD-index. In deriving the mean number of bed-days per episode, individuals with long hospitalization

Table 2 Psychiatric comorbidity in the study population, expressed as at least one record of the condition prior to (or at the time of) ADHD-index¹

	Females		Males		Females versus males with ADHD		
	With ADHD ¹ N = 37,591 n (%)	Without ADHD ² N = 187,946 n (%)	With ADHD ¹ N = 47,739 n (%)	Without ADHD ² N = 238,680 n (%)	Absolute difference (95% CI) ³	p-Value ⁴	Adjusted p-value ⁵
Anxiety disorders including stress ICD-10-codes: F40-F48	18,932 (50.4)	28,772 (15.3)	12,359 (25.9)	14,429 (6.1)	24.5 (23.8–25.1)	<.001	<.001
Mood (affective) disorders ICD-10-codes: F30-F31; F32-F34; F38-F39	14,103 (37.5)	15,390 (8.2)	9,296 (19.5)	7,269 (3.1)	18.0 (17.4–18.7)	<.001	<.001
Substance use disorders ICD-10-codes: F10-F19	4,834 (12.9)	4,845 (2.6)	5,703 (12.0)	5,396 (2.3)	0.9 (0.5–1.4)	<.001	<.001
Autism ICD-10-code: F84	3,732 (9.9)	1,876 (1.0)	5,955 (12.5)	3,753 (1.6)	–2.5 (–3.0 – -2.1)	<.001	<.001
Sleep disorders ICD-10-code: F51	2,812 (7.5)	3,924 (2.1)	2,300 (4.8)	3,103 (1.3)	2.7 (2.3–3.0)	<.001	<.001
Eating disorders ICD-10-code: F50	2,094 (5.6)	2,522 (1.3)	273 (0.6)	545 (0.2)	5.0 (4.8–5.2)	<.001	<.001
Personality disorders ICD-10-code: F60	2,357 (6.3)	977 (0.5)	1,001 (2.1)	369 (0.2)	4.2 (3.9–4.5)	<.001	<.001
Conduct disorder ICD-10-code: F91	994 (2.6)	222 (0.1)	2,001 (4.2)	539 (0.2)	–1.5 (–1.8 – -1.3)	<.001	<.001
Tics/Tourette ICD-10-code: F95	266 (0.7)	313 (0.2)	836 (1.8)	1,326 (0.6)	–1.0 (–1.2 – -0.9)	<.001	<.001
Psychotic disorders ICD-10-codes: F20-F29	443 (1.2)	575 (0.3)	603 (1.3)	905 (0.4)	–0.1 (–0.2–0.1)	.278	<.001
Mental retardation ICD-10-code: F70	403 (1.1)	595 (0.3)	596 (1.3)	801 (0.3)	–0.2 (–0.3–0.0)	.019	.093

¹Females and males with at least one record of ICD10: F90 and/or at least one record of an ADHD-medication (Amphetamine, Dexamphetamine, Methylphenidate, Atomoxetine, Lisdexamphetamine, Guanfacine) during the study period. Index date is the date of first record.

²Up to five population controls without ADHD matched to each individual with ADHD, by age, sex, and socioeconomic status. Population controls were given the same index date as the matched individual.

³Absolute difference (95% confidence interval) in percentages with comorbid condition between females and males with ADHD.

⁴p-value for difference between females and males with ADHD, based on the two-sample proportion test.

⁵p-value for difference between females and males with ADHD adjusted for age at ADHD-index, based on logistic regression analyses.

episodes (several years) were included as a ‘new’ hospitalization during each studied year. These individuals were given a length of hospitalization of 365 days for that year. For example, if an individual was admitted to hospital 6 years prior to index and discharged 1 year prior to index, that individual contributes to one hospitalization episode of 365 days, both at 5 and 2 years prior to index in our analyses.

Statistical analyses

All patient characteristics were described in relation to ADHD-index. Sociodemographic characteristics (sex, age, and SES), psychiatric comorbidity, and comorbidity related to intentional self-harm or events of undetermined intent, as well as psychiatric and non-psychiatric health care utilization were described and summarized using descriptive statistics. Means, standard deviations (SD), medians, and interquartile ranges (IQR) were used to describe numerical variables

depending on distribution; *n* (%), frequency distributions, and absolute differences with 95% confidence intervals (CI) were used to describe categorical variables. We used the Pearson’s Chi-square test and the independent sample proportion test to compute *p*-values for differences between females and males with ADHD in regard to categorical variables. For normally distributed numerical variables, differences between females and males with ADHD were tested by means of the Welch independent sample *t*-test (i.e., assuming unequal variances), and for non-normally distributed numerical variables the Mann–Whitney *U*-test was used. As females with ADHD tended to be older than males at ADHD-index, we also performed binary logistic regression analyses on the secondary outcomes of psychiatric comorbid conditions and intentional self-harm/event of undetermined intent prior to ADHD-index in which we controlled for age at ADHD-index. The dependent variables were each condition respectively, and independent variables in all models were sex

Table 3 Annual percentage on pharmacological treatment, psychotherapy, and psychoeducation at 5 and 2 years prior to, and at 2 and 5 years after ADHD-index

