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Anxiety, mood, and substance use disorders in adult men and women with and without attention-deficit/hyperactivity disorder: A substantive and methodological overview

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ABSTRACT

Knowledge on psychiatric comorbidity in adult ADHD is essential for prevention, detection, and treatment of these conditions. This review (1) focuses on large studies (n > 10,000; surveys, claims data, population registries)

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to identify (a) overall, (b) sex- and (c) age-specific patterns of comorbidity of anxiety disorders (ADs), major depressive disorder (MDD), bipolar disorder (BD) and substance use disorders (SUDs) in adults with ADHD relative to adults without ADHD; and (2) describes methodological challenges relating to establishing comorbidity in ADHD in adults as well as priorities for future research. Meta-analyses (ADHD: n = 550,748; no ADHD n = 14,546,814) yielded pooled odds ratios of 5.0(CI:3.29–7.46) for ADs, 4.5(CI:2.44–8.34) for MDD, 8.7 (CI:5.47–13.89) for BD and 4.6(CI:2.72–7.80) for SUDs, indicating strong differences in adults with compared to adults without ADHD. Moderation by sex was not found: high comorbidity held for both men and women with sex-specific patterns as in the general population: higher prevalences of ADs, MDD and BD in women and a higher prevalence of SUDs in men. Insufficient data on different phases of the adult lifespan prevented conclusions on developmental changes in comorbidity. We discuss methodological challenges, knowledge gaps, and future research priorities.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a childhood onset disorder with a prevalence of around 5–7% in childhood (Polanczyk et al., 2007; Thomas et al., 2015) and 2–3% in adulthood (Fayyad et al., 2017; Simon et al., 2009). ADHD is often comorbid with other psychiatric disorders. For example, common conditions that co-occur with ADHD in childhood are Oppositional Defiant Disorder (ODD), Autism Spectrum Disorder (ASD) and anxiety disorders (ADs) (Antshel et al., 2016; Cordova et al., 2022; Grzadzinski et al., 2016; Jensen et al., 2001; Noordermeer et al., 2017; Spencer et al., 1999). Adult disorders that often co-occur with ADHD are ADs, Mood disorders (i.e., major depressive disorder (MDD), bipolar disorder (BD)) and substance use disorders (SUDs). The focus of this review is on the comorbidity of ADHD with ADs, MDD, BD and SUDs in adults.

Comorbidity refers to the co-occurrence of two conditions. For psychiatric disorders, comorbidity rates tend to be high. These high rates may partly be artifactual due to, for example, symptom overlap between disorders, classification and measurement errors, and so forth (Klein and Riso, 1993; Lilienfeld, 2003). Yet symptom overlap does not account for all comorbidity and many conclude that it is unlikely that comorbidity is merely artifactual (e.g., Angold et al., 1999; Biederman et al., 1995; Katzman et al., 2017; Mak et al., 2021; Milberger et al., 1995). This review assumes that ADHD, ADs, MDD and SUDs are distinguishable and valid conditions and we use the term comorbidity to refer to the co-occurrence of ADHD with these different conditions. In line with this, we see the presence of comorbidity as etiologically meaningful (Klein and Riso, 1993; Lilienfeld, 2003), such that ADHD may be a risk factor for the other, later onset, disorders (i.e., prognostic) or that ADHD and, respectively, ADs, MDD, BD or SUDs may share a common etiology (i.e., pathogenic). Indeed, genomewide association studies have shown that ADHD shares causal loci with other psychiatric disorders (Smoller et al., 2019) and neuroimaging studies indicate that pathophysiology is, in part, shared (Radonjić et al., 2021).

Apart from etiology, the presence of comorbidity is also clinically meaningful. In childhood, comorbidity is associated with greater ADHD symptom severity, greater cognitive and functional impairments, and response to interventions and an overall poorer prognosis (Antshel et al., 2016; Ashwood et al., 2015; Blader et al., 2021; Elwin et al., 2020; Halldorsdottir et al., 2016; Jarrett et al., 2016; Reale et al., 2017; Schatz and Rostain, 2006; Weye et al., 2021). The presence or absence of psychiatric comorbidity in children with ADHD is thus critical in relation to daily functioning, treatment and prognosis. In adulthood, comorbidity is associated with reduced quality of life, functional impairments and premature death (Chen et al., 2022; Cherkasova et al., 2022; Dalsgaard et al., 2015; Joseph et al., 2018; Kessler et al., 2006; Mak et al., 2021; Sobanski et al., 2007; Stickley at al, 2018; Sun et al., 2019; Weye et al., 2021). Thus, etiological and clinical considerations illustrate why studying comorbidity is important.

Although ADHD has been diagnosed in youth for over a century, ADHD in adults was not widely recognized until the 1990 s after the first small longitudinal studies of clinically referred youth reported the persistence of ADHD into young adulthood and the first clinical studies of adult patients using cross-sectional data to document the validity of the disorder in adulthood (Barkley et al., 2006; Biederman et al., 1993, 1994, 2000; Faraone et al., 2006a; Gittelman et al., 1985; Hechtman, 2011; Spencer et al., 1994, 1998; Wood et al., 1976). It is now generally acknowledged that persistence into adulthood is substantial, such that around two thirds of all individuals with childhood ADHD, either at full syndromal or subthreshold level, with fluctuations over time and continued functional impairments in quality of life, social relations, and functioning at work (Cherkasova et al., 2022; Faraone et al., 2006b; Joseph et al., 2018; Sibley et al., 2016, 2022). Compared to childhood, substantial uncertainty nonetheless remains on the overall prevalence of ADHD in adulthood, given (a) the availability of few studies compared to far more studies performed on childhood ADHD, (b) variability in adult diagnostic criteria and methods (Sibley et al., 2016), and (c) variability in estimates in different parts of the world (Fayyad et al., 2017). With regard to comorbidity, the early literature on the persistence of childhood ADHD into adulthood has from the outset been focused on differentiating characteristics of ADHD from other common adult psychiatric disorders and on the impairments tied specifically to adult ADHD and not explained by the presence of comorbid disorders (Able et al., 2007; Biederman et al., 1998, 2006, 2012; Garcia et al., 2012; Katzman et al., 2017; Montano et al., 2011; Uchida et al., 2018). Through this focus on how adult ADHD differs from the other, better established, adult psychiatric disorders (e.g., MDD), the presence of comorbidity has been a central theme.

The present review aims to compare adults with ADHD with adults without ADHD on overall prevalences, sex-, and age-specific prevalences of ADs, MDD, BD and SUDs based on large representative samples from the general population. Most knowledge on psychiatric comorbidity in adult ADHD has been derived from relatively small-sized clinical samples. These studies have described the frequent presence of ADs, MDD, BD and SUDs in adults with ADHD, but interpretation is often hindered due to absence of a comparison group (i.e., difficult to establish if comorbidity is high or low; e.g., Duran et al., 2014; Leung and Chan, 2017; Wilens et al., 2009) or use of a clinical comparison group (possible underestimation, e.g., Cumyn et al., 2009; Gorlin et al., 2016; Murphy and Barkley, 1996). However, other clinical studies included an adequate comparison group and report on high rates of MDD, BD, SUDs and to a lesser extent ADs (e.g., McGough et al., 2005; Miller et al., 2007; Sobanski et al., 2007), but estimates vary widely potentially due to the combination of small sample size and specific clinical characteristics of the recruited patient sample. Similar interpretational problems hold for establishing sex differences in comorbidity (e.g., Edvinsson et al., 2013; Wilens et al., 2009), although two small-sized clinical studies with an appropriate comparison group have been conducted which evaluated if differences between men and women were different in persons with ADHD than in persons without ADHD. Both found no modification by sex (Biederman et al., 1994, 2004). While taking the first step in determining if the presence of ADHD alters well-known population-based sex differences in psychopathology, the finding that this is not the case should be seen as preliminary as these two studies were underpowered for the identification of interaction effects. With regard to potential lifespan differences in comorbidity, two studies reporting on

different follow up waves of a clinical sample indicated that the presence of comorbidity co-occurred with persistence of ADHD symptoms during adulthood but estimates of comorbidity in different parts of adulthood were not provided (Grevet et al., 2022; Karam et al., 2017). In all, the findings derived from mostly small clinical studies indicate high comorbidity in adults with ADHD but more definite conclusions, including on potential sex and lifespan differences in comorbidity, require representative general population-based estimates of the prevalence of comorbid conditions in persons with and without ADHD.

The first aim of this narrative review is to describe the extent to which adults diagnosed with ADHD have comorbid ADs, MDD, BD and SUDs by bringing together findings from large studies representative of the general population of which in recent years quite a number have been published. We confined ourselves to ADs, mood disorders (i.e., MDD and BD) and SUDs, as these are the most common psychiatric disorders in adulthood *and* have been studied frequently as comorbid conditions of adult ADHD.

The second aim is to synthesize findings on sex-differences in the patterns of comorbidity of ADHD in adulthood. ADHD manifests differently in girls than in boys, with attention problems being more prominent in girls with ADHD and hyperactivity-impulsivity more prominent in boys with ADHD (Gaub and Carlson, 1997; Staller et al., 2006). These different manifestations may go together with respectively, more internalizing and externalizing problems (Hinshaw et al., 2022), although this sex specific pattern is also found in the general population and it is uncertain if it is more outspoken in ADHD. Sex differences in the manifestation of ADHD may be less outspoken in adults (Young et al., 2020; Williamson and Johnston, 2015), although this also needs further research due to the potential presence of sex-specific diagnostic biases (Mowlem et al., 2019) as well as that adult (sex-specific) symptoms are typically not probed in current ADHD instruments (Hinshaw et al., 2022). Sex differences in the prevalence of ADs, MDD, BD and SUDs in the adult general population are well-known (e.g., Kessler et al., 1994; Pedersen et al., 2014; Sundquist et al., 2017) but potential etiological differences shared by men and women with ADHD (e.g., enhanced exposure due to adverse events or failure experiences; a shared genetic etiology between ADHD and comorbid conditions) could make the prevalence of ADs, MDD, BD and SUDs in women and men with ADHD being more alike. All of these findings raise the question if sex differences in ADs, MDD, BD and SUDs are altered when ADHD is present compared to sex specific prevalence estimates of these conditions in the general population and this will be addressed in this review.

The third aim is to summarize potential changes in comorbidity across the adult lifespan. Starting adolescence, longitudinal studies show that particularly hyperactivity declines (Biederman et al., 2000; Vos et al., 2022), although this varies for different symptoms and associated impairments (Niina et al., 2022) and whether or not comorbidity and adverse circumstances are present (Hartman et al., 2019). Furthermore, longitudinal findings in clinical sample show that up to 30% of adults with ADHD may show symptom attenuation or remission of ADHD during adulthood (Edvinsson and Ekselius, 2018; Karam et al., 2015) which is in line with decreasing ADHD symptom levels based on longitudinal population cohorts (Wootton et al., 2022) and a gradual decline of ADHD across the adult lifespan found in a recent meta-analysis (Song et al., 2021) and a large study in the general population (Vos and Hartman, 2022), both based on cross-sectional data. With regard to the comorbid conditions studied here, peak incidence periods in the general population differ for ADs, MDD, BD and SUDs, respectively (Andreas et al., 2017, 2019; Pedersen et al., 2014; Schulte et al., 2014; Solmi et al., 2022; Volkert et al., 2013) and so does the course of these conditions throughout the lifespan (Beller et al., 2021; Hasin and Grant, 2004; Plana-Ripoll et al., 2020; Sajatovic et al., 2015; Scott et al., 2008; Walker et al., 2015). Together changes in ADHD and changes in ADs, MDD, BD and SUDs raise the question if type and extent of comorbidity in ADHD also changes throughout the lifespan, which we aim to document.

