Neuroscience and Biobehavioral Reviews 124 (2021) 100–123

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Comorbidity of ADHD and adult bipolar disorder: A systematic review and meta-analysis

Carmen Schiweck [a,*], Gara Arteaga-Henriquez [b,c,d], Mareike Aichholzer [a], Sharmili Edwin Thanarajah [a,e], Sebastian Vargas-Cáceres [b,f], Silke Matura [a], Oliver Grimm [a], Jan Haavik [g,h], Sarah Kittel-Schneider [i], Josep Antoni Ramos-Quiroga [b,c,d], Stephen V. Faraone [j], Andreas Reif [a]

[a] Department for Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt- Goethe University, Germany
[b] Department for Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain
[c] Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Barcelona, Catalonia, Spain
[d] Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Catalonia, Spain
[e] Max-Planck-Institute for Metabolism Research, Cologne, Germany
[f] Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Catalonia, Spain
[g] Department of Biomedicine, University of Bergen, Bergen, Norway
[h] Bergen Center of Brain Plasticity, Division of Psychiatry, Haukeland University Hospital, Bergen, Norway
[i] Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, University Hospital, University of Würzburg, Würzburg, Germany
[j] Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA

ARTICLE INFO

Keywords:
Comorbidity
ADHD
Attention deficit hyperactivity disorder
Adult bipolar disorder
Prevalence
Age of onset

ABSTRACT

Attention-deficit / hyperactivity disorder (ADHD) and Bipolar Disorder (BD) are common mental disorders with a high degree of comorbidity. However, no systematic review with meta-analysis has aimed to quantify the degree of comorbidity between both disorders. To this end we performed a systematic search of the literature in October 2020. In a meta-analysis of 71 studies with 646,766 participants from 18 countries, it was found that about one in thirteen adults with ADHD was also diagnosed with BD (7.95 %; 95 % CI: 5.31–11.06), and nearly one in six adults with BD had ADHD (17.11 %; 95 % CI: 13.05–21.59 %). Substantial heterogeneity of comorbidity rates was present, highlighting the importance of contextual factors: Heterogeneity could partially be explained by diagnostic system, sample size and geographical location. Age of BD onset occurred earlier in patients with comorbid ADHD (3.96 years; 95 % CI: 2.65–5.26, $p < 0.001$). Cultural and methodological differences deserve attention for evaluating diagnostic criteria and clinicians should be aware of the high comorbidity rates to prevent misdiagnosis and provide optimal care for both disorders.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder with a worldwide prevalence between 5 and 8% in children (Asherson et al., 2016; Polanczyk et al., 2007). Up to 65 % of patients (Faraone et al., 2006a) continue to experience impairing symptoms into adulthood (adult ADHD, aADHD), although symptoms change over time; hyperactivity seems to diminish, while inattention and emotional problems prevail or even become more important (Chang et al., 2013; Larsson et al., 2011). The prototypic symptom complex that can be observed in aADHD (Asherson et al., 2016) comprises concentration problems and inattention, mind wandering, problems staying on task or keeping deadlines, and also impulsive behaviour, restlessness, and difficulty regulating emotions triggered by external stimuli. The trajectory of ADHD over the life span is characterized by a high degree of comorbidity (Franke et al., 2018) that, at least partially, could be tracked back to shared genetic vulnerability which is especially pronounced for major depressive disorder (MDD) (Demontis et al., 2019). Among the disorders shown to occur more often in aADHD than chance predicts, is bipolar disorder (BD) (Torres et al., 2015).

Like ADHD, BD is a common mental disorder with a prevalence of 1%–3%, depending on how narrowly diagnostic criteria are applied (Merikangas et al., 2007, 2011). The core feature of BD is the lifespan

* Corresponding author at: Department for Psychiatry, Psychosomatics and Psychotherapy, Heinrich-Hoffmann Str. 10, 60528. Frankfurt am Main, Germany.
E-mail address: carmen.schiweck@kgu.de (C. Schiweck).

https://doi.org/10.1016/j.neubiorev.2021.01.017
Received 12 September 2020; Received in revised form 12 January 2021; Accepted 19 January 2021
Available online 27 January 2021

occurrence of depressive as well as manic episodes, the latter of which are defined by increased energy and drive, psychomotor hyperactivity, restlessness, euphoria or irritability, and increased impulsivity in a state-like manner. In between mood episodes, patients are mostly euthymic and free of disease symptoms, although up to 40 % of patients continue to suffer from a varying degree of cognitive deficits (Volkert et al., 2015). Especially in bipolar-II disorder (BD-II), which is characterized by the exclusive presence of hypomania, the differential diagnosis between aADHD and BD can be challenging when not considering the trait-like nature of aADHD in contrast to the state-like features of BD. This is further complicated by the inter-episode cognitive deficits in BD as well as common sub-syndromal mood states and phenomena such as mixed episodes and rapid cycling, i.e., high-frequency mood swings, both occurring more often in BD-II. Thus, there is considerable overlap in the diagnostic criteria and associated features between BD and aADHD. Since diagnostic criterion overlap may not entirely explain the comorbidity of both (Milberger et al., 1995), it is possible that other shared clinical features are due to shared genetic or environmental risk factors.

Unsurprisingly so, aADHD and BD have been found to be comorbid in cross-sectional studies, with comorbidity rates ranging between 5 % (McGough et al., 2005) and 47 % (Wilens et al., 2003) when the primary sample was aADHD. Family-based studies suggest a relative risk of about 2% for the comorbid phenotype in first-degree relatives (Faraone et al., 2012). Also, longitudinal follow-ups - especially from a family-based Canadian study (Duffy et al., 2014)- argue for a trajectory from childhood ADHD to adult comorbid BD/ADHD. This is also supported by recent cross-disorder meta-analyses from genome-wide association studies which found an overlap in common genetic risk variants for ADHD and BD (Consortium et al., 2019).

To date, and to the best of our knowledge, no systematic review and meta-analysis has quantified the degree of comorbidity between ADHD and adult BD. The comorbidity of ADHD and BD is also a highly relevant and timely topic in paediatric psychiatry: Especially in the Americas, the number of children diagnosed with paediatric bipolar disorder has risen in the last years (Dickstein and Leibenluft, 2012). Since the reason for this increased diagnostic occurrence is still heavily debated and may be due to different American and European diagnostic traditions (Carlson, 2018; Goldstein et al., 2019; Parry et al., 2018), we here opted for the description of BD comorbidity occurring in adolescence and adulthood only. For an overview on comorbidity of ADHD in paediatric BD, see reference (Joshi and Wilens, 2009). Furthermore, we updated a previous meta-analysis on family-based studies (Faraone et al., 2012) on this topic and undertook a systematic review on large genetic studies investigating this comorbidity.

2. Methods

2.1. Literature search

To conduct the review, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015) were followed. The review protocol was registered on PROSPERO (ID: CRD42020179855). In- and exclusion criteria were discussed and approved by all authors. Databases were searched independently, and title, abstract and full text screening, as well as assessment of article eligibility were independently performed by authors CS and GAH. Disagreements as to eligibility of articles was discussed after completion of the screening phase and any difference of opinion was discussed with a third author to reach a decision.

2.2. Search strategy

To carry out the systematic review, databases *PubMed* and *World of Knowledge* (including the databases *WOS, BCI, CCC, DRCI, DIIDW, KJD, MEDLINE, RSCI, SciELO, ZOOREC*) were searched for relevant articles, without year limitations prior to 14th October 2020. The search strategy consisted of a combination of the keywords '*ADHD'* OR *'attention deficit'* OR *'hyperactive*'* OR *'hyperkinetic'* together with (AND) *'Bipolar Disorder'* OR *'bipolar*'* OR *'manic'* OR *'mania*'*, or a combination of the key terms *'comorbidity'* AND *'ADHD'* or *'comorbidity'* AND *'Bipolar Disorder'* OR *'bipolar*'* OR *'manic'* OR *'mania*'*. The 'NOT' connection was used to exclude articles mentioning *'mouse'* OR *'rat'* OR *'animal'* OR *'zebrafish'* as topic. In *World of Knowledge*, article type restrictions were set for patents, case reports, news, editorials, data sets, reference material, meetings, corrections, biographies, abstracts, or books. In addition, reference lists of articles were searched to identify further suitable articles.

2.3. Study selection

2.3.1. In- and exclusion criteria

Original full-text articles published in English, Spanish, German, Dutch or French (*i.e.*, all languages the research team was able to read) were included, without limitations for publication dates or origin. Publications had to provide numbers or percentages of participants with BD who did or did not have comorbid ADHD, or vice versa, numbers of participants with ADHD who were or were not affected by BD. For family-studies only, numbers or percentages of ADHD and non-ADHD relatives (for family studies of BD participants) or the numbers or percentages of BD and non-BD relatives (for family studies of ADHD participants) needed to be given. This practice was adopted to update and directly compare the newly identified studies with the results obtained in a recent large meta-analytic study (Faraone et al., 2012). For BD, diagnosis according to International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM) was required, with exclusive focus on diagnosed adolescents and adults (15 years or older at the time of BD assessment). For ADHD, a reported diagnosis according to DSM/ICD criteria during childhood and/or adulthood (including symptom onset during childhood, i.e., before age 12) was required.

To identify relevant articles, studies were excluded if they did not mention a diagnosis of BD and ADHD, or if the sample size was smaller than 50 participants for prevalence reports. Studies were also excluded if they reported on childhood BD, or if patients were younger than 15 years of age at the time of assessment, were not peer-reviewed or used targeted sampling strategies (i.e., specifically selected patients with comorbidity). In addition, given that a recent meta-analysis (Faraone et al., 2012) has covered all family-based studies up to 2011, only family studies published in 2011 or later were included to provide a short qualitative update. The authors of possibly relevant articles, which were either not available as full text, or could qualify, but where information on eligibility was judged insufficient, were contacted by email. An overview of excluded articles can be found in Supplementary Table 1.

2.4. Quality assessment and information extraction

Quality assessment of the included articles was based on an adapted version of the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist (Supplementary Table 2). The respective points for quality assessment were title and abstract; for the introduction and methods: context, objectives, study design, context, participants, variables, data sources/measures, bias, sample size, quantitative variables, statistical methods, participants; for the results: descriptive data, variable results data, other analysis, key findings; for the discussion: limitations, interpretations and external validity and funding, yielding a total of 22 points. A low risk of bias was given when the study had more than 15 points, a medium risk of bias when the study had between 10 and 15 points, and a high risk of bias was given when the study had less than 10 points. In addition, we extracted and examined 3 variables to directly test the effect of diagnostic procedures on comorbidity rates. For this purpose, we extracted information on the interviewer (mental health professional/other); the nature of the

interview (semi-) structured interviews compared with clinical diagnosis, or diagnosis supported by questionnaires, or register-based studies); and whether diagnosis of ADHD was or was not validated by a third party.

2.5. Information extraction

Information extraction from articles was independently performed by two authors (CS and GAH or SET and MA) using a piloted data extraction form. Information extracted from the publications followed the Population, Intervention, Comparison and Outcome (PICO) guidelines. Specifically, we extracted population (patient- or register- and population-based), geographic location, baseline age or follow-up age if applicable, proportions of participants with female sex, diagnostic criteria and version used (DSM/ICD), diagnostic instruments used ((semi-)structured/unstructured, name and descriptive text in the article), the period of diagnosis for ADHD (childhood/current or adult ADHD), the diagnosis of BD (current/lifetime), the age of onset for BD, and the comorbidity rate in numbers or percentages for ADHD in BD and for BD in ADHD. Given that this is a meta-analysis of comorbidity rates, the comparison is a test against zero-prevalence; where given, prevalence in healthy controls was also extracted, but was not used in this analysis. In addition, we aimed to extract percentages of patients on psychotropic medication, age of onset and percentages of subtypes for ADHD (inattentive, hyperactive or combined) or BD type (BD-I, BD-II or BD not otherwise specified (NOS)). Where BD NOS was included and information was given separately for BD-I and BD-II, only comorbidity rates for BD-I and BD-II were extracted. BD age of onset for patients with BD and those with comorbid ADHD was also extracted (mean, standard deviation, and n). For studies reporting on the same population, the most complete article was used for extraction. Register-based studies reporting on a part of the same population(Chen et al., 2018; Kristiansen et al., 2015; Larsson et al., 2013; Meier et al., 2018) were reviewed thoroughly and included if the part of the population was deemed to be significantly different from each other by 3 assessors (CS, MA and GAH). All disagreements could be solved during discussion of the extracted results.

2.6. Statistical analysis

In order to assess comorbidity of ADHD and BD in the respective other disorder, we used the software packages *meta* (Schwarzer, 2007; Schwarzer et al., 2015) and *metaphor* (Viechtbauer, 2010) in R version 3.1.5 (R Core Team, 2013). Random-effects meta-analysis of proportions was performed, and comorbidity estimates were derived by pooling individual study prevalence with a pooled estimate for between study heterogeneity. As per recent recommendations when considering individual study weights (Schwarzer et al., 2019), the arcsine transformation was applied to achieve an approximate normal distribution. No continuity correction was applied. The (transformed) proportions of included studies were weighted by the inverse of the variances of the (transformed) proportion to estimate the comorbidity rates of ADHD in patients with BD and the comorbidity rates of BD in participants with ADHD. Random effect models using the restricted maximum likelihood method were used to calculate overall effects. Restricted maximum likelihood was chosen as estimator. Heterogeneity was tested using the I^2 statistics, with an I^2 above 75 % considered heterogeneous. Sensitivity analysis was performed to estimate the effect of potential outliers using leave-one-out analyses. Stratified meta-analysis and meta-regression were performed to explore variables statistically accounting for heterogeneity (including population, geographic location (continent), diagnostic status (current/lifetime), diagnostic system (DSM/ICD), the diagnostic quality variables (see above for a description) and for continuous variables (age, sex and overall quality score). Where reported, the percentage of heterogeneity accounted for refers to the proportional reduction in the amount of heterogeneity after including moderators/covariates in the model and reflects the value of (pseudo) R^2 in the model. Funnel plots and Egger's test were used to explore publication bias.

Additional analyses were performed to compare comorbidity rates in function of BD subtype (BD-I and BD-II) in subgroup analysis. Furthermore, to assess whether age of BD onset differed between those with and without comorbid ADHD, we used the raw mean difference as effect size, not assuming homoscedasticity. For this, data was analysed with the *metafor* (Viechtbauer, 2010) package in R. All displayed p values are uncorrected estimates.

3. Results

3.1. Study characteristics

After duplicate removal, 4812 titles and 1027 abstracts of unique articles were screened. Four hundred thirty-one full-text articles were assessed for eligibility. Three hundred fifty-eight articles were excluded, of which 6 were not available and 352 were excluded with reasons (Supplementary Information 1). In total, 71 studies involving 646,766 participants of 18 countries were included in the meta-analysis of ADHD and BD comorbidity (see PRISMA Flow diagram in Fig. 1). Thirty-eight of those articles (Agosti et al., 2011; Anastopoulos et al., 2018; Arnold et al., 2020; Biederman et al., 2006, 2010; Breda et al., 2016; Brunkhorst-Kanaan et al., 2020; Chen et al., 2015, 2018; Faraone et al., 2006b; Garcia et al., 2012; Gorlin et al., 2016; Halmoy et al., 2010; Halperin et al., 2011; Harpold et al., 2007; Hodgkins et al., 2011; Kessler et al., 2005; Kooij et al., 2001; Kristiansen et al., 2015; Larsson et al., 2013; Mannuzza et al., 1993; Meier et al., 2018; Miesch and Deister, 2019; Milberger et al., 1995; Pehlivanidis et al., 2020; Pineiro-Dieguez et al., 2016; Rasmussen and Levander, 2009; Secnik et al., 2005; Silva et al., 2014; Smalley et al., 2007; Sobanski et al., 2008; Solberg et al., 2018; Stahlberg et al., 2004; Tsai et al., 2019; Westmoreland et al., 2010; Wilens et al., 2009; Yoshimasu et al., 2018; Young et al., 2015b) involving 234,833 participants assessed comorbidity of BD in ADHD patients. Thirty-five articles (Aedo et al., 2018; Andersen et al., 2013; Angst et al., 2013; Bennett et al., 2019; Berkol et al., 2014; Bernardi et al., 2010; Di Nicola et al., 2014; Ghaffary et al., 2013; Harmanci et al., 2016; Henin et al., 2007; Hossain et al., 2019; Karaahmet et al., 2013; Karanti et al., 2019; Kerner and Lambert, 2011; Marin et al., 2013; McIntyre et al., 2010; Meier et al., 2018; Merikangas et al., 2007, 2011; Nierenberg et al., 2005; Oguz et al., 2014; Papachristou et al., 2013; Perroud et al., 2014; Perugi et al., 2013; Pinna et al., 2019; Propper et al., 2015; Rubino et al., 2009; Ryden et al., 2009; Sachs et al., 2000; Sentissi et al., 2008; Song et al., 2015; Tamam et al., 2008; Torres et al., 2015; Walsh et al., 2020; Young et al., 2015a) involving 411,933 participants assessed ADHD comorbidity in BD. Two articles (Meier et al., 2018; Young et al., 2015a) assessed both, therefore the total number of articles is 71. An overview of sample characteristics for ADHD and BD samples can be found in Table 1A and B, comorbidity rates can be found in Table 2A and B. Furthermore, 9 family studies (Arman et al., 2018; Axelson et al., 2015; Biederman et al., 2013; Chen et al., 2019a; Palacio-Ortiz et al., 2017; Turkyilmaz et al., 2012; Walsh et al., 2020; Wei et al., 2019) (including n = 596,985 relatives of participants with ADHD or BD) were identified for the qualitative update of the family-based meta-analysis.

An overview of diagnostic procedures and instruments used can be found in Supplementary Table 1. Most studies relied on two structured interviews to derive diagnoses of aADHD and BD (n = 41, 58 %) or used at least one structured interview for either diagnosis of ADHD or BD (n = 9, 13 %). Other studies derived diagnoses from medical registers or medical records (n = 16, 23 %). A small minority of studies used unstructured interviews and/or questionnaires to support a clinical diagnosis of ADHD (n = 4, 6%) or referred to unspecified clinical diagnosis, mentioning adherence to DSM criteria (n = 1, 1%).