	Females		Males		Females versus males with ADHD	
	With ADHD ¹ n (%)	Without ADHD ² n (%)	With ADHD ¹ n (%)	Without ADHD ² n (%)	Absolute difference (95% CI) ³	p-Value ⁴
FIVE YEARS PRIOR TO INDEX						
Analgesics ⁵	N = 22,541 1,782 (7.9)	N = 107,746 3,937 (3.7)	N = 26,141 1,142 (4.4)	N = 125,624 2,496 (2.0)	3.5 (3.1–4.0)	<.001
Anticonvulsants (mood stabilizers) ⁶	628 (2.8)	754 (0.7)	438 (1.7)	778 (0.6)	1.1 (0.8–1.4)	<.001
Neuroleptics, sedatives, and hypnotics ⁷	2,995 (13.3)	4,373 (4.1)	1,854 (7.1)	2,929 (2.3)	6.2 (5.6–6.7)	<.001
Psychoanaesthetics ⁸	3,303 (14.7)	3,957 (3.7)	1,679 (6.4)	1,734 (1.4)	8.2 (7.7–8.8)	<.001
SUD treatment ⁹	110 (0.5)	74 (0.1)	141 (0.5)	106 (0.1)	–0.1 (–0.2–0.8)	.468
Psychotherapy ¹⁰	1,024 (4.5)	1,362 (1.3)	457 (1.7)	513 (0.4)	2.8 (2.5–3.1)	<.001
TWO YEARS PRIOR TO INDEX						
Analgesics ⁵	N = 32,798 3,299 (10.1)	N = 161,883 7,126 (4.4)	N = 40,971 2,203 (5.4)	N = 203,264 4,507 (2.2)	4.7 (4.3–5.1)	<.001
Anticonvulsants (mood stabilizers) ⁶	1,707 (5.2)	1,564 (1.0)	1,150 (2.8)	1,595 (0.8)	2.4 (2.1–2.7)	<.001
Neuroleptics, sedatives, and hypnotics ⁷	8,127 (24.8)	8,937 (5.5)	5,724 (14.0)	5,884 (2.9)	10.8 (10.2–11.4)	<.001
Psychoanaesthetics ⁸	8,528 (26.0)	8,616 (5.3)	5,097 (12.4)	3,748 (1.8)	13.6 (13.0–14.1)	<.001
SUD treatment ⁹	288 (0.9)	127 (0.1)	453 (1.1)	229 (0.1)	–0.2 (–0.4 – –0.1)	.002
Psychotherapy ¹⁰	4,217 (12.9)	4,357 (2.7)	2,275 (5.6)	1,465 (0.7)	7.3 (6.9–7.7)	<.001
TWO YEARS AFTER INDEX						
Analgesics ⁵	N = 26,749 3,103 (11.6)	N = 136,690 7,723 (5.7)	N = 35,739 2,108 (5.9)	N = 182,890 5,266 (2.9)	5.7 (5.2–6.2)	<.001
Anticonvulsants (mood stabilizers) ⁶	2,037 (7.6)	1,643 (1.2)	1,485 (4.2)	1,808 (1.0)	3.5 (3.1–3.8)	<.001
Neuroleptics, sedatives, and hypnotics ⁷	11,954 (44.7)	9,705 (7.1)	12,018 (33.6)	6,497 (3.6)	11.1 (10.3–11.8)	<.001
Psychoanaesthetics ⁸	8,778 (32.8)	10,092 (7.4)	5,891 (16.5)	4,513 (2.5)	16.3 (15.6–17.0)	<.001
ADHD ¹¹	16,398 (61.3)	NA	21,857 (61.2)	NA	0.1 (–0.6–0.9)	.717
SUD treatment ⁹	291 (1.1)	164 (0.1)	440 (1.2)	258 (0.1)	–0.1 (–0.3–0.0)	.107
Psychotherapy ¹⁰	5,329 (19.9)	5,650 (4.1)	3,192 (8.9)	2,062 (1.1)	11.0 (10.4–11.6)	<.001
FIVE YEARS AFTER INDEX						
Analgesics ⁵	N = 14,778 1,943 (13.1)	N = 77,961 5,128 (6.6)	N = 20,905 1,319 (6.3)	N = 111,396 3,862 (3.5)	6.8 (6.2–7.5)	<.001
Anticonvulsants (mood stabilizers) ⁶	1,268 (8.6)	1,219 (1.6)	965 (4.6)	1,212 (1.1)	4.0 (3.4–4.5)	<.001
Neuroleptics, sedatives, and hypnotics ⁷	6,275 (42.5)	6,650 (8.5)	6,682 (32.0)	4,624 (4.2)	10.5 (9.5–11.5)	<.001
Psychoanaesthetics ⁸	4,925 (33.3)	7,406 (9.5)	3,471 (16.6)	3,515 (3.2)	16.7 (15.8–17.6)	<.001
ADHD ¹¹	7,095 (48.0)	NA	9,958 (47.6)	NA	0.4 (–0.7–1.4)	.490
SUD treatment ⁹	193 (1.3)	101 (0.1)	302 (1.4)	195 (0.2)	–0.1 (–0.4–0.1)	.291
Psychotherapy ¹⁰	2,486 (16.8)	4,563 (5.9)	1,516 (7.3)	1,946 (1.7)	9.5 (8.9–10.3)	<.001

¹Females and males with at least one record of ICD-10: F90 and/or at least one record of an ADHD-medication (Amphetamine, Dexamphetamine, Methylphenidate, Atomoxetine, Lisdexamphetamine, Guanfacine) during the study period. Index date is the date of first record.

²Up to five population controls without ADHD matched to each individual with ADHD, by age, sex, and socioeconomic status. Population controls were given the same index date as the matched individual.

³Absolute difference (95% confidence interval) in percentages with treatment between females and males with ADHD.

⁴p-value for difference between females and males with ADHD, based on the two-sample proportion test.

⁵ATC-codes: N02A Opioids, N02C Migraine. Note that the data does not cover medications sold over the counter.

⁶ATC-codes: N03AB02 Phenytoin, N03AD01 Etosuximide, N03AE01 Benzodiazepine derivatives (Klonazepam), N03AF Karboxamidderivat (Hermolepsin, Tegretol, Trileptal), N03AG Fettsyraderivat (N03AG 01Valproinsyra (Absenor, Ergenyl), N03AX Other anticonvulsants ie mood stabilizers (N03AX09 Lamotrigine, N03AX11 Topiramate, N03AX12 Gabapentin, N03AX14 Keppra, N03AX15 Zonégren, N03AX16 Pregabalin, N03AX17 Diacomit, N03AX18 Lacosamide).

⁷ATC-codes: N05A Neuroleptics + N05AN Lithium, N05B Sedative + hypnotics, N05BA Benzodiazepines, N05BB01 Hydroxyzine (Atarax), N05BE01 Buspiron, N05C Hypnotics + sedatives, N05CD Bzd derivatives, N05CF Bzd-like (Zolpidem, Zopiklon), N05CH Melatonin, N05CM (N05CM02 Hemineurin, N05CM06 Propiomazine).