A final aim of this review is to point out methodological difficulties that need to be considered when interpreting current and future findings on comorbid psychiatric conditions of ADHD in adulthood and related to this, to point out the gaps in current knowledge and to outline future research priorities.

2. Methods

2.1. Study selection

The following search terms were used:*(ADHD[Title] or Attention Deficit Hyperactivity Disorder[Title] or Attention Deficit / Hyperactivity Disorder [Title]) AND (adult[Title] OR adults[Title] OR adulthood[Title]) AND (comorbidity or comorbid or co-morbid or co-occurrence)*. For a study to be included in the review the following criteria were used (1) the study had no exclusion criteria related to ADHD or ADs, MDD, BD and SUDs; (2) the presence of ADHD and of comorbid conditions was established on the basis of diagnoses, i.e., clinical diagnoses, semi-structured or structured interviews. Thus, studies using a cut-off based on symptom counts of ADHD or of ADs, MDD, BD or SUDs derived from a self-report questionnaire were excluded; also, studies in which the single question "were you ever diagnosed with …" was posed and thus had no direct information on ADD or comorbid conditions based on clinical diagnoses, semi-structured or structured interviews were excluded (4) the sample was representative of the general population and diagnostic information was provided on ADs, MDD, BD for adults with and without ADHD. Studies with a clinical comparison sample (e.g., referred patients with other diagnoses than ADHD) or a healthy comparison sample (individuals with ADs, MDD, BD or SUDs removed from the sample) were excluded. Also, studies that started from the comorbid condition rather than from ADHD to investigate the prevalence of ADHD (e.g. the prevalence of ADHD in individuals with and without MDD) were excluded; (4) the total sample size was at least 10,000. The rationale to focus on relatively large studies was based on considerations regarding the stability of the estimates. When sampled from the general population, based on the population prevalence of 2–3% (Fayyad et al., 2017; Simon et al., 2009), at least 200 persons would be expected.

The final search was completed at January 1, 2023 and yielded 1001 papers in Pubmed. Abstracts were carefully screened by both the first (CAH) and third (MV) author and the full text of the paper was read in case of doubt. In addition, references were checked for potentially missed papers. Disagreements were solved by rechecking the paper against the inclusion criteria. The selection procedure yielded in total nine studies that fitted our inclusion criteria. The selected studies were performed in samples representative of the general population (surveys; 2 studies), in large parts of the full population (insurance claims data; 3 studies) or in the full population (registry data; 4 studies).

2.2. Included studies

Selected studies are described in detail in supplementary information (SI), sections S1-S5. Table 1 summarizes relevant background characteristics of included studies. Briefly, the first selected population survey was the World Health Organization World Mental Health Surveys (WHO-WMHS; Fayyad et al., 2017). Among the 20 sites taking part in the WHO-WMHS was the National Comorbidity Survey Replication (NCSR) that took place in the Unites States of America (USA; Kessler and Merikangas, 2004; Kessler et al., 2006). Diagnostic procedures in the NCSR were more extensive than those at the other sites that contributed to the WHO-WMHS. Therefore, findings are separately reported in this review for the NCSR in addition to the results from the WHO-WMHS. The second selected survey was the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), performed in the USA (Bernardi et al., 2012; Grant et al., 2004a, 2004b; Cortese et al., 2016). Two of the three selected studies based on insurance claims data were

Table 1
Study characteristics, ADHD prevalence rates and male:female ratios[a].

	Country	total number of persons analyzed[b]	number of persons with ADHD in total sample	birth years	age range	mean age total sample	mean age subsample ADHD	period of ADHD retrieved and source[c]	response rate	prevalence ADHD %[d]	male-female ratio[d]
S	International WHO-WHMS	26,744	749[e]	1957–1994	18–44	∅[f]	~29[e]	2001–2012	68,5	2.8[e]	1.6:1[e]
S	USA NCSR[g]	3199	141[e]	1957–1984	18–44	∅[f]	~31[e]	2001–2002	70,9	4.4[e]	1.6:1[e]
S	USA NESARC[h]	34,653	807/340	≤ 1984	≥ 18	~47	~39/~37	2004–2005	70,5[i]	2.5/1	1.4:1/ 1.1:1
C	USA-Babinski	775,936[j]	387,968	1980–1996	18–25	21	21	2005–2014	N/A	6.0	1.4:1
C	USA-Secnik	4504[k]	2252	1934–1983	18–65	~33	~33	1999–2001	N/A	∅	1.8:1
C	Germany	10,940 [l]	5470	1914–1997	18–96	< 25	< 25	2009–2014	N/A	0.2 [m]	1.9:1 [m]
R	Norway	1701,206	40,103	1967–1997	18–48	33	31	2004–2015	N/A	2.4	1.5:1
R	Sweden-Chen	5551,807	61,129	1949–1995	18–64	41	30	1973–2013	N/A	1.1	1.3:1
R	Sweden-Sundquist	5397,675	25,891	≤ 1999[n]	≥ 18	∅	∅	1998–2016[o]	N/A	0.5	1.2:1
R	Denmark	1603,943	31,302	1981–2013	0–32	N/A[p]	N/A[p]	1981–2013	N/A	2.0	2.4:1

Notes ADHD: Attention-Deficit/Hyperactivity Disorder; N/A: not applicable; ∅: Information was not provided; ~: approximate estimate. S: Survey. C: Claims data. R: Registry data

[a] part of the content of this table was calculated from the information provided in the original papers for the purpose of the present study rather than directly retrieved.

[b] total sample size analyzed to determine presence of anxiety disorders, major depressive disorder, bipolar disorder and substance use disorders.

[c] international WHO-WHMS, USA-NCSR: past 12-months interview-based diagnosis. NESARC: lifetime respectively past 2-month interview-based diagnosis. Norway: ADHD based on prescription data 2004–2015; ADHD based on diagnosis 2008–2015. Sweden-Chen: inpatient diagnosis since 1973; outpatient diagnosis since 2001. Sweden-Sundquist: diagnosis from primary care. USA-Babinski: diagnosis includes primary and specialist care; USA-Secnik: diagnosis includes primary and specialist care; Germany: diagnosis includes primary and specialist care; while ADHD was based on 2009–2014; anxiety, mood and substance use disorders were based on 2014; Denmark: inpatients diagnosis during 1981–2013; outpatients and emergency contact diagnosis between 1995 and 2013.

[d] estimates rounded at 1 decimal place.

[e] estimated by multiple imputation rather than actual number of persons with ADHD.

[f] age not provided but most of the samples including USA-NCSR were nationally representative at the time study was performed.

[g] this study is part of the International WHO-WHMS study. Given more extensive reporting in this study we described its results separately.

[h] information on both lifetime and past 2-month diagnoses is provided. Lifetime ADHD with age of onset of ADHD < 18 years old and regardless of whether ADHD persisted or remitted; past 2-months (sex specific) comorbidity based on persistent ADD with age of onset of ADHD < 12 years old and present in past 2 months.

[i] ADHD in NESARC assessed at wave 2. Wave 1 response rate was 81%; wave 2 response rate was 87% of wave 1, which yields an overall wave 2 response rate of 70%.

[j] total sample includes ADHD sample identified in the database combined with 1:1 age-, gender-, metropolitan statistical area- and type of insurance plan-matched sample of adults without ADHD; total number of adults in database was n = 6466,133.

[k] total sample includes ADHD sample identified in the database combined with age, gender, metropolitan statistical area and type of insurance plan; total number of adults in database was not provided.

[l] total sample includes ADHD sample identified in the database combined with 1:1 age- and sex-matched sample of adults without ADHD; total number of adults in database in 2014 was n = 3705,952.

[m] original paper provided separate estimates for ages 18–30 and 31 and older; current estimates calculated from these separate estimates.

[n] start date of observational period varied among regions between 1998 and 2008; reported start date is the earliest retrieval date. End date of observational period varied among regions between 2013 and 2016; reported end date is the latest retrieval date.

[o] end date of observational period varied among regions between 2013 and 2016; reported birthyears are based on age ≥ 18 at the latest retrieval date.

[p] longitudinal analyses; mean age not provided.

performed in the USA (Babinski et al., 2020; Secnik et al., 2005) and one in Germany (Libutzki et al., 2019). All three studies selected a 1:1 comparison sample from the total database, matched to the ADHD sample on the basis of sex and age (and in Secnik et al., 2005, in addition, by region and insurance type). Finally, the four whole population-based studies selected for the review were based on, respectively, Norwegian (Solberg et al., 2018; secondary and inpatient care and ATC codes), Swedish (Chen et al., 2018: secondary and inpatient care; Sundquist et al., 2017: primary care) and Danish registries (Ottosen et al., 2019: secondary and inpatient care). Among these nine studies that provided information with regard to overall comorbidity estimates (aim 1), six provided sex-specific results (aim 2, Babinski et al., 2020; Chen et al., 2018; Cortese et al., 2016; Libutzki et al., 2019; Ottosen et al., 2019; Solberg et al., 2018). Finally, with regard to aim 3, two studies reported on different age groups (Chen et al., 2018; Libutzki et al., 2019).

2.3. Outcome parameters

We focused on absolute differences and relative differences between persons with and without ADHD, which are both calculated on the basis of the prevalence rate. The prevalence rate captures the absolute risk of ADs, MDD, BD and SUDs in the two groups of individuals, i.e., with and without ADHD, in percentages. Individuals with and without ADHD are compared by the prevalence difference which is calculated by subtracting the prevalence rate of respectively ADs, MDD, BD and SUDs found in individuals with ADHD from that found in individuals without ADHD. A value above zero thus indicates that the prevalence of these conditions is higher in ADHD. The prevalence difference is particularly relevant when the research is focused on determining if relative to the population prevalence, there is an excess of ADs, MDD, BD and SUDs among individuals with ADHD who, if this would be the case, could be specifically targeted for prevention or treatment (e.g., VanderWeele et al., 2014). As an estimate of the relative risk of respectively ADs, MDD, BD and SUDs in adults with ADHD compared with adults without ADHD, we report both the prevalence ratio and the odds ratio, in line with the included studies reporting one, or the other, outcome parameter. As ratios, they adjust for the prevalence rate of each of the studied conditions in the general population which facilitates comparing across different conditions that vary in their prevalence in the general population (such as, here, ADs, MDD, BD and SUDs) answering the question which condition, if any, is most strongly associated with ADHD. Prevalence or odds ratios above one indicate that ADHD is associated with an increased relative risk of the condition studied when compared to

individuals without ADHD (e.g., Gnardellis et al., 2022; VanderWeele et al., 2014). To maximize comparability across the studies we additionally calculate odds ratios for studies that provided the prevalence ratio (vice versa calculation is not possible due to insufficient information in the original papers) and, likewise, the meta-analyses of the findings are focused on odds ratios (described in Section 2.4, below). Finally, SI, section S4, provides additional background information on study specific outcome parameters, including on incidence ratios provided by Denmark in longitudinal analyses. To address potential sex differences in comorbidity, we report prevalence rates for women and men separately, sex-specific prevalence differences as well as sex specific prevalence and odds ratios. We report the same outcome parameters to address the potential presence of age differences, in that case comparing different age groups instead of women and men.