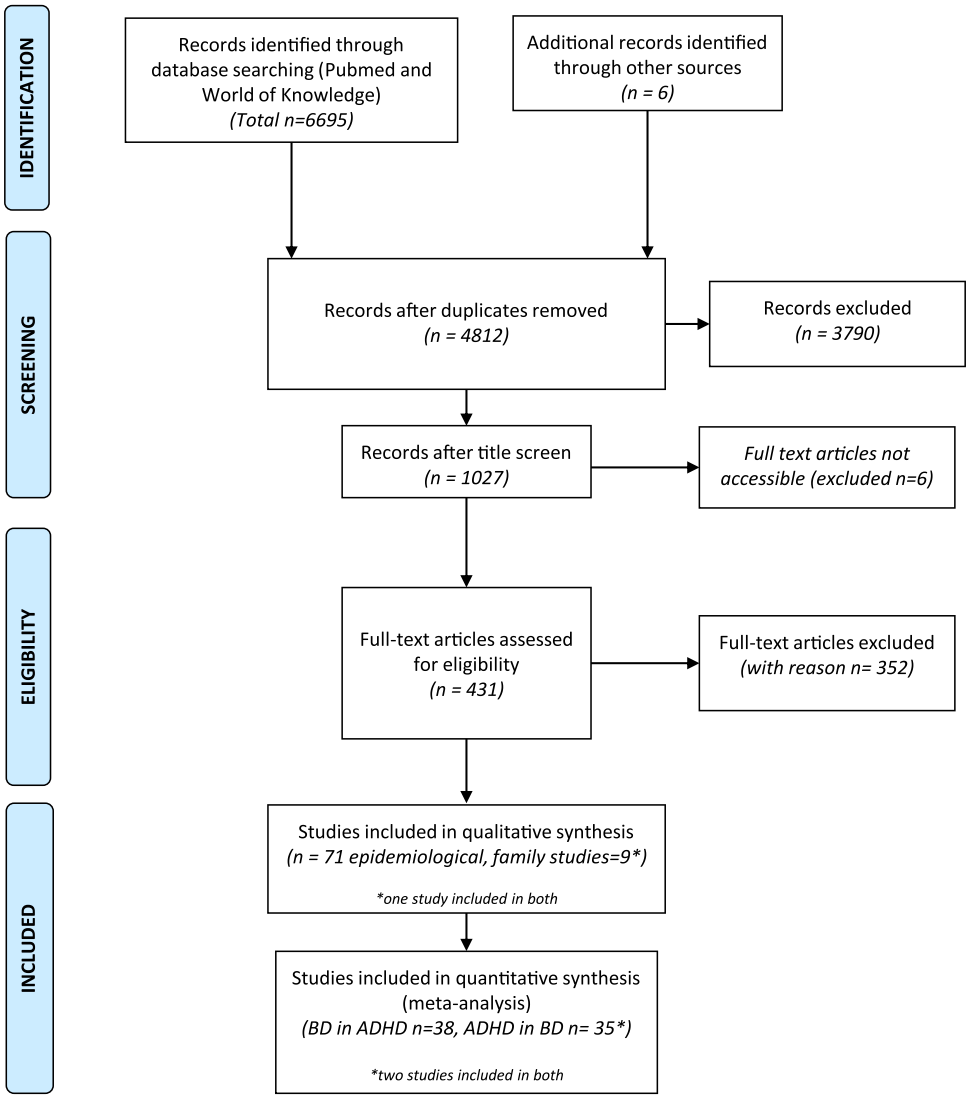

Fig. 1. PRISMA Flow Diagram for the systematic review process.

3.2. Comorbidity of BD in patients with ADHD

3.2.1. Overall and current vs lifetime comorbidity of BD

Of the 38 studies, 27 (n cases = 221,443) assessed lifetime comorbidity of BD in ADHD and 11 studies (n cases = 13,322) assessed current/12-month comorbidity of BD. Our meta-analysis of *lifetime* BD yielded a pooled comorbidity of 9.43 % (CI 95 %: 5.66–14.03). However, leave-one-out-analysis identified one influential outlier (Westmoreland et al., 2010) (Supplementary Fig. 1A and 1B). Since the outlier changed comorbidity rates substantially ($z = 4.84$), and the study was the only study to report on a prison population, we excluded this outlier from analysis, as results would likely not represent the general population. This yielded an overall lifetime comorbidity of 7.95 % (CI 95 %: 5.31–11.06), see Fig. 2. Pooled estimates of studies assessing *current* BD yielded a pooled comorbidity of 2.98 % (CI 95 %: 1.02–5.91), see Fig. 3. Substantial heterogeneity between studies was present in both meta-analyses (for lifetime comorbidity: $Q = 5533.78$, $p < 0.001$, $I^2 = 100$ %; for current comorbidity $Q = 165.32$, $p < 0.001$, $I^2 = 94$ %), see Figs. 2 and 3. To investigate potential sources of heterogeneity, meta-analyses stratifying by population and continent of origin were conducted and effects of diagnostic system (DSM/ICD), age and sex were explored. Given that we are interested in overall comorbidity rates, in the following we will report estimates for studies reporting lifetime comorbidity only.

3.2.2. Comorbidity per sample size

No statistical difference emerged for comorbidity of lifetime BD between small (74 % patient-based) and large (all population-based) samples (estimate = 0.09, $z = 1.59$, $p = 0.111$), although comorbidity rates in the patient-based samples were numerically higher than for population-based samples (9.59, CI 95 % 6.22–13.60 and 4.99, 95 % CI 1.80–9.64 respectively), see Supplementary Fig. 2. Heterogeneity in subsamples was still significant ($I^2 = 94$ %, $p < 0.01$ and $I^2 = 100$ %, $p < 0.001$).

3.2.3. Comorbidity per continent

The difference between continents (Asia, Europe and America including both North and South America) was significant ($Q = 12.95$, $df = 2$, $p = 0.002$). Follow-up analyses revealed a much higher lifetime comorbidity of BD in the Americas compared with Europe (estimate=-0.15, z=-3.24, $p = 0.001$) and significantly lower comorbidity in Taiwan compared with America (estimate=-0.25, z=-2.15, $p = 0.032$). The difference between Europe and Taiwan was not significant (estimate = 0.10, $z = 0.85$, $p = 0.396$). Lifetime comorbidity in the US was 12.64 (95 % CI 8.80–17.06). Comorbidity in Taiwan was 1.36 (95 % CI from combined comorbidity 0.00–10.69) and in Europe it was 4.54(95

Table 1

A. Demographic and sample characteristics for ADHD patients. **B.** Demographic and sample characteristics for BD patients. Note: where relevant and possible, mean age and sex distribution were recalculated for the relevant patient subset. Abbreviations: FU-Follow-up, ADHD subtype I: Inattentive, H: Hyperactive, C: Combined. BD subtype: I-Bipolar Disorder I; BD II- Bipolar Disorder II; NOS-Bipolar Disorder Not Otherwise Specified; nr-not reported.

1st author, year	sample size	mean age (SD)	female (%)	sample specification	country	continent	diagnostic system	version (ADHD)	version (BD)	comorbid substance abuse	ADHD subtype			FU into adulthood
											I	H	C	
Agosti 2011	365	nr	49%	register/ population	US	AMERICA	DSM	IV	IV	yes	nr	nr	nr	no
Anastopoulos 2016	220	18(5)	52%	register/ population	US	AMERICA	DSM	V	IV	nr	47.00%	5.00%	48.00%	no
Arnold 2020	419	nr	24%	in-/out- patients	US	AMERICA	DSM	NA	IV	nr	nr	nr	nr	yes
Biederman 2006	112	22(3)	0%	in-/out- patients	US	AMERICA	DSM	III	IV	nr	nr	nr	nr	yes
Biederman 2010	96	21.6 (4)	100%	in-/out- patients	US	AMERICA	DSM	III-R	IV	nr	nr	nr	nr	yes
Breda 2015	277	33(2)	49%	in-/out- patients	BRAZIL	AMERICA	DSM	IV	IV	yes	nr	nr	nr	no
Brunkhorst Kanaan 2020	94	35	43%	in-/out- patients	GERMANY	EUROPE	both	5	ten	nr	nr	nr	nr	no
Chen 2015	6160	nr	nr	register/ population	TAIWAN	ASIA	ICD	nine-cm	nine-cm	yes	nr	nr	nr	yes
Chen 2018	61129	nr	44%	register/ population	SWEDEN	EUROPE	ICD	nine or ten	nine or ten	nr	nr	nr	nr	no
Garcia 2012	211	34(11)	49%	in-/out- patients	BRAZIL	AMERICA	DSM	IV	IV	yes	nr	nr	nr	no
Faraone 2006	127	36 (11	nr	in-/out- patients	US	AMERICA	DSM	IV	unclear	yes	nr	nr	nr	no
Gorlin 2016	204	35(13)	50%	in-/out- patients	US	AMERICA	DSM	IV	IV	yes	43	9.00%	49.00%	no
Halmoy 2009	50	nr	nr	in-/out- patients	NORWAY	EUROPE	both	ten(modified)	IV	nr	nr	nr	nr	nr
Halperin 2011	90	18(2)	13%	in-/out- patients	US	AMERICA	DSM	unclear	IV	yes	nr	nr	nr	yes
Harpold 2007	207	38(10)	42%	in-/out- patients	US	AMERICA	DSM	III-R	III-R	yes	nr	nr	nr	no
Hodgkins 2011	31752	32(13)	45%	register/ population	US	AMERICA	ICD	nine-cm	nine-cm	nr	nr	nr	nr	no
Kessler 2005	346	nr	36%	register/ population	US	AMERICA	DSM	IV	IV	nr	nr	nr	nr	no
Kooij 2001	116*	33(nr)	nr	in-/out- patients	THE NETHERLANDS	EUROPE	DSM	IV	IV	yes	16.00%	~2%	82.00%	no
Kristiansen 2014	1577	30(9)	38%	register/ population	DK	EUROPE	ICD	ten	ten	yes	nr	nr	nr	no
Larsson 2013	60655*	nr	32%	register/ population	SWEDEN	EUROPE	ICD	nine/ten	eight/nine/ ten	nr	nr	nr	nr	no
Manuzza 1993	91	26(1)	0%	in-/out- patients	US	AMERICA	DSM	III-R	III-R	nr	nr	nr	nr	yes
Meier 2018	13628	nr	nr	register/ population	DENMARK	EUROPE	ICD	eight/ten	ten	yes	nr	nr	nr	yes
Miesch 2017	98	39(13)	62%	in-/out- patients	GERMANY	AMERICA	both	IV-TR	ten	yes	29.00%	7.00%	64.00%	no
Milberger 1995	186	nr	nr	in-/out- patients	US	AMERICA	DSM	III-R	III-R	nr	nr	nr	nr	no
Pineiro-Dieguez 2016	367	33(1)	28%	in-/out- patients	SPAIN	EUROPE	DSM	IV-TR	nr	yes	27	31.00%	42.00%	no
Phelivandis 2020	180	31	31%	in-/out- patients	GREECE	ERUOPE	DSM	5	5	no	nr	nr	nr	no
Rasmussen 2009	458	30(9)	31%	in-/out- patients	NORWAY	EUROPE	ICD	ten	ten	yes	25.00%	2.00%	68.00%	no
Secnik 2005	2252	32(13)	36%	register/ population	US	AMERICA	ICD	nine	nine	yes	nr	nr	nr	no
Silva 2013	329	33(11)	50%	in-/out- patients	BRAZIL	AMERICA	DSM	IV	IV	yes	nr	nr	nr	no
Smalley 2007	188	nr	30%	register/ population	FINLAND	EUROPE	DSM	IV	unclear	nr	nr	nr	nr	no
Sobanski 2008	118	37(9)	46%	in-/out- patients	GERMANY	EUROPE	DSM	IV	IV	yes	51.40%	0.00%	48.60%	no
Solberg 2018	40103	31(8)	44%	register/ population	NORWAY	EUROPE	ICD	ten	ten	yes	nr	nr	nr	no
Stahlberg 2004	161	32(9)	47%	in-/out- patients	SWEDEN	EUROPE	DSM	IV	IV	yes	nr	nr	nr	no
Tsai 2019	214	25(5)	34%	in-/out- patients	TAIWAN	ASIA	DSM	IV	IV	yes	40.00%	0.00%	60.00%	no
Westmoreland 2009	68	29(8)	12%	register/ population	US	AMERICA	DSM	IV	IV	yes	nr	nr	nr	no
Wilens 2009	107	37(10)	51%	in-/out- patients	US	AMERICA	DSM	IV	IV	yes	31.00%	7.00%	62.00%	no

(*continued on next page*)

Table 1 (*continued*)

1st author, year	sample size	mean age (SD)	female (%)	sample specification	country	continent	diagnostic system	version (ADHD)	version (BD)	comorbid substance abuse	ADHD subtype			FU into adulthood
											I	H	C	
Yoshimasu 2018	232	27(nr)	28%	register/ population	US	AMERICA	DSM	IV	IV	yes	nr	nr	nr	yes
Young 2015	11846	36(14)	48%	register/ population	US	AMERICA	ICD	nine	nine	yes	nr	nr	nr	no

*only 116 used for analysis

1st author, year	sample size	mean age (SD)	BD mean age of onset	ADHD mean age of onset	female (%)	sample specification	country	continent	diagnostic system	version (ADHD)	version (BD)	comorbid substance abuse	BD subtype			BD NOS included in analysis	ADHD diagnosis	ADHD subtype			FU into adulthood
													I	II	NOS						
Aedo 2018	235*	38 (14)	22	nr	63%	in-/out-patients	Chile	AMERICA	DSM	IV-TR	IV-TR	yes	64%	35%	1%	yes	lifetime	nr	nr	nr	no
Andersen 2013	784	nr	28	nr	62%	register/ population	Denmark	EUROPE	ICD	eight/ ten	eight/ ten	yes	nr	nr	nr	na	lifetime	nr	nr	nr	no
Angst 2013	903	nr	nr	nr	59%	in-/out-patients	Multiple	MULTI	DSM	IV	IV	nr	nr	nr	nr	na	current	nr	nr	nr	no
Bennett 2019	469	nr	nr	nr	58%	in-/out-patients	Multiple	MULTI	DSM	IV	IV	nr	84%	14%	2%	yes	current	nr	nr	nr	no
Berkol 2014	129	nr	nr	nr	nr	in-/out-patients	Turkey	ASIA	DSM	IV	IV	nr	91%	4%	4%	no	current	nr	nr	nr	no
Bernardi 2010	100	29(2)	17	6.5	49%	in-/out-patients	Italy	EUROPE	DSM	IV	IV	nr	67%	33%	0%	na	lifetime	nr	nr	nr	no
Di Nicola 2014	102	47(13)	32	nr	62%	in-/out-patients	Italy	EUROPE	DSM	IV-TR	IV-TR	nr	48%	39%	13%	yes	current	50%	31%	19%	no
Ghaffary 2013	152	34(11)	25	nr	33%	in-/out-patients	Iran	ASIA	DSM	unclear	IV	nr	100%	0%	0%	na	lifetime	nr	nr	nr	no
Harmanci 2016	100	nr	27	nr	nr	in-/out-patients	Turkey	ASIA	DSM	IV-TR	IV-TR	nr	87%	13%	0%	na	current	38%	20%	42%	no
Henin 2007b	83	42(8)	23	4.9	68%	in-/out-patients	US	AMERICA	DSM	IV	IV	nr	72%	28%	0%	na	lifetime	nr	nr	nr	no
Hossain 2019	316025	nr	nr	nr	58%	register/ population	US	AMERICA	ICD	nine	nine	yes	nr	nr	nr	na	lifetime	nr	nr	nr	no
Karaahmet 2013	90	36	22	nr	47%	in-/out-patients	Turkey	ASIA	DSM	IV	IV	yes	nr	nr	nr	na	lifetime	24%*	24%	52%	no
Karanti 2019	8463	48(16)	nr	nr	62%	register/ population	Sweden	EUROPE	DSM	IV	IV	yes	55%	45%	0%	na	current	nr	nr	nr	no
Kerner 2011	1000	42(13)	nr	nr	50%	register/ population	US	AMERICA	DSM	III-R/IV	III-R/IV	yes	100%	0%	0%	na	lifetime	nr	nr	nr	no
Marin 2013	50	38(13)	nr	nr	48%	in-/out-patients	Canada	AMERICA	DSM	IV	IV	nr	nr	nr	nr	na	current	nr	nr	nr	no
McIntyre 2010	176	39(13)*	24.2	nr	64%	in-/out-patients	US,Canada	AMERICA	DSM	IV	IV	nr	68%	32%	0%	na	lifetime	nr	nr	nr	no
Meier 2018	9250	nr	33	nr	57%	register/ population	Denmark	EUROPE	ICD	eight/ ten	eight/ ten	nr	nr	nr	nr	na	lifetime	nr	nr	nr	no
Merikangas 2007	195	nr	20	nr	nr	register/ population	US	AMERICA	DSM	IV	IV	nr	nr	nr	nr	na	current	nr	nr	nr	no
Merikangas 2011	721	nr	nr	nr	nr	register/ population	Multiple	MULTI	DSM	IV	IV	yes	27%	18%	nr	na	lifetime	nr	nr	nr	no
Nierenberg 2005	870	nr	nr	nr	nr	in-/out-patients	US	AMERICA	DSM	IV	IV	yes	69%	26%	5%	no	lifetime	nr	nr	nr	no
Oguz 2014	121	34(nr)	nr	nr	59%	in-/out-patients	Turkey	ASIA	DSM	IV	IV	yes	100%	0%	0%	na	current	nr	nr	nr	no
	56	19(nr)	nr	nr	nr			EUROPE	DSM	unclear	IV	nr	100%	0%	0%	na	lifetime	nr	nr	nr	yes

(*continued on next page*)

Table 1 (*continued*)

1st author, year	sample size	mean age (SD)	BD mean age of onset	ADHD mean age of onset	female (%)	sample specification	country	continent	diagnostic system	version (ADHD)	version (BD)	comorbid substance abuse	BD subtype			BD NOS included in analysis	ADHD diagnosis	ADHD subtype			FU into adulthood
													I	II	NOS						
Papachristou 2013						register/ population	The Netherlands														
Perroud 2014	124	42(12)	25	nr	55%	in-/out-patients	Switzerland	EUROPE	DSM	IV	IV	yes	55%	34%	11%	yes	current	nr	nr	nr	no
Perugi 2013	96	nr	nr	nr	41%	in-/out-patients	Italy	EUROPE	DSM	IV-TR	IV-TR	yes	67%	33%	0%	na	current	nr	nr	nr	no
Pinna 2019	703	46(nr)	26	nr	55%	in-/out-patients	Italy	EUROPE	DSM	IV-TR	IV-TR	yes	52%	48%	0%	na	lifetime	nr	nr	nr	no
Propper 2015	363	44(13)	24	nr	65%	in-/out-patients	Canada	AMERICA	DSM	IV	IV	yes	65%	35%	0%	na	lifetime	nr	nr	nr	no
Rubino 2009	132	44(13)	nr	nr	61%	in-/out-patients	Italy	EUROPE	DSM	unclear	IV-TR	yes	nr	nr	nr	na	lifetime	nr	nr	nr	no
Ryden 2009	159*	39(13)	22	nr	62%	in-/out-patients	Sweden	EUROPE	DSM	IV	IV	yes	50%	40%	9%	no	lifetime	nr	nr	nr	no
Sachs 2000	56	nr	nr	nr	nr	in-/out-patients	US	AMERICA	DSM	III-R	unclear	yes	88%	13%	0%	na	lifetime	nr	nr	nr	no
Sentissi 2008	73	44(12)	25	nr	53%	in-/out-patients	France	EUROPE	DSM	IV	IV	yes	85%	15%	0%	na	current	nr	nr	nr	no
Song 2015	54723	nr	nr	nr	nr	register/ population	Sweden	EUROPE	ICD	eight/ nine/ten	eight/ nine/ten	yes	nr	nr	nr	na	lifetime	nr	nr	nr	no
Tamam 2008	159	34(10)	25	nr	50%	in-/out-patients	Turkey	ASIA	DSM	IV-TR	IV-TR	nr	92%	6%	2%	yes	lifetime	nr	nr	nr	no
Torres 2015	163	43(13)	27	nr	54%	in-/out-patients	Spain	EUROPE	DSM	IV-TR	IV-TR	yes	76%	24%	0%	na	lifetime	nr	nr	nr	no
Walsh 2020	182	46	16	nr	66%	non-clinical/ population	US	AMERICA	DSM	IV-TR	IV-TR	yes	60%	40%	0%	na	lifetime	nr	nr	nr	no
Young 2015	14943	44(15)	nr	nr	nr	register/ population	US	AMERICA	ICD	nine-cm	nine-cm	nr	nr	nr	nr	na	lifetime	nr	nr	nr	no

*numbers may differ from numbers in meta-analysis because BD-NOS are included

Table 2

A. Prevalence rate of BD in the primary sample of ADHD. Diagnosis for ADHD is given as cADHD if only a childhood diagnosis was given, as lifetime if diagnosis occurred at any time point and as adult ADHD if diagnosis was mentioned as being present during adulthood. **B**. Prevalence rate of ADHD in the primary sample of BD. Lifetime ADHD diagnosis refers to any diagnosis of ADHD, current refers to current psychopathology of aADHD.

