Prevalence of cocaine use and cocaine use disorder among adult patients with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis

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ABSTRACT

We conducted this systematic review and meta-analysis (registered with PROSPERO CRD42020142039) of the literature to estimate the lifetime prevalence of cocaine use and cocaine use disorder among adult patients with attention-deficit/hyperactivity disorder (ADHD). The literature search was performed on the electronic databases PubMed and PsychINFO without date or language restrictions. Additional studies were identified by hand searching of citations. Inclusion criteria were: studies involving adult patients with ADHD and reporting cocaine use and/or cocaine use disorders. Data were pooled in the meta-analyses using a generalized linear mixed model with random effects. Statistical heterogeneity was assessed using the Cochran Q test. Sensitivity analyses were conducted. Twelve studies were included in the review: six in the meta-analysis of cocaine use and nine in the meta-analysis of cocaine use disorder. The estimated prevalence of cocaine use was 26.0% (95% CI 0.18–0.35) and the estimated prevalence of cocaine use disorder was 10.0% (95% CI 0.08–0.13). Heterogeneity in both meta-analyses was high but decreased to non-significance in the meta-analysis on cocaine use disorder after excluding the outlier study. In conclusion, one out of four adult patients with ADHD use cocaine and one out of ten develop a lifetime cocaine use disorder. Since cocaine use can lead to more severe and complex disorders ofv impaired systemic functioning, adult patients with ADHD should be assessed for cocaine use disorder and promptly referred for treatment.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder in which a persistent pattern of inattention and/or hyperactivity-impulsivity results in functional impairment (Americani Psychiatric Association, 2013). It is one of the most frequently observed psychiatric disorders during childhood (estimated prevalence 4–8%) (Faraone et al., 2003). It persists throughout adulthood in up to 57% of patients (Fayyad et al., 2017), with some degree of functional impairment in nearly 90% of cases (Biederman et al., 2000). A recent cross-national survey estimated a mean prevalence of 2.8% among adults, ranging from 0.6% to 7.3% depending on country income level (Fayyad et al., 2017). This rate is similar to the pooled prevalence of 2.5% obtained by Simon and co-workers (Simon et al., 2009) in their meta-analysis, which also reported 51.7% of adult patients with ADHD had at least one psychiatric comorbid disorder and 11.5% a substance use disorder (SUD), with ADHD onset preceding the SUD in 99.1% of cases (Fayyad et al., 2017).
Previous epidemiologic studies have reported a SUD in 15.2% of ADHD patients (lifetime prevalence 36%) (Adler, 2008; Kessler et al., 2006). A meta-analysis of longitudinal studies concluded that childhood ADHD prospectively predicts SUD in adolescents and adults and that it is 1.5-fold more likely to develop in children with ADHD than in those without the disorder (Lee et al., 2011). A prospective study by Levy reported that children with ADHD were more likely than controls to have a SUD diagnosed in adolescence and more likely to experience alcohol and drug dependence in adulthood (Levy et al., 2014). Also in cases that did not meet the diagnostic criteria for SUD, ADHD

patients were more likely to experiment with licit and illicit substances during their lifetime than those not diagnosed with the disorder (Baker et al., 2012; Est´evez et al., 2016; Kooij et al., 2019; Lee et al., 2011).

On the other side, a meta-analysis published in 2012 found that ADHD is present in almost one out of four patients with SUD (van Emmerik-van Oortmerssen et al., 2012). More recently, a prevalence of ADHD from 5.4% to 32% was reported in patients with SUD (Kaye et al., 2014; van de Glind et al., 2014) and from 15.1% to 25% in those with cocaine use disorder (Daigre et al., 2013; Martinez-Luna et al., 2019).

One explanation for the high rates of SUD in ADHD patients is the self-medication hypothesis, which posits that such patients experiment with substances in an attempt to ameliorate their ADHD symptoms (Mariani et al., 2014; Wilens, 2004). Evidence supporting the hypothesis has come from neuroimaging studies that revealed dopamine deficits in the mesolimbic reward pathways of ADHD patients (Volkow et al., 2007a, 2007b), which explains to some extent that substance use among ADHD patients may be an attempt to compensate for dopamine deficits. The hedonic effect of substances and other addictive behaviours would occur with increased dopamine transmission in the mesolimbic reward pathway (Volkow et al., 2011).

The self-medication hypothesis may be useful in studying cocaine use, as it shares psychoactive properties with methylphenidate, one of the most effective stimulant medications prescribed for ADHD treatment (Volkow et al., 1997; Volkow and Swanson, 2003). The density of dopamine membrane transporters (DATs) is higher in ADHD patients than healthy controls. Therefore, dopamine re-uptake in the pre-synaptic neurons of ADHD patients is too rapid to produce adequate post-synaptic effects (Krause et al., 2003), dopamine activity in the antero-medial frontal cortex and the nucleus accumbens is decreased, and this was found to be associated with the hyperactivity and attention deficit typical of patients with ADHD (Le Moal and Simon, 1991; Solanto, 1998). Both cocaine and methylphenidate bind DATs, thus reducing dopamine re-uptake and increasing dopamine levels in thesynaptic cleft (Dresel et al., 2000; Volkow et al., 1995). Furthermore, they increase dopamine levels in the nucleus accumbens (Di Chiara and Imperato, 1988) and the striatum (Volkow et al., 1995), abolishing dopamine deficit and reducing hyperactivity and inattention in ADHD (Solanto, 1998).

The high co-occurrence of SUD and cocaine use disorder in subjects with ADHD may also reflect the tendency toward the impulsive risktaking behaviour characteristic of ADHD (Evren et al., 2018; Ortal et al., 2015). High levels of impulsivity were indeed observed in patients with ADHD and SUD (Crunelle et al., 2013b; Perez de Los Cobos et al., 2011). Also, subjects with ADHD often have a history of conduct disorders in childhood and display antisocial personality disorder in adulthood, which are recognized predictors of impulsive behaviour and substance use (Biederman et al., 1995; Brook et al., 2010; Fergusson et al., 2007). Neuroimaging studies in ADHD patients revealed hyperactivation of the motivation-reward processing brain network during tasks testing impulsive choices, hypoactivation of inhibitory control brain network during inhibitory control tasks, decreased white matter microstructure coherence, and reduced cortical thickness (Adisetiyo and Gray, 2017). Furthermore, neuroimaging studies have also shown a more profound reduction in striatal grey matter (van Wingen et al., 2013), a lower baseline DAT availability, and an attenuated DAT occupancy by methylphenidate (Crunelle et al., 2013a) in adult ADHD patients with cocaine dependence than in those without dependence, suggesting these neurobiological differences as possible explanations for the reduced effectiveness of treatment in adults with ADHD and cocaine dependence.