2.4. Meta-analyses

Meta-analyses combining the nine different studies described in Section 2.2 are performed to determine if the prevalence of, respectively, ADs, MDD, BD and SUDs in adults with ADHD differs from adults without ADHD (aim 1; Babinski et al., 2020; Bernardi et al., 2012, Chen et al., 2018; Fayyad et al., 2017; Libutzki et al., 2019; Ottosen et al., 2019; Secnik et al., 2005; Solberg et al., 2018; Sundquist et al., 2017). For this purpose, we focus on the 20-site WHO-WMHS (Fayyad et al., 2017) which includes the NCSR from the WHO-WMHS (Kessler et al., 2006). We focus on the relative difference in prevalence and calculate the natural logarithm of the odds ratio (LogOR) and its variance. Meta-analyses are conducted in *R 4.1.2* (R Core team, 2020) to estimate the pooled LogOR across studies for each disorder. Random-effects meta-analytic models are fitted to the data in *metafor* (Viechtbauer, 2020). The Restricted Maximum-Likelihood (REML) estimator is used with Knapp-Hartung confidence interval adjustment (Langan et al., 2019). The Cochran's Q test is used to investigate the potential presence of significant heterogeneity in estimates across studies (Cochran, 1954). Publication bias is assessed visually using funnel plots. In follow-up analyses, we perform meta-regressions to investigate if (a) observation time to identify comorbidity, (b) upper limit of the sample age range, (c) type of study (survey vs insurance claims or registry data, and (d) male-to-female ratio in the sample have an influence on the findings of the meta-analyses.

In a similar manner, we perform meta-analyses for five studies providing sex-specific results to estimate if sex differences in ADs, MDD, BD ad SUDs differ between men and women with and without ADHD (aim 2; Babinski et al., 2020; Chen et al., 2018; Libutzki et al., 2019; Ottosen et al., 2019; Solberg et al., 2018). Although the study by Cortese et al. (2016) also provides sex-specific findings, it is not included in the meta-analyses, given that prevalence rates of ADs, MDD, BD and SUDs were not provided for males and females without ADHD. Finally, the two identified studies that stratified by age used different age cut-offs (i.e. age 30 versus age 50. This hinders comparability and thus findings are not meta-analysed (aim 3; Chen et al., 2018; Libutzki et al., 2019).

3. Results

3.1. ADs, MDD, BD ad SUDs in adults with ADHD compared to adults without ADHD

Table 2 provides for all included studies prevalence rates, prevalence differences and prevalence / odds ratios for ADs, MDD, BD ad SUDs. For each of these four conditions, prevalence rates vary strongly across the studies, both in individuals with and in individuals without ADHD. Accordingly, prevalence differences also vary strongly, with ranges of 2.2–44.3 for ADs, 1.0–41.6 for MDD, 0.3–27.3 for BD, and 2.4–31.5 for SUDs (Table 2). With regard to the prevalence/odds ratios, ADHD was associated with a 2.2–9.1-fold increased risk of ADs, a 1.6–9.0-fold increased risk of MDD, a 3.4–20.0-fold increased risk of BD and a 2.3–9.7-fold increased risk of SUDs.

Visual inspection of Table 2 suggests that prevalence differences and ratios are associated with observation time to identify comorbidity (ranging from 1 year to lifetime; Table 2) and the average age at end of follow-up (mean age in studies roughly varied from 20 to 40 years; Table 1). The findings from Swedish primary and specialist care, respectively, show the largest prevalence differences and ratios, in line with these studies' longest observation time to identify comorbidity combined with their highest average age. Conversely, the two studies focused on young adults (i.e., USA-Babinski and Denmark) tend to have the lowest prevalence differences and ratios, in line with that not all onsets of ADs, MDD, BD and SUDS have yet occurred.

Comparisons among ADs, MDD, BD and SUDs *within* each of the studies (thereby removing variability in results due to methodological differences between studies) indicate that prevalence differences are similar for ADs, MDD and SUDs, which are higher compared to BD. This pattern in absolute risk is associated with the lower prevalence of BD in the general population, compared to the other three conditions. With regard to relative risk as indicated by the prevalence / odds ratios, *within* country comparisons among ADs, MDD, BD and SUDs show that ADHD and BD have the strongest association. Thus, accounting for the prevalence differences between ADs, MDD, BD and SUDs in the general population, the highest risk is with BD.

Meta-analyses combining the studies described in Sections 2.2 and 2.3 indicate that ADHD is significantly associated with increased ADs (logOR = 1.60, SE = 0.21, 95% CI = [1.19; 2.01], $z = 7.66$, $p < 0.001$), MDD (logOR = 1.51, SE = 0.31, 95% CI = [0.89; 2.12], $z = 4.80$, $p < 0.001$), BD (logOR = 2.17, SE = 0.24, 95% CI = [1.70; 2.63], $z = 9.12$, $p < 0.001$) and SUDs (logOR = 1.53, SE = 0.27, 95% CI = [1.00; 2.05], $z = 5.68$, $p < 0.001$). Table 3 and Fig. 1 show pooled odds ratios of 5.0 for ADs, 4.5 for MDD, 8.7 for BD and 4.6 for SUDs.

Cross-study heterogeneity is significant in all four meta-analyses (Table 3). Publication bias is not evident from the funnel plots (SI, section S6). The meta-regressions exploring the heterogeneity of the pooled estimates revealed that the male-to-female ratio in the sample influences the estimate of BD, for which studies with a larger male-to-female ratio have a smaller prevalence of BD in adults with compared to adults without ADHD, in line with the overall lower prevalence of BD in males compared to females. None of the other meta-regressions yield statistically significant findings (SI, section S7). While suggesting that the main findings are not affected by observation time to identify comorbidity, upper limit of the sample age range or type of study (survey vs insurance claims data/registry data), these findings may be due to limited statistical power (i.e., few studies in the meta-analysis to explore these effects).

3.2. Sex differences in ADs, MDD, BD ad SUDs in men and women with ADHD compared to men and women without ADHD

Six studies reported on sex differences in comorbidity. Table 4 provides sex specific prevalence rates, prevalence differences as well as prevalence ratios and odds ratios for adults with and without ADs, MDD, BD ad SUDs. Here, the main question is whether sex differences in these conditions are similar or different in adults with ADHD compared to sex differences in the general population.

Table 4 shows that for ADs, MDD and BD, the prevalence differences described in Section 3.2 (Table 2) in individuals with ADHD compared to individuals without ADHD are larger for females than males. This excess risk for women with ADHD (i.e., female-male difference of the prevalence difference, Table 4, before-last column) varies between 0.9%− 13.2% for ADs, 1.3%− 11.4% for MDD, and 0.4%− 8.6% for BD. Excess risks are lowest in the Danish study compared to the other studies, in line with the younger participants in the study and censored data (i.e., not all onsets of ADs, MDD and BD have yet occurred).

The six studies do not converge on sex differences in SUDs: an excess number of females with ADHD compared with males with ADHD is

Table 2
Occurrence, absolute risk and relative risk of anxiety disorders, major depressive disorder, bipolar disorder and substance use disorders in individuals with and without ADHD, estimated by prevalence rates, prevalence differences, and prevalence/odds ratios in surveys, registries and insurance claims data[a,b].

		maximum years comorbidity identified[c]	ADHD	no ADHD	absolute risk in ADHD compared to no ADHD	relative risk in ADHD compared to no ADHD[d]	
Anxiety disorders							
			prevalence %	prevalence %	prevalence difference %	prevalence ratio	odds ratio
S	International WHO-WHMS	1	34.2	∅	∅	∅	3.7
S	USA NCSR	1	47.1	19.5	27.6	2.4	3.7
S	USA NESARC[e]	1/lifetime	42.7/60.7	14.4/27.2	28.4/33.5	3.0/2.2	4.4/4.1
C	USA-Babinski[f]	1	15.9	7.3	8.6	2.2	2.7
C	USA-Secnik[g]	3	13.8	3.5	10.3	4.0	4.5
C	Germany[h,i]	1	43.8	14.7	29.1	3.0	4.5
R	Norway[j,k]	7	21.8	5.0	16.8	4.4	5.3
R	Sweden-Chen[l,m]	40	44.7	4.9	39.8	9.1	13.8
R	Sweden-Sundquist[n]	17	54.0	9.7	44.3	4.4	10.9
R	Denmark[o]	26	3.7	1.5	2.2	2.5	2.5
Major depressive disorder							
			prevalence %	prevalence %	prevalence difference %	prevalence ratio	odds ratio
S	International WHO-WHMS	1	15.0	∅	∅	∅	2.5
S	USA NCSR	1	18.6	7.8	10.8	2.4	2.7
S	USA NESARC[e]	1/lifetime	11.2/26.4	5.5/16.2	5.7/10.2	2.0/1.6	2.2/1.9
C	USA-Secnik	3	17.1	2.9	14.2	5.8	6.8
R	Norway[j,k]	7	24.1	5.8	18.3	4.2	5.2
R	Sweden-Chen[l,m]	40	42.3	4.7	37.6	9.0	12.2
R	Sweden-Sundquist[n]	17	53.8	12.2	41.6	5.6	8.4
R	Denmark[o]	22	2.6	1.6	1.0	1.6	1.7
Bipolar disorder							
			prevalence %	prevalence %	prevalence difference %	prevalence ratio	odds ratio
S	International WHO-WHMS	1	9.4	∅	∅	∅	5.4
S	USA NCSR	1	19.4	3.1	16.3	6.3	7.4
S	USA NESARC[e]	1/lifetime	22.7/33.6	3.2/6.2	19.5/27.3	7.1/5.4	8.9/7.6
C	USA-Secnik	3	4.5	0.6	3.9	7.7	8.0
R	Norway[j,k]	11	10.7	1.3	9.3	8.0	8.8
R	Sweden-Chen[l,m]	40	14.3	0.7	13.6	20.0	18.3
R	Denmark[o]	22	0.4	0.1	0.3	3.4	3.4
Mood disorders							
			prevalence %	prevalence %	prevalence difference %	prevalence ratio	odds ratio
C	Germany[h,i,p]	1	40.7	8.2	32.5	5.0	7.7
Substance use disorders							
			prevalence %	prevalence %	prevalence difference %	prevalence ratio	odds ratio
S	International WHO-WHMS	1	11.4	∅	∅	∅	3.8
S	USA NCSR	1	15.2	5.7	9.6	2.7	3.0
S	USA NESARC[e]	1/lifetime	46.0/71.7	20.5/44.5	25.4/27.2	2.2/1.6	3.3/3.2
C	USA-Babinski[f]	1	2.3/3.8	1.3/1.9	1.0/1.9	1.8/2.0	1.8/2.0
C	USA-Secnik	3	5.1	1.9	3.2	2.7	2.8
R	Germany[h,i]	12	15.9	4.7	11.2	3.4	3.8
R	Norway[j,k]	7	22.5	2.9	19.6	7.9	9.9
R	Sweden-Chen[l,m]	40	35.1	3.6	31.5	9.7	12.5
R	Sweden-Sundquist[n,q]	17	17.2/23.1	2.0/2.5	15.3/20.5	8.8/9.1	10.4/11.5
R	Denmark[o]	22	4.2	1.8	2.4	2.3	2.4

Notes ADHD: Attention-Deficit/Hyperactivity Disorder; ∅: Information was not provided; S: Survey. C: Claims data. R: Registry data.