study	ADHD diagnosis	BD state	total N	cases N
Agosti 2011	aADHD	lifetime	365	56
Anastopoulos 2018	aADHD	current	220	0
Arnold 2020	lifetime	lifetime	419	52
Biederman 2006	cADHD	lifetime	112	21
Biederman 2010	cADHD	current	96	7
Breda 2016	lifetime	lifetime	277	45
Chen 2015	lifetime	lifetime	6160	84
Chen 2018	aADHD	lifetime	61129	7123
Garcia 2012	aADHD	lifetime	211	32
Faraone 2006	aADHD	lifetime	127	23
Gorlin 2016	aADHD	current	204	15
Halmoy 2010	lifetime	lifetime	50	13
Halperin 2011	cADHD	current	90	1
Harpold 2007	aADHD	lifetime	207	20
Hodgkins 2011	lifetime	lifetime	31752	1207
Kessler 2005	aADHD	lifetime	346	36
Kooij 2001	aADHD	current	116	1
Kristiansen 2015	aADHD	lifetime	1577	100
Larsson 2013	lifetime	lifetime	60655	2989
Manuzza 1993	lifetime	current	91	0
Meier 2018	lifetime	lifetime	13628	182
Miesch 2019	aADHD	current	98	5
Milberger 1995	aADHD	current	186	20
Pineiro-Dieguez 2016	aADHD	lifetime	367	9
Rasmussen 2009	aADHD	lifetime	458	14
Secnik 2005	aADHD	lifetime	2252	101
Silva 2014	aADHD	lifetime	329	51
Smalley 2007	lifteime	lifetime	188	0
Sobanski 2008	aADHD	lifetime	118	0
Solberg 2018	aADHD	lifetime	40103	4271
Stahlberg 2004	aADHD	current	161	8
Tsai 2019	aADHD	current	214	1
Westmoreland 2010	aADHD	lifetime	68	49
Wilens 2009	aADHD	lifetime	107	20
Yoshimasu 2018	lifetime	lifetime	232	35
Young 2015	aADHD	current	11846	936
Brunkhorst-Kanaan 2020	aADHD	lifetime	94	2
Pehlivanidis 2020	aADHD	lifetime	180	18
Total			**234833**	**17547**

study	ADHD diagnosis	BD state	total N	cases N
Aedo 2018	lifetime	lifetime	233	23
Andersen 2013	lifetime	current	784	33
Angst 2013	current	lifetime	903	9
Bennett 2019	current	lifetime	469	64
Berkol 2014	current	lifetime	129	23
Bernardi 2010	lifetime	lifetime	100	18
Di Nicola 2014	current	lifetime	102	16
Ghaffary 2013	lifetime	lifetime	152	56
Harmanci 2016	current	current	100	48
Henin 2007b	lifetime	lifetime	83	18
Hossain 2019	lifetime	lifetime	316025	16433
Karaahmet 2013	lifetime	lifetime	90	34
Karanti 2019	current	current	8463	309
Kerner 2011	lifetime	lifetime	1000	97
Marin 2013	current	current	50	13
McIntyre 2010	lifetime	lifetime	176	31
Meier 2018	lifetime	lifetime	9250	182
Merikangas 2007	current	lifetime	195	81
Merikangas 2011	lifetime	lifetime	721	198
Nierenberg 2005	lifetime	lifetime	870	84
Oguz 2014	current	lifetime	121	26
Papachristou 2013	lifetime	lifetime	56	12
Perroud 2014	current	current	124	27
Perugi 2013	current	lifetime	96	19
Pinna 2019	lifetime	lifetime	703	173
Propper 2015	lifetime	lifetime	363	15
Rubino 2009	lifetime	current	132	41
Ryden 2009b	lifetime	lifetime	144	43
Sachs 2000	lifetime	lifetime	56	8
Sentissi 2008	current	lifetime	73	22
Song 2015	lifetime	lifetime	54723	2064
Tamam 2008	lifetime	lifetime	159	43
Torres 2015	lifetime	lifetime	163	29
Walsh 2020	lifetime	lifetime	182	58

(*continued on next page*)

Table 2 (*continued*)

study	ADHD diagnosis	BD state	total N	cases N
Young 2015	lifetime	current	14943	941
Total			**411933**	**21291**

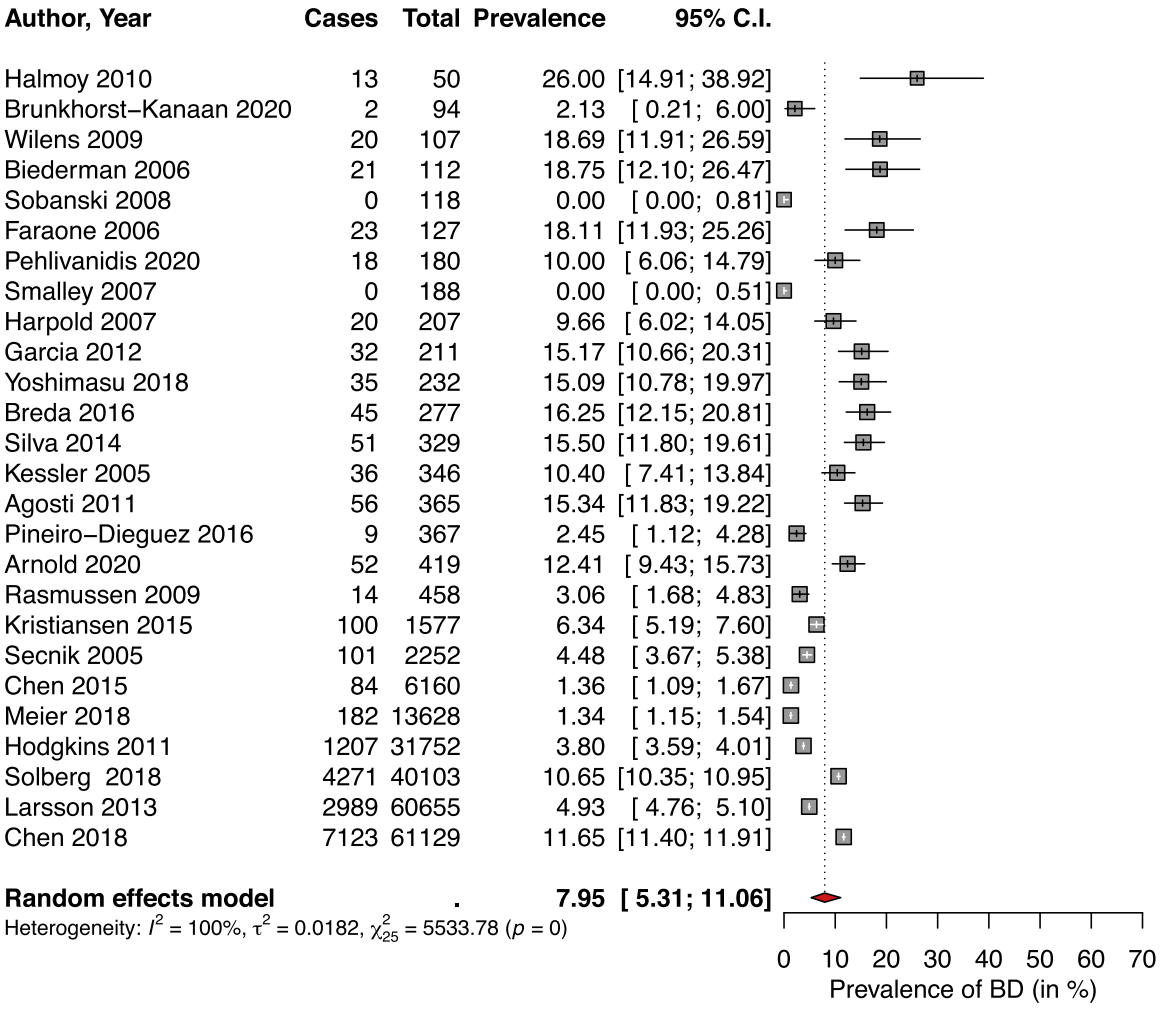

Fig. 2. Lifetime comorbidity rate of BD in patients with ADHD.

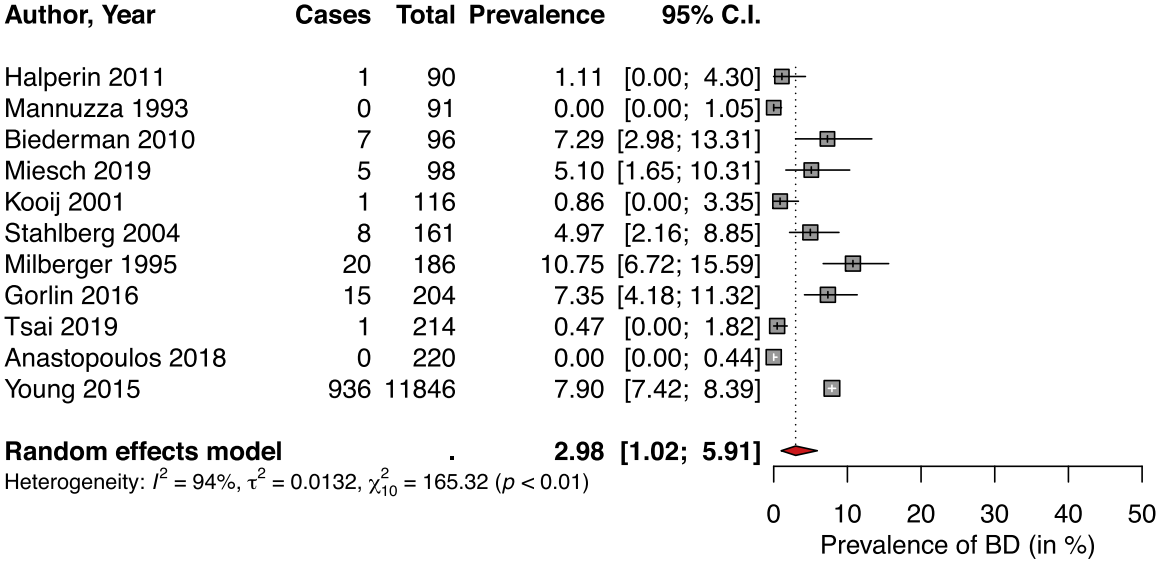

Fig. 3. Comorbidity rate of current BD in patients with ADHD.

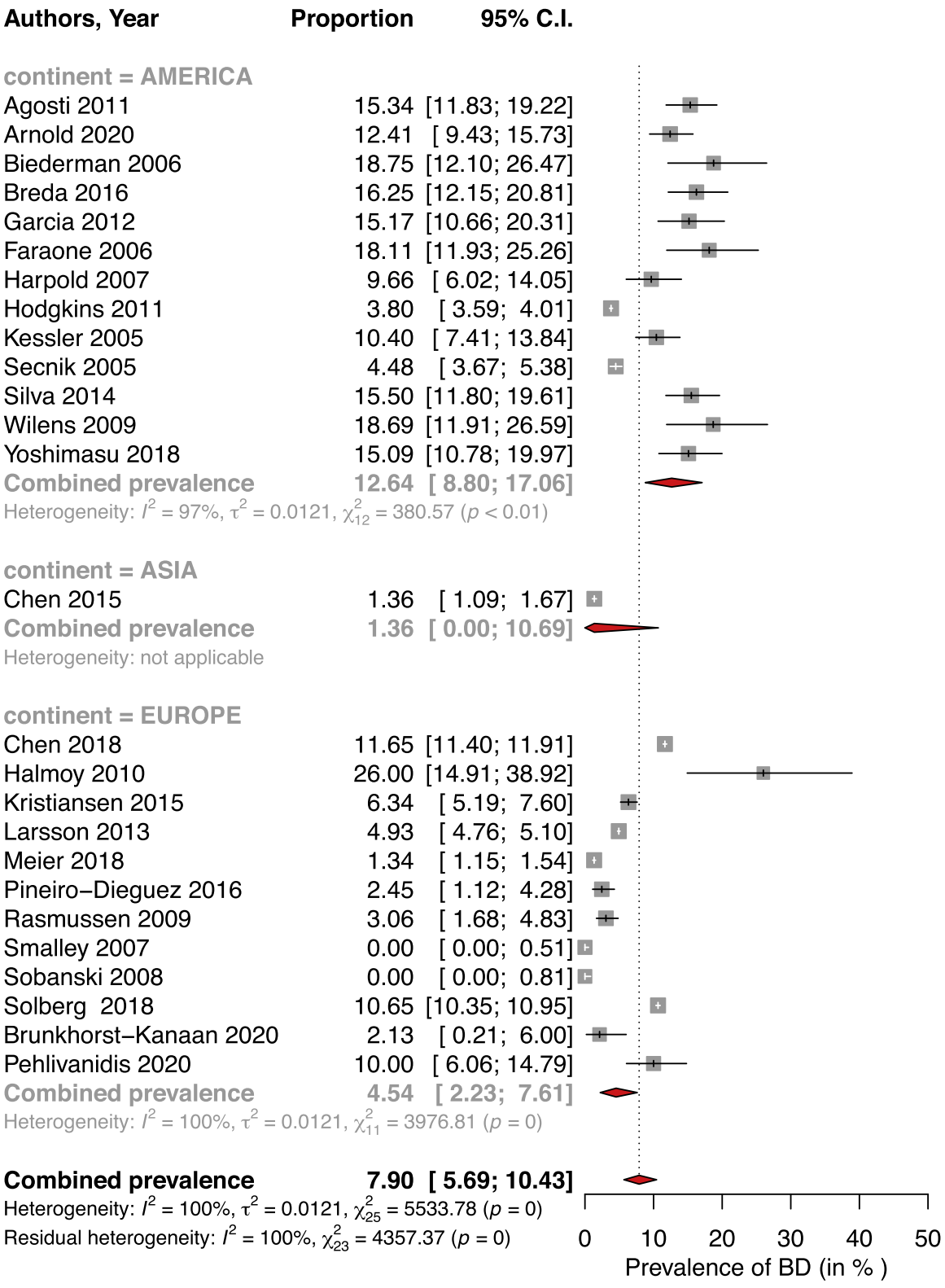

Fig. 4. Comorbidity rate of BD in patients with ADHD by continent. America includes both North and South America, Asia refers to the study from Taiwan.

% CI 2.23–7.61), see Fig. 4. Continent explained a significant amount of heterogeneity (R^2 = 33.38 %), but residual heterogeneity was still significant (I^2 = 100 %, p < 0.001). Recomputed combined comorbidity was 7.90 (95 % CI: 5.69–10.43).

3.2.4. *Influence of diagnostic system*

Fifteen studies used the DSM, 9 studies used the ICD and 2 studies used both instruments for diagnosis. Stratified analysis by diagnostic system (only including ICD or DSM) did reveal significant effects (estimate = 0.10, df = 1, p = 0.049). Comorbidity with DSM was 10.06 (95 % CI: 6.53–14.26), and 4.76 with the ICD (95 %CI: 1.94–8.74), see Supplementary Fig. 3. Importantly, to determine if the effect of country was driven by sample size or diagnostic system, we conducted a meta regression with these terms. The difference between Europe and

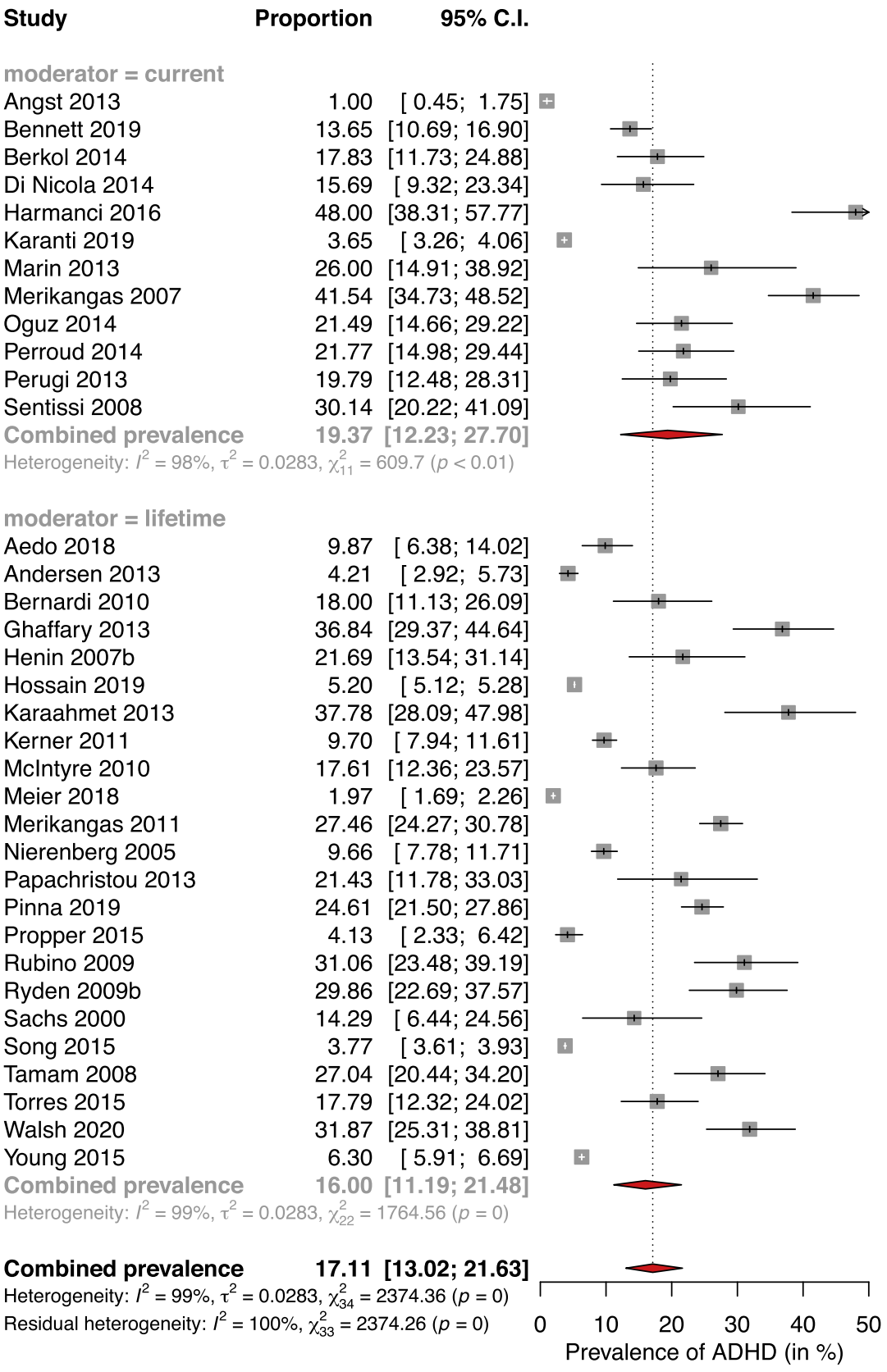

Fig. 5. Comorbidity rate of current and lifetime diagnoses of ADHD in patients with BD.