⁸ATC-codes: N06AA Tricyclic, N06AB SSRI, N06AC Tetracyclic, N06AG + AF MAO-inhibitors, N06AX Others (N06AX03 Mianserin, N06AX11 Mirtazapine, N06AX12 Bupropion, N06AX16 Venlafaxin, N06AX18 Edronax, N06AX21 Duloxetine, N06AX22 Agomelatine (sleep), N06AX26 Vortioxetine).

⁹SUD = substance use disorder N07BB (Alcohol), N07BC (Opioids).

¹⁰Psychotherapy is defined as by procedure codes: DU008 Psychodynamic therapy, DU009 Psychotherapy, other, DU010 Psychotherapy, cognitive, DU011 Psychotherapy, CBT, DU013 Psychotherapy, MBT, DU020 Psychotherapy, systemic, DU021 Psychotherapy, DBT, DU022 Psychotherapy, IPT, and DU023 Psychopedagogical therapy.

¹¹ATC-codes: Amphetamine (N06BA01), N06BA02 Dexamphetamine, N06BA04 MPH, N06BA09 Atomoxetine, N06BA12 Lisdexamphetamine, C02AC02 Guanfacine *Alfaadrenergic with CNS- effect*.

and age at ADHD-index. Although small differences in proportions, means and medians may show p -values of $<.05$ in large sample sizes, we decided to present percentages, as well as absolute differences in percentages with 95% CI:s, in addition to p -values for transparency. Due to immigration and emigration to and from Region Stockholm during the study period, individuals will have different follow-up time prior to, and after, ADHD-index. Consequently, proportion estimates per year presented in Table 3, and in Figures 3 and 4, were based on different denominators.

Results

Figure 1 is a flow chart of the derivation of the study population, showing the total sample of 85,330 individuals with ADHD identified. Overall, the proportion of the different ADHD presentations was evenly distributed. However, the proportion of females with a record of ADHD predominately inattentive presentation (ADD) during the study period was higher compared to males (31.5% vs. 28.1%, respectively) (Table S1). Of the 85,330 individuals with an ADHD-index, 5.5% of the females and 5.4% of the males never had a record of an ICD-10 F90 diagnosis during the study period.

Age at diagnosis

A visual representation of the difference in the distribution of age at ADHD-index in females and males is shown in Figure 2. Table 1 shows age and SES at ADHD-index, with population controls matched for age at index, sex, and SES. Females had their ADHD-index at a median age of 19.0 years (IQR 13.0–32.0), and males at the age of 14.0 years (IQR 9.0–28.0). On average, ADHD-index was 3.9 years later in females compared with males (95% CI of difference: 3.74–4.11). SES did not differ between females and males with ADHD.

Psychiatric comorbidity including self-harm

Psychiatric comorbidities expressed as ever had the ICD-10 diagnosis prior to (or at) ADHD-index is shown in Table 2. The two most common psychiatric comorbid conditions for both sexes with ADHD as well as for population controls were anxiety disorders and mood disorders, respectively. Females with ADHD were approximately twice as likely compared to males with ADHD to be diagnosed with both anxiety disorders (50.4% vs. 25.9%) and mood disorders (37.5% vs. 19.5%). Males in contrast had higher rates of autism spectrum disorders, conduct disorder, tics, and Tourette's disorder. The highest relative differences between females and males with ADHD were observed for eating disorders (5.6% vs. 0.6%) and personality disorders (6.3% vs. 2.1%). In addition, Tables S2A and S2B show that females with ADHD more often than males with ADHD had a diagnosis of self-harm events both prior to, and after ADHD-index. Ingestion or inhalation with intent to self-harm and/or of undetermined intent was reported in 5.0% of females with ADHD, versus 1.6% of males with ADHD prior to ADHD-index, and 3.1% versus 1.2% respectively after ADHD-index. Age at index was statistically significant in all logistic regression models. There was little change in p -values for sex differences between adjusted and unadjusted results, with two exceptions. When adjusting for age at index, the difference between females and males with ADHD regarding psychotic disorders became statistically significant ($p < .001$), and the sex difference in mental retardation was no longer statistically significant ($p = .093$). Females with ADHD had a higher psychiatric comorbidity burden compared to population controls for the majority of conditions, across the entire study period.

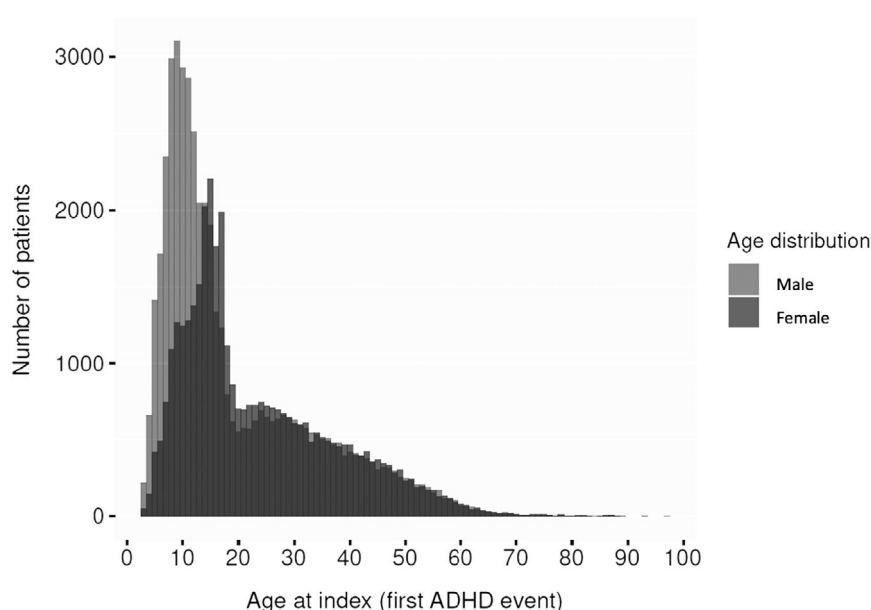


Figure 2 Age distribution at ADHD-index by sex

Pharmacological treatment and psychotherapy

Table 3 displays the annual proportion of pharmacological treatment and psychotherapy at 5 and 2 years prior to, and at 2 and 5 years after ADHD-index. The proportion of individuals prescribed ADHD-medication was similar across sex at both 2 and 5 years after index. Five years prior to ADHD-index females showed a higher use of anticonvulsants, neuroleptics, sedatives, and hypnotics, as well as psychoanaleptics, compared to males. For both females and males with ADHD, an increase in the use of all medications was observed between 5 years prior to index and 2 years prior to index. Two