Accordingly, our hypothesis was that the rates of cocaine use and lifetime cocaine use disorder will be high among adults with ADHD. To our best knowledge, few systematic reviews and meta-analyses have investigated the co-occurrence of ADHD with substance use disorders in general (Lee et al., 2011; Wilens and Morrison, 2012) and none to date has focused on the prevalence of cocaine use or cocaine use disorder. Therefore, an accurate estimation of the lifetime prevalence of cocaine use and cocaine use disorder among adult patients with ADHD is lacking. To fill this gap, we conducted a systematic review and meta-analysis of the literature to estimate the lifetime prevalence of cocaine use and cocaine use disorder among adult patients with ADHD.

2. Methods

The protocol of the review was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020142039).

2.1. Search strategy

The literature search was performed on the electronic databases PubMed and PsychINFO (up to July 16, 2019) without restrictions on publication date or language. The search string was originally developed for PubMed and then adapted to the PsychINFO database to fit it to the database controlled vocabulary and syntax rules. For the PubMed search, the string was: ("Substance-Related Disorders"[MeSH] OR "Cocaine"[MeSH] OR cocain*[tw]) AND ("Attention Deficit Disorder with Hyperactivity"[MeSH] OR ADHD[tw] OR attention-deficit-disord* [tw]). Exploded MeSH terms were used. Keywords followed by a [tw] field tag were searched in all text fields of the records. For the PsychINFO search, the string was: (DE "Substance Use Disorder" OR DE "Drug Usage" OR DE "Drug Abuse" OR DE "Intravenous Drug Usage" OR DE "Drug Dependency" OR DE "Polydrug Abuse" OR DE "Drug Addiction" OR DE "Drug Seeking" OR DE "Cocaine" OR TX cocain*) AND (DE "Attention Deficit Disorder with Hyperactivity" OR TX ADHD OR TX attention-deficit-disord*), where DE denotes controlled vocabulary terms and TX denotes keywords searched in all searchable fields of the records.
Additional studies were identified by handsearching the citations in the reviews (n = 64) and the studies (n =89) that were considered pertinent on abstract screening. The study flow diagram is illustrated in Fig. 1.

2.2. Inclusion and exclusion criteria

Inclusion criteria were studies 1) involving adults; 2) patients diagnosed with adult ADHD; and 3) reporting cocaine use and/or cocaine use disorder. To obtain results representative of the general population of patients with adult ADHD, studies on subpopulations (e.g., prisoners, military veterans, only males or females, and patients with addictions) were excluded. Also excluded were studies involving patients diagnosed with ADHD in childhood but without a chronic course of symptoms in adulthood.

2.3. Procedures

Citations were downloaded to a Procite reference database. Double records were checked and eliminated. Initial screening of titles and abstracts was performed by two reviewers (FVT and IS) separately. Studies not addressing ADHD or substance use or unspecific psychiatric disorders were excluded, whilst all others underwent abstract screening. Abstracts were examined by two independent reviewers and screened for inclusion (FVT and FO; FVT and GN). Disagreement was discussed between the two reviewers until agreement was reached. After abstract screening, full texts of studies (n = 89) were reviewed for inclusion or exclusion by two independent reviewers (FVT and CM; FVT and FO; FVT and GN). Disagreement was resolved by discussion. The two reviewers coded the reasons for exclusion of studies and extracted the data from the included studies. Titles, abstracts, methods, and results of studies and reviews published in a language other than English were translated with the help of a mother tongue consultant. Data were extracted using a standardised form including information on country, age, sample characteristics (clinical or community), inclusion and exclusion criteria, recruitment method, assessment tools for adult ADHD and cocaine use and cocaine use disorder, kind of indicator (lifetime or last month), sample size of adult patients with ADHD included in the analysis, number of patients using cocaine or with cocaine use disorder, prevalence, and 95% confidence interval. Prevalence of comorbid psychiatric conditions in adult patients with ADHD were also extracted for each study. Two study authors were contacted via email for obtaining missing information but neither provided the requested information. The prevalence of use was re-calculated for the studies providing cocaine use data separately by patient subgroup. This was done for the studies by De Alwis et al. (2014), Liebrenz et al. (2015), and Scully et al. (2014).

The risk of bias of studies was assessed using the checklist developed by Munn (Munn et al., 2015) and issued by the Johanna Briggs Institute. Assessment was performed by two independent reviewers (FVT and GN), and disagreement was resolved by consensus. Studies were graded at low, moderate, and high risk of bias if judged positive for 7–9, 4–6, and 0–3 appraisal criteria, respectively. Table 1 presents the results of risk of bias assessment.

2.4. Statistical analysis

A random effects meta-analysis model via a generalized linear mixed effect method was fitted to pool data in the meta-analyses. Both 95% confidence intervals and 95% prediction intervals were estimated (Fig. 2 and Fig. 3). Statistical heterogeneity was assessed using the Cochran Q test. Heterogeneity was quantified using the I2 statistic, as proposed by Higgins and Thompson (Higgins et al., 2003). Values of I2 of 0–24.9%, 25–49.9%, 50–74.9%, and >75% suggested no, low, moderate or high heterogeneity, respectively.

Sensitivity analyses were conducted. A leave-one-out analysis was carried out to identify the most influential studies that could distort the pooled effect (Fig. 4). Studentized deleted residuals were employed to detect influential studies (Viechtbauer and Cheung, 2010). The standardized squared difference between the pooled result estimated with and without the study was computed to assess the contribution of each study to the overall heterogeneity. No study was identified as being influential in the meta-analysis of prevalence of cocaine use (Fig. 4a). The study by Pi˜neiro-Dieguez et al. (2016) was identified as being influential in the meta-analysis of prevalence of cocaine use disorder (Fig. 4b). The meta-analysis omitting this study is presented in Fig. 3b. Further sensitivity analysis was conducted leaving out the two studies assessing cocaine use through self-report of patients (Scully et al., 2014; Vingilis et al., 2015). The difference in the pooled prevalence was not statistically significant: 0.22 (95% CI 0.14–0.33; 95% PI 0.02–0.78) vs 0.26 (95% CI 0.18–0.35; 95% PI 0.07–0.62).