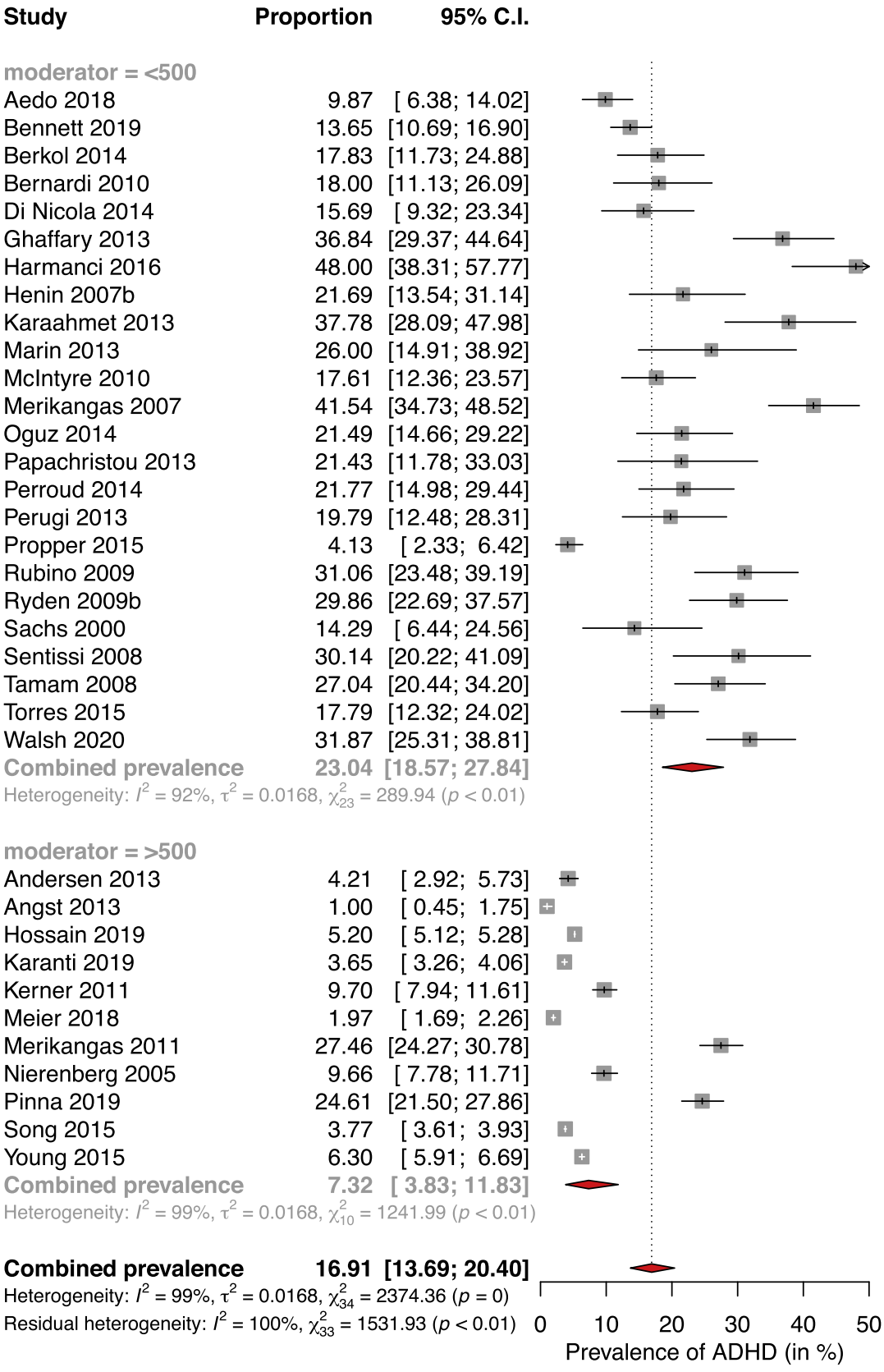

Fig. 6. Comorbidity rate of ADHD in patients with BD per sample size. Small refers to less than 500 people and large sample size refers to more than 500 people).

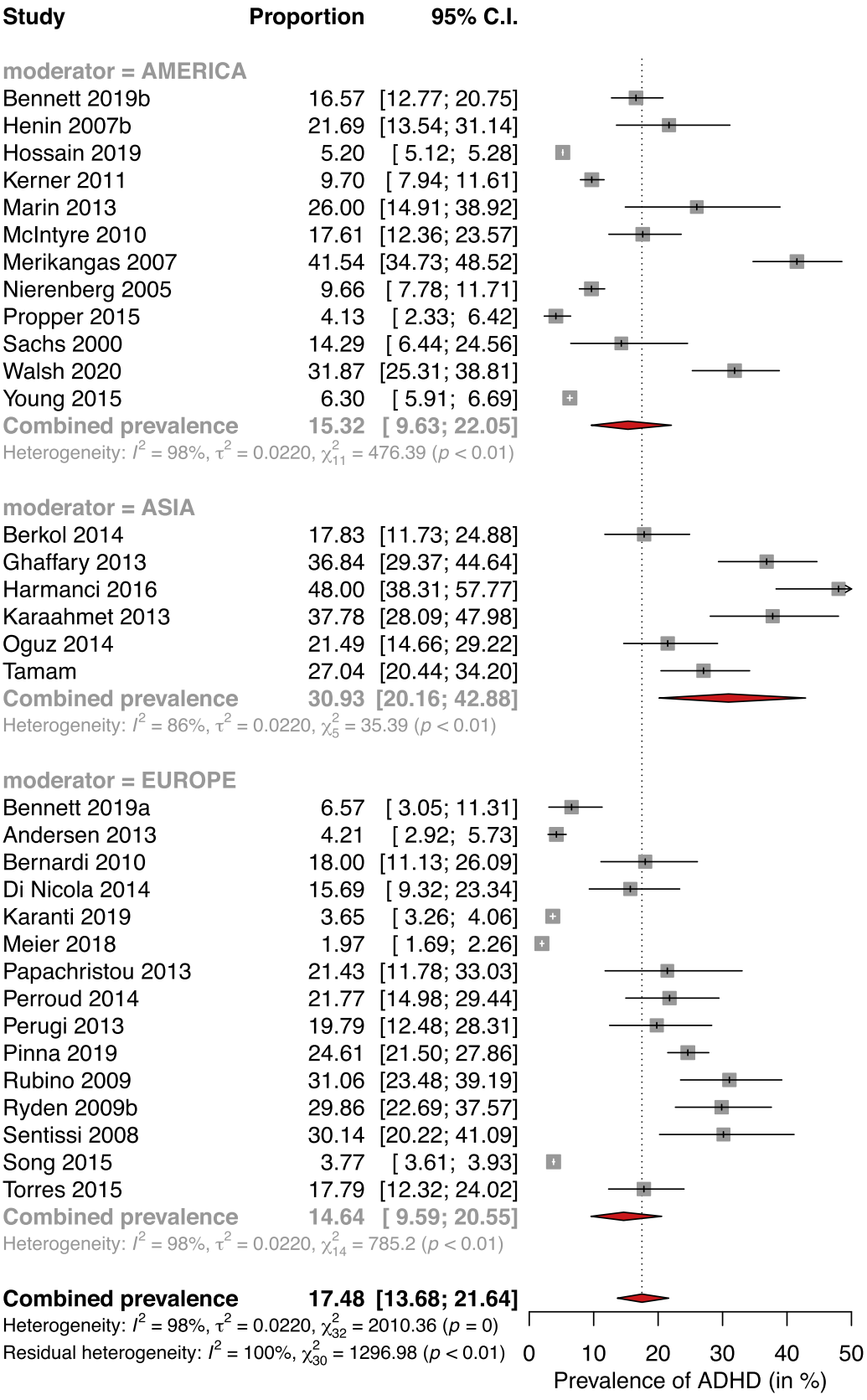

Fig. 7. Comorbidity rate of ADHD in patients with BD by continent. America includes both North and South America, Asia refers to studies from Turkey and Iran.

America remained significant (estimate=-0.16, z=-3.04, p = 0.002).

3.2.5. Effects of sex and age

Since not all studies reported sex and age, separate meta-regressions were conducted for these factors. Eighteen studies reporting on lifetime comorbidity of BD also reported mean age at assessment and 24 reported the percentage of women in the sample. No significant effect emerged for age (estimate=-0.01, z=-0.73, p = 0.463) or sex (estimate = 0.15, z = 0.61, p = 0.543).

3.2.6. Publication bias

Visual inspection of the funnel plot did not indicate evidence for publication bias in studies reporting lifetime BD comorbidity in ADHD (when excluding the influential outlier study), confirmed by Egger's test (z = 1.68 p = 0.092) (Supplementary Fig. 4).

3.2.7. Effects including the outlier

Including the outlier did not alter effects majorly: In a meta-regression including diagnostic system, and sample size, continent remained significant (Europe-America p = 0.012), while sample size (p = 0.963) and diagnostic system (ICD compared with DSM: p = 0.833) were not significant.

3.3. Comorbidity of ADHD in patients with BD

3.3.1. Overall and current vs lifetime diagnosis of ADHD

Of the 35 studies, 23 (n cases = 401,108) assessed lifetime diagnosis of ADHD, whereas 12 studies (n cases = 10,825) (also) assessed current/aADHD. Pooled comorbidity of any ADHD diagnosis in the overall BD sample was 17.11 % (95 % CI: 13.05–21.59), but again, substantial heterogeneity was present (Q = 2374.36, p < 0.001, I^2 = 99.81 %). No significant outlier was identified in leave-one-out analysis. Since the diagnosis of aADHD requires presence of symptoms during childhood, we used lifetime/aADHD as a moderator for preliminary analysis. Comorbidity of BD in patients with a lifetime diagnosis of ADHD was 16.00 % (95 % CI: 11.19–21.48). For patients with current/aADHD, BD comorbidity was 19.37 % (95 % CI: 12.23–27.70), see Fig. 5. Both comorbidity rates did not differ significantly from each other (Q = 0.51, df = 1, p = 0.473). Therefore, in the following, comorbidity rates of lifetime/current ADHD and potential moderators are explored jointly.

3.3.2. Comorbidity per sample size

Visual inspection of the forest plot indicated a larger effect for smaller studies, mostly from patient-based studies (88 %) and a lower comorbidity for larger studies with a majority (73 %) of population/register-based samples. Subgroup analysis using a common between-study variance component in large and small studies confirmed a lower comorbidity rate in larger studies (>500 participants) compared with smaller studies (estimate=−0.23, z=−4.69, p < 0.001). Comorbidity in smaller studies was 23.04 (95 % CI:18.57−27.84) compared with 7.32 (95 % CI: 3.83–11.83) in larger studies. The combined comorbidity was 16.91 (95 % CI: 13.69–20.40) (Fig. 6).

3.3.3. Comorbidity per continent

Given the large difference by continent in the first part of the results section, we also explored the effect of country on comorbidity rates. One study (Bennett et al., 2019) reported comorbidity for Europe and the Americas separately and was split for this purpose (Bennett 2019/a and 2019/b in the graphs). In America, the comorbidity rate of ADHD in BD was 15.32 (95 % CI:9.63−22.05) and comparable to Europe, where it was 14.64 (95 % CI: 9.59–20.55) (estimate=-0.01, z=-0.16, p = 0.873). However, in Western Asia (i.e., Turkey and Iran) comorbidity amounted to 30.93 (95 % CI: 20.16–42.88) and was significantly higher than in America (estimate = 0.19, z = 2.43, p = 0.015) and Europe (estimate=-0.20, z=-2.64, p = 0.008) (Fig. 7). The recomputed comorbidity rate was 17.48 (95 % CI:13.68−21.64). Two studies included participants from multiple continents and were not included in the moderator analysis. The study by Angst et al. (2013) included a large minority of patients from China, Taiwan, Korea and Vietnam and a small majority of studies from Europe, whereas more than 2/3 of the participants described in Merikangas et al. (2011) were from New Zealand and the US. Comorbidity rates were 1.00 % (CI 95 %: 0.45–1.75) and 27.46 % (CI 95 % 24.27–30.78 %) respectively.

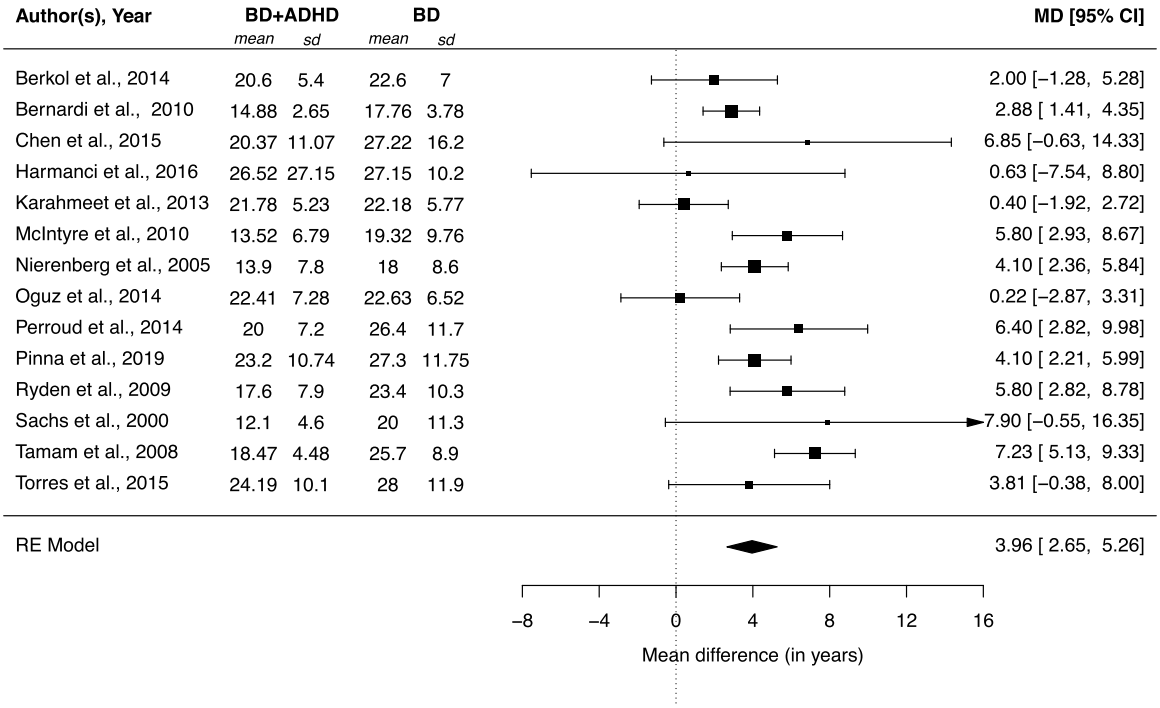

Fig. 8. Age of onset between patients with BD and patients without BD. Effects are derived from a random effects model, effect size used is the raw mean difference, using age in years.

Table 3
Prevalence of ADHD in relative of BD an vice versa. Abbreviations: FDR- First degree Relative, w/= with, nr = not reported; ~ indicates an estimation based on the provided data.

	Family of cases						Family of control group						
study	Proband disorder	relation	total N relatives	N w/ ADHD or BD	Mean age (years)	% female	relation	total N relatives	N w/ ADHD or BD	Mean age (years)	% female	p value	Comment
Arman 2018	BD	offspring	250	61*	11.4	54 %	offspring	250	28*	11.6	50 %	<0.001	*clear disorder during lifetime
Axelson 2015	BD	offspring	391	120	18.1*	49 %	offspring	248	45	18.0*	54 %	0.01	*age at last assessment
Biederman 2013b	BD*	FDR	61	~3	nr	nr	FDR	411	~29	nr	nr	ns	*children with BD I
	BD + ADHD	FDR	626	~140	nr	nr	FDR	nr	nr	nr	nr	<0.05	
Chen 2019	BD	FDR	188290	2749	34.8	50.10 %	nr	nr	nr	nr	nr	<0.001*	*compared to general population
Palacio-Ortiz 2017	BD	offspring	127	35	17.6	45 %	offspring	150	19	17.7	47 %	0.001	
Turkyilmaz 2012	BD	FDR	73	14*	18−44	49 %	FDR	68	6*	NA	49 %	0.08	*cADHD
Walsh 2020	BD	FDR	227	37	51*	64 %	FDR	176	20	49	63 %	BD I: $p < 0.03$/ BD II $p > 0.7$	*association not significant after controlling for mood disorders in relatives
Biederman 2013b	ADHD	FDR	511	~ 28	NA	NA	FDR	411	~21	NA	NA	ns	(~5,5%/ 511 in ADHD) (~5%/411 HC)
Chen 2019b	ADHD	FDR	401301	~2689	29.7	50 %	FDR	1605204	~4976	29.7	50 %	<0.001	
Wei 2019	ADHD	siblings	5128	14	18	58 %	siblings	20512	26	18	58 %	0,027	

Table 4
Age of Onset for patients with BD and with or without comorbid ADHD. The comparison (p) refers to values extracted from each article and does not reflect meta-analytic data. Significance: *<0.05, **<0.01, ***<0.001.

author year	pure BD			BD + ADHD			direction	significance	conclusion	comment
	n	*age of onset, mean*	*sd*	*n*	*age of onset, mean*	*sd*	*age of onset*	*comparison (p)*		
Berkol 2014	32	*22.6*	*7,0*	*23*	*20.6*	*5.4*	~(↓)	*ns*	non-significantly lower in BD + ADHD	*pure BD was a subgroup of all BD patients tested
Bernardi 2010	82	*17.8*	*3.8*	*18*	*14.9*	*2.7*	↓	**< 0.001*****	significantly younger age of onset	Overall group onset (16.93−18.68)
Chen 2015	20	27.2	16,0	84	20.4	11	↓	**p < 0.001*****	significantly lower age of onset for BD in people with ADHD compared to "pure BD" i.e. controls	*only study where primary sample was ADHD
Harmanci 2016	52	*27.2*	*10.2*	*48*	*26.5*	*27*	~(↓)	*p = 0.759*	no difference	*p value recalculated based on lifetimeADHD
Karahmeet 2013	56	*22.2*	*5.8*	34	*21.8*	*5.2*	~(↓)	p = 0.74	no difference	
McIntyre 2010	145	*19.3*	*9.8*	31	*13.5*	*6.8*	↓	**p = 0.005****	significanty younger at onset of first depression	*age for depression onset
Nierenberg 2005	830	*18.0*	*8.6*	87	*13.9*	*7.8*	↓	**p< 0.001*****	significantly younger age of onset	
Oguz 2014	95	*22.6*	*6.5*	26	*22.4*	*7.3*	~(↓)	p = 0.880	no difference	
Perroud 2014	97	26.4	*11.7*	27	20,0	*7.2*	↓	**p = 0.01***	significantly younger age of onset of BD and at onset of depressive episode (p = 0.006) but not for mania	*sd derived with formula SD= $\sqrt{N}$x (upper limit of CI – lower limit of CI)/3.92
Pinna 2019	530	27.3	*11.8*	173	23.2	*11*	↓	**p < 0.001***	significantly lower age of onset	p value recomputed for combined group
Ryden 2009	114	*23.4*	*10.3*	45	*17.6*	*7.9*	↓	**p < 0.001*****	significantly lower age of onset	
Sachs 2000	8	*20.0*	*11.3*	8	*12.1*	*4.6*	↓	**p < 0.01****	significantly lower age of onset	mean and sd combined for cADHD and aADHD samples
Tamam 2008	116	*25.7*	*8.9*	43	*18.5*	*4.5*	↓	**p < 0.001*****	significantly lower age of onset	
Torres 2015	134	*28.0*	*11.9*	29	*24.2*	*10*	~(↓)	p = 0.066	no difference (trend for lower age of onset)	

3.3.4. Influence of diagnostic system

Five studies used the ICD and 30 used the DSM. Use of the DSM led to considerably higher comorbidity rates: 20.07 (95 %CI: 16.04–24.42) for DSM-based studies vs. 4.16 (95 %CI: 0.67–10.41) in ICD based studies (estimate = 0.26, z = 3.79, $p < 0.001$), see Supplementary Fig. 5. This effect was no longer significant when adding continent and sample size into the model (estimate: -0.13, z=-1.75, p = 0.080). In the full model, comorbidity in Western Asia remained higher compared with Europe, and the Americas (p = 0.056 and p = 0.043), although the effect for Europe was no longer significant. The effect of sample size remained significant (p = 0.031). The full model explained a significant amount of heterogeneity ($R^2 = 52.60$ %), but residual heterogeneity was still significant ($I^2 = 99.85$, $p < 0.001$).

3.3.5. Effects of age and sex

Separate meta-regression showed that mean sample age reported by 24 studies had no impact on comorbidity rates (estimate=-0.01, z=-1.38, p = 0.168), and did not explain heterogeneity. Sex distribution, reported by 27 studies, also did not have significant effects (estimate=-0.73, z=-1.92, p = 0.055).