years after index females with ADHD still showed a significantly higher use of anticonvulsants, neuroleptics, sedatives, hypnotics, and psychoanaleptics, compared to males with ADHD. A two- to threefold rise in these same medications was observed between 5 years prior to index and 2 years after index, for both females and males with ADHD. The prescription rates remained relatively constant at 2 and 5 years following ADHD-index, with gender differences in the ADHD population remaining largely constant. At 2 years prior to ADHD-index, females with ADHD were less likely to receive SUD-treatment than males with ADHD (0.9% vs. 1.1%), despite a higher liability of having a SUD diagnosis,

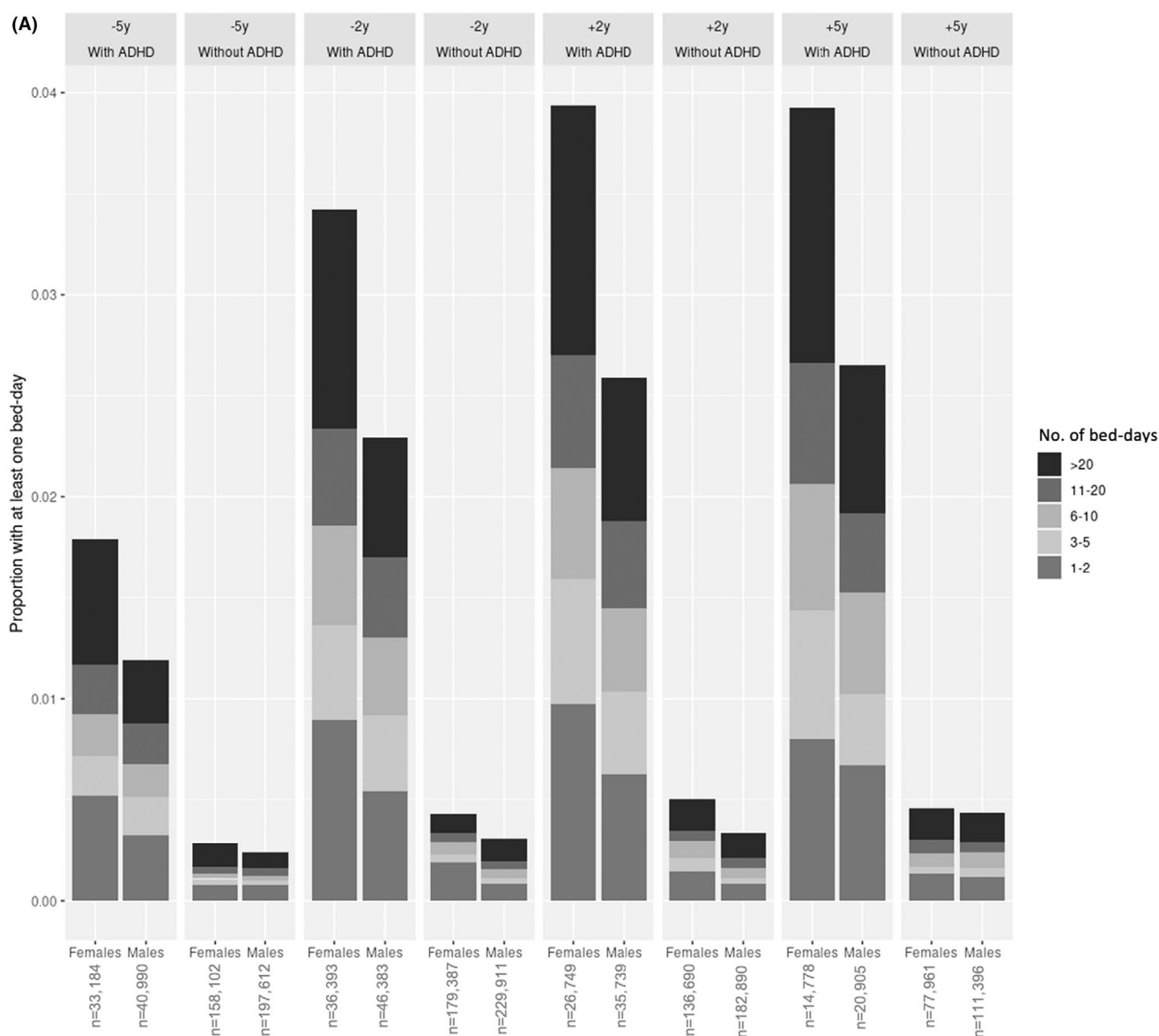
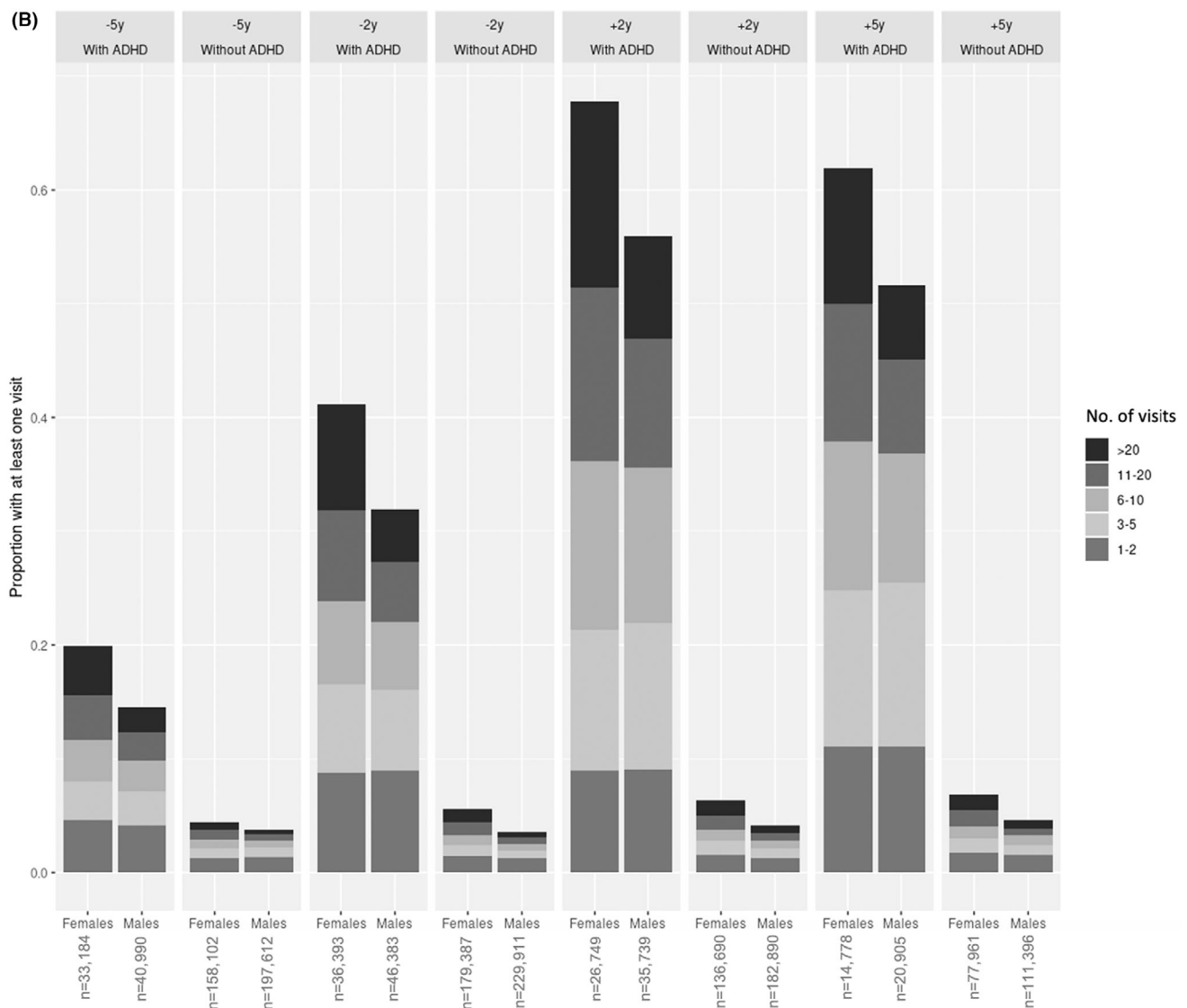