Statistical analyses were performed using the meta package of R, version 3.6.1 (Schwarzer, 2007).

3. Results

The search strategy retrieved 1936 records from PubMed and 1376 from PsychINFO. After the double records were deleted, 2565 remained in the database (Fig. 1). After exclusion of titles and abstracts deemed not pertinent, a total of 137 papers underwent full-text assessment. The full text was obtained for 89 studies, 73 identified from abstract screening and 16 from hand searching of citations. After reading the full text, we excluded 77 studies. Most (n = 56) did not report cocaine use or cocaine use disorder. Nine involved children or samples of adults that had received a childhood ADHD diagnosis. Three assessed both children and adult patients. Five involved selected populations: cocaine users, cigarette smokers, patients attending youth social integration centres, and patients attending sexually transmitted disease clinics. Two studies presented secondary analyses of included studies. Two studies presented an analysis of preliminary subsamples of included studies (Jacob et al., 2007; Vingilis et al., 2014).

Twelve studies were included in the review (Table 2) (Biederman et al., 1995; De Alwis et al., 2014; Faraone et al., 2007; Groβ-Lesch et al., 2016; Huntley and Young, 2014; Liebrenz et al., 2015; Murphy and Barkley, 1996; Ohlmeier et al., 2011; Pi˜neiro-Di´eguez et al., 2016; Scully et al., 2014; Sizoo et al., 2009; Vingilis et al., 2015). Six (De Alwis et al., 2014; Faraone et al., 2007; Huntley and Young, 2014; Murphy and Barkley, 1996; Scully et al., 2014; Vingilis et al., 2015) reported data for the meta-analysis of cocaine use (Fig. 2) and nine (Biederman et al., 1995; De Alwis et al., 2014; Faraone et al., 2007; Groβ-Lesch et al., 2016; Liebrenz et al., 2015; Ohlmeier et al., 2011; Pi˜neiro-Di´eguez et al., 2016; Scully et al., 2014; Sizoo et al., 2009) reported data for the meta-analysis of cocaine use disorder (Fig. 3).

3.1. Study characteristics

Table 2 presents the descriptive characteristics of the 12 studies. Four (33.3%) were from the United States (Biederman et al., 1995; De Alwis et al., 2014; Faraone et al., 2007; Murphy and Barkley, 1996), two (16.7%) from Germany (Groβ-Lesch et al., 2016; Ohlmeier et al., 2011), two (16.7%) from the UK (Huntley and Young, 2014; Scully et al., 2014), one each from Switzerland (Liebrenz et al., 2015), Spain (Pi˜neiro-Di´eguez et al., 2016), the Netherlands (Sizoo et al., 2009), and Canada (Vingilis et al., 2015). Overall, more than half (58.3%) were from Europe.

All studies involved adults. The range in mean age was from 25 to 39 years in the studies that provided the mean age (Faraone et al., 2007; Groβ-Lesch et al., 2016; Huntley and Young, 2014; Liebrenz et al., 2015; Murphy and Barkley, 1996; Ohlmeier et al., 2011; Scully et al., 2014; Sizoo et al., 2009).

The majority of the studies (93.3%) involved patients recruited from a clinical context, two recruited patients from the community (De Alwis et al., 2014; Vingilis et al., 2015), and one recruited participants from both settings (Faraone et al., 2007). Referral methods to recruit participants were reported in eight studies (56.7%). Two (Faraone et al., 2007; Pi˜neiro-Di´eguez et al., 2016) recruited patients through both referrals and advertisements, whilst two (De Alwis et al., 2014; Vingilis et al., 2015) used surveys.

Inclusion criteria for adult ADHD were quite similar across studies, and basically followed the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV) criteria for adult diagnosis. In some cases, exclusion criteria were explicitly described. The main reasons given for exclusion were other psychiatric disorders (Faraone et al., 2007; Groβ-Lesch et al., 2016; Huntley and Young, 2014; Murphy and Barkley, 1996; Sizoo et al., 2009), an IQ lower than 70 or 80 (Faraone et al., 2007; Groβ-Lesch et al., 2016; Huntley and Young, 2014; Murphy and Barkley, 1996; Sizoo et al., 2009), and inadequate language level (Faraone et al., 2007; Sizoo et al., 2009; Vingilis et al., 2015).

Various different tools were used to diagnose adult ADHD. The Structured Clinical Interview for DSM Disorders (SCID) was used in five studies (Biederman et al., 1995; Faraone et al., 2007; Groβ-Lesch et al., 2016; Huntley and Young, 2014; Murphy and Barkley, 1996). Three used the SCID coupled with other tools, including the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Biederman et al., 1995); the ADHD Diagnostic Checklist (ADHD-DC), and the Wender Utah Rating Scale-short form (WURS-K) (Groβ-Lesch et al., 2016); and DCS and ADHD-Assessment Functional Impairment (AFI) (Huntley and Young, 2014). Murphy and Barkley (1996) combined the SCID for DSM-III with interview modules constructed ad hoc to assess symptoms according to DSM–III–R and Symptoms Checklist-90-Revised (SCL-90-R). Liebrenz et al. (2015) used five different assessment tools: Wender-Reimherr Interview (WRI), Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), SCL-90-R, WURS-K, and ADHD-Self-rating Scale (SB). Ohlmeier et al. (2011) used different assessment tools for ADHD diagnosis in adulthood (Conners' Adult ADHD Rating Scales, CAARS) and, retrospectively, in childhood (Brown Attention Deficit Scales). Scully et al. (2014) used the Barkley Adult ADAH Rating Scale (BAARS), whilst Vingilis et al. (2015) used the Adult ADHD Self-Report Scale (ASRS v1.1) together with questions investigating previous diagnosis and ADHD treatment. Finally, Sizoo et al. (2009) used a semi-structured interview based on the developmental history of each patient and the DSM-IV checklist, whereas Pi˜neiro-Di´eguez et al. (2016) used DSM-IV-TR criteria.