3.3.6. Effects of BD I and BD II

Of the thirty-five studies describing ADHD in BD, 19 studies (n cases = 9,826) provided estimates of ADHD in BD I and 15 studies (n cases = 5,603) provided estimates for BD II disorder. Comorbidity of ADHD did not differ between patients with BD I and BD II (estimate = 0.01, z = 0.16, p = 0.870), heterogeneity was high ($I^2 = 98.08$ %, $p < 0.001$).

3.3.7. Assessment of publication bias

There was a visual indication for publication bias in studies reporting ADHD in BD. This was confirmed using Egger's test (z = 5.14, $p < 0.001$) (Supplementary Fig. 6A). Calculation of comorbidity rates with the trim and fill method estimated that 5 studies (SE = 3.92) are missing from the left side of the mean, which if imputed would lead to lower estimated comorbidity (Supplementary Fig. 6B).

3.4. Effects of quality and diagnostic accuracy in ADHD and in BD

Quality ratings for the studies included in the quantitative synthesis showed that most studies were of moderate quality (low quality:10 %, medium quality: 68 %, high quality: 23 %). The detailed overview of quality ratings can be found in Supplementary Table 2. The general quality ratings (as a continuous variable) had no effect on comorbidity rates, neither for patients with a primary diagnosis of ADHD, hereafter referred to as "ADHD studies" (estimate = 0.00, z = 0.02, p = 0.981), nor for patients with a primary diagnosis of BD, hereafter referred to as "BD studies" (estimate=-0.02, z=-1.51, p = 0.131).

Yet, analyses using the three diagnostic quality determinants (i.e., the use of (semi-)structured interviews, interviewer with a mental health background, and validation of ADHD through a third party) revealed significantly lower estimates of comorbidity in register-based studies compared with studies using two interviews (for ADHD studies: estimate = 0.18 z = 3.15, p = 0.002 and for BD studies: estimate = 0.29, z = 4.19, $p < 0.001$). Studies only using one diagnostic interview were not significantly different from register-based studies for ADHD studies (estimate = 0.06, z = 0.42, p = 0.671), but had significantly higher estimates for BD studies (estimate = 0.32, z = 3.63, $p < 0.001$ compared with register-based studies). Studies using questionnaires to support the diagnosis also had higher estimates (only applicable for BD studies: estimate = 0.39, z = 4.30, $p < 0.001$ compared with register-based studies).

Validation of ADHD diagnosis by a third party decreased comorbidity estimates significantly when introduced in one model with diagnostic interviews (for ADHD: estimate=-0.15, z=-2,22, p = 0.027, n = 7 studies) but had no significant effect in BD studies (estimate = 0.02, z = 0,32, p = 0.746, n = 10 studies). No significant difference occurred for diagnosis by a mental-health professional compared with lay interviewers or register-based diagnoses for BD studies (estimate=-0.08, z=-1.47, p = 0.141). This item was not assessed for ADHD studies since it was redundant with interview status in the same model.

3.5. Age of BD onset in patients with and without comorbid ADHD

Fourteen studies compared the age of BD onset between those with and without comorbid ADHD. Where both onset of the first depressive episode and of mania were given, we used the episode that occurred earliest. Interestingly, all studies reported a younger age of onset in patients who had ADHD, and this difference reached significance in 9 of 14 studies (Table 4). The raw mean difference for age of onset in a random effects model comparing BD and BD with comorbid ADHD could be estimated at approximately 4 years (μ = 3.96, CI 95 %: 2.65–5.26, estimate = 3.06, z = 5.94, $p < 0.001$). Significant heterogeneity was present ($I^2 = 64.98$ %, p = 0.001), but continent or age did not explain the heterogeneity ($p > 0.50$). Results are presented in Fig. 8.

3.6. Comorbidity of ADHD and BD in relatives

We also identified studies assessing the risk of ADHD in relatives of patients with BD and of BD in relatives of patients with ADHD (Biederman et al., 2003) to update the meta-analysis by Faraone et al. (2012). We identified 7 new studies assessing risk of ADHD in relatives of participants with BD (Arman et al., 2018; Axelson et al., 2015; Biederman et al., 2013; Chen et al., 2019b; Palacio-Ortiz et al., 2017; Turkyilmaz et al., 2012) and 3 new studies assessing the risk of BD in relatives of patients with ADHD (Biederman et al., 2013; Chen et al., 2019a; Wei et al., 2019). In line with the previously published review, most studies (4 of 7) reported a significantly higher comorbidity of ADHD in relatives of patients with BD. One study found a trend for significance while one study found no difference. Another study first found a significant difference for BD-I (not for BD-II), but this association was no longer significant after controlling for BD comorbidity in relatives (Walsh et al., 2020), see Table 3 for an overview. For relatives of ADHD, two studies found significantly higher comorbidity of BD in relatives of participants with ADHD, and one study found no difference. Given the much larger data set meta-analysed previously (Faraone et al., 2012), these new data do not change their conclusion that first degree relatives of ADHD patients are at elevated risk for BD and first degree relatives of BD patients are at elevated risk for ADHD. Family studies of ADHD and BD also show that the two disorders are usually transmitted together (Biederman et al., 2003; Doyle and Faraone, 2002).

4. Discussion

In the here examined studies, 1 in 13 patients with ADHD had BD and nearly 1 in 6 patients with BD were diagnosed with ADHD. These numbers are strikingly high. Given the published lifetime prevalence for ADHD of 6.5 % and a lifetime BD prevalence of 1–2 % (these number however vary widely across studies and represent the rough median of published data) (Fayyad et al., 2017; Polanczyk et al., 2007, 2014), one could tentatively estimate that, based on the few population based studies included in this meta-analysis, comorbid BD and ADHD could occur in around 0.12 % of the population, or up to 0.38 % if taking into account the smaller studies that used scientifically valid diagnostic criteria, to ascertain comorbidity with interviews and questionnaires (see Supplementary information 2 for details on the calculation). Although speculative, this rate would correspond to nearly 4 Million affected people in the combined population of the European Union and the United States, and calls for clinical and research efforts addressing this important comorbidity, which is characterized by high disease burden, large impairment (Torres et al., 2018) and challenging clinical management (Viktorin et al., 2017).

The comorbidity rates given above are higher than to be expected by chance: 8.39 % vs. 1–2 % in the case of BD, and 18 % vs. 6.5 % in the case of ADHD, i.e., a three to five times increased comorbidity rate. However, these rates are far from being homogeneous across studies and at least partially depend on study characteristics which we outline below. First, we will discuss the current literature regarding some factors contributing to this heterogeneity, which will enable the reader to critically assess the presented comorbidity estimates. Next, we discuss possible reasons for the comorbid manifestation of ADHD and BD and discuss its clinical relevance.

4.1. Inter-continental differences of comorbidity rates

Intriguingly, we found a pronounced difference for comorbidity rates between continents. The impact of geographical location on comorbidity rates has been discussed in previous reports addressing BD and ADHD separately. For BD, it was suggested that prevalence may be higher in the Americas (particularly in South-America) compared with Asia and (some) European countries (Merikangas et al., 2011; Roser and Ritchie, 2016), but this is not the case for ADHD: Polanczyk et al. (2014) (Polanczyk et al., 2014) found that the initially significant difference between continents was better explained by methodological variables, indicating that geographic origin only plays a minimal role for ADHD prevalence (Canino and Alegría, 2008; Polanczyk et al., 2014). We here found a significant difference of comorbidity rates between America and Europe when ADHD was our primary sample, but not when BD was our primary sample. This finding is intriguing and deserves further exploration.

The high rate of comorbidity in Turkey is surprising, but does reflect findings of previous reports showing not only a higher prevalence of (childhood) ADHD (Ercan et al., 2019) and slightly elevated prevalence of BD in Turkey (0.85) compared with some European (i.e., Germany, Poland) or American (0.65 %) countries (Roser and Ritchie, 2016). It also fits well with increased rate of mood disorders in school-aged children with ADHD in Turkey (Ercan et al., 2015). The reduced comorbidity rate of BD and ADHD comorbidity in the single (though large) study from Taiwan, may also be explained by generally lower prevalence rates of mental disorders in Taiwan compared with the US (Compton et al., 1991). Indeed a more recent meta-analysis showed that while prevalence rates of ADHD in China and Hong Kong were 6.5 % and 6.2 % (and therefore comparable to European and American prevalence rates), prevalence in Taiwan was lower (4.2 %) (Liu et al., 2018). Also, given that the number of studies from Western and East Asia is comparatively low, these findings should not be overstated. Nevertheless, since the continent of origin explained such an important part of heterogeneity in the present analysis, this factor deserves further attention, notwithstanding the methodological differences among studies, which we discuss below.

4.2. Cultural and ethnic impact on diagnosis and conceptualization in current diagnostic classification systems

Firstly, an important contributing factor to the increased comorbidity rate of BD in ADHD patients between continents is the potential for cultural difference in diagnosing disorders. The role of culture in diagnostic classification stretches well beyond the ADHD and BD association reported in this review, and is still a topic of debate for revisions of diagnostic manuals (most recently, the DSM-5 and ICD-11, see also (Ecks, 2016; Gureje et al., 2020)). Opposing perspectives of this discussion are best (though crudely) summarized as the universalist and relativistic approaches to diagnosis, which are reviewed elsewhere (Canino and Alegría, 2008; DeMarinis, 2018). Briefly, from a universalist point of view, psychiatric disorders define the same underlying (internal) construct across cultures, albeit with a distinct manifestation of symptoms that reflect cultural influences (Canino and Alegría, 2008). In contrast, from the relativistic perspective, cultural aspects take on a more prominent role in the (biological and psychological) development of psychiatric disorders, to the extent that current primordial diagnostic criteria (e.g., length and number of symptom manifestation) depend on cultural norms for their interpretation. For example, the degree of deviance required for a symptom to be coded as present may vary among cultures.

The relativistic and universalist viewpoints are particularly important in light of current diagnostic manuals: The commonly used diagnostic criteria of the DSM gave little attention to (non-Western) cultural aspects in the first versions of the DSM (Littlewood, 1992). There has been increasing recognition of the importance of cultural norms in the newer versions of the DSM (i.e., the introduction of the Outline for Cultural Formulation (OCF) in the DSM IV-TR and the related cultural formulation interview (CFI) in the DSM-5). Most studies in this meta-analysis used earlier versions of the DSM. In fact, the varying integration and role of cultural norms across the different versions of the DSM and ICD, that form the core of the aforementioned debates, may have contributed to the significant amount of heterogeneity between the here mentioned studies.

An example from the literature to demonstrate the role of cultural norms on diagnosis is a study by Mellsop and colleagues (Mellsop et al., 2007). The authors showed that Maori populations had more manic episodes and manic symptoms compared with New Zealanders of European ancestry (Mellsop et al., 2007) and argued that this may be due to cultural differences in the experience and reporting of hyperactivity and the impression of the Maoris as more “talkative, over-reactive and loud” compared with white, European descendants. Similarly, a review of US studies showed that patients with BD of African ancestry were more often misdiagnosed with a disorder other than BD, compared with patients with BD of non-African ancestry (Akinhanmi et al., 2018).

From a psychological perspective, another hypothesis adds to understanding differences among countries. Novelty Seeking and Risk Taking are personality traits which are more pronounced in ADHD (Jacob et al., 2014, 2007). People with these traits might be more likely to migrate to foreign countries, such that genetic ADHD risk may be enriched in countries with a migratory background and / or after genetic bottlenecks, such as the Americas. This is speculative at present. The here reported differences may be due to true lower/higher prevalence, and/or to under/over-diagnoses possibly because of cultural norms, but evidence for this claim is currently lacking. It is however important to realize that several other factors including language, religion and beliefs, gender roles, as well as tradition, a history of migration including familial- and socio-economic context, and cultural acclimatization (Alarcón, 2009) all have powerful influences to what is conceived as normal and thus likely affect diagnosis and therefore may influence the rate of comorbidity.

In summary, the evidence for cultural influences on comorbidity rates of ADHD and BD alone and when comorbid is not consistent so far. Importantly, a large majority of studies were conducted in Europe and the US. In multi-ethnic countries, symptoms might be presented and rated differently, influenced by the ethnicity of the patient and/or the assessor. Further studies from near, middle and far east countries as well as African countries are needed. Cultural differences between assessors and patients should also be taken into account in future studies. With the publication of DSM-5, it is likely that many of the patients who were diagnosed as BD under DSM-IV would be given the diagnosis of Disruptive Mood Dysregulation Disorder in DSM-5 (DMDD). This may diminish the intercontinental differences we observed.

4.3. The effect of sample size

In our BD sample, larger studies showed smaller effects. This is an indication of publication bias. However, since publication bias is usually introduced by underrepresentation of negative results in the literature, and this logic does not fully apply to comorbidity data (i.e., results do not need to reach statistical significance for reporting rates of

comorbidity), the observed trend may not be entirely due to bias introduced by publication patterns. Another explanation is that patients with comorbid disorders may be more likely to display help-seeking behaviour (i.e., Berkson's bias) (Fine et al., 2018; Galbaud du Fort et al., 1993; Regeer et al., 2009). This would yield higher comorbidity rates in patient-based samples compared with population samples. Indeed, our results indicate that for ADHD prevalence in patients with BD, the small (mostly clinical) samples had much higher prevalence rates than the larger (mostly register-based) studies.

In addition, the diagnostic ascertainment in bigger samples may be less precise than in smaller studies with extensive clinician contact, due to constraints on internal and external validity of the diagnostic procedures (Munk-Jørgensen and Dinesen Østergaard, 2011). For example, some population-based studies considered the use of prescription medication for ADHD as approximating a valid diagnosis. While this presumption does seem reasonable and is commonly accepted practice, register-based studies which use medical registers may underestimate actual comorbidity rates. Some of the reasons contributing to this, are the overrepresentation of samples with help-seeking behaviour or who make use of the health-care system. The error rate for diagnoses when using prescription medication as proxy for diagnosis may be further increased since stimulants can also be prescribed for patients with narcolepsy or other conditions. In summary, register-based studies may underestimate comorbidity rates and to overcome this methodological issue, epidemiological, representative population samples are needed.

4.4. Effect of sex and age

In the present review, we found no pronounced effects for age and sex on prevalence rates, neither for the primary ADHD population, nor the primary adult BD population. This is surprising, given that one could suspect higher rates of lifetime comorbidity in older populations. Because 2 of 3 cases who had childhood ADHD show persistent symptoms of ADHD in adulthood (Asherson, 2012) and BD prevalence increases steadily up to the late 20′s and then decreases (Ferrari et al., 2016), so one may expect a difference for lifetime compared with 12 month comorbidity rates. A possible explanation is that for lifetime diagnosis, patients who might have had a childhood diagnosis of ADHD but were no longer symptomatic when diagnosed with BD, may have not been diagnosed as comorbid in studies. Nevertheless, comorbidity rates in studies of participants with BD who assessed the childhood diagnosis of ADHD were not strikingly different than studies assessing lifetime comorbidity without specific emphasis on cADHD. It is also interesting that there was no difference in sex for comorbidity rates, which may well reflect the fact that BD has a roughly equal sex distribution and so does adult ADHD (in contrast to childhood ADHD, which is more commonly diagnosed in boys).

4.5. Methodological factors

Next to culture and ethnic factors, it should be noted that methodological differences likely contribute to the observed heterogeneity among studies. Some of these factors include but are not limited to the ascertainment of ADHD diagnoses (including different information sources), the version of the diagnostic system used, and the heterogeneous reporting of results. As such, the level of diagnostic ascertainment played a crucial role in prevalence rates: we observed increased prevalence rates when (semi-)structured interviews were used, and decreased prevalence rates in studies which used register studies. Furthermore, third-party validation significantly decreased prevalence rates for ADHD. This points out the need for careful and multi-level diagnostic assessment. It is also likely that comorbidity rates differ between diagnostic systems used (i.e., DSM vs ICD), but also within a different diagnostic system, depending on the version used. For instance, it has been reported that rates of attention deficit disorder are broader and thus much higher when using the *Diagnostic Statistical Manual*, fourth edition (DSM-IV) of the American Psychiatric Association classificatory system as compared with the *International Statistical Classification of Diseases and Related Health Problems*, 10th edition (ICD-10) (Döpfner et al., 2008; Polanczyk et al., 2007; Tripp et al., 1999). We also observed this trend in our samples: Generally speaking, the comorbidity rate of ADHD and BD in samples diagnosed with ICD-criteria was lower than in studies using the DSM. In addition, the version of the DSM used may lead to between study variability. Recent studies have shown that the DSM-5 version may differ from prior versions when it comes to the diagnosis of ADHD (van de Glind et al., 2014) and current BD (Machado-Vieira et al., 2017), though lifetime diagnosis may not be as affected (Gordon-Smith et al., 2017). In the present analysis, only 3 studies used the DSM-5, showing comorbidity rates of 0 % (Anastopoulos et al., 2018), 2 % (Brunkhorst-Kanaan et al., 2020) and 10 % (Pehlivanidis et al., 2020) respectively. Yet, since most studies in the present analysis have used older versions of the DSM i.e., III and IV or IV-TR), a statistical comparison between DSM-III or DSM-IV and DSM-5 was not possible. Previous studies have shown that DSM-III and DMS-IV versions do correlate well: for instance, 93 % of patients received an ADHD diagnosis with both instruments (Biederman et al., 1997). Nevertheless, the different methodology between studies is quite striking and becomes evident when considering the quality ratings, with most studies showing low to moderate quality, and the important contribution of diagnostic accuracy.

Therefore, it is likely that although not easy to quantify, study methodology played a considerable role for the encountered heterogeneity.

Interestingly, one outlier study was identified in the present analysis, showing unusually high comorbidity rates. A possible explanation for this high estimate is that the study by Westmoreland et al. (2010), as only study in our meta-analysis, reports on prison inmates (Westmoreland et al., 2010). A previous meta-analysis showed a five to tenfold increase of ADHD prevalence in prison populations (Young et al., 2015b), and BD may also be significantly higher (Falissard et al., 2006). Special attention is therefore warranted in prison populations and further research on the comorbidity in these samples is needed.

To summarize, the cultural, methodological, diagnostic and demographic factors mentioned above are all important contributors that may contribute to the found heterogeneity. However, these factors alone do not explain the reasons for the high rates of comorbidity that we found. In the following we will explore some of the reasons that may lead to the significant association between BD and ADHD.

4.6. Reasons for comorbidity: genetic effects

Possible reasons for comorbidity include shared genetic effects, given the high occurrence of BD and ADHD in family-based studies: In a 2012 meta-analysis, relatives of probands with BD had a significantly higher chance of having ADHD and among relatives of ADHD probands, BD-I occurred more frequently (Faraone et al., 2012); the relative risk was doubled each way. Our update confirms this previous meta-analysis: most studies reported much higher comorbidity rates of ADHD or BD in first degree relatives of probands with BD or ADHD respectively, compared with relatives of controls. Recent GWASs provide further evidence for shared heritability, that is however considerably lower than the estimates resulting from family studies. The genome-wide genetic correlation largely varies between different generations of GWAS, yielding genetic correlation estimates (r_g) between 0.05 (Lee et al., 2013) and 0.71 {van Hulzen, 2017 #180}. However, the most recent study with the largest data sample provides only a small significant genetic correlation ($r_g = 0.14$, $p < 0.001$) (Consortium et al., 2019). This small genetic correlation suggests that rare variants, main effects of environmental risk factors or gene by environment interactions must explain the extent of cross-transmission of ADHD and BD seen in family studies. The GWAS mentioned above performed a cross-disorder meta-analysis of eight psychiatric disorders including BD and ADHD and

identified eight pleiotropic loci with shared risk (Consortium et al., 2019). Interestingly, among the most significant pleiotropic loci showing association with both ADHD and BD were *RBFOX1* (RNA--binding Fox-1 Homolog 1), *DCC* and *RIMS1*, all genes that are involved in neuronal development and corticogenesis (Manitt et al., 2013) or synaptic functioning (Hamada et al., 2015). This is of interest, as delayed cortical and subcortical maturation may have a role in the pathophysiology of both disorders (Najt et al., 2016; Shaw et al., 2012); however, neuroimaging data indicates that volumetric deficits and cortical thinning are negatively correlated between ADHD and BD (Radonjić et al., 2021).