[a] Part of the content of this table is calculated from the information provided in the original papers rather than directly retrieved (see section 3.2.3).

[b] All estimates rounded at 1 decimal place.

[c] Maximum period during which the presence of anxiety disorders, MDD, bipolar disorder and SUDs could be identified.

[d] both prevalence ratios and odds ratios are provided so that studies can be compared on the same metric.

[e] NESARC: 12-months and lifetime comorbidity estimates based on lifetime ADHD which was defined as onset before age 18 regardless of whether ADHD persisted thereafter.

[f] paper does not report observation time for ADs and SUDs, which is most likely 1 year, in line with the 1 year observation period that was reported for MDD in this study (however, the reporting on MDD comorbidity was insufficient for incorporation is this table.).

[g] social phobia was separately analyzed from the remaining anxiety disorders but had a very low prevalence which likely overlaps with the anxiety disordered group and was therefore not included.

[h] inpatient, day patient or outpatient diagnoses. ADHD based on 2009–2014; anxiety, mood and substance use disorders based on 2014.

[i] original paper provided separate estimates for ages 18–30 and 31 and older; current estimates calculated from these separate estimates.

[j] ADHD and bipolar disorder based on prescription data 2004–2015; ADHD and bipolar disorder based on diagnosis 2008–2015; anxiety disorders, MDD, and SUDs diagnoses based on diagnosis 2008–2015.

[k] estimates adjusted for birthyear.
[l] inpatient diagnoses since 1973; outpatient diagnoses since 2001. while the retrieval period was 40 years maximally, the 12 year period covering outpatient diagnoses since 2001 provide the bulk of the data, particularly on ADHD.
[m] estimates adjusted for age and sex.
[n] the observation time differed among different regions. The longest period of observation was 1998–2014 which is reported here.
[o] inpatient diagnoses during 1981–2013; outpatients and emergency contacts diagnoses between 1995 and 2013. ADHD identified from birth (maximum age is 32 years); comorbid anxiety disorders from age 6 years (maximum observed period 26 years); comorbid MDD, bipolar disorder, and SUDs from age 10 (maximum observed period for anxiety is 22 years).
[p] the German study combined MDD and bipolar disorder into a single category of mood disorders.
[q] This study provided separate estimates for respectively alcohol use disorder and other substance use disorders; note that summing these percentages would introduce error given possible overlap in patients.

Table 3
Meta-analytic results of the relative risk (odds ratios) of anxiety disorders, major depressive disorder, bipolar disorder and substance use disorders in individuals with and without ADHD[a,b,c].

Outcome	# Studies	Association			Heterogeneity	
		OR	*95% CI*	*p*	*Q*	*p*
Anxiety disorders (ADs)	9	4.95	[3.29; 7.46]	< 0.001	31028.44	< 0.001
Major depressive disorder (MDD)	7	4.51	[2.44; 8.34]	< 0.001	8209.44	< 0.001
Bipolar disorder (BD)	6	8.72	[5.47; 13.89]	< 0.001	2301.38	< 0.001
Substance abuse disorders (SUDs)	9	4.60	[2.72; 7.80]	< 0.001	18579.24	< 0.001

Notes ADHD: Attention-Deficit/Hyperactivity Disorder; OR Odds Ratio; CI confidence interval; Q Cochran's Q test
[a] The 20-site WHO-WMHS (Fayyad et al., 2017) which includes the NCSR subsample from the WHO-WMHS (Kessler et al., 2006) was used in the meta-analysis.
[b] The mood disorder category which combined MDD and BD into a single category in the German sample (Table 2; see Libutzki et al., 2019) was left out of the meta-analysis.
[c] Prevalence rates were reported separately for Alcohol Use Disorder and Drug-Addiction (Table 2; see Sundquist et al., 2017) but were pooled for the purpose of this meta-analysis. The two prevalence rates were summed followed by subtraction of the estimated overlap in persons with both conditions as provided for the whole population in the original paper. The pooled prevalence is overestimated to the extent that the overlap in alcohol use Disorder and Drug-Addiction is stronger is persons with than without ADHD.

found for SUDs in the Danish study and the USA-Babinski study (i.e., for alcohol use disorder; but not for other substance use disorders). NESARC, Norway and Sweden report an excess number of males compared to females with ADHD and SUDs. The Danish and USA-Babinsky studies included young adults; the excess risk in women with ADHD in these studies may reflect an earlier onset of SUDs in females with ADHD while this pattern reverses later in life as found in the studies that included older adults.

Sex specific prevalence ratios and odds ratios (i.e., the ratio of the female ADHD versus non-ADHD and male ADHD versus non-ADHD ratios, as reported in Table 4, last column) are mostly small and inconsistent across the studies (i.e., they are slightly below or above 1, indicating small difference between sexes which are sometimes stronger for males and sometimes stronger for females, respectively). Slightly higher ratios, consistently above 1 in the Danish (BD, SUDs, and including ADs and MDD when based on the incidence ratios) and USA-Babinski (ADs, MDD, BD, SUDs) studies hint at stronger associations for studied conditions for young adult women with ADHD.

Meta-analyses combining five studies that stratified by sex, as described in Sections 2.2 and 2.4 (Babinski et al., 2020; Chen et al., 2018; Libutzki et al., 2019; Ottosen et al., 2019; Solberg et al., 2018), determine if the relative difference in risk between men and women with ADHD of, respectively, ADs MDD, BD and SUDs, differs from the relative difference in risk of these conditions between men and women without ADHD. The meta-analyses of sex-specific relative risk show, pooled across samples, a lower relative risk for male than female adults, for ADs (logOR = −0.64; 95% C.I. [−0.75; −0.52]), MDD (logOR = −0.74; 95% C.I. [−0.89; −0.58]) and BD (logOR = −0.61; 95% C.I. [−0.76; −0.47]), yet these sex differences in relative risk are independent of whether ADHD is present or not (i.e., no moderation effect by sex, see SI section S8). In contrast, the meta-analysis of SUDs shows, pooled across samples, a higher relative risk for male than female adults, for SUDs (logOR = 0.3710; 95% C.I. [0.1884; 0.5535]), which holds, again, independent of the presence of ADHD (i.e., no moderation effect by sex, see SI section S8). Fig. 2 shows the forest plots depicting sample specific and pooled estimates of the relative sex differences in the prevalence of ADs, MDD, BD and SUDs in, respectively, adults without and with ADHD. The forest plots illustrate that sex differences in ADs, MDD, BD and SUDs in adults without ADHD are similar to sex differences in these conditions in adults with ADHD. All four sex-specific meta-analyses report statistically significant heterogeneity in the pooled estimates. See SI, section S8, for the results of the heterogeneity of findings in these sex specific meta-analyses.

3.3. Age differences in ADs, MDD, BD ad SUDs in adults with ADHD compared to adults without ADHD

Here, the main question is whether age differences in ADs, MDD, BDs and SUDs are similar or different in adults with ADHD compared to potential age differences in the general population. Only two studies stratified the findings by age: the Swedish study provided separate estimates for adults age 50–64 in addition to the findings in the total sample and the German study reported separately on adults with ages 18–30 years and ages 30 and older. Given little age-specific information overall and these different age cutoffs, prevalence rates, prevalence differences and prevalence ratios in the older subset of adults of the Swedish and German studies relative to the total adult sample are described in SI, section S9 and Table S1. Very tentatively we hypothesized, there, that the prevalence of AD, MDD, BD or SUD remains higher throughout the lifespan in individuals with ADHD than individuals without ADHD and that the relative risk of having an AD, MDD, BD or SUD when diagnosed with ADHD increases somewhat across the adult lifespan.

4. Methodological challenges

An additional aim of this paper is to review the methodological difficulties that need consideration when evaluating current and future evidence on comorbid conditions of ADHD in adulthood. Survey data and registry data have each strengths and weaknesses and are partly complementing one another. Part of the weaknesses are specifically related to adult ADHD and co-occurring conditions. We review these here.

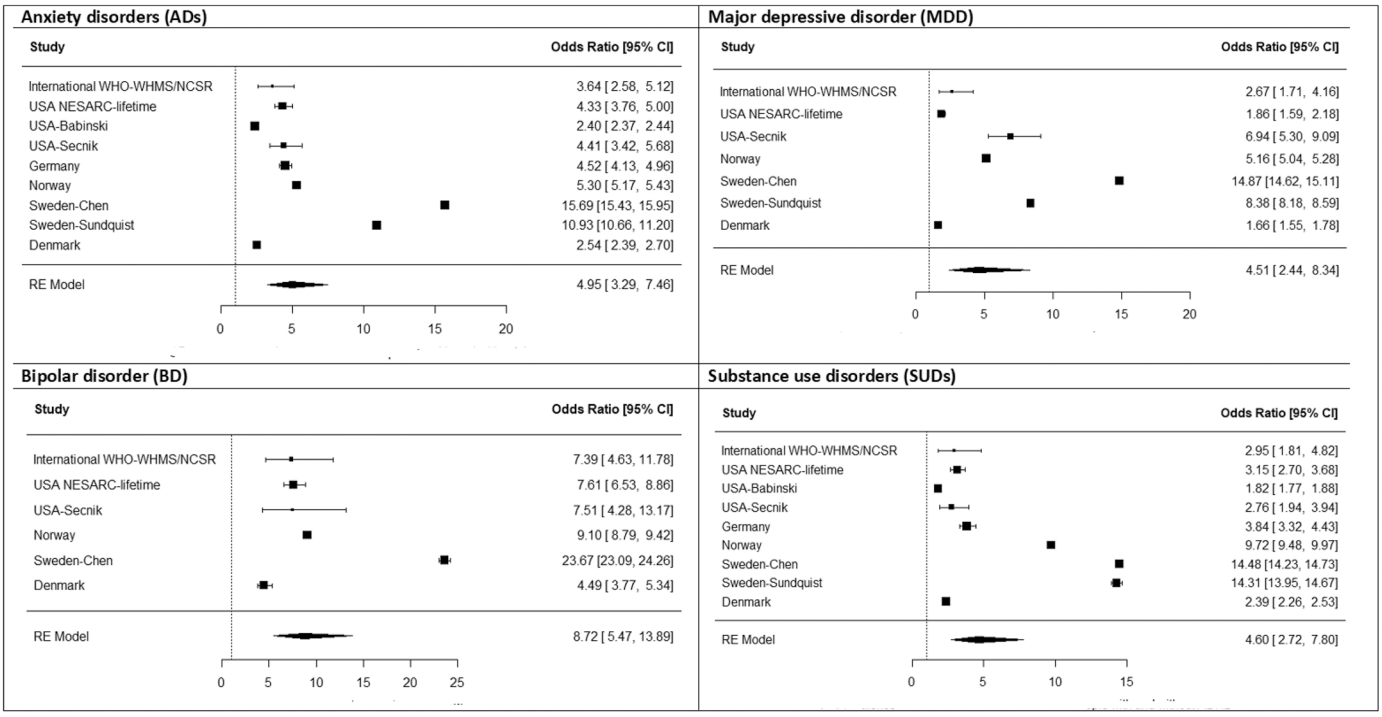

Fig. 1. Pooled and study specific relative risk (OR) of anxiety disorders, major depressive disorder, bipolar disorder and substance use disorders in individuals with compared to individuals without ADHD. ADHD: Attention-Deficit/Hyperactivity Disorder; OR Odds Ratio: positive values indicate a higher risk in individuals with ADHD; CI confidence interval; the diamond shape at the bottom of each panel is the pooled differences between adults with and without ADHD.