Figure 3 (A) Annual proportion of inpatient psychiatric healthcare utilization in the study population expressed as at least one inpatient bed-day at 5 and 2 years prior to, and at 2 and 5 years after ADHD-index.^{1,2} (B) Annual proportion of outpatient psychiatric health care utilization in the study population expressed as at least one visit at 5 and 2 years prior to, and at 2 and 5 years after ADHD-index.^{1,2} ¹With ADHD: Females and males with at least one record of ICD10: F90 and/or at least one record of an ADHD-medication (Amphetamine, Dexamphetamine, Methylphenidate, Atomoxetine, Lisdexamphetamine, Guanfacine) during the study period. Index date is the date of first record. ²Up to five population controls without ADHD matched to each individual with ADHD, by age, sex, and socioeconomic status. Population controls were given the same index date as the matched individual with ADHD. The population controls were given the same index date as the individual with ADHD they were matched to.



prior to, or at time of ADHD-index (12.9% vs. 12.0%) (Table 2).

The use of therapeutic psychological interventions increased in the period between 5 and 2 years prior to index, as well as from 2 years prior to 2 years after index, for both females and males with ADHD (Table 3). In females with ADHD, the use of psychological interventions declined in the period between 2 and 5 years after index. At 2 and 5 years after index, psychological interventions were still about twice as common for females with ADHD compared to males with ADHD. Compared to matched population controls, females with ADHD showed a higher use of pharmacological as well as psychological interventions across the entire study period.

Health care utilization

Figure 3A,B show the annual proportion of in- and outpatient psychiatric health care utilization, expressed as at least one inpatient bed-day or one outpatient visit, respectively, at 5 and 2 years prior

to, and at 2 and 5 years after index by sex, among individuals with and without ADHD. Females with ADHD were more likely than males with ADHD to have both an in- and outpatient psychiatric health care event across the entire study period. For both females and males with ADHD the proportion of inpatient psychiatric health care utilization increased from 5 years prior to index up until 2 years after index, after which it remained largely unchanged at 5 years after index (Figure 3A). The annual proportion of individuals with at least one outpatient psychiatric health care visit at 5 years prior to ADHD-index was 19.9% for females with ADHD compared with 14.6% for males with ADHD (Figure 3B). Corresponding proportions at 2 years prior to index was 41.2% for females with ADHD and 32% for males with ADHD. Figure 4A,B shows the annual proportion of inpatient and outpatient non-psychiatric health care utilization expressed as at least one inpatient bed-day or one visit, respectively, at 5 and 2 years prior to, and at 2 and 5 years after index by gender, among individuals with and without ADHD. Females with ADHD had higher annual