Analysing the same dataset focused on shared heritability just between ADHD and BPD, O'Connel et al. (2019) (O'Connell et al., 2019) identified five other loci jointly associated with both disorders with concordant effect directions. Two of these loci were novel for both disorders, the others were previously known to be associated with either ADHD or BPD. Moreover, in a previous and smaller iteration of the PGC data, Van Hulzen et al. (2017) (van Hulzen et al., 2017) reported two independent loci on chromosome six and ten with same direction of effect for ADHD and BD. Interestingly, a different gene (*ADCY2* on chromosome 5) was identified if the BD sample was restricted to early onset participants (<21 years) possibly indicating a different aetiology of early- and late onset BD.

In conclusion, a growing body of evidence hints towards a genetic overlap between both conditions that may impact processes involved in brain maturation and neuronal signalling (Delghandi et al., 2005; Hamada et al., 2015; Manitt et al., 2013). However, findings are still inconsistent, because no lead SNP was shared between studies. Hence, future studies with much larger samples will be needed to reveal shared genetic risk factors.

4.7. Joint non-genetic risk factors for ADHD and BD

Beyond the genetic contribution, environmental risk factors might have a role in the aetiology of the comorbid disorder. Respective pre- and perinatal risk factors include, among others, premature birth, low birth weight (Tole et al., 2019), maternal substance abuse (Eilertsen et al., 2017), maternal stress during pregnancy (Marangoni et al., 2016; Sciberras et al., 2017) and childhood maltreatment (Capusan et al., 2016; Stern et al., 2018; Teicher and Samson, 2013). While these risk factors have been shown to contribute to the development of ADHD as well as BD, these associations are still insufficiently explored to draw firm conclusions for comorbidity. Also, at least some of these risk factors might not be entirely environmental in nature but reflect a joint underlying genetic factor; methods such as Mendelian randomization are needed to study causal rather than correlational relationships.

For instance, a recent study showed a significant association for BD diagnosis and maternal substance abuse (Marangoni et al., 2016), and likewise, maternal substance abuse has previously been identified as a risk factor for ADHD (Sciberras et al., 2017). However, in a recent longitudinal study maternal substance abuse was associated with ADHD symptoms, but not with a clinical diagnosis (Eilertsen et al., 2017). Another risk factor for several psychopathological disorders, is maternal stress exposure. A recent review found that maternal stress exposure during the first trimester significantly increased risk for BD (Marangoni et al., 2016). Similarly, maternal stress has been identified as risk factor for ADHD (Manzari et al., 2019). But, because mothers suffering from ADHD also experience more maternal stress (Perez Algorta et al., 2018), this finding might be partially due to genetic variants. Another noteworthy risk factor are early traumatic life events (Bortolato et al., 2017). In their large-scale study, Brown and colleagues found that children with ADHD were more likely to have experienced childhood trauma (Brown et al., 2017). For BD, childhood adversity has also been identified as risk factor (Palmier-Claus et al., 2018) and may lead to worse clinical outcomes (Agnew-Blais and Danese, 2016). All these risk factors are not specific (which is true of some genetic risk variants as well (Smoller et al., 2019).

4.8. ADHD and BD comorbidity: a diagnostic artefact?

There might be a much simpler explanation for the observed ADHD/BD overlap. Because diagnostic manuals list partially overlapping symptoms for BD and ADHD, their comorbidity might be a diagnostic artefact rather than a true finding. Indeed, Youngstrom et al. (2010) have discussed this possibility, considering some of the concepts that may contribute to 'artificial' or false, and 'true' comorbidity (Youngstrom et al., 2010): In brief, the authors discuss several reasons for possibly 'false 'comorbidity (including the use of categorical labels instead of dimensional approaches for diagnosis, over-splitting of symptoms leading to inflated comorbidity rates, and the overlap between diagnostic criteria such as irritable mood, poor concentration and impulsivity). The latter possibility was investigated by Milberger et al. (1995) (Milberger et al., 1995) in one of the included studies in this meta-analysis. The authors showed that, when overlapping symptoms were removed from the diagnostic criteria, the association between ADHD and bipolar disorder remained significant. Fifty-six percent of those diagnosed with the comorbid condition maintained their diagnosis of BD after the symptoms were subtracted. They thus concluded that most cases of comorbidity could not be accounted for by diagnostic overlap.

One of the possible contributors to falsely inflated comorbidity rates noted by Youngstrom et al. (2010) (Youngstrom et al., 2010) is developmental sequencing (i.e., that one disorder is a developmental stage that precedes development of the other disorder). Some have thus suggested that ADHD may be a precursor for BD (Tillman and Geller, 2006). The clinical rationale is simple: ADHD can start before the age of 7, while BD usually manifests in the early twenties and several symptoms are shared between both disorders. Two questions arise when investigating this potential association: 1) Do children with ADHD and/or a higher ADHD Polygenic Risk Score (PRS) develop BD more often, and 2) does the offspring of parents suffering from BD show a diagnosis of ADHD more often?

A possible answer to the first question is given by the Avon Longitudinal Study of Parents and Children (ALSPAC), a large birth cohort in the UK that characterized the course of developmental trajectories in children with ADHD between age 4 and 17 (Kim et al., 2015). In their analysis, the authors identified a persistent group of patients (i.e., 40 % of patients with high ADHD symptoms during childhood). This persistent class was predominantly male, had lower IQ, demonstrated higher conduct problems, and problems of social behaviour. While this group had the highest ADHD genetic liability, as reflected by ADHD PRS, it did not have higher BD PRS as compared with the other latent classes. In contrast, the childhood-limited latent class numerically had the highest BD PRS although this was far from significant (Riglin et al., 2016). This suggests that ADHD is not a simple bipolar prodrome: It can lead to a different and distinct clinical course.

The second question was approached by cross-sectional high-risk studies which reported an increased lifetime risk of a wide range of psychiatric disorders in (adult) offspring of BD affected parents. The longitudinal and transgenerational Canadian High-Risk Offspring cohort (Duffy, 2012; Duffy et al., 2007, 2018) showed that affected offspring from parents suffering from BD falls into two categories. One displays a relatively homogenous trajectory from mood disorders to lithium-sensitive BD, the other class begins early in life, includes cADHD and has a much more variable outcome from depression to non-lithium responsive BD, and even psychosis(Lieberman et al., 2019). This may indicate that the observed ADHD-BD trajectory and hence comorbidity is a separate disease group, and distinct from lithium-sensitive BD. This finding however has yet to be replicated. Similarly, the Pittsburgh Bipolar Offspring Study (BIOS) studied the offspring of patients suffering from BD (Kim et al., 2015). One-hundred and twenty-two children with ADHD whose parents had BD and 48 offspring with ADHD of control

parents were included. While children with ADHD of parents with BD had more psychopathology than ADHD offspring of the control parents, there was no significant difference between the ADHD *trajectories* between the groups. However, phenotyping differed from the Canadian study. Together with the results obtained from family-based studies, reviewed above and elsewhere (Faraone et al., 2012), there are strong arguments that offspring of BD-affected parents may first manifest as ADHD which later on is complicated by comorbid BD. Whether this is a subgroup of BD, with a potentially differing clinical phenotype (e.g., less lithium sensitivity, higher rate of BD II cases, more rapid cycling, more chronic mood fluctuations and less "pure" mania) is an open question, although clinical experience points towards such a subgroup. The fact that we here found earlier age of onset for BD in patients with comorbid ADHD does seem to support this notion

4.9. Clinical implications of comorbidity

Regardless of above-mentioned diagnostic debates, clinicians should be aware that almost 8% of their patients diagnosed with ADHD could be at risk for BD. Because a wide range of emotional symptoms co-occur with ADHD (Faraone et al., 2019), the diagnoses of BD in adulthood or Disruptive Mood Dysregulation Disorder (DMDD) in childhood (which has been reported to affect as much as 21.8 % of children with ADHD) can be mistaken as being severe ADHD. That diagnostic error is serious as it may inadvertently deny patients treatment options for BD and DMDD (Krieger and Stringaris, 2013).

The assessment of comorbidity between ADHD and BD is challenging due to the clinical similarity of some symptoms. To identify comorbid patients, a routine examination of ADHD and BD symptoms is required. In addition, clinical red flags such as BD treatment resistance, history of school problems or early onset of disease may index comorbidity. It is necessary to consider not only the presence of the symptom as such, but its course over time, as ADHD symptoms have a chronic and persistent course whereas BD is episodic. However, the distinction can be difficult during childhood where the mood disturbance is typically irritable, and episodes of extreme irritability are superimposed on chronic irritability or moodiness. After a comorbid ADHD/BD diagnosis has been established, both diseases call for evidence-based treatment according to pertinent guidelines. Psychoeducation about the conditions is of high importance; targeted psychotherapy is warranted that should also aim at self-empowerment and coping with symptoms; and finally, mood stabilizers are essential in the treatment of BD, while pharmacologic treatment for ADHD is typically warranted. Recent evidence from a large-scale, register-based study shows that while methylphenidate treatment alone can lead to a considerably increased risk for treatment-emergent mania, this risk is lower when co-administrated with mood stabilizers: in their study, considering 3 months of follow-up after treatment with methylphenidate, Viktorin et al. (2017) found a higher risk ratio for manic episodes in patients treated with methylphenidate alone, but a reduced risk ratio for manic episodes when methylphenidate was combined with a mood-stabilizer (Viktorin et al., 2017). In line with this, a small, randomized clinical trial has shown that combined mood stabilizing and amphetamine treatment for paediatric bipolar disorder with ADHD did not lead to worsening of manic symptoms effectively (Scheffer et al., 2005). We are not aware of any other large-scale studies that accounted for a confound-by-indication effect, which is in our opinion the only design that allows meaningful clinical conclusions. First evidence thus seems to suggest no general disadvantage of combining mood stabilizing medication with methylphenidate for the treatment of ADHD with comorbid BD, but further large-scale, well-controlled, randomized clinical trials assessing the efficacy of stimulant medication on top of mood stabilizers in adult patients with BD and ADHD are needed.

4.10. Limitations

Like all meta-analyses, we inherit the limitations of the constituent studies. It should be noted that previous meta-analyses have found a significant difference of ADHD by geographical location, but that these effects were no longer significant when other methodological factors were introduced (Polanczyk et al., 2014), suggesting that the effect of geographical location is negligible. In addition, while the random effects meta-analyses used in the present meta-analyses were arguably the best choice for our heterogeneous sample, it also attributes a smaller weight to larger studies, and may therefore have over-estimated comorbidity rates of ADHD in the BD sample. It is likely that other models such as generalized linear mixed models, which do not assign such weights, would reach lower estimates. It should also be noted that we here focused on studies derived from patient registers and for a large part, clinical samples. Therefore, the here reported heterogeneity for comorbidity rates likely does not reflect prevalence in the general population. They do, however, give an indication of what could be expected in clinical samples, if diagnostic interviews are systematically used. Especially in ADHD, administrative data based on insurance claims or superficial population sampling are notorious for under-estimating the prevalence of ADHD (Libutzki et al., 2019). Furthermore, the article selection was restricted to the five languages that the authors were able to understand, such that other relevant articles may have been missed. Lastly, data were insufficient to reliably estimate the effect of different versions within a diagnostic system (i.e., between DSM-IV and DSM-5), which may have reduced heterogeneity and should be investigated in future reports.

5. Conclusion

Our review found that the co-occurrence of ADHD and BD is much higher than expected by chance. We found important variations depending on geographic location (and/or cultural norms), the diagnostic system used (ICD vs DSM) and sample size and an earlier age of onset for BD with comorbid ADHD. Our study highlights that clinicians should be aware of this diagnostic co-occurrence, which can have important implications for diagnostic specification and potentially treatment.

CRediT authorship contribution statement

Carmen Schiweck: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Gara Arteaga-Henriquez:** Conceptualization, Methodology, Validation, Investigation, Writing - original draft. **Mareike Aichholzer:** Conceptualization, Methodology, Validation, Investigation, Writing - original draft. **Sharmili Edwin Thanarajah:** Conceptualization, Methodology, Validation, Investigation, Writing - original draft. **Sebastian Vargas-Cáceres:** Methodology, Validation, Writing - original draft. **Silke Matura:** Conceptualization, Writing - original draft. **Oliver Grimm:** Methodology, Writing - original draft. **Jan Haavik:** Conceptualization, Writing - original draft, Writing - review & editing. **Sarah Kittel-Schneider:** Conceptualization, Writing - original draft. **Josep Antoni Ramos-Quiroga:** Conceptualization, Writing - original draft. **Stephen V. Faraone:** Conceptualization, Resources, Writing - original draft, Writing - review & editing, Supervision. **Andreas Reif:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

Carmen Schiweck, Gara Arteaga-Henríquez, Mareike Aichholzer, Sharmili Edwin-Thanarajah, Sebastián Vargas-Cáceres and Silke Matura have no conflict of interest to declare. Oliver Grimm has received

honoraria as speaker from Medice Arzneimittel Pütter & Co KG GmbH. Sarah Kittel-Schneider received speaker's honoraria from Shire/Takeda and Medice Arzneimittel Pütter GmbH&Co KG.Josep Antoni Ramos-Quiroga reports grants and personal fees from Takeda, grants and personal fees from Janssen, grants and personal fees from Roche, personal fees from Lilly, personal fees from Novartis, personal fees from Bial, personal fees from Shionogui, grants and personal fees from Lundbeck, grants and personal fees from Almirall, grants and personal fees from Braingaze, grants and personal fees from Sincrolab, personal fees from Medice, grants and personal fees from Rubio, and grants from Psious outside the submitted work. Jan Haavik has served as a speaker for Medice, HB Pharma, Biocodex, Takeda and Shire. In the past year, Stephen V. Faraone received income, potential income, travel expenses continuing education support and/or research support from Takeda, OnDosis, Tris, Otsuka, Arbor, Ironshore, Rhodes, Akili Interactive Labs, Sunovion, Supernus 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.adhdinadults.com. Andreas Reif received speaker's honoraria, and / or served on advisory boards, from Shire/Takeda, Medice, Janssen, Servier, and SAGE.

Acknowledgements

This work was supported by the European Union's Horizon 2020 research and innovation programme under COCA grant agreement number 667302, EudaMed BipoLIfe A3: CIV-15-07-013687, Eat2beNice Grant Agreement 728018 and PRIME Grant Agreement 847879.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.01.017.

References

Aedo, A., Murru, A., Sanchez, R., et al., 2018. Clinical characterization of rapid cycling bipolar disorder: association with attention deficit hyperactivity disorder. J. Affect. Disord. 240, 187–192. https://doi.org/10.1016/j.jad.2018.07.051.

Agnew-Blais, J., Danese, A., 2016. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry 3, 342–349. https://doi.org/10.1016/S2215-0366(15)00544-1.

Agosti, V., Chen, Y., Levin, F.R., 2011. Does Attention Deficit Hyperactivity Disorder increase the risk of suicide attempts? J. Affect. Disord. 133, 595–599. https://doi.org/10.1016/j.jad.2011.05.008.

Akinhanmi, M.O., Biernacka, J.M., Strakowski, et al., 2018. Racial disparities in bipolar disorder treatment and research: a call to action. Bipolar. Disord. 20, 506–514. https://doi.org/10.1111/bdi.12638.

Alarcón, R.D., 2009. Culture, cultural factors and psychiatric diagnosis: review and projections. World Psychiatry 8, 131–139. https://doi.org/10.1002/j.2051-5545.2009.tb00233.x.

Anastopoulos, A.D., DuPaul, G.J., Weyandt, L.L., et al., 2018. Rates and patterns of comorbidity among first-year college students with ADHD. J. Clin. Child. Adolesc. Psychol. 47, 236–247. https://doi.org/10.1080/15374416.2015.1105137.

Andersen, S.M., Randers, A., Jensen, C.M., et al., 2013. Preceding diagnoses to young adult bipolar disorder and schizophrenia in a nationwide study. BMC Psychiatry 13, 343. https://doi.org/10.1186/1471-244x-13-343.

Angst, J., Gamma, A., Bowden, C.L., Azorin, et al., 2013. Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. Eur. Arch. Psychiatry Clin. Neurosci. 263, 663–673. https://doi.org/10.1007/s00406-013-0393-4.

Arman, S., Salimi, H., Maracy, M.R., 2018. Parenting styles and psychiatric disorders in children of bipolar parents. Adv. Biomed. Res. 7, 147. https://doi.org/10.4103/abr.abr_131_18.

Arnold, L.E., Van Meter, A.R., Fristad, M.A., et al., 2020. Development of bipolar disorder and other comorbidity among youth with attention-deficit/hyperactivity disorder. J. Child. Psychol. Psychiatry 61, 175–181. https://doi.org/10.1111/jcpp.13122.

Asherson, P., 2012. ADHD across the lifespan. Medicine 40, 623–627. https://doi.org/10.1016/j.mpmed.2012.08.007.

Asherson, P., Buitelaar, J., Faraone, S.V., et al., 2016. Adult attention-deficit hyperactivity disorder: key conceptual issues. Lancet Psychiatry 3, 568–578. https://doi.org/10.1016/s2215-0366(16)30032-3.

Axelson, D., Goldstein, B., Goldstein, T., et al., 2015. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. Am. J. Psychiatry 172, 638–646. https://doi.org/10.1176/appi.ajp.2014.14010035.

Bennett, F., Hodgetts, S., Close, A., et al., 2019. Predictors of psychosocial outcome of bipolar disorder: data from the Stanley Foundation Bipolar Network. Int. J. Bipolar Disord. 7, 28. https://doi.org/10.1186/s40345-019-0169-5.

Berkol, T.D., Yargic, I., Ozyildirim, I., et al., 2014. Comorbidity of adult attention deficit and hyperactivity disorder in bipolar patients: prevalence, sociodemographic and clinical correlates. Noro. Psikiyatr. Ars. 51, 97–102. https://doi.org/10.4274/npa.y6376.

Bernardi, S., Cortese, S., Solanto, M., et al., 2010. Bipolar disorder and comorbid attention deficit hyperactivity disorder. A distinct clinical phenotype? Clinical characteristics and temperamental traits. World J. Biol. Psychiatry 11, 656–666. https://doi.org/10.3109/15622971003653238.

Biederman, J., Faraone, S.V., Weber, W., et al., 1997. Correspondence between DSM-III-R and DSM-IV attention-deficit/hyperactivity disorder. J. Am. Acad. Child. Adolesc. Psychiatry 36, 1682–1687. https://doi.org/10.1097/00004583-199712000-00016.

Biederman, J., Mick, E., Wozniak, J., et al., 2003. Can a subtype of conduct disorder linked to bipolar disorder be identified? Integration of findings from the Massachusetts General Hospital Pediatric Psychopharmacology Research Program. Biol. Psychiatry 53, 952–960. https://doi.org/10.1016/s0006-3223(03)00009-x.

Biederman, J., Monuteaux, M.C., Mick, E., et al., 2006. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychol. Med. 36, 167–179. https://doi.org/10.1017/s0033291705006410.

Biederman, J., Petty, C.R., Monuteaux, M.C., et al., 2010. Adult psychiatric outcomes of girls with attention deficit hyperactivity disorder: 11-year follow-up in a longitudinal case-control study. Am. J. Psychiatry 167, 409–417. https://doi.org/10.1176/appi.ajp.2009.09050736.