4.1. Methodological challenges that are particularly relevant for surveys

4.1.1. Two- or multi-phase sampling to estimate ADHD prevalence and comorbidity

NESARC used a single-phase sampling approach with face-to-face surveys conducted in all respondents. However, surveys estimating prevalence and comorbidity rates often use two- or multi-phase sampling to keep a study feasible financially and timewise. (Dunn et al., 1999) The WHO-WMHS built on NCSR (Fayyad et al., 2017; Kessler et al., 2006) which used a three-phase sampling approach. Two- or multi-phase sampling approaches introduce error in estimating the prevalence rates (Prince, 2003) depending, among other things, on the psychometric quality of the phase 1 screener (i.e., sensitivity and specificity for the condition studied) and the sample sizes of interviewed participants among screen positive and screen negative strata. The complexities involved in in each step of a multi-phase sampling approach are illustrated in the WHO-WMHS/NCSR. The first sampling phase did not involve an ADHD screener. Rather, the subset selected for ADHD interviewing was based on participants' responses on the interview on ADs, MDD, BD and SUDs using the Composite International Diagnostic Interview (CIDI) version 3.0 (Kessler and Ustün, 2004; see section S2.1), in three strata of decreasing risk (i.e., 100% of respondents with any of these disorders, 59% with subthreshold problems, and 25% without symptoms). These selection percentages were thus geared towards the comorbid conditions studied here instead of ADHD (i.e., screening for ADHD was based on symptoms of anxiety and mood disorders and SUDs) which may have led to overestimating the prevalence of comorbidity. In addition, the precision with which individuals with ADHD without comorbid ADs, MDD, AD and SUDs could be detected in the relatively small 25% stratum that received ADHD interviewing remains uncertain; it may have led to underestimation of the prevalence of ADHD. In the second phase, a lay person administered interview was used as an extensive screener for establishing the potential presence of childhood ADHD. Only a single question was asked to establish if childhood ADHD persisted in adulthood, which may have introduced error in estimating the prevalence of ADHD in adulthood. That is, it remains uncertain if the minimum number of ADHD symptoms were present and if criteria of impairment and cross-situational presence of ADHD symptoms were met to warrant an adult diagnosis of ADHD. The third phase involved a blinded clinician-based interview which provided the gold standard ADHD diagnosis. To impute the presence or absence of a clinical ADHD diagnosis in the total sample, a subset of 154 respondents, from the USA, received a blinded clinical interview, in four strata of decreasing risk (40% with both childhood and current ADHD symptoms, 20% with childhood but not current ADHD symptoms, 20% with subthreshold ADHD symptoms in childhood, and 20% without symptoms). Findings on the relation between the lay-based interview and the clinician-administered interview, along with scores on other variables assessed in the study, were used to estimate the presence or absence of clinical ADHD for all participants by multiple imputation. This was done given that a strong monotonic relationship was found between sampling strata and presence of clinical ADHD diagnosis. One potential source of error in this third phase is the small sample size of 154 individuals who received the clinical diagnostic interview. A second potential source of error, as discussed by the authors (Fayyad et al., 2017), is that imputation for all other 19 sites around the world was based on the association between the lay-administered and clinician administered interviews in the USA. This association could have turned out differently if clinical interviews had been feasible in each of these sites. The extent of error in the reported prevalence of ADHD and its comorbidities in the WHO-WMHS is therefore unknown.

Feasibility in terms of financial constraints and time investment play no role in registries and insurance claims data which are collected primarily for other reasons than research.

4.1.2. Underestimation due to non-response

Surveys may have a bias due to the inherent less-than-100% response rate. It is well-known that individuals who do not participate in surveys are a selective subgroup including less healthy or poorer individuals (e.g., Bjertness et al., 2010; Howe et al., 2013), with the potential

Table 4
Occurrence, absolute risk and relative risk of anxiety disorders, major depressive disorder, bipolar disorder and substance use disorders in females and males with and without ADHD, estimated by sex-specific prevalence/incidence rates, prevalence/incidence differences, and prevalence/hazard/odds ratios, and sex specific modifications on the linear scale (differences) and mutiplicative scale (ratios) in surveys, registries and insurance claims data[a,b].

		ADHD		no ADHD		ADHD compared to no ADHD female	ADHD compared to no ADHD male	ADHD compared to no ADHD female	ADHD compared to no ADHD male	Additive effect modification by sex[c]	Multiplicative effect modification by sex[d,e]	
		female	male	female	male					female-male difference of the	female/male ratio of the	
		prevalence (%)		prevalence (%)		prevalence difference		prevalence ratio		prevalence difference	prevalence ratio	odds ratio
Anxiety disorders (ADs)												
S	USA-NESARC[f,g]	57.7/ 79.1	36.6/ 49.3	∅	∅	∅	∅	∅	∅	∅	∅	1.1/ 1.9
C	USA-Babinski	20.7	12.5	8.8	6.2	11.9	6.2	2.4	2.0	5.7	1.2	1.3
C	Germany[h,i]	56.3	37.4	23.5	10.1	32.7	27.3	2.4	3.7	5.4	0.6	1.0
R	Norway[j,k]	28.7	14.8	6.6	3.4	22.1	11.4	3.7	5.3	10.7	0.7	0.8
R	Sweden[l,m]	52.7	37.0	6.2	3.6	46.6	33.4	8.5	10.2	13.2	0.8	1.1
R	Denmark[n,o,p,q]	4.8 [121.3]	3.2[58.0]	1.8 [15.8]	1.1 [9.9]	3.0 [105.6]	2.1 [48.1]	2.7 [3.7]	2.8 [3.5]	0.9 [57.5]	0.9 [1.1]	1.0
Major depressive disorder (MDD)												
S	USA-NESARC[f,g]	11.3/ 31.7	11.3 (19.5)	∅	∅	∅	∅	∅	∅	∅	∅	0.4/ 0.9
C	USA-Babinski	∅	∅	∅	∅	∅	∅	2.7	2.2	∅	∅	1.2
R	Norway[j,k]	31.9	17.1	7.5	4.1	24.4	13.1	3.7	5.1	11.3	0.7	0.8
R	Sweden[l,m]	49.3	35.6	5.9	3.6	43.4	32.1	8.4	10.0	11.4	0.8	1.0
R	Denmark[n,o,p,q]	4.5 [133.7]	1.8 [38.5]	2.3 [27.8]	0.9 [10.6]	2.2 [106.0]	1.0 [28.0]	2.0 [2.8]	2.1 [2.5]	1.3[78.0]	0.9 [1.1]	1.0
Bipolar disorder (BD)												
S	USA-NESARC[f,g]	27.3/ 39.3	17,2/ 29.1	∅	∅	∅	∅	∅	∅	∅	∅	1.2/ 1.3
R	Norway[j,k]	13.5	8.9	1.6	1.1	11.9	7.9	8.0	8.9	4.0	0.9	1.0
R	Sweden[l,m]	19.0	10.0	0.9	0.5	18.0	9.4	20.8	18.9	8.6	1.1	1.2
R	Denmark[n,o,p,q]	0.8 [21.4]	0.3 [6.2]	0.2 [2.0]	0.1 [1.1]	0.6 [19.3]	0.2 [5.0]	4.8 [5.7]	3.2 [4.3]	0.4 [14.3]	1.5 [1.3]	1.5
Mood disorders (MDD or BD)												
C	Germany[h,i,r]	53.2	34.3	13.4	5.5	39.8	28.8	4.0	6.2	11.0	0.6	1.0
Substance use disorders (SUDs)												
S	USA-NESARC[f,g]	32.5/ 61.2	50.1/ 75.5	∅	∅	∅	∅	∅	∅	∅	∅	0.9/ 1.3
C	USA-Babinski[s]	1.8/2.7	2.6/ 4.6	0.7/ 1.0	1.7/ 2.6	1.0/1.7	1.0/2.0	2.4/2.6	1.6/1.8	0.1/− 0.4	1.5/1.5	1.5/ 1.4
C	Germany[h,i]	15.3	16.1	4.4	4.8	10.9	11.4	3.4	3.4	-0.5	1.0	0.9
R	Norway[j,k]	15.8	26.6	2.1	3.6	13.7	23.0	7.2	7.6	-9.3	0.9	0.9
R	Sweden[l,m]	30.9	39.4	2.8	4.4	28.1	35.1	11.1	9.0	-7.0	1.2	1.1
R	Denmark[n,o,p,q]	4.2 [120.3]	4.2 [91.2]	1.6 [18.9]	2.0 [24.4]	2.7 [101.5]	2.1 [66.7]	2.7 [3.5]	2.1 [2.9]	0.5 [34.7]	1.3 [1.2]	1.3

Notes ADHD: Attention-Deficit/Hyperactivity Disorder; ∅: Information was not provided; S: Survey. C: Claims data. R: Registry data.

[a] part of the content of this table is calculated from the information provided in the original papers rather than directly retrieved (see section 3.2.3).

[b] estimates rounded at 1 decimal place.

[c] positive values indicate an excess difference for females relative to males.

[d] values higher than 1 indicate an excess risk for females relative to males.

[e] both prevalence ratios and odds ratios are provided so that studies can be compared on the same metric.

[f] estimates are based on persistent ADHD, i.e., onset before age 12 and present in the two months preceding diagnostic interviewing.

[g] we report the inverse of the odds ratios that were reported in paper (i.e., reported in paper for ADs:.88/0.52; MDD: 2.34/1.11; BD: 0.83/0.77; SUDs: 1.12/0.79) given switch in reference category in current table.

[h] inpatient, day patient or outpatient diagnoses. ADHD based on 2009–2014; ADs, MDD, BD and SUDs based on 2014.

[i] original paper provided separate estimates for ages 18–30 and 31 and older; current estimates are calculated from these separate estimates.