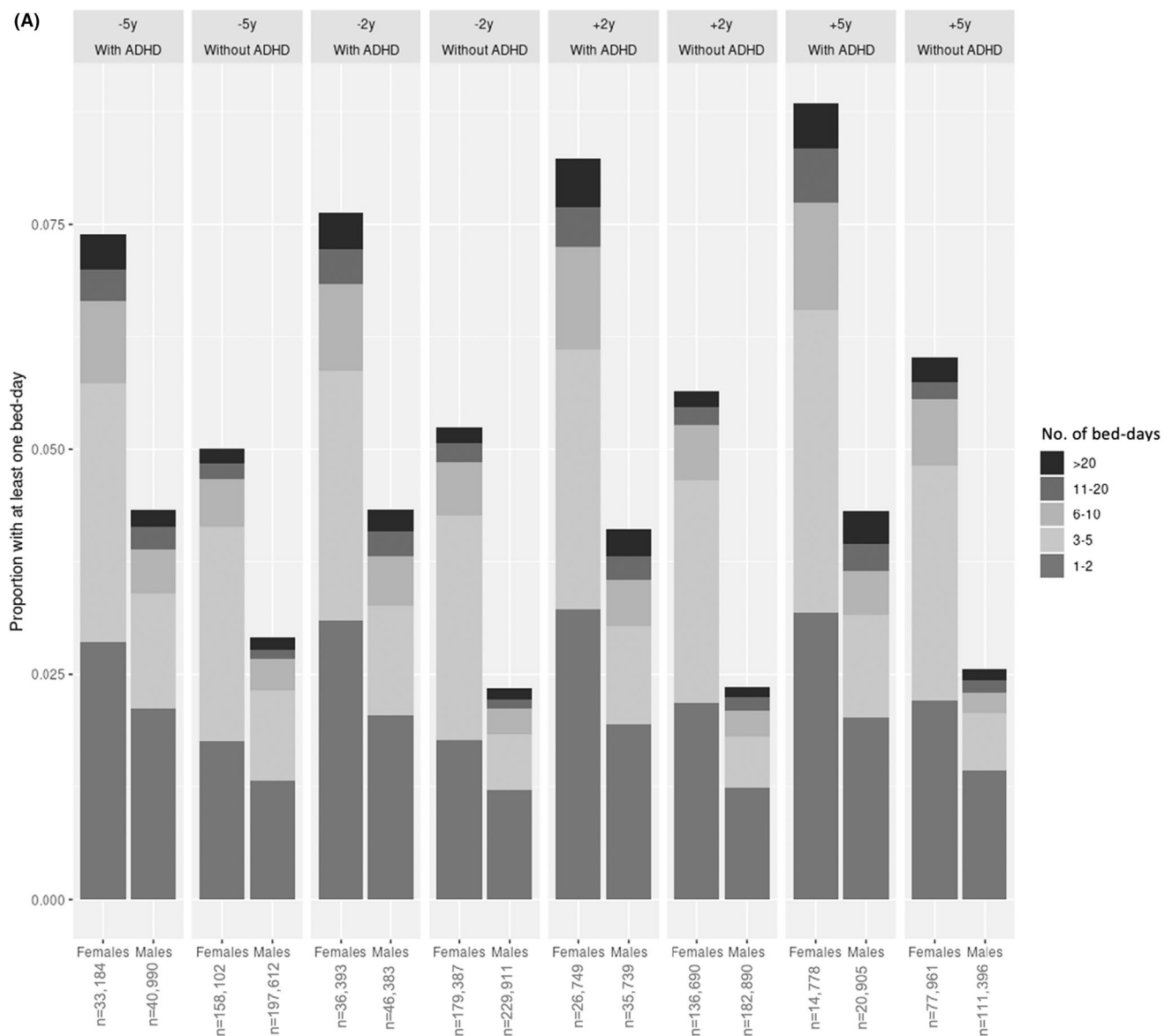


Figure 4 (A) Annual proportion of inpatient non-psychiatric health care utilization in the study population expressed as at least inpatient bed-day at 5 and 2 years prior to, and at 2 and 5 years after, first record of ICD10: F90 and/or ADHD-medication^{1,2}. (B) Annual proportion of outpatient non-psychiatric health care utilization in the study population expressed as at least one visit at 5 and 2 years prior to, and at 2 and 5 years after, ADHD-index^{1,2}. ¹With ADHD: Females and males with at least one record of ICD10: F90 and/or at least one record of an ADHD-medication (Amphetamine, Dexamphetamine, Methylphenidate, Atomoxetine, Lisdexamphetamine, Guanfacine) during the study period. Index date is the date of first record. ²Up to five population controls without ADHD matched to each individual with ADHD, by age, sex, and socioeconomic status. Population controls were given the same index date as the matched individual.