Biederman, J., Martelon, M., Faraone, S.V., et al., 2013. Personal and familial correlates of bipolar (BP)-I disorder in children with a diagnosis of BP-I disorder with a positive child behavior checklist (CBCL)-severe dysregulation profile: a controlled study. J. Affect. Disord. 147, 164–170. https://doi.org/10.1016/j.jad.2012.10.028.

Bortolato, B., Köhler, C.A., Evangelou, E., et al., 2017. Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. Bipolar Disord. 19, 84–96. https://doi.org/10.1111/bdi.12490.

Breda, V., Rovaris, D.L., Vitola, E.S., et al., 2016. Does collateral retrospective information about childhood attention-deficit/hyperactivity disorder symptoms assist in the diagnosis of attention-deficit/hyperactivity disorder in adults? Findings from a large clinical sample. Aust. N. Z. J. Psychiatry 50, 557–565. https://doi.org/10.1177/0004867415609421.

Brown, N.M., Brown, S.N., Briggs, R.D., et al., 2017. Associations between adverse childhood experiences and ADHD diagnosis and severity. Acad. Pediatr. 17, 349–355. https://doi.org/10.1016/j.acap.2016.08.013.

Brunkhorst-Kanaan, N., Verdenhalven, M., Kittel-Schneider, S., et al., 2020. The quantified behavioral test-A confirmatory test in the diagnostic process of adult ADHD? Front. Psychiatry 11, 216. https://doi.org/10.3389/fpsyt.2020.00216.

Canino, G., Alegría, M., 2008. Psychiatric diagnosis–is it universal or relative to culture? J. Child. Psychol. Psychiatry 49, 237–250, 10.111/j.1469-7610.2007.1854.x.

Capusan, A.J., Kuja-Halkola, R., Bendtsen, P., et al., 2016. Childhood maltreatment and attention deficit hyperactivity disorder symptoms in adults: a large twin study. Psychol. Med. 46, 2637–2646. https://doi.org/10.1017/s0033291716001021.

Carlson, G.A., 2018. Commentary: bipolar disorder in youth – what is it and where is it? – a commentary on Parry et al. (2018). Child. Adolesc. Ment. Health 23, 23–25. https://doi.org/10.1111/camh.12243.

Chang, Z., Lichtenstein, P., Asherson, P.J., et al., 2013. Developmental twin study of attention problems: high heritabilities throughout development. JAMA Psychiatry 70, 311–318. https://doi.org/10.1001/jamapsychiatry.2013.287.

Chen, M.H., Wei, H.T., Chen, L.C., et al., 2015. Autistic spectrum disorder, attention deficit hyperactivity disorder, and psychiatric comorbidities: a nationwide study. Res. Autism Spectrum Disord. 10, 1–6. https://doi.org/10.1016/j.rasd.2014.10.014.

Chen, Q., Hartman, C.A., Haavik, J., et al., 2018. Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: a population-based cross-sectional study. PLoS One 13. https://doi.org/10.1371/journal.pone.0204516 e0204516.

Chen, M.-H., Pan, T.-L., Huang, K.-L., et al., 2019a. Coaggregation of major psychiatric disorders in first-degree relatives of individuals with attention-deficit/hyperactivity disorder: a nationwide population-based study. J. Clin. Psychiatry 80, 18m12371. https://doi.org/10.4088/JCP.18m12371.

Chen, M.H., Hsu, J.W., Huang, K.L., et al., 2019b. Risk and coaggregation of major psychiatric disorders among first-degree relatives of patients with bipolar disorder: a nationwide population-based study. Psychol. Med. 49, 2397–2404. https://doi.org/10.1017/s003329171800332x.

Compton, W.M., Helzer, J.E., Hwu, H.-g., et al., 1991. New methods in cross-cultural psychiatry: psychiatric illness in Taiwan and the United States. Am. J. Psychiatry 148, 1697–1704. https://doi.org/10.1176/ajp.148.12.1697.

Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell 179, 1469–1482. https://doi.org/10.1016/j.cell.2019.11.020.

Delghandi, M.P., Johannessen, M., Moens, U., 2005. The cAMP signalling pathway activates CREB through PKA, p38 and MSK1 in NIH 3T3 cells. Cell Signal. 17, 1343–1351. https://doi.org/10.1016/j.cellsig.2005.02.003.

DeMarinis, V., 2018. Mental health diagnosis: Is It relative or universal in relation to culture? In: Steinmark, M., Fuller, S., Zackariasson, U. (Eds.), Relativism and Post-Truth in Contemporary Society, pp. 101–121.
Demontis, D., Walters, R.K., Martin, J., et al., 2019. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat. Genet. 51, 63–75. https://doi.org/10.1038/s41588-018-0269-7.
Di Nicola, M., Sala, L., Romo, L., et al., 2014. Adult attention-deficit/hyperactivity disorder in major depressed and bipolar subjects: role of personality traits and clinical implications. Eur. Arch. Psychiatry Clin. Neurosci. 264, 391–400. https://doi.org/10.1007/s00406-013-0456-6.
Dickstein, D.P., Leibenluft, E., 2012. Beyond dogma: from diagnostic controversies to data about pediatric bipolar disorder and children with chronic irritability and mood dysregulation. Isr. J. Psychiatry Relat. Sci. 49, 52–61.
Döpfner, M., Breuer, D., Wille, N., et al., 2008. How often do children meet ICD-10/DSM-IV criteria of attention deficit-/hyperactivity disorder and hyperkinetic disorder? Parent-based prevalence rates in a national sample – results of the BELLA study. Eur. Child. Adolesc. Psychiatry 17, 59–70. https://doi.org/10.1007/s00787-008-1007-y.
Doyle, A.E., Faraone, S.V., 2002. Familial links between attention deficit hyperactivity disorder, conduct disorder, and bipolar disorder. Curr. Psychiatry. Rep. 4, 146–152. https://doi.org/10.1007/s11920-002-0049-y.
Duffy, A., 2012. The nature of the association between childhood ADHD and the development of bipolar disorder: a review of prospective high-risk studies. Am. J. Psychiatry 169, 1247–1255. https://doi.org/10.1176/appi.ajp.2012.11111725.
Duffy, A., Alda, M., Crawford, L., et al., 2007. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. Bipolar Disord. 9, 828–838. https://doi.org/10.1111/j.1399-5618.2007.00421.x.
Duffy, A., Horrocks, J., Doucette, S., et al., 2014. The developmental trajectory of bipolar disorder. Br. J. Psychiatry 204, 122–128. https://doi.org/10.1192/bjp.bp.113.126706.
Duffy, A., Goodday, S., Keown-Stoneman, C., et al., 2018. The emergent course of bipolar disorder: observations over two decades from the Canadian high-risk offspring cohort. Am. J. Psychiatry 176, 720–729. https://doi.org/10.1176/appi.ajp.2018.18040461.
Ecks, S., 2016. The strange absence of things in the “culture” of the DSM-V. CMAJ 188, 142–143. https://doi.org/10.1503/cmaj.150268.
Eilertsen, E.M., Gjerde, L.C., Reichborn-Kjennerud, T., et al., 2017. Maternal alcohol use during pregnancy and offspring attention-deficit hyperactivity disorder (ADHD): a prospective sibling control study. Int. J. Epidemiol. 46, 1633–1640. https://doi.org/10.1093/ije/dyx067.
Ercan, E.S., Bilac, O., Uysal Ozaslan, T., et al., 2015. Is the prevalence of ADHD in Turkish elementary school children really high? Soc. Psychiatry Psychiatr. Epidemiol. 50, 1145–1152. https://doi.org/10.1007/s00127-015-1071-9.
Ercan, E.S., Polanczyk, G., Akyol Ardıc, U., et al., 2019. The prevalence of childhood psychopathology in Turkey: a cross-sectional multicenter nationwide study (EPICPAT-T). Nord. J. Psychiatry 73, 132–140. https://doi.org/10.1080/08039488.2019.1574892.
Falissard, B., Loze, J.-Y., Gasquet, I., et al., 2006. Prevalence of mental disorders in French prisons for men. BMC Psychiatry 6, 33. https://doi.org/10.1186/1471-244X-6-33.
Faraone, S.V., Biederman, J., Mick, E., 2006a. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol. Med. 36, 159. https://doi.org/10.1017/S003329170500471X.
Faraone, S.V., Biederman, J., Spencer, T., et al., 2006b. Diagnosing adult attention deficit hyperactivity disorder: are late onset and subthreshold diagnoses valid? Am. J. Psychiatry 163, 1720–1729. https://doi.org/10.1176/ajp.2006.163.10.1720.
Faraone, S.V., Biederman, J., Wozniak, J., 2012. Examining the comorbidity between attention deficit hyperactivity disorder and bipolar I disorder: a meta-analysis of family genetic studies. Am. J. Psychiatry 169, 1256–1266. https://doi.org/10.1176/appi.ajp.2012.12010087.
Faraone, S.V., Rostain, A.L., Blader, J., et al., 2019. Practitioner review: emotional dysregulation in attention-deficit/hyperactivity disorder - implications for clinical recognition and intervention. J. Child. Psychol. Psychiatry 60, 133–150. https://doi.org/10.1111/jcpp.12899.
Fayyad, J., Sampson, N.A., Hwang, I., Adamowski, et al., 2017. The descriptive epidemiology of DSM-IV adult ADHD in the world health organization world mental health surveys. Atten. Defic. Hyperact. Disord. 9, 47–65. https://doi.org/10.1007/s12402-016-0208-3.
Ferrari, A.J., Stockings, E., Khoo, J.-P., et al., 2016. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. Bipolar Disord. 18, 440–450. https://doi.org/10.1111/bdi.12423.
Fine, A., Nasiri, K., Fotinos, K., et al., 2018. Examining predictors of help-seeking behaviours in patients with mood and anxiety symptoms. Psychiatry Res. 265, 190–197. https://doi.org/10.1016/j.psychres.2018.04.040.
Franke, B., Michelini, G., Asherson, P., et al., 2018. Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. Eur. Neuropsychopharmacol. 28, 1059–1088. https://doi.org/10.1016/j.euroneuro.2018.08.001.
Galbaud du Fort, G., Newman, S.C., Bland, R.C., 1993. Psychiatric comorbidity and treatment seeking. Sources of selection bias in the study of clinical populations. J. Nerv. Ment. Dis. 181, 467–474.
Garcia, C.R., Bau, C.H.D., Silva, K.L., et al., 2012. The burdened life of adults with ADHD: impairment beyond comorbidity. Eur. Psychiatry 27, 309–313. https://doi.org/10.1016/j.eurpsy.2010.08.002.
Ghaffary, A., Bidaki, R., Hosseinpoor, S., 2013. Determining the prevalence of attention deficit hyperactivity disorder in patients with bipolar disorder type I within their remission phase. Galen. Med. J. 2, 174–178.
Goldstein, B.I., Post, R.M., Birmaher, B., 2019. Debate: fomenting controversy regarding pediatric bipolar disorder. Child Adolesc. Ment. Health 24, 95–96. https://doi.org/10.1111/camh.12318.
Gordon-Smith, K., Jones, L.A., Forty, L., et al., 2017. Changes to the diagnostic criteria for bipolar disorder in DSM-5 make little difference to lifetime diagnosis: findings from the UK Bipolar Disorder Research Network (BDRN) study. Am. J. Psychiatry 174. https://doi.org/10.1176/appi.ajp.2017.17010109, 803-803.
Gorlin, E.I., Dalrymple, K., Chelminski, I., et al., 2016. Diagnostic profiles of adult psychiatric outpatients with and without attention deficit hyperactivity disorder. Compr. Psychiatry 70, 90–97. https://doi.org/10.1016/j.comppsych.2016.06.015.
Gureje, O., Lewis-Fernandez, R., Hall, B.J., et al., 2020. Cultural considerations in the classification of mental disorders: why and how in ICD-11. BMC Med. 18, 25. https://doi.org/10.1186/s12916-020-1493-4.
Halmoy, A., Halleland, H., Dramsdahl, M., et al., 2010. Bipolar symptoms in adult attention-deficit/hyperactivity disorder: a cross-sectional study of 510 clinically diagnosed patients and 417 population-based controls. J. Clin. Psychiatry 71, 48–57. https://doi.org/10.4088/JCP.08m04722ora.
Halperin, J.M., Rucklidge, J.J., Powers, R.L., et al., 2011. Childhood CBCL bipolar profile and adolescent/young adult personality disorders: a 9-year follow-up. J. Affect. Disord. 130, 155–161. https://doi.org/10.1016/j.jad.2010.10.019.
Hamada, N., Ito, H., Iwamoto, I., et al., 2015. Role of the cytoplasmic isoform of RBFOX1/A2BP1 in establishing the architecture of the developing cerebral cortex. Mol. Autism 6, 56. https://doi.org/10.1186/s13229-015-0049-5.
Harmanci, H., Cam Celikel, F., Etikan, I., 2016. Comorbidity of adult attention deficit and hyperactivity disorder in bipolar and unipolar patients. Noro. Psikiyatr. Ars 53, 257–262. https://doi.org/10.5152/npa.2015.11328.
Harpold, T., Biederman, J., Gignac, M., et al., 2007. Is oppositional defiant disorder a meaningful diagnosis in adults? Results from a large sample of adults with ADHD. J. Nerv. Ment. Dis. 195, 601–605. https://doi.org/10.1097/NMD.0b013e318093f448.
Henin, A., Biederman, J., Mick, E., A. A, et al., 2007. Childhood antecedent disorders to bipolar disorder in adults: a controlled study. J. Affect. Disord 99, 51–57. https://doi.org/10.1016/j.jad.2006.09.001.
Hodgkins, P., Montejano, L., Sasane, R., et al., 2011. Cost of illness and comorbidities in adults diagnosed with attention-deficit/hyperactivity disorder: a retrospective analysis. Prim. Care Companion CNS. Disord. 13 https://doi.org/10.4088/PCC.10m01030. PCC.10m01030.
Hossain, S., Mainali, P., Bhimanadham, et al., 2019. Medical and psychiatric comorbidities in bipolar disorder: insights from national inpatient population-based study. Cureus 11, e5636. https://doi.org/10.7759/cureus.5636.
Jacob, C.P., Romanos, J., Dempfle, A., et al., 2007. Co-morbidity of adult attention-deficit/hyperactivity disorder with focus on personality traits and related disorders in a tertiary referral center. Eur. Arch. Psychiatry. Clin. Neurosci. 257, 309–317. https://doi.org/10.1007/s00406-007-0722-0726.
Jacob, C., Gross-Lesch, S., Jans, T., et al., 2014. Internalizing and externalizing behavior in adult ADHD. Atten. Defic. Hyperact. Disord. 6, 101–110. https://doi.org/10.1007/s12402-014-0128-z.
Joshi, G., Wilens, T., 2009. Comorbidity in pediatric bipolar disorder. Child Adolesc. Psychiatr. Clin. N. Am. 18, 291–319. https://doi.org/10.1016/j.chc.2008.12.005.
Karaahmet, E., Konuk, N., et al., 2013. The comorbidity of adult attention-deficit/hyperactivity disorder in bipolar disorder patients. Compr. Psychiatry 54, 549–555. https://doi.org/10.1016/j.comppsych.2012.11.005.
Karanti, A., Kardell, M., Joas, E., et al., 2019. Characteristics of bipolar I and II disorder: a study of 8766 individuals. Bipolar Disord. 22, 392–400. https://doi.org/10.1111/bdi.12867.
Kerner, B., Lambert, C.G., 2011. Genome-wide association study in bipolar patients stratified by Co-morbidity. Plos One 6, e28477. https://doi.org/10.1371/journal.pone.0028477.t001.
Kessler, R.C., Adler, L.A., Barkley, R., et al., 2005. Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. Biol. Psychiatry 57, 1442–1451. https://doi.org/10.1016/j.biopsych.2005.04.001.
Kim, J.-W., Yu, H., Ryan, N.D., et al., 2015. Longitudinal trajectories of ADHD symptomatology in offspring of parents with bipolar disorder and community controls. J. Clin. Psychiatry 76, 599–606. https://doi.org/10.4088/jcp.14m09095.
Kooij, J.J., Aeckerlin, L.P., Buitelaar, J.K., 2001. Functioning, comorbidity and treatment of 141 adults with attention deficit hyperactivity disorder (ADHD) at a psychiatric outpatient department. Ned. Tijdschr. Geneeskd. 145, 1498–1501.
Krieger, F.V., Stringaris, A., 2013. Bipolar disorder and disruptive mood dysregulation in children and adolescents: assessment, diagnosis and treatment. Evid. Based Ment. Health 16, 93–94. https://doi.org/10.1136/eb-2013-101400.
Kristiansen, C.B., Shanmuganathan, J.W.D., Gustafsson, L.N., et al., 2015. Increasing incidence and diagnostic instability in adult attention-deficit hyperactivity disorder nationwide between 1995 and 2012. Atten. Defic. Hyperact. Disord. 7, 151–156. https://doi.org/10.1007/s12402-014-0155-9.
Larsson, H., Dilshad, R., Lichtenstein, P., Barker, E.D., 2011. Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology. J. Child. Psychol. Psychiatry 52, 954–963. https://doi.org/10.1111/j.1469-7610.2011.02379.x.
Larsson, H., Ryden, E., Boman, M., et al., 2013. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. Br. J. Psychiatry 203, 103–106. https://doi.org/10.1192/bjp.bp.112.120808.
Lee, S.H., Ripke, S., Neale, B.M., et al., 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat. Genet. 45, 984–994. https://doi.org/10.1038/ng.2711.