Cocaine use and cocaine use disorder were assessed using the SCID interview in four studies (Biederman et al., 1995; Faraone et al., 2007; Groβ-Lesch et al., 2016; Murphy and Barkley, 1996). One study used both the SCID and the Drug Use Screening Inventory (DUSI) tools (Faraone et al., 2007). DSM-IV criteria were used in three studies (De Alwis et al., 2014; Pi˜neiro-Di´eguez et al., 2016; Sizoo et al., 2009), whilst one study used International Classification of Disease 10th edition (ICD-10) criteria (Liebrenz et al., 2015). Ohlmeier et al. (2011) used several scales: ICD-10, DSM-IV-TR, International Diagnostic Checklists (IDCL), European adaptation of a multidimensional assessment instrument (Europ ASI), and Quality Outcomes Database (QOD). One study (Huntley and Young, 2014) used the ADHD-AFI. Finally, two studies evaluated cocaine use via self-reported questionnaires or interviews(Scully et al., 2014; Vingilis et al., 2015).

Sample size differed across the studies and ranged from less than 100 (Huntley and Young, 2014; Ohlmeier et al., 2011; Scully et al., 2014; Sizoo et al., 2009) to nearly 800 patients (De Alwis et al., 2014; Groβ-Lesch et al., 2016).
Prevalence of psychiatric comorbidities was reported in most studies, albeit considering different conditions (Supplementary Table 1). Four studies included information on comorbid SUDs only (Biederman et al., 1995; Faraone et al., 2007; Ohlmeier et al., 2011; Sizoo et al., 2009).
Prevalence of mood disorders ranged from 17,6% to 33,3% in five studies (Liebrenz et al., 2015; Murphy and Barkley, 1996; Pi˜neiro-Di´eguez et al., 2016; Scully et al., 2014; Vingilis et al., 2015) whilst affected about 50% of patients with adult ADHD in the studies by De Alwis et al. (2014) and Groβ-Lesch et al. (2016). Anxiety disorders affected 15,0%-35,6% of patients in five studies (Groβ-Lesch et al., 2016; Liebrenz et al., 2015; Murphy and Barkley, 1996; Pi˜neiro-Di´eguez et al., 2016; Vingilis et al., 2015) but more than 50% of patients in the studies by De Alwis et al. (2014) and Scully et al. (2014).
Scores indicating low risk of bias were obtained for nine studies (75%) (Biederman et al., 1995; Faraone et al., 2007; Huntley and Young, 2014; Groβ-Lesch et al., 2016; Liebrenz et al., 2015; Ohlmeier et al., 2011; Pi˜neiro-Di´eguez et al., 2016; Sizoo et al., 2009; Vingilis et al., 2015), moderate risk for three (25%) (De Alwis et al., 2014; Murphy and Barkley, 1996; Scully et al., 2014), and high risk for none (Table 1).

3.2. Prevalence of cocaine use

Six studies (De Alwis et al., 2014; Faraone et al., 2007; Huntley and Young, 2014; Murphy and Barkley, 1996; Scully et al., 2014; Vingilis et al., 2015), involving a total of 1557 patients, provided data on adults with ADHD using cocaine. Five studies measured lifetime prevalence of use and only one study recorded last month use (Faraone et al., 2007).
Three studies were conducted in the United States (De Alwis et al., 2014; Faraone et al., 2007; Murphy and Barkley, 1996), two in the UK (Huntley and Young, 2014; Scully et al., 2014), and one in Canada (Vingilis et al., 2015).
The estimated average prevalence of cocaine use was 26% (95% CI 0.18–0.35; 95% PI 0.07–0.62) (Fig. 2). Heterogeneity across studies was statistically significant ($p < 0.01$; $I2 = 91\%$). The prevalence of cocaine use ranged from 12.1% in the US study (Faraone et al., 2007) to 42.5% in the UK study (Scully et al., 2014). Differences in the prevalence of cocaine use did not seem to be related to the year when the studies were conducted. A low prevalence of use was reported in the study by Faraone et al. conducted in 2007 in the study by De Alwis et al. conducted in 2014, whilst a high prevalence was recorded in the studies by Huntley and Young, Scully et al. and Vingilis et al. conducted in 2014 and 2015, and in the study by Murphy and Barkley conducted in 1996.
The differences in the prevalence of cocaine use may be related to enrolment setting and participant age. Studies conducted in the community or through epidemiologic surveys (Faraone et al., 2007, 12.1%; prevalence rates than studies conducted in clinics or psychiatric services, which reported prevalence rates of over 30% and enrolled younger patients (32.5% reported by Murphy and Barkley, 1996; 34% by Huntley and Young, 2014; 42.5% by Scully et al., 2014).

3.3. Prevalence of cocaine use disorder

Nine studies (Biederman et al., 1995; De Alwis et al., 2014; Faraone et al., 2007; Groβ-Lesch et al., 2016; Liebrenz et al., 2015; Ohlmeier et al., 2011; Pi˜neiro-Di´eguez et al., 2016; Scully et al., 2014; Sizoo et al., 2009), involving a total of 2965 patients, provided data on adult patients with ADHD and cocaine use disorder. Seven reported the lifetime prevalence of cocaine use disorder, one study in the last month (Faraone et al., 2007), and one study at the time of ADHD diagnosis (Pi˜neiro-Di´eguez et al., 2016).
Three studies were conducted in the United States (Biederman et al., 1995; De Alwis et al., 2014; Faraone et al., 2007), two in Germany (Groβ-Lesch et al., 2016; Ohlmeier et al., 2011), one each in