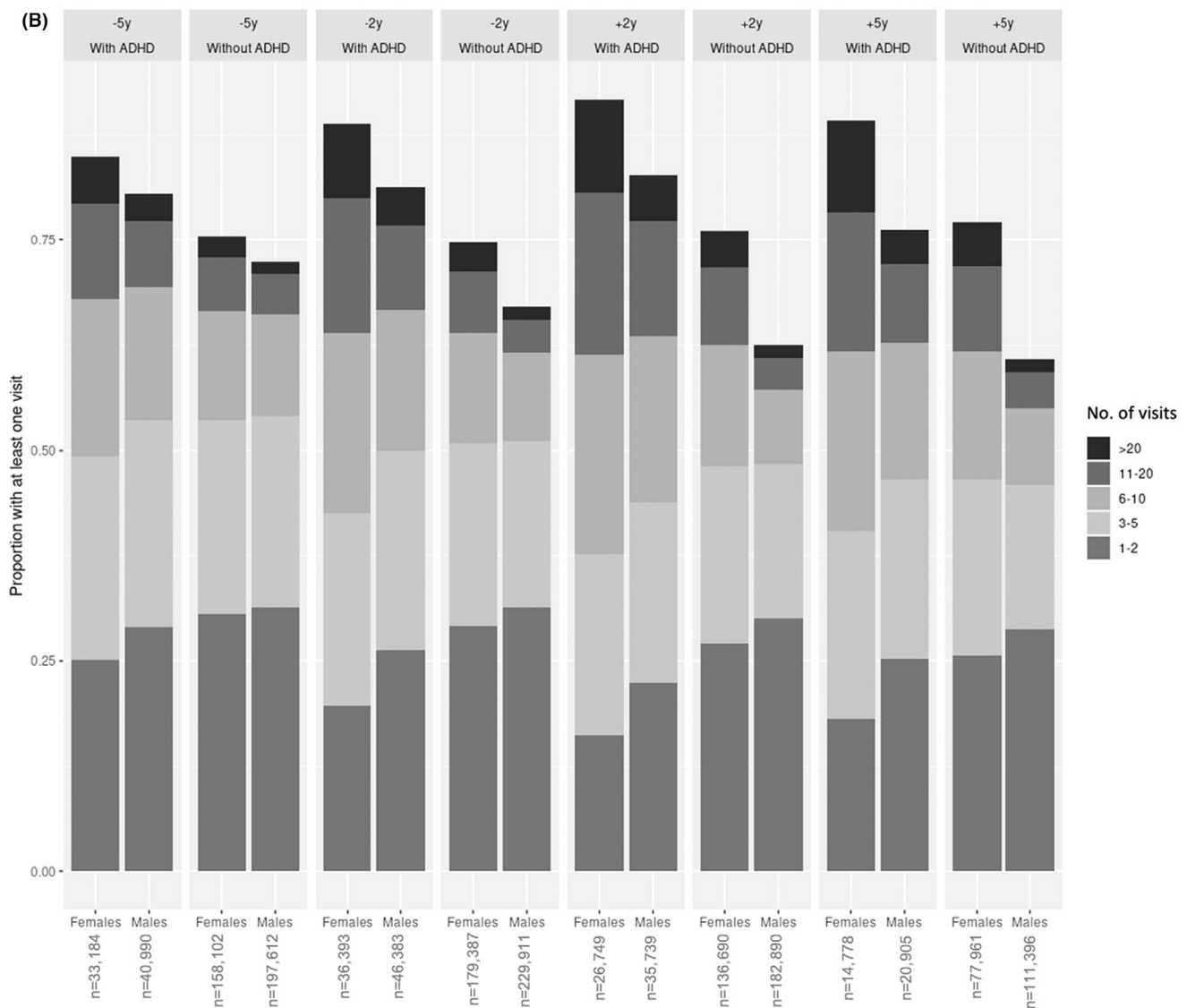
proportions of inpatient and outpatient non-psychiatric health care utilization, compared to males with ADHD, at 2 and 5 years prior to index, as well as at 2 and 5 years after index. Comparing females with ADHD to female population controls, differences in annual proportions of inpatient, non-psychiatric health care were observed across the whole study period (Figure 4A).

Discussion

In this population-based cohort study, we found that females had their ADHD-index approximately 4 years later than males, that is, at 23.5 versus 19.6 years. In addition, females with ADHD were

more often diagnosed with psychiatric comorbidity and had a significantly higher use of psychotropic drugs and health care utilization compared to males with ADHD and population controls of both sexes both prior to and after ADHD-index. Equal, evidence based, and timely interventions should be at the core of sustainable and effective health care. Early detection and interventions applying multi modal treatment approaches is crucial to prevent decremental psychosocial outcomes due to ADHD, regardless of sex (Faraone et al., 2021). However, our results indicate that there are still barriers to evidence-based care for females with ADHD.

A central hypothesis regarding the diagnostic delay in females is that they exhibit less disruptive



or externalizing symptoms than males. Our data partly supports this, as females were more often diagnosed with predominately inattentive ADHD (ADD) (Gershon, 2002). Our findings support studies that suggest that females in fact do exhibit hyperactivity and impulsivity traits, but that these are displayed as externalizing emotional or verbal hyperactivity and impulsivity symptoms, that are misinterpreted (e.g. as e.g. anxiety, borderline personality disorder, or bipolar disorder; Hollingdale, Woodhouse, Asherson, Gudjonsson, & Young, 2014; Quinn & Madhoo, 2014; Stepp, Burke, Hipwell, & Loeber, 2012). These symptoms may also explain why females receive more therapeutic psychological interventions whereas males receive a referral for ADHD assessment (Klefsjo et al., 2021; Petrovic & Castellanos, 2016).

According to Swedish National Guidelines central stimulant ADHD medication can only be prescribed by licensed psychiatrist specialized in child- and adolescent, adult psychiatry, forensic psychiatry, or habilitation in cases where other interventions have failed or are deemed insufficient

(Läkemedelsverket, 2016). Treatment for ADHD can thus only be provided by specialized psychiatric care, whereas assessment and treatment for many non-ADHD psychiatric conditions, such as depression, anxiety, disrupted sleep, and stress related conditions is conducted in primary care. Our results show that females with ADHD use non-ADHD-medications significantly more often than males with ADHD. One hypothesis is that central stimulant medication may mitigate direct ADHD symptoms but may not be effective for comorbid disorders. Another hypothesis is that females develop more severe, treatment resistant comorbidity, due to diagnostic delay. A third yet unexplored hypothesis is that the menstrual cycle may influence mood, emotional regulation and brain dopamine function, implicated in ADHD-symptomatology (Dorani, Bijlenga, Beekman, van Someren, & Kooij, 2021; Zhang, Yang, Yang, Jin, & Zhen, 2008) and that hormonal status may interact with comorbidity display as well as pharmacological effect. Indeed, a recent comprehensive review showed that psychiatric symptoms are most prominent in the luteal phase (Handy,

Greenfield, Yonkers, & Payne, 2022), when many females also report increased emotional dysregulation and worsening of ADHD symptoms (Roberts, Eisenlohr-Moul, & Martel, 2018).

In our data females with ADHD are overrepresented in overall health care utilization compared to males with ADHD as well as female population controls. Furthermore, and congruent with previous research, our data show that females with ADHD have more inpatient visits due to acute psychiatric stressors compared to males with ADHD (Klefsjö et al., 2021). In line with previous findings of substantial health care related costs associated with ADHD, our results clearly show that females with ADHD are severely impaired, generating substantial costs driven primarily by inpatient care and need for psychological interventions (Garcia-Argibay et al., 2021; Libutzki et al., 2019). Identification of health care utilization patterns indicative of ADHD symptoms may be a feasible way to detect ADHD in females and prevent some of the socioeconomic burden and personal suffering of ADHD.