Libutzki, B., Ludwig, S., May, M., et al., 2019. Direct medical costs of ADHD and its comorbid conditions on basis of a claims data analysis. Eur. Psychiatry 58, 38–44. https://doi.org/10.1016/j.eurpsy.2019.01.019.
Lieberman, J.A., Small, S.A., Girgis, R.R., 2019. Early detection and preventive intervention in schizophrenia: from fantasy to reality. Am. J. Psychiatry 176, 794–810. https://doi.org/10.1176/appi.ajp.2019.19080865.
Littlewood, R., 1992. DSM–IV and culture: is the classification internationally valid? Psychiatr. Bull. 16, 257–261. https://doi.org/10.1192/pb.16.5.257.
Liu, A., Xu, Y., Yan, Q., Tong, L., 2018. The prevalence of attention deficit/hyperactivity disorder among Chinese children and adolescents. Sci. Rep. 8, 1–15. https://doi.org/10.1038/s41598-018-29488-2.
Machado-Vieira, R., Luckenbaugh, D.A., Ballard, E.D., et al., 2017. Increased activity or energy as a primary criterion for the diagnosis of bipolar mania in DSM-5: findings from the STEP-BD study. Am. J. Psychiatry 174, 70–76. https://doi.org/10.1176/appi.ajp.2016.15091132.
Manitt, C., Eng, C., Pokinko, M., et al., 2013. Dcc orchestrates the development of the prefrontal cortex during adolescence and is altered in psychiatric patients. Transl. Psychiatry 3. https://doi.org/10.1038/tp.2013.105 e338-e338.
Mannuzza, S., Klein, R.G., Bessler, A., et al., 1993. Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. Arch. Gen. Psychiatry 50, 565–576. https://doi.org/10.1001/archpsyc.1993.01820190067007.
Manzari, N., Matvienko-Sikar, K., Baldoni, F., et al., 2019. Prenatal maternal stress and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis. Soc. Psychiatry Psychiatr. Epidemiol. 54, 1299–1309. https://doi.org/10.1007/s00127-019-01745-3.
Marangoni, C., Hernandez, M., Faedda, G.L., 2016. The role of environmental exposures as risk factors for bipolar disorder: A systematic review of longitudinal studies. J. Affect. Disord. 193, 165–174. https://doi.org/10.1016/j.jad.2015.12.055.
Marin, A., Scott, D., Groll, D.L., 2013. Bipolar disorder comorbid with attention-deficit/hyperactivity disorder in adult inpatients with acute relapse. Prim. Care Companion CNS Disord. 15 https://doi.org/10.4088/PCC.12m01495. PCC.12m01495.
McGough, J.J., Smalley, S.L., McCracken, J.T., et al., 2005. Psychiatric comorbidity in adult attention deficit hyperactivity disorder: findings from multiplex families. Am. J. Psychiatry 162, 1621–1627. https://doi.org/10.1176/appi.ajp.162.9.1621.
McIntyre, R.S., Kennedy, S.H., Soczynska, J.K., et al., 2010. Attention-deficit/hyperactivity disorder in adults with bipolar disorder or major depressive disorder: results from the international mood disorders collaborative project. Prim. Care Companion J. Clin. Psychiatry 12. https://doi.org/10.4088/PCC.09m00861gry. PCC.09m00861.
Meier, S.M., Pavlova, B., Dalsgaard, S., et al., 2018. Attention-deficit hyperactivity disorder and anxiety disorders as precursors of bipolar disorder onset in adulthood. Br. J. Psychiatry 213, 555–560. https://doi.org/10.1192/bjp.2018.111.
Mellsop, G., Dutu, G., El-Badri, S., 2007. CAOS contribution to understanding cultural/ethnic differences in the prevalence of bipolar affective disorder in New Zealand. Aust. N. Z. J. Psychiatry 41, 392–396. https://doi.org/10.1080/00048670701264636.
Merikangas, K.R., Akiskal, H.S., Angst, J., et al., 2007. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch. Gen. Psychiatry 64, 543–552. https://doi.org/10.1001/archpsyc.64.5.543.
Merikangas, K.R., Jin, R., He, J.P., et al., 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch. Gen. Psychiatry 68, 241–251. https://doi.org/10.1001/archgenpsychiatry.2011.12.
Miesch, M., Deister, A., 2019. Attention-deficit/hyperactivity disorder (ADHD) in adult psychiatry: data on 12-month prevalence, risk factors and comorbidity. Fortschr. Neurol. Psychiatr. 87, 32–38. https://doi.org/10.1055/s-0043-119987.
Milberger, S., Biederman, J., Faraone, S.V., et al., 1995. Attention deficit hyperactivity disorder and comorbid disorders: issues of overlapping symptoms. Am. J. Psychiatry 152, 1793–1799. https://doi.org/10.1176/ajp.152.12.1793.
Moher, D., Shamseer, L., Clarke, M., et al., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4 https://doi.org/10.1186/2046-4053-4-1.
Munk-Jørgensen, P., Dinesen Østergaard, S., 2011. Register-based studies of mental disorders. Scand. J. Public Health 39, 170–174. https://doi.org/10.1177/1403494810390728.
Najt, P., Wang, F., Spencer, L., Johnston, J.A., et al., 2016. Anterior cortical development during adolescence in bipolar disorder. Biol. Psychiatry 79, 303–310. https://doi.org/10.1016/j.biopsych.2015.03.026.
Nierenberg, A.A., Miyahara, S., Spencer, T., et al., 2005. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. Biol. Psychiatry 57, 1467–1473. https://doi.org/10.1016/j.biopsych.2005.01.036.
O'Connell, K.S., Shadrin, A., Bahrami, S., et al., 2019. Identification of genetic overlap and novel risk loci for attention-deficit/hyperactivity disorder and bipolar disorder. Mol. Psychiatry. https://doi.org/10.1038/s41380-019-0613-z.
Oguz, N., Oral, T., Oguz, M., 2014. Temperament and personality traits of bipolar disorder I patients comorbid with adult attention deficit hyperactivity disorder. Anadolu. Psikiyatri. Dergisi. 15, 221–229. https://doi.org/10.5455/apd.37031.
Palacio-Ortiz, J.D., Pena-Quintero, C.E., Gomez-Valero, M.A., et al., 2017. Lifetime psychiatric disorders: a comparision study between offspring of parents with bipolar disorder Type-I versus the offspring of community controls parents. Rev. Colomb. Psiquiatr. 46, 129–139. https://doi.org/10.1016/j.rcp.2016.06.007.
Palmier-Claus, J.E., Berry, K., Bucci, S., et al., 2018. Relationship between childhood adversity and bipolar affective disorder: systematic review and meta-analysis. Br. J. Psychiatry 209, 454–459. https://doi.org/10.1192/bjp.bp.115.179655.
Papachristou, E., Ormel, J., Oldehinkel, A.J., et al., 2013. Child behavior checklist-mania scale (CBCL-MS): development and evaluation of a population-based screening scale for bipolar disorder. PLoS One 8, e69459. https://doi.org/10.1371/journal.pone.0069459.
Parry, P., Allison, S., Bastiampillai, T., 2018. 'Paediatric bipolar disorder' rates are lower than claimed – a reexamination of the epidemiological surveys used by a meta-analysis. Child Adoles. Ment. Health 23, 14–22. https://doi.org/10.1111/camh.12231.
Pehlivanidis, A., Papanikolaou, K., Mantas, V., et al., 2020. Lifetime co-occurring psychiatric disorders in newly diagnosed adults with attention deficit hyperactivity disorder (ADHD) or/and autism spectrum disorder (ASD). BMC Psychiatry 20, 423. https://doi.org/10.1186/s12888-020-02828-1.
Perez Algorta, G., Kragh, C.A., Arnold, L.E., et al., 2018. Maternal ADHD symptoms, personality, and parenting stress: differences between mothers of children with ADHD and mothers of comparison children. J. Atten. Disord. 22, 1266–1277. https://doi.org/10.1177/1087054714561290.
Perroud, N., Cordera, P., Zimmermann, J., et al., 2014. Comorbidity between attention deficit hyperactivity disorder (ADHD) and bipolar disorder in a specialized mood disorders outpatient clinic. J. Affect. Disord. 168, 161–166. https://doi.org/10.1016/j.jad.2014.06.053.
Perugi, G., Ceraudo, G., Vannucchi, G., et al., 2013. Attention deficit/hyperactivity disorder symptoms in Italian bipolar adult patients: a preliminary report. J. Affect. Disord. 149, 430–434. https://doi.org/10.1016/j.jad.2012.12.010.
Pineiro-Dieguez, B., Balanza-Martinez, V., Garcia-Garcia, P., et al., 2016. Psychiatric comorbidity at the time of diagnosis in adults with ADHD: the CAT study. J. Atten. Disord. 20, 1066–1075. https://doi.org/10.1177/1087054713518240.
Pinna, M., Visioli, C., Rago, C.M., et al., 2019. Attention deficit-hyperactivity disorder in adult bipolar disorder patients. J. Affect. Disord. 243, 391–396. https://doi.org/10.1016/j.jad.2018.09.038.
Polanczyk, G., de Lima, M.S., Horta, B.L., et al., 2007. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am. J. Psychiatry 164, 942–948. https://doi.org/10.1176/ajp.2007.164.6.942.
Polanczyk, G.V., Willcutt, E.G., Salum, G.A., et al., 2014. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int. J. Epidemiol. 43, 434–442. https://doi.org/10.1093/ije/dyt261.
Propper, L., Ortiz, A., Slaney, C., et al., 2015. Early-onset and very-early-onset bipolar disorder: distinct or similar clinical conditions? Bipolar Disord. 17, 814–820, 10.111/bdi.12346.
R Core Team, 2013. R: a Language and Environment for Statistical Computing: Vienna, Austria.
Rasmussen, K., Levander, S., 2009. Untreated ADHD in adults: are there sex differences in symptoms, comorbidity, and impairment? J. Atten. Disord. 12, 353–360. https://doi.org/10.1177/1087054708314621.
Radonjić, N.V., Hess, J.L., Rovira, P., et al., 2021. Structural brain imaging studies offer clues about the effects of the shared genetic etiology among neuropsychiatric disorders. Mol Psychiatry. https://doi-org.ezp.lib.cam.ac.uk/10.1038/s41380-020-01002-z.
Regeer, E.J., Krabbendam, L., De Graaf, R., et al., 2009. Berkson's bias and the mood dimensions of bipolar disorder. Int. J. Methods Psychiatr. Res. 18, 279–286. https://doi.org/10.1002/mpr.290.
Riglin, L., Collishaw, S., Thapar, A.K., et al., 2016. Association of genetic risk variants with attention-deficit/hyperactivity disorder trajectories in the general population. JAMA Psychiatry 73, 1285–1292. https://doi.org/10.1001/jamapsychiatry.2016.2817.
Roser, M., Ritchie, H., 2016. Burden of disease. Our World in Data (Accessed on 18/12/2020). https://ourworldindata.org/.
Rubino, I.A., Frank, E., Croce Nanni, R., et al., 2009. A comparative study of axis I antecedents before age 18 of unipolar depression, bipolar disorder and schizophrenia. Psychopathology 42, 325–332. https://doi.org/10.1159/000232975.
Ryden, E., Thase, M.E., Straht, D., et al., 2009. A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. Acta Psychiatr. Scand. 120, 239–246. https://doi.org/10.1111/j.1600-0447.2009.01399.x.
Sachs, G.S., Baldassano, C.F., Truman, C.J., et al., 2000. Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. Am. J. Psychiatry 157, 466–468. https://doi.org/10.1176/appi.ajp.157.3.466.
Scheffer, R.E., Kowatch, R.A., Carmody, T., et al., 2005. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. Am. J. Psychiatry 162, 58–64. https://doi.org/10.1176/appi.ajp.162.1.58.
Schwarzer, G., 2007. meta: An R Package for Meta-Analysis. R. news 7, pp. 40–45.
Schwarzer, G., Carpenter, J.R., Rücker, G., 2015. Meta-Analysis With R, vol. 4784. Springer.
Schwarzer, G., Chemaitelly, H., Abu-Raddad, L.J., et al., 2019. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. Res. Synth. Methods 10, 476–483. https://doi.org/10.1002/jrsm.1348.
Sciberras, E., Mulraney, M., Silva, D., et al., 2017. Prenatal risk factors and the etiology of ADHD—Review of existing evidence. Curr. Psychiatry Rep. 19, 1. https://doi.org/10.1007/s11920-017-0753-2.
Secnik, K., Swensen, A., Lage, M.J., 2005. Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. Pharmacoeconomics 23, 93–102. https://doi.org/10.2165/00019053-200523010-00008.
Sentissi, O., Navarro, J.C., De Oliveira, H., et al., 2008. Bipolar disorders and quality of life: the impact of attention deficit/hyperactivity disorder and substance abuse in euthymic patients. Psychiatry Res. 161, 36–42. https://doi.org/10.1016/j.psychres.2007.06.016.

Shaw, P., Malek, M., Watson, B., et al., 2012. Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder. Biol. Psychiatry 72, 191–197. https://doi.org/10.1016/j.biopsych.2012.01.031.

Silva, K.L., Rovaris, D.L., Guimaraes-da-Silva, P.O., et al., 2014. Could comorbid bipolar disorder account for a significant share of executive function deficits in adults with attention-deficit hyperactivity disorder? Bipolar Disord. 16, 270–276. https://doi.org/10.1111/bdi.12158.

Smalley, S.L., McGough, J.J., Moilanen, I.K., et al., 2007. Prevalence and psychiatric comorbidity of attention-deficit/hyperactivity disorder in an adolescent finnish population. J. Am. Acad. Child Adolesc. Psychiatry 46, 1575–1583. https://doi.org/10.1097/chi.0b013e3181573137.

Smoller, J.W., Andreassen, O.A., Edenberg, H.J., et al., 2019. Psychiatric genetics and the structure of psychopathology. Mol. Psychiatry 24, 409–420. https://doi.org/10.1038/s41380-017-0010-4.

Sobanski, E., Brüggemann, D., Alm, B., Kern, S., Philipsen, A., Schmalzried, H., Hesslinger, B., Waschkowski, H., Rietschel, M., 2008. Subtype differences in adults with attention-deficit/hyperactivity disorder (ADHD) with regard to ADHD-symptoms, psychiatric comorbidity and psychosocial adjustment. Eur. Psychiatry 23 (Mar. (2)), 142–149. https://doi.org/10.1016/j.eurpsy.2007.09.007. Epub 2007 Nov 19. PMID: 18024089.

Solberg, B.S., Halmoy, A., Engeland, A., et al., 2018. Gender differences in psychiatric comorbidity: a population-based study of 40 000 adults with attention deficit hyperactivity disorder. Acta. Psychiatr. Scand. 137, 176–186. https://doi.org/10.1111/acps.12845.

Song, J., Bergen, S.E., Kuja-Halkola, R., et al., 2015. Bipolar disorder and its relation to major psychiatric disorders: a family-based study in the Swedish population. Bipolar Disord. 17, 184–193. https://doi.org/10.1111/bdi.12242.

Stahlberg, O., Soderstrom, H., Rastam, M., et al., 2004. Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. J. Neural. Transm (Vienna) 111, 891–902. https://doi.org/10.1007/s00702-004-0115-1.

Stern, A., Agnew-Blais, J., Danese, A., et al., 2018. Associations between abuse/neglect and ADHD from childhood to young adulthood: a prospective nationally-representative twin study. Child Abuse. Negl. 81, 274–285. https://doi.org/10.1016/j.chiabu.2018.04.025.

Tamam, L., Karakus, G., Ozpoyraz, N., 2008. Comorbidity of adult attention-deficit hyperactivity disorder and bipolar disorder: prevalence and clinical correlates. Eur. Arch. Psychiatry Clin. Neurosci. 258, 385–393. https://doi.org/10.1007/s00406-008-0807-x.

Teicher, M.H., Samson, J.A., 2013. Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am. J. Psychiatry 170, 1114–1133. https://doi.org/10.1176/appi.ajp.2013.12070957.

Tillman, R., Geller, B., 2006. Controlled study of switching from attention-deficit/hyperactivity disorder to a prepubertal and early adolescent bipolar I disorder phenotype during 6-year prospective follow-up: rate, risk, and predictors. Dev. Psychopathol. 18, 1037–1053. https://doi.org/10.1017/s0954579406060512.

Tole, F., Kopf, J., Schröter, K., et al., 2019. The role of pre-, peri-, and postnatal risk factors in bipolar disorder and adult ADHD. J. Neural. Transm. 126, 1117–1126. https://doi.org/10.1007/s00702-019-01983-4.

Torres, I., Gómez, N., Colom, F., et al., 2015. Bipolar disorder with comorbid attention-deficit and hyperactivity disorder. Main clinical features and clues for an accurate diagnosis. Acta Psychiatr. Scand. 132, 389–399. https://doi.org/10.1111/acps.12426.

Torres, I., Garriga, M., Sole, B., et al., 2018. Functional impairment in adult bipolar disorder with ADHD. J. Affect. Disord. 227, 117–125. https://doi.org/10.1016/j.jad.2017.09.037.

Tripp, G., Luk, S.L., Schaughency, E.A., et al., 1999. DSM-IV and ICD-10: a comparison of the correlates of ADHD and hyperkinetic disorder. J. Am. Acad. Child Psy. 38, 156–164. https://doi.org/10.1097/00004583-199902000-00014.

Tsai, F.-J., Tseng, W.-L., Yang, L.-K., et al., 2019. Psychiatric comorbid patterns in adults with attention-deficit hyperactivity disorder: treatment effect and subtypes. Plos One 14, e0211873. https://doi.org/10.1371/journal.pone.0211873.

Turkyilmaz, E., Yavuz, B.G., Karamustafalioglu, O., et al., 2012. Prevalence of adult attention deficit hyperactivity disorder in the relatives of patients with bipolar disorder. Int. J. Psychiatry Clin. Pract. 16, 223–228. https://doi.org/10.3109/13651501.2012.674532.

van de Glind, G., Konstenius, M., Koeter, et al., 2014. Variability in the prevalence of adult ADHD in treatment seeking substance use disorder patients: results from an international multi-center study exploring DSM-IV and DSM-5 criteria. Drug. Alcohol. Depend. 134, 158–166. https://doi.org/10.1016/j.drugalcdep.203.09.026.

van Hulzen, K.J.E., Scholz, C.J., Franke, B., Ripke, S., Klein, M., McQuillin, A., Sonuga-Barke, E.J., Kelsoe, J.R., Landén, M., Andreassen, O.A., Lesch, K.P., Weber, H., Faraone, S.V., Arias-Vasquez, A., Reif, A., 2017. Genetic overlap between attention-deficit/hyperactivity disorder and bipolar disorder: evidence from genome-wide association study meta-analysis. Biol. Psychiatry 82, 634–641. https://doi.org/10.1016/j.biopsych.2016.08.040.

Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36, 1–48. https://doi.org/10.18637/jss.v036.i03.

Viktorin, A., Ryden, E., Thase, et al., 2017. The risk of treatment-emergent mania with methylphenidate in bipolar disorder. Am. J. Psychiatry 174, 341–348. https://doi.org/10.1176/appi.ajp.2016.16040467.

Volkert, J., Kopf, J., Kazmaier, J., et al., 2015. Evidence for cognitive subgroups in bipolar disorder and the influence of subclinical depression and sleep disturbances. Eur. Neuropsychopharmacol. 25, 192–202. https://doi.org/10.1016/j.euroneuro.2014.07.017.

Walsh, R.F.L., Sheppard, B., Cui, L., et al., 2020. Comorbidity and patterns of familial aggregation in attention-deficit/hyperactivity disorder and bipolar disorder in a family study of affective and anxiety spectrum disorders. J. Psychiatr. Res. 130, 355–361. https://doi.org/10.1016/j.jpsychires.2020.08.017.

Wei, H.-T., Pan, T.-L., Hsu, J.-W., et al., 2019. Risks of bipolar disorder, depressive disorder, and traumatic brain injury among siblings of patients with attention-deficit hyperactivity disorder. J. Affect. Disord. 245, 335–339. https://doi.org/10.1016/j.jad.2018.11.057.

Westmoreland, P., Gunter, T., Loveless, P., et al., 2010. Attention deficit hyperactivity disorder in men and women newly committed to prison: clinical characteristics, psychiatric comorbidity, and quality of life. Int. J. Offender. Ther. Comp. Criminol. 54, 361–377. https://doi.org/10.1177/0306624x09332313.

Wilens, T.E., Biederman, J., Wozniak, J., et al., 2003. Can adults with attention-deficit/hyperactivity disorder be distinguished from those with comorbid bipolar disorder? Findings from a sample of clinically referred adults. Biol. Psychiatry 54, 1–8. https://doi.org/10.1016/s0006-3223(02)01666-9.

Wilens, T.E., Biederman, J., Faraone, S.V., et al., 2009. Presenting ADHD symptoms, subtypes, and comorbid disorders in clinically referred adults with ADHD. J. Clin. Psychiatry 70, 1557–1562. https://doi.org/10.4088/JCP.08m04785pur.

Yoshimasu, K., Barbaresi, W.J., Colligan, R.C., et al., 2018. Adults with persistent ADHD: gender and psychiatric comorbidities A population-based longitudinal study. J. Atten. Disord. 22, 535–546. https://doi.org/10.1177/1087054716676342.

Young, J.Q., Kline-Simon, A.H., Mordecai, et al., 2015a. Prevalence of behavioral health disorders and associated chronic disease burden in a commercially insured health system: findings of a case-control study. Gen. Hosp. Psychiatry 37, 101–108. https://doi.org/10.1016/j.genhosppsych.2014.12.005.

Young, S., Moss, D., Sedgwick, O., Fridman, M., et al., 2015b. A meta-analysis of the prevalence of attention deficit hyperactivity disorder in incarcerated populations. Psychol. Med. 45, 247–258. https://doi.org/10.1017/s0033291714000762.

Youngstrom, E.A., Arnold, L.E., Frazier, T.W., 2010. Bipolar and ADHD comorbidity: both artifact and outgrowth of shared mechanisms. Clin. Psychol. 17, 350–359. https://doi.org/10.1111/j.1468-2850.2010.01226.x.