Switzerland (Liebrenz et al., 2015), Spain (Pi˜neiro-Di´eguez et al., 2016), the UK (Scully et al., 2014), and the Netherlands (Sizoo et al., 2009).
The estimated average prevalence of cocaine use disorder was 10.0% (95% CI 0.08–0.13; 95% PI 0.04–0.23) (Fig. 3a). Heterogeneity across the studies was statistically significant ($p < 0.01$; $I2 = 85\%$). There was no substantial difference in the prevalence of cocaine use disorder by study period. The prevalence ranged from 7% to 11% in six out of nine studies providing data on the prevalence of cocaine use disorder (7.2% in Groβ-Lesch et al., 2016; 8.3% in Liebrenz et al., 2015; 8.4% in Biederman et al., 1995; 9.4% in Sizoo et al., 2009; 10.6% in De Alwis et al., 2014; 11% in Scully et al., 2014). Among the three apparently outlier studies, the study by Faraone et al. (2007) reported a prevalence of 5.1%, whereas the studies by Ohlmeier et al. (2011) and Pi˜neiro-Di´eguez et al. (2016) reported a prevalence of 14.8% and 20.8%, respectively.
Prevalence did not differ by recruitment setting. Only two studies providing data on the prevalence of cocaine use disorder were conducted in the community. One reported a prevalence of 5.1% (Faraone et al., 2007), whereas the 10.6% prevalence reported by the other was near to the average (De Alwis et al., 2014). All the other studies providing data on the prevalence of cocaine use disorder were conducted in clinics or psychiatric services.
Patient age did not appear to be influential. The age range was 29–39 years in all the studies in the meta-analysis of cocaine use disorder, except for the one by De Alwis et al.
Finally, after omitting the study identified as influential in the outlier analysis (Pi˜neiro-Di´eguez et al., 2016) from the meta-analysis, the prevalence of cocaine use disorder was slightly reduced to 9% (95% CI 0.07–0.10; 95% PI 0.07–0.10), and heterogeneity lost statistical significance ($p = 0.14$; $I2 = 28\%$) (Fig. 3b).

4. Discussion

To our best knowledge, this is the first systematic review estimating the prevalence of lifetime cocaine use among adult patients with ADHD. The review included 12 studies involving overall 3357 patients.
The meta-analysis showed an estimated average prevalence of 26% of cocaine use among adult patients and a high degree of heterogeneity across the study populations. This did not appear to be related to the year the study was published, since low and high prevalence rates were reported by older and more recent studies. Prevalence rates appeared to differ by recruitment setting; studies conducted in the community or through epidemiologic surveys had a lower prevalence of cocaine use than those that recruited from clinical settings or psychiatric services. This could be due to a higher risk of substance use in patients attending clinical/psychiatric services and to a higher underreporting of cocaine use in the general population than among patients seeking treatment in clinical settings. Another possible explanation for the difference could be the age of the sample, which was lower in the studies that reported a high prevalence of cocaine use.
The estimated average prevalence of cocaine use disorder was less than half that of cocaine use (10.0% vs. 26.0%). Again, there was high statistical heterogeneity between the samples, which however disappeared when the outlier study was excluded from the analysis. No clear differences were observed between older and recently published studies, and as regards recruitment setting. This may have been due to the general propensity of patients to report a problem for which they received a formal diagnosis and to the ability of clinicians to detect it with validated assessment tools or interviews. Patient age did not appear related to the observed differences. The far lower prevalence of cocaine use disorder compared to cocaine use appears to be a reasonable estimate.
The lifetime prevalence of cocaine use and cocaine use disorder among adult patients with ADHD seems to be more similar to that of patients with other psychiatric disorders than to that of the general population. In a national US survey, about 0.6% of people aged 12 or older were current users of cocaine (Hedden et al., 2015). Conversely, a higher prevalence of cocaine use disorder was found in patients with psychiatric disorders: cocaine use disorder was reported in 2.8% of individuals with antisocial personality disorder (Compton et al., 2005), 6.6–11% of those with bipolar disorder (Hunt et al., 2016a, 2016b), and 16% of those with borderline personality disorder (Trull et al., 2018).

A high prevalence of mood disorders, anxiety disorders, and SUDs affected patients with adult ADHD in the included studies, a result in line with the current literature (Fayyad et al., 2017; Kooij et al., 2019). Albeit the sparse and heterogenous information, the prevalence of cocaine use and cocaine use disorders did not appear to be related to the reported psychiatric comorbidities.

Assessing and taking into account the presence of SUDs in the overall management of ADHD patients is important not only because the prevalence of SUDs is higher than one would expect, but also because SUDs seem to be more severe and chronic in patients with ADHD than in those without the disorder (Wilens, 2007). This poses an increased risk of severe emotional problems and impaired interpersonal functioning in individuals with ADHD (van Emmerik-van Oortmerssen et al., 2012), making it important to screen ADHD patients for SUDs and refer them for prompt treatment.

Although cocaine dependence remains a challenge and research has yet to delineate effective treatment, promising intervention strategies are available. And while existing evidence has not yet clearly demonstrated the efficacy of pharmacological treatment for cocaine dependence, substitution therapy with psychostimulants holds promise (Castells et al., 2016) and psychosocial interventions appear to be effective as first-line treatments (De Crescenzo et al., 2018; Minozzi et al., 2016). Moreover, combination therapies with high-dose ADHD medications and cognitive behavioural therapy has been shown to reduce ADHD symptoms and abuse of amphetamine and cocaine (Konstenius et al., 2014; Levin et al., 2015). ADHD medications, albeit effective in reducing the severity of core ADHD symptoms, seem to have limited effect on comorbid substance use (Cunill et al., 2015). However, they don't appear to precipitate substance use in adults without previous SUD (Torgensen et al., 2013) or worsen SUD in patients with comorbid SUD (Klassen et al., 2012). Decreased long-term risk of substance-related events among SUD patients treated for ADHD was recently reported (Quinn et al., 2017), and an improvement in ADHD symptoms appeared to precede cocaine abstinence rather than cocaine abstinence preceding ADHD symptom improvement among patients with both ADHD and cocaine use disorder treated with stimulants (Levin et al., 2018). This finding suggests a direct link between ADHD symptoms and cocaine use and that abstinence from cocaine use can be achieved by reducing impulsivity, increasing cognitive control, and decreasing the need to self-medicate (Levin et al., 2018).

This review has some strengths. The search strategy did not restrict study publication date or language, thus ensuring a systematic search of search and review and disagreements were resolved by consensus. The sample was large and included studies from different countries, thus enhancing reliability of estimated prevalence rates. The diagnosis of adult ADHD was based on standardised assessment scales. The outcome under study is unlikely to be affected by publication bias. Separate prevalence estimates were calculated for cocaine use and cocaine use disorder, and sensitivity analyses were performed. Average prevalence estimates were obtained by statistical meta-analysis using random effects.