[j] ADHD and BD based on prescription data 2004–2015; ADHD and bipolar disorder based on diagnosis 2008–2015; ADs, MDD, and SUDs diagnoses based on diagnosis 2008–2015.

[k] estimates adjusted for birthyear.

[l] inpatient diagnoses 1973–2013; outpatient diagnoses 2001–2013.

[m] estimates adjusted for age.

[n] inpatient diagnoses during 1981–2013; outpatients and emergency contacts diagnoses between 1995 and 2013. ADHD identified from birth (maximum age is 32 years); ADs from age 6 years (maximum observed period 26 years); MDD, BD, and SUDs from age 10 (maximum observed period for anxiety is 22 years).

[o] The Danish study performed longitudinal analyses (see sections S3.1 and S4). Incidences, incidence differences, and hazard ratios (HR) based on longitudinal analyses as provided in the original paper are reported here ([second estimate]), in addition to the estimates based on the prevalence (first estimate); estimates are adjusted for age, calendar time, gestational age, birthweight, 5-minute Apgar score, maternal education, paternal income, maternal and paternal ages at time of child's birth, and history of psychiatric disorders in the mother, father, siblings and halfsiblings.

[p] incidence rates and incidence rate differences per 10,000 person-years of time at risk.

[q] incidence rate ratios were estimated as hazard ratios.

[r] the German study combined MDD and BD into a single category of mood disorders.

[s] This study provided separate estimates for respectively alcohol use disorder and other substance use disorders; note that summing these percentages woud introduce error given possible overlap in patients.

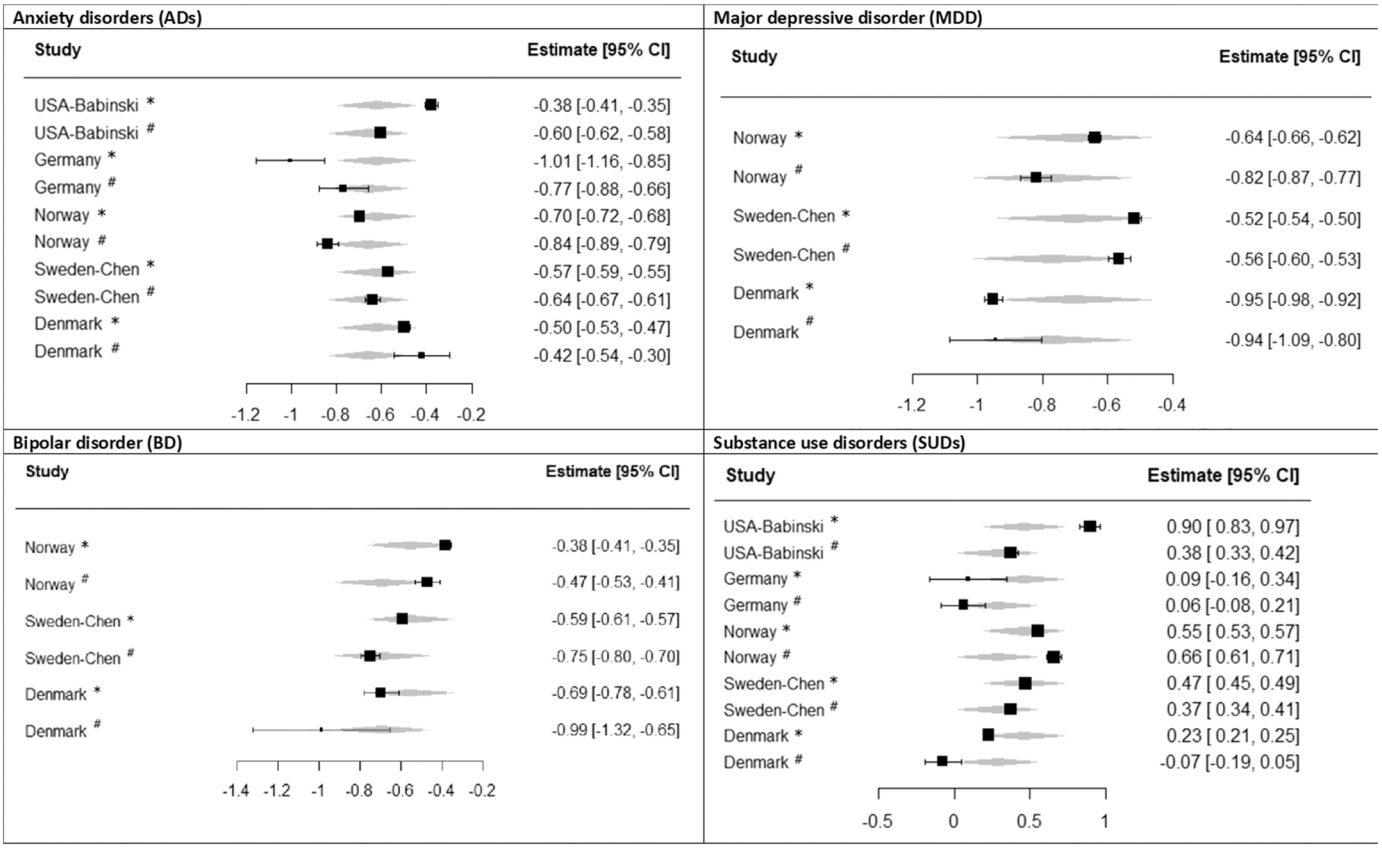

Fig. 2. Pooled and study specific relative risk (logOR) of anxiety disorders, major depressive disorder, bipolar disorder and substance use disorders of men compared to women with and without ADHD. ADHD: Attention-Deficit/Hyperactivity Disorder; * without ADHD; # with ADHD; LogOR: the natural logarithm of the Odds Ratio: negative values indicate a lower risk and positive values a higher risk for males; CI confidence interval; the diamond shapes depict the two pooled differences across the studies for adults without * and # with ADHD, respectively.

implication that prevalence and comorbidity rates derived from the survey data may be underestimated. The NCSR in the USA (Kessler et al., 2006) had a response rate of 70,9% and the WHO-WMHS (Fayyad et al., 2017) had a weighted average response rate of 68.5% (range 45.9%–97.2%) across the 20 sites that evaluated ADHD. In NESARC, the response rate in wave 1 was 81% (Grant et al., 2005) and in wave 2, when assessment of ADHD was performed, the response rate was 86.7% of wave 1 respondents. All studies applied sound, elaborate, weighting techniques to correct for deviations between the sample and the population. These corrections for non-response are a very important asset of these studies but may not fully compensate for underestimation of prevalence of ADHD and comorbidity with ADs, MDD, BD and SUDs. Biases due to non-response play a much less important role in registries and insurance claims data that cover the whole population and are based on mandatory reporting from the health care system.

4.1.3. Recall bias

Surveys depend on individuals' recall of the symptoms and impairments of the disorder. This may lead to underestimation. Due to its onset in childhood, recall of the potential presence of ADHD symptoms and functional impairments associated with these symptoms should go back to age 12 and before (i.e., age 12 is the current age at onset requirement in DSM-5; in earlier versions this was age 7). Therefore, recall bias with regard to childhood symptoms plays an important role in ADHD which presumably becomes worse with increasing age of the respondents (Fayyad et al., 2017; Lundervold et al., 2014; Simon et al., 2009; Vos and Hartman, 2022). Furthermore, it has been shown that higher self-reported current symptoms of ADHD, anxiety or depression are associated with higher recalled childhood ADHD symptoms (Grogan and Bramham, 2016; Lundervold et al., 2021). It remains unclear if this reflects the severity of the condition already from childhood on, a temporary increase in ADHD symptoms (e.g., as a direct effect of the comorbid condition, or environmental stressors influencing both ADHD and comorbid conditions (Grevet et al., 2021; Karam et al., 2017; Sibley et al., 2022), or overestimation of childhood symptoms as a function of current symptom levels (the so-called "state effect"; Ormel et al., 2004). The WHO-WMHS (including the NCSR) excluded individuals aged 45 and older from ADHD assessment to avoid recall bias, but there were some suggestions of recall bias nonetheless (e.g. lower prevalence of ADHD in childhood than adulthood). In contrast to the NCRS and WHO-WMHS, NESARC did not define an upper age limit for establishing the presence of ADHD and the extent to which recollection bias played a role in the findings is unknown. The lifetime prevalence of ADHD was 2.5% based on an age of onset before age 18 (Bernardi et al., 2012) while it was 1.8% based on an onset before age 12 (Cortese et al., 2016). The difference may reflect a mixture of respondent failing to recall when they had their first symptoms and true adolescent onset ADHD. Also, the low prevalence of persistent ADHD (1%, onset before age 11 and presence of ADHD in last 2 months; Cortese et al., 2016) may in part reflect recollection problems.

Failure to recall the presence of symptoms during childhood also plays a role in registry data if ADHD was not diagnosed during childhood

and thus needs to be determined retrospectively. Presumably, however, clinical examination allows for extensive developmental probing questions on the presence of ADHD symptoms and functional impairments during childhood, which may be complemented with information from external informants (e.g., parents, older siblings). Clinician-based interviewing is not feasible in large scale epidemiological surveys as illustrated in the WHO-WMHS/NCSR (only in stage 3 and only in the NCSR sample). Therefore, recall bias is particularly associated with surveys.

4.1.4. Underestimation of adult ADHD when based on self-report in fully structured interviews

Not only need symptoms of ADHD be recalled from the past but they also need to be recognized in the here and now. In childhood, ADHD is diagnosed based on parent and teacher information, while in adulthood the diagnosis is mostly based on self-report. Studies comparing adult self-reports and informant reports of ADHD symptoms show lower estimates of ADHD based on self-reports in both children and adults, as well as reduced self-insight into ADHD-related functional impairments (Mörstedt et al., 2015). Likewise, under-reporting is evident when self-reports are compared with clinician-based semi-structured interviews (Luderer et al., 2019). It has also been suggested that women may be more accurate in reporting their ADHD symptoms than men, potentially biasing research on ADHD in adulthood, although this needs further research (Hinshaw et al., 2022). Together, this suggests (potential male-specific) underestimation of ADHD based on fully structured interviews performed by trained lay-interviewers, like in NESARC. Clinical diagnoses from registry and insurance claims data may be less affected by under-reporting (e.g. due to the possibility to pose additional probing questions on the presence of ADHD symptoms and functional impairments).

4.1.5. Imprecise estimates and the need for large sample sizes

This review included only large surveys pe($N > 10{,}000$) and showed that even in large samples the number of individuals with adult ADHD which form the basis of our findings was still modest. For example, the NESARC sample included $n = 34{,}653$ individuals among whom only 340 individuals were identified with adult ADHD that persisted into adulthood. As an example of the consequences, there was only limited statistical power to identify sex differences in AD, MDD, BD, and SUDs in adults with ADHD. The presence of millions of people is one of the main advantages of registry and insurance claims data.