This regional health care register included approximately 24% of the Swedish population. The register has a considerably broader range of data, with higher granulation, compared to national population-based registries and we could include age and SES-matched controls. However, our results also need to be interpreted in the context of some limitations. Identification of ADHD diagnosis was based on an ICD-10 record of F90 or an ATC-code record of at least one dispensed prescription of a medication for ADHD. Swedish national guidelines state that medication should be reserved for ADHD-cases where other supportive interventions have failed (Läkemedelsverket, 2016). Our definition of exposure could probably not avoid false negatives; however, we consider bias due to false positives more unlikely. In addition, as in all observational studies, we could not fully rule out selection bias due to a lack of information on exposure and outcome variables. By design, this study can only capture individuals who actively have been in contact with the health care services. Also, we did not assess the level of functional impairment or severity of the different disorders and diagnoses, or how many times an individual sought care for a specific condition. Nor did we link a specific condition or diagnosis to a specific intervention or prescription of a specific pharmacological treatment.

Importantly, although an approximately 4-year age difference in diagnosis between males and females is notable, both males and females in this sample on average are diagnosed quite late (Rocco, Corso, Bonati, & Minicuci, 2021). This suggests that opportunities for early detection and consequently early interventions are missed also for males. Diagnosing ADHD in adults, in Sweden, is a relatively new phenomenon and central stimulant medication (Methylphenidate) was formally

approved for treatment of adult ADHD in 2014. Although off-label prescriptions for adults have increased since 2003 when the first central stimulant medication for childhoods ADHD was approved in Sweden, there was no formal pharmacological treatment available for adults with ADHD until the last decade. This may have influenced the possibility of receiving an ADHD diagnosis and Sweden may consequently be playing 'catch up' by diagnosing previously undiagnosed adults. Another possible explanation for the relatively late diagnosis in both males and females in our sample may be a lack of recourses for assessment and treatment. In Sweden, guidelines state that diagnostic assessment for ADHD should be made by a team of licensed and experienced psychiatrist and psychologist. Thus, ADHD assessment is a costly and time-consuming process and time between symptom display, referral, and actual diagnosis is not seldom several years in the Swedish health care system.

Conclusions

This study shows that females receive their ADHD diagnosis close to 4 years later than males. We also demonstrate that females with ADHD have high rates of comorbidity, psychopharmacological treatment, and overall health care utilization, accentuated in the years around ADHD index. Our results indicate a need for increased knowledge about early symptom display, comorbidity, and health care utilization prior to ADHD diagnosis as well as a better understanding of neurobiological underpinnings and, specifically, the influence of biological sex through sex hormones on ADHD symptoms and treatment outcomes in females. Together, these factors may inform future research and decrease diagnostic delay, polypharmacy, and multimorbidity and aid in improving the efficacy of the multimodal treatment for females with ADHD.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Proportion of different presentations of ICD10 F90 ADHD diagnosis in the total sample ($N = 85,330$)^{1,2}.

Table S2A. Intentional self-harm and/or event of undetermined intent expressed as at least one event prior to, or at ADHD-index.

Table S2B. Intentional self-harm and/or event of undetermined intent expressed as at least one event after ADHD-index.

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The study was approved by the research ethics committee at Uppsala University, Dnr 2021-02624), July 05, 2021. The study was designed, conducted, and

consequently reported adhering to the 22-item STROBE-checklist (Cuschieri, 2019). No patient or patient organization was involved in the planning or execution of the study. The data for this study is governed by the research authority of Uppsala University. Data were pseudonymized before being transferred to Uppsala University.

C.S. takes responsibility for the integrity of the data and the accuracy of the data analysis. C.S. is a member of the Scientific Council at the Swedish Medical Products Agency SE-75103 Uppsala Sweden. The views expressed in this paper are not necessarily the view of the Government agency. C.S. is the founder and owner of a private Swedish clinic for assessment and treatment of ADHD in children and adults (SMART Psykiatri) and the founder of a digital tool for screening and precision health for female ADHD (Letterlife). C.S. has participated at advisory boards, served as invited speaker and, received honorariums/travel expenses from Shire/Takeda, Nordic Drugs, UCB Pharma, DNE Pharma, Novartis and Evolan, Lundbeck A/S, and Medice during 2016–2023. She served as PI for research supported by Takeda 2022–2023 and currently receive book royalties from publishing houses in Sweden, Denmark, Estonia, the UK, and Korea (NoK, Presto, TNP, JKP, and Koonja). I.S.-P. served occasionally on advisory boards or acted as invited speaker at scientific meetings for Gedeon Richter,

MSD, Bayer Health Care, Peptonics, Shire, and Lundbeck A/S. S.Y. is employed full time in private practice providing assessment and psychological treatment for children and adults with ADHD. Over the past 3 years S.Y. has received honoraria for consultancy and educational talks years from Janssen, Medice and Takeda. She is author of the ADHD Child Evaluation (ACE), ACE+ for adults, and lead author of R&R2 for ADHD Youths and Adults. T.C. is a co-owner of Sence Research which is an independent company in epidemiology and biostatistics. K.E.S. is employed by Sence Research. M.G. has participated in advisory boards, served as invited speaker for Shire/Takeda, Jansen Cilag and Eli Lilly. Takeda AB financially supported the analytical work for this study via Sence Research (an independent company in biostatistics and epidemiology). Authors received no compensation for manuscript writing. The remaining authors have declared that they have no competing or potential conflicts of interest.

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Key points

- ADHD is a prevalent neurodevelopmental disorder associated with a plethora of adverse health outcomes. Sex differences in the prevalence of ADHD have previously been reported.
- In this register-based study, age at diagnosis, psychiatric comorbidity, pharmacological treatment, and health care utilization were compared between females and males with ADHD.
- Our results indicate that females with ADHD risk diagnostic delay, as well as higher rates of comorbidity, polypharmacy, and health care utilization, compared to males with ADHD.
- Future research and standard of care should explore and develop methods for early detection and treatment, to mitigate the personal suffering and societal burden of diagnosed as well as undiagnosed female ADHD.

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