On the other side, the review has also limitations. A number of studies were excluded because they did not measure cocaine use or cocaine use disorder outcomes separately and reported only general "drug use" or "substance use disorder" outcomes. The exclusion of studies involving special population samples could have led to underestimation of the prevalence. Both the prevalence of cocaine use and of cocaine use disorder was heterogeneous in the studies included. It was sometimes difficult to determine how the study authors calculated prevalence, and in some cases the data were re-calculated with the risk of errors.

In conclusion, according to the present review, few studies to date have investigated the prevalence of cocaine use and cocaine use disorder among adult patients with ADHD. Albeit with high heterogeneity, the findings suggest a high rate of lifetime cocaine use among these patients. This could lead to more severe and complex disorder with impairment of systemic functioning. Further studies on stimulants and other ADHD treatments to reduce or avoid cocaine use by improving attention, hyperactivity, and impulsivity are needed. As recommended by the international consensus on ADHD and SUD (Crunelle et al., 2018), adult patients with ADHD should be assessed for cocaine use disorder and promptly referred for treatment.

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Author contribution

FVT and FO conceptualised the review. FVT and the biomedical librarian NC developed the search strategy. FVT developed the Procite database for managing the references. FVT, IS, GN, CM and FO screened titles and abstracts. GN, CM, and NC collected papers. FVT, FO, CM and GN evaluated the papers for inclusion and extracted data. FVT and FO drafted the paper. PB carried out the statistical analysis. All authors provided critical revision, contributed to, and approved the final manuscript.

Data availability

Data are available upon request. Federica Vigna-Taglianti is responsible for the data.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.11.021.

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Figure 1. Flow chart of search strategy.

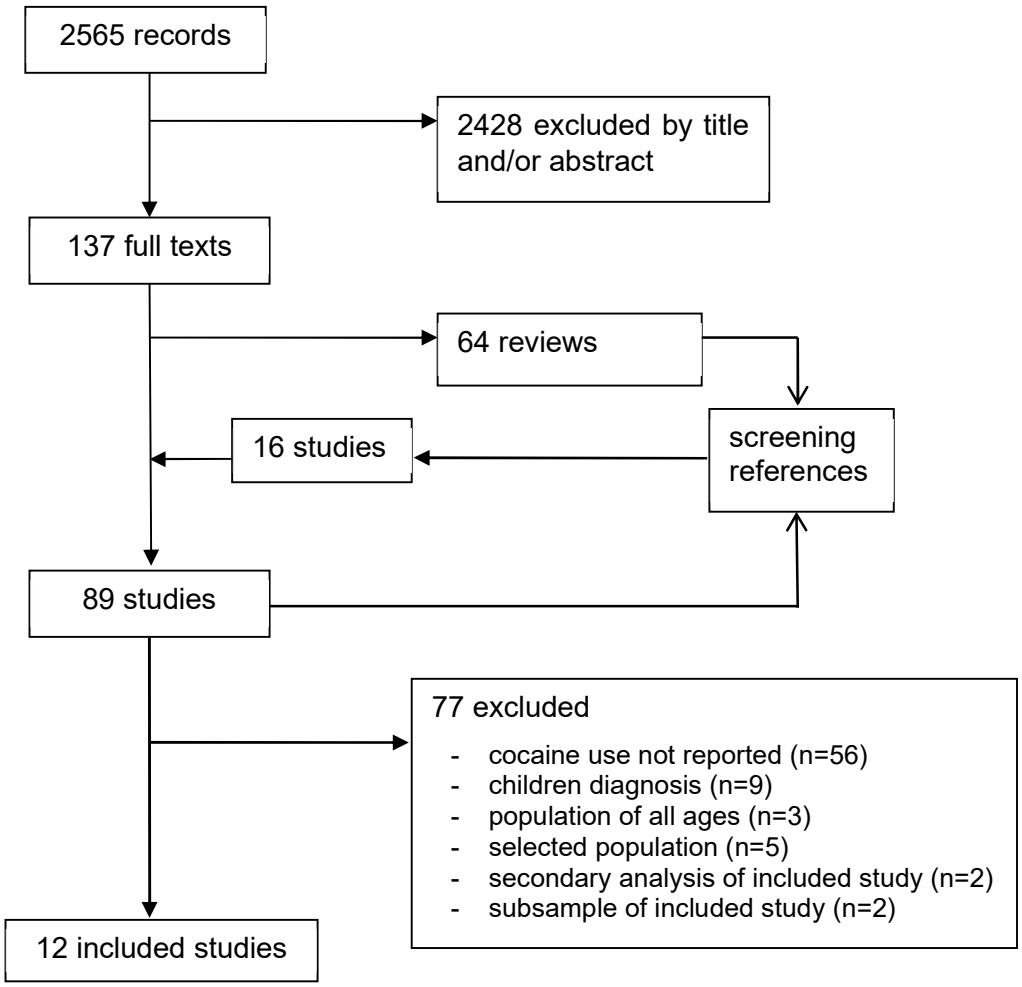


Figure 2. Meta-analysis on prevalence of cocaine use.