4.2. Methodological challenges particularly relevant for registry and insurance claims data

4.2.1. Primary care, specialist care, or both

The Danish and Norwegian studies included data from specialist (i.e., secondary and inpatient) care but not primary care. The Norwegian study used pharmacotherapy from the Norwegian Prescription Database (NorPD) to identify individuals with ADHD and BD, as such partly compensating for the absence of primary care data. The two registry studies from Sweden reported respectively on comorbidity of ADHD in primary (Sundquist et al., 2017) and specialist care (Chen et al., 2018). In contrast, the studies using insurance claims data from the USA and Germany (Babinski et al., 2020; Libutzki et al., 2019; Secnik et al., 2005) combined data from primary and specialist care.

Estimates of comorbidity reported in this review may in part depend on whether patients with ADHD, ADs, MDD, BD and SUDs were registered in primary care or specialized care, or both. As a general rule, patients who have more severe problems, which includes the presence of comorbidity, tend to be more often treated in specialist care. Along similar lines, individuals without comorbid conditions, which form the comparison group when calculating prevalence differences and ratios, tends to be less common in specialist care. Thus, as a general rule, estimates of comorbidity in individuals with ADHD identified from specialist care registers would be inflated. However, who gets to be referred to primary of secondary care will depend on many other (unknown) factors than disorder severity, including differences in health care and insurance systems which differs across countries. The study by Sundquist et al. (2017) in this review showed how patients were distributed between primary care and specialist care and illustrated that it is very complex to track down potential biases if a study is focused on either primary of specialist care. More than 80% of patients with ADs, MDD and drug abuse were registered only in primary care. For ADHD and Alcohol Use Disorder this was, respectively, 54% and 46% (BD was a priori expected to be treated in secondary or inpatient care and therefore not investigated in the study). Further, across diagnoses only a small proportion of patients were registered for the same diagnosis in primary care as in specialist and inpatient care. If a patient is registered in primary care for one condition and in specialist care for another comorbidity remains undetected. We conclude that studies focused only on primary or only on specialist care have unknown biases in comorbidity estimates.

4.2.2. Unknown variability in diagnostic assessment

The WHO-WMHS went to great lengths to assure that assessment procedures and instruments were the same across the different countries. Examples to guarantee consistency across countries are standardized translation and backtranslation, harmonization protocols, and extensive training in data collection by bilingual supervisors. In sharp contrast, diagnoses from registry and insurance claims data are not under the investigators' control, and may differ from one clinician, setting, timepoint, and country to another. In addition, guidelines regarding the nature and frequency of diagnostic assessments also depend on features of the health care and insurance systems, which differ across countries. All of this may yield variability in the findings. Note that the problem of non-uniform diagnostic assessment and variability in findings is also present in surveys. Even though in surveys the diagnostic instrument is under the control of the investigator, surveys typically differ in which instrument was used.

4.2.3. Inflated comorbidity estimates in referred patients

The prevalence of comorbid conditions is inflated when based on treatment seeking individuals in registries and insurance claims data than when assessed by research instruments applied to the general population in surveys. This stems, first, from selection bias: individuals with two disorders are more impaired than individuals with a single disorder and are therefore more likely to seek treatment (Cohen and Cohen, 1984; Dalsgaard et al., 2020; Harris et al., 2016; Steinhausen et al., 2017; Williamson et al., 2015). Another bias is the so called Berkson's bias which applies to the situation that the chance of receiving a diagnosis for a disease is increased due to the presence of another disease, which holds in case of comorbidity (e.g., when being monitored over time for one disease another condition may be uncovered that otherwise might have gone unnoticed), and which increases the number of persons with comorbidity in the study (Berkson, 1946). Surveys, in contrast, are able to include all individuals with the condition, irrespective of whether they did or did not seek treatment for the conditions studied. Survey data are, therefore, more representative of a condition and yield more valid estimates of comorbidity. In contrast, register and insurance claims data better reflect the levels of comorbidity to be expected in clinical practice. Further, to the extent that seeking help and being co-diagnosed differs for men and women (e.g., Biederman et al., 2004) or differs in different parts of the lifespan (e.g., Price et al., 2019), conclusions on sex and developmental differences in comorbidity rates may be erroneous when based on registries and insurance claims data.

4.2.4. Referred ADHD patients differ in comorbidity in different phases of the adult lifespan due to cohort effects

A special case of bias which is particularly relevant to ADHD is present in lifespan comparisons, due to a cohort effect, based on when

adults were born. This bias is due to the history of ADHD, which began to be widely recognized in clinical practice only in the 1990 s. As such, there is a discrepancy between the comparatively higher numbers of individuals with ADHD in registries up till the age of around 30 who were diagnosed in childhood, and a much smaller number of adults with ADHD from around age 30 or older. Importantly, the issue here is not so much that numbers of individuals with ADHD differ based on when they are born, but rather that individuals diagnosed with ADHD in adulthood for the first time are likely to qualitatively differ from individuals diagnosed in childhood, especially with regards to comorbidity. That is, help seeking in individuals from age 30 or older may be influenced strongly by the impairments involved in ADs, MDD, BD or SUDs rather than ADHD as such. A noted in Section 4.2.3, psychiatric comorbidity is an important reason for help seeking (Harris et al., 2016) and it is to be expected that this age group has more extensive comorbidity compared to young adults who already received an ADHD diagnosis in childhood irrespective of whether they would develop (future) comorbidity. Thus, an apparent rise in comorbidity around the age of 30 may be due to help seeking for the comorbid conditions. Firm conclusions on comorbidity patterns across the lifespan need to come from population surveys or need to await the segment of the population diagnosed with ADHD in childhood to grow older to allow for valid comparisons, preferably in longitudinal research. An example is provided by the Danish study reported on here, but which was currently limited by an upper age limit of 32 years (Ottosen et al., 2019).

5. Discussion of findings and outlook

5.1. Prevalence of ADs, MDD, BD and SUDs in adults with and without ADHD

Evidence from large surveys, register and insurance claims studies on the presence of ADs, mood disorders and SUDs in adults with ADHD shows that these common adult disorders are much more frequent in individuals with ADHD compared with those without ADHD. This finding corroborates earlier findings based on many smaller studies in which adults with ADHD were compared to individuals without ADHD (e.g., Biederman, 1993; 1995a,b; McGough et al., 2005; Miller et al., 2017; Sobanski et al., 2007). Pooled across studies, our meta-analyses yielded relative risks (odds ratios) comparing adults with and without ADHD of 5.0 for ADs, 4.5 for MDD, 8.7 for BD and 4.6 for SUDs. Even though the present study focused on large studies to ensure stable estimates and on diagnoses rather than a rough estimate of whether ADHD and comorbid conditions were present of not based on questionnaire scores, high variability in the estimates of comorbidity was found. High variability is not surprising. Although heterogeneity in estimates could not be addressed in full due to low statistical power in the meta-analyses, it matters if comorbidity is assessed over 1 year or many years, if primary care is part of the database or not, if older aged individuals with ADHD are included or only young adults, if people need to recall past symptoms of ADHD and comorbid conditions or if these were registered at the time of diagnosis, and so on and so forth. We draw two conclusions. First, despite the variability in specific estimates, the pooled estimates should be approximately correct and it is unlikely that the conclusion of high comorbidity of ADs, MDD, BD, and SUDs in adults with ADHD derived from general population studies will be overturned by future studies. Second, more precise estimates can only be achieved through the use of a common analysis protocol with the same methodological decisions applied to the different databases followed by meta-analysis.

5.2. Sex differences in comorbid conditions of ADHD

A consensus statement (Young et al., 2020) and research review (Hinshaw et al., 2022) highlighted that knowledge on females with ADHD falls short of that of males, and that what we do know about sex differences in ADHD is mostly based on childhood rather than the full lifespan. Here, we aimed to enhance knowledge on sex differences in comorbid conditions of ADHD during adulthood. The literature often reports that (in childhood) anxiety and depression are more common in girls with ADHD while externalizing problems are more common in boys with ADHD (e.g., Hinshaw et al., 2022; Staller and Faraone, 2006). However, these suggested sex specific patterns of comorbidity coincide with well-known normative sex differences in psychopathology in the general population while the more pertinent yet unanswered question for etiological research and clinical practice is if sex differences are increased or reduced if ADHD is present compared with the general population (e.g., Tung et al., 2016). To address this question, studies with estimates in men and women with and without ADHD are required, of which we identified six. The findings showed that women with ADHD outnumbered men in the frequency of having ADs, MDD, or BD, and in young adulthood, SUDs. Men, beyond young adulthood, outnumbered women in the frequency of having SUDs. However, the findings form the meta-analyses showed that there was no modification by sex. Together, the results are in line with two earlier small-sized studies (Biederman et al., 1994, 2004) and the NESARC study (Cortese et al., 2016; not included in the meta-analyses) showing that high comorbidity holds for both men and women and that sex differences in ADs, MDD, BD and SUDs remain roughly unaltered whether ADHD is present or not. One open question may be if this conclusion is influenced by differences in help seeking between men and women. In general, women more often seek professional help than men (Harris et al., 2016; Johansen, 2021, Tseregounis et al., 2020). However, current findings could only be influenced if enhanced help seeking patterns differ in men and women with ADHD compared to these overall differences which may require more research. Another topic deserving additional study is if onset of ADs, MDD, BD and SUDs starts earlier in females than males with ADHD relative to an onset difference in females compared to males without ADHD. The findings in the two studies exclusively focused on young adulthood hinted at this possibility (Babinski et al., 2020; Ottosen et al., 2019).

5.3. Lifespan differences in comorbid conditions of ADHD

Patterns of comorbidity in individuals with ADHD may change during development, but we showed that the available knowledge in the literature is scant. Very tentatively, we hypothesize that ADs, MDD, BD and SUDs may persist longer over the lifespan in adults with than without ADHD at the same time acknowledging that even in studies that included older aged individuals the average age was around 30 or younger, strongly overrepresenting young adults with ADHD. Note further that the most important complication in interpreting the current findings from a lifespan angle is not the lower number of mid- and older-aged adults with ADHD in the databases but rather that middle and older aged adults likely represent a selective over-representation of individuals with comorbid ADs, MDD, BD, or SUDs who sought help for these comorbid conditions rather than for ADHD as such. Thus, individuals with a registered diagnosis in childhood may or may not develop an AD, MDD, BD or SUD later on in life. In contrast, individuals diagnosed with ADHD in adulthood are likely to be a more severely affected subgroup of adults with ADHD which might not have sought help at all if it were not for the burden due to an additional onset of an AD, MDD, BD or SUD. Firm conclusions on how the presence of ADs, MDD, BD and SUDs may change across the lifespan in individuals with ADHD compared to individuals without ADHD thus need to be postponed.