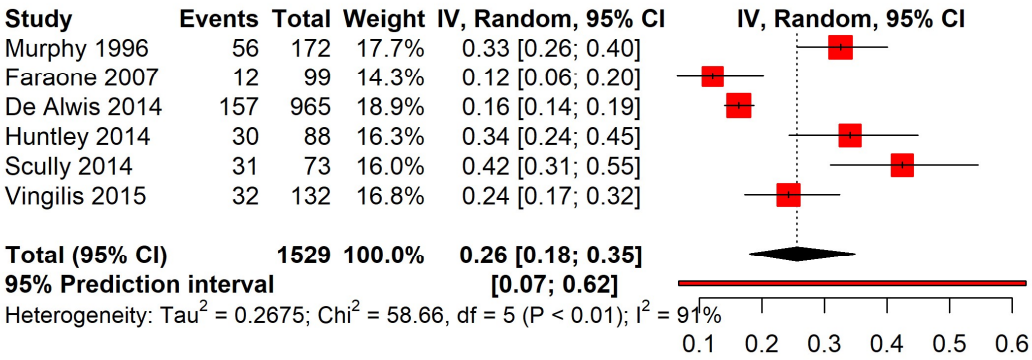
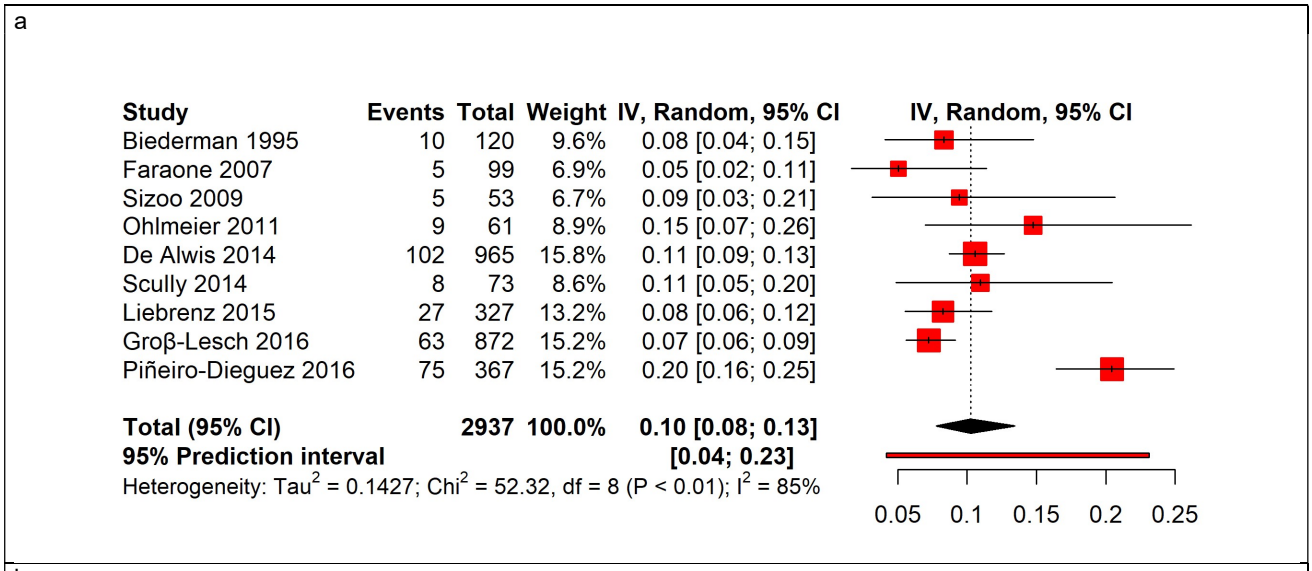


Figure 3. Meta-analysis on prevalence of cocaine use disorder including all studies (a), and omitting the study identified as outlier (b).

a



b

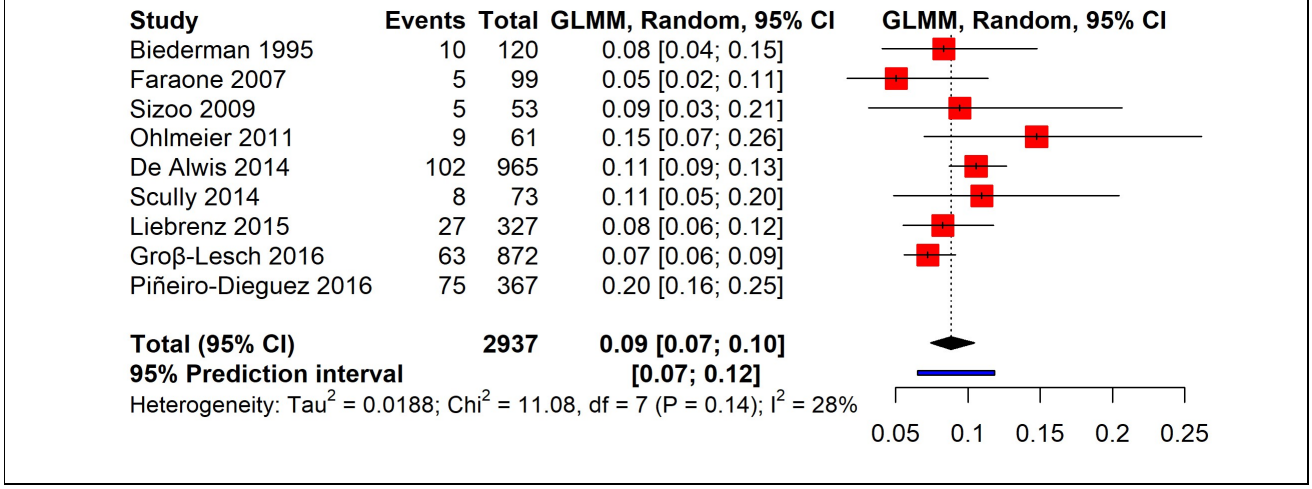
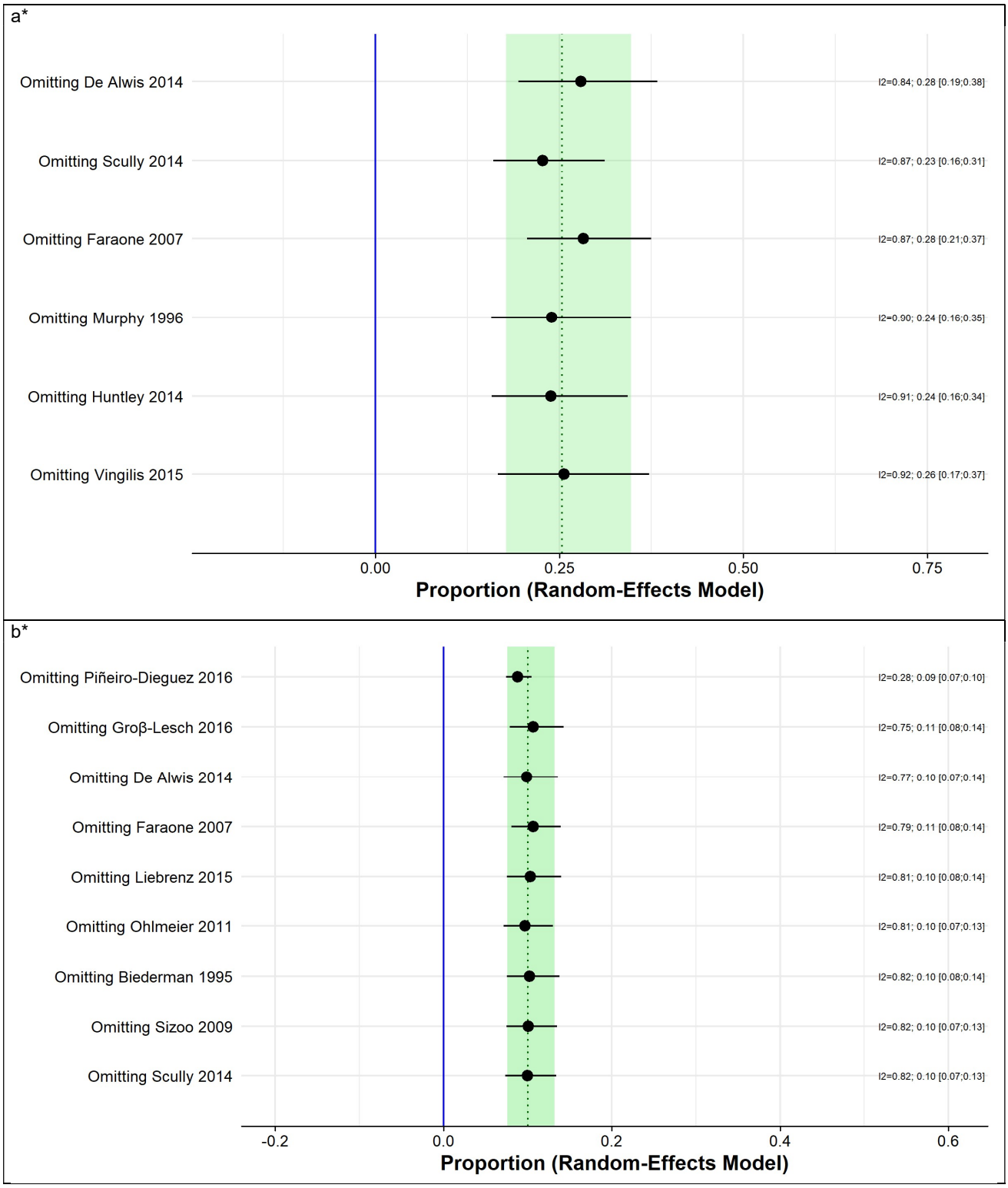