5.4. Comorbid conditions of ADHD in old age

There is an absence of data on comorbid conditions of ADHD in old age, which is concerning given, e.g., recent findings showing ADHD to be a risk factor for dementia. As was shown in section 4.3, our data were

not at all informative on comorbidities of ADHD in old age, as older aged adults with ADHD were excluded by design from the WHO-WMHS, not separately analyzed with regard to comorbidity in NESARC (there were only n = 33 adults with ADHD aged ≥ 65; see Dobrosavljevic et al., 2020), and hardly present in registry and insurance data. A recent meta-analysis documented for the first time what is known about the prevalence of ADHD in adults aged approximately 50 years and older (Dobrosavljevic et al., 2020). The study showed a prevalence rate of 2.18% based on questionnaires, but this estimate is likely too high because neither age of onset nor impairment were systematically assessed in questionnaires. For clinical diagnoses of ADHD, the prevalence was 0.2% and it was 0.01% based on ADHD treatment rates, emphasizing that ADHD in older adults is extremely rare in clinical practice. These estimates illustrate that mid-to-older age adults with ADHD have not routinely found their way numbers into the services and/or that clinicians underdiagnose ADHD among those who sought help. Another recent meta-analysis of surveys or other diagnostic tools in the general population (Song et al., 2021) and an independent follow-up study (Vos and Hartman, 2022) showed a gradual decline in prevalence across the adult lifespan and provided separate prevalence estimates per decade. Best estimate prevalence rates beyond age 60 were around 1%, i.e., 0.8% in Song et al. (2021) and 1.1% in Vos and Hartman (2022). These estimates are markedly higher than the prevalence of ADHD of 0,2% in older adulthood in referred samples (Dobrosavljevic et al., 2020), confirming that ADHD in adults is not sufficiently identified in clinical practice. The scarcity of data on the prevalence of ADHD in old age illustrates why there are also no data on comorbid conditions. Accounting for early mortality among individuals with psychiatric disorders, it is generally found that the prevalence of ADs, MDD, BD and SUDs declines in old age (Beller et al., 2021; Hasin and Grant, 2004; Plana-Ripoll et al., 2020; Sajatovic et al., 2015; Scott et al., 2008; Walker et al., 2015). Yet, it is debated if this age-decline is a true decline or a consequence of the absence of age-sensitive diagnostic instruments adapted to how disorders manifest in elderly people (e.g., Andreas et al., 2017; Andreescu et al., 2023; Beekman, 2018; Muñoz et al., 2018). Thus, in as much as diagnostic criteria of common adult psychiatric disorders have not crystallized for old age, estimates of their comorbidity with ADHD will be equally variable. Furthermore, in relation to ADHD, discussion of the potential need for age specific criteria has so far focused on differences in the presentation of ADHD between childhood and early adulthood (Faraone et al., 2006b; Reimherr et al., 1985) but is highly important for old age as well, due to blurring of diagnostic boundaries with for example mild cognitive decline or early phases of dementia (Ivanchak et al., 2012; Kooij et al., 2016). This provides a good example of old-age specific problems in assessing ADHD and we additionally refer to Sections 4.1.3 and 4.1.4 on respectively recall problems about age of onset and use of self-report in the assessment of ADHD, both of which are accentuated in old age. We conclude that while old age psychiatric epidemiology is overall a relatively young research field, the knowledge on old age ADHD runs behind knowledge available for other psychiatric disorders.

5.5. Prevention and early treatment of conditions comorbid with ADHD

The findings from this review have strong clinical relevance and provide guidance for both mental health professionals and general practitioners. The implications can coarsely be categorized into two domains: I) awareness regarding comorbidity and, consequently, early detection and treatment; and II) prevention of comorbid conditions by appropriate ADHD treatment.

ADHD has a much earlier onset (before age 12) than most ADs, and MDD, BD and SUDs (Carvalho et al., 2020; Penninx et al., 2021; Solmi et al., 2022). As our data indicate that ADHD is a risk factor for these later-life conditions – however the causal patterns might be –, knowledge about these relationships will raise awareness and hence enable early detection (and, possibly, treatment) of comorbidities. Conceptualized this way, ADHD can be considered a risk constellation for other mental disorders just like metabolic syndrome is considered a risk factor for diabetes and cardiovascular disorders, and, accordingly, an imperative to act. For most mental disorders, staging approaches have been suggested (e.g., BD (Frank et al., 2015) or MDD (Cosci et al., 2022) and there is consensus that early detection improves their outcome, especially as a variety of low-intensity interventions with favorable risk-benefit and cost-benefit ratio are recommended for early stages. For instance, there is good evidence for digital applications in early stage depression treatment (Twomey et al., 2020; Wu et al., 2021). Whether or not such low-threshold interventions are equally effective in the context of ADHD remains to be determined; however, meta-analytic evidence suggests that preventive treatment for at-risk groups is efficacious e.g., in MDD (Salazar de Pablo et al., 2021), alcohol use (Hennessy and Tanner-Smith (2015), and ADs (Lawrence et al., 2017). While an extensive review of indicated prevention in mental disorders is beyond the scope of this review, a large body of work recommends to implement such approaches. Thus, patients with ADHD should be included as an at-risk group for the above disorders and be offered preventive measures if sub-threshold symptoms occur to prevent their full onset. Current and other emerging evidence suggest that peak onsets of ADs, MDD, BD and SUDs may be earlier in individuals with ADHD than in individuals without ADHD (Bartoli et al., 2023; Babinski et al., 2020; Libutzki et al., 2019; Milberger et al., 1997; Miola et al., 2022; Molina et al., 2018; Nierenberg et al., 2005; Norén Selinus et al., 2016; Ottosen et al., 2019), prevention of comorbidity may need to be timed earlier in individuals with ADHD than without ADHD. Even if we could only maintain emerging comorbidities at the level of subthreshold symptoms and postpone a full onset during childhood, adolescence and young adulthood, their lifelong consequences on school functioning (e.g., school drop-out) and social functioning (e.g., becoming fully isolated from peers) may be avoided.

However, beyond increasing awareness to detect comorbidity and low intensity interventions to treat comorbidity, is there any evidence that adequate ADHD treatment can directly decrease the risk of comorbid disorders? Evidence is sparse, which is not unusual for long-term trajectories which are not accessible to randomized controlled trials, but amounting evidence suggests that the treatment of ADHD may reduce the incidence of downstream comorbid disorders (Biederman et al., 2009; Katzman et al., 2017; Sayal et al., 2018; Wang et al., 2016; Wilens et al., 2003). Medication with stimulants is the gold standard ADHD treatment and recommend by pertinent guidelines; Chang and colleagues (Chang et al., 2019) used a meta-analytic approach to synthesize findings from linked prescription databases (k = 40 studies in total, thereof 18 that employed a within-person design to account for confound-by-indication), in order to study the effect of stimulant medication in ADHD on neurobehavioral outcomes including MDD, SUDs and BD. Although almost all short-term outcomes favored stimulant medication, there was only limited data on long-term effects. However, a nation-wide study from Taiwan including > 70,000 patients suffering from ADHD showed that longer use of stimulants was protective against depression later in life (aOR, 0.91) (Lee et al., 2016). This finding was supported by another study from South Korea on 3500 patients with ADHD, where long-term stimulant use reduced the risk towards depression as well (HR=0.7) (Park et al., 2022). The same was true for bipolar disorder, where long-term stimulant medication in childhood ADHD reduced the prevalence of later-life BD (aOR 0.7; n > 140,000 patients; Taiwan; Wang et al., 2016). Findings for other disorders, especially substance use disorders (where small studies suggested preventive effects as well; e.g., Coetzee et al., 2023), are less clear, calling for more research as also suggested by other researchers (e.g., Ivanov et al., 2022). Given the prevalence of ADHD and the potential huge impact of its treatment in the prevention of comorbidity, conducting such studies (likely via utilizing large-scale, longitudinal registries) is clearly warranted. Finally, in adults with ADHD who have already developed a comorbid condition, initial evidence suggests that

treatment of ADHD enhances the effectiveness of treatment of comorbid conditions, promotes remission and reduces recurrence (Galanter et al., 2003; Reale et al., 2017). As failure to treat individuals with ADHD potentially widens the gaps between the prevalence of adult-onset psychiatric conditions in individuals with and without ADHD (Hossain et al., 2020), the risk-benefit ratio of ADHD treatment regarding comorbidity however can be regarded favorable when considering all the above.

6. Limitations

We end this review by pointing out that, except for the WHO-WMHS, the studies included in this review collected data from high-income European countries and the USA. In the WHO-WMHS comorbidity estimates were estimated across all countries. It should thus be emphasized that the current review does not generalize to non-western countries and that scarce knowledge necessitates future research. Another limitation is our focus on ADs, MDD, BD and SUDs, while other comorbid conditions of ADHD such as autism spectrum disorder or personality disorders are also important, but these have been much less studied in adults with and without ADHD, awaiting further research before estimates can be pooled.

7. Conclusions

We propose monitoring of sub-threshold symptoms of ADs, MDD, BD. and SUDs in persons with ADHD to facilitate early detection and preventive measures to prevent or postpone full onset of comorbidity. We propose further that additional research is needed on whether adequate ADHD treatment can directly decrease the risk of comorbid disorders. These proposals are based on this review's finding that the prevalence rates of ADs, MDD, BD and SUDs in adults with ADHD are substantially higher compared with the prevalence rates in adults without ADHD. Our review shows further that the association of ADs, MDD, BD and SUDs with ADHD is not modified by sex, implying that high comorbidity holds for both men and women with ADHD, while sex differences in the patterns of comorbidity are roughly similar in men and women with, compared to men and women without, ADHD (women higher prevalence rates of ADs, MDD and BD; men a higher prevalence rate of SUDs). No firm conclusions about developmental changes in comorbid conditions of ADHD in adulthood could be drawn, due to the absence of data, although a preliminary hypothesis to be tested in future research is that in individuals with ADHD, onset of ADs, MDD, BD and SUDs is earlier (and potentially even earlier in women with ADHD) and persists longer during the adult lifespan compared to individuals without ADHD. Longitudinal developmental studies spanning different phases in the adult lifespan in men and women are needed to further address such lifespan patterns.

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Conflicts of interest

KK, SD, QC, BC, MV report no conflicts of interest. CAH has received speaker's honoraria for Medice. HL reports receiving grants from Shire Pharmaceuticals; personal fees from and serving as a speaker for Medice, Shire/Takeda Pharmaceuticals and Evolan Pharma AB; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire/Takeda Pharmaceuticals and Evolan Pharma AB, all outside the submitted work. Henrik Larsson is editor-in-chief of JCPP Advances. BL is employed at Janssen-Cilag AG, which however has no connection to this work. EDR has served as a speaker for Shire Sweden AB outside the submitted work. SC declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD. SKS has received speaker's and authors' honoraria from Medice Arzneimittel Pütter GmbH Co KG and Takeda. JH has received speaker's honoraria from Medice, Shire and Takeda. BSS has received authors's honoraria from Takeda. AR has received honoraria from and/or serves on advisory boards for Medice, Shire/Takeda, SAGE/Biogen, Janssen, Boehringer Ingelheim and cyclerion. SF received, In the past year, Dr income, potential income, travel expenses continuing education support and/or research support from Aardvark, Aardwolf, Tris, Otsuka, Ironshore, KemPharm/Corium, Akili, Supernus, Atentiv, Noven, Sky Therapeutics, Axsome and Genomind. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. He also receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health, Oxford University Press: Schizophrenia: The Facts and Elsevier: ADHD: Non-Pharmacologic Interventions. He is Program Director of www.ADHDEvidence.org and www.ADHDinAdults.com.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105209.

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