Figure 4. Leave-one-out pooled results and heterogeneity. Meta-analysis on prevalence of cocaine use (a) and prevalence of cocaine use disorder (b).



* Sorted by heterogeneity (from low to high)

Table 1. Characteristics of included studies

Study	Country	Mean age (years)	Sample	Inclusion criteria	Exclusion criteria	Recruitment method	Assessment of adult ADHD*	Assessment of cocaine use*	Adult ADHD sample** (n)	Cocaine use prevalence	Cocaine use disorder prevalence
Biederman 1995	US	35.7-38.5	clinical	age>18; clinical diagnosis of childhood-onset ADHD; chronic course; current diagnosis	-	referral	SCID; Kiddle SADS-E	SCID	120		n=10, 8.4%°
De Alwis 2014	US	49.1	community	non institutionalized citizens and non-citizens aged >18 years	-	NESARC survey	AUDADIS-IV; DSM-IV	DSM-IV	965	n=157, 16.3%°	n=102, 10.6%°
Faraone 2007	US	36.1	clinical and community	age>18	major sensorimotor handicaps; psychosis; inadequate English; IQ<80	referral; advertisements	SCID	SCID; DUSI	99	n=12, 12.1%^	n=5, 5.1%^
Groβ-Lesch 2016	Germany	30.7-36.7	clinical	age>18; onset before the age of 7 years; chronic course of ADHD; current diagnosis	any organic disorder with symptoms ADHD like; IQ<80; bipolar disorder; ADHD symptoms only during a psychiatric disorder; symptoms better accounted for by another diagnosis.	referral	SCID-I; ADHS-DC; WURS-K	SCID-I	872		n=63, 7.2%°
Huntley 2014	UK	25.2	clinical	age>18	IQ<70; severe mental illness or brain damage or pervasive developmental disorder.	referral	SCID for DSM-IV; DCS; ADHD-AFI	ADHD-AFI	88	n=30, 34%°	
Liebrenz 2015	Switzerland	38.7	clinical	adults ADHD; information on substance use		referral	WRI; WRAADDS; SCL-90-R; WURS-K; ADHS-SB	ICD-10	327		n=27, 8.3%°

Murphy 1996	US	32.0	clinical	age>18; at least 8 symptoms of ADHD; childhood onset; symptoms persistent into adulthood	schizophrenia, other psychoses, manic depression; epilepsy; head trauma needing hospital treatment; mental retardation; serious sensory or motor impairments	referral	SCID for DSM-III-R; SCL90-R; interview modules from DSM-III-R	SCID	172	n=56, 32.5%°	
Ohlmeier 2011	Germany	35.1	clinical	age>18; diagnosis of ADHD	acute psychosis; severe impairment by illness and not able to self-care	referral	DSM-IV-R; WURS-K; CAARS; Brown Attention Deficit Scales	DSM-IV-R; IDCL ICD-10 EuropASI QOD	61		n=9, 14.8%°
Piñeiro-Diéguez 2016	Spain	32.7	clinical	age>18; first ADHD diagnosis according to DSM IV-TR; minimum set of data (date of diagnosis, date of birth, gender)		referral; advertisements through retail network of the sponsor	DSM IV-TR	DSM IV-TR	367		n=75, 20.8%^^
Scully 2014	UK	30.9-31.8	clinical	adult ADHD diagnosis from multidisciplinary team assessment; details on offending history		referral	BAARS	self-reported	73	n=31, 42.5%°	n=8, 11.0%°
Sizoo 2009	Netherlands	29.0-35.7	clinical	age>18; first ADHD diagnosis according to semi-structured developmental history and DSM-IV criteria	psychotic disorder; bipolar disorder; IQ<80; insufficient inadequate Dutch; uncorrected visual or auditory impairment	referral	DSM-IV-TR; semi-structured developmental history	DSM-IV	53		n=5, 9.4%°
Vingilis 2015	Canada	-	community	age>18; ability to complete the interview in English		computer-assisted telephone survey	ASRS V-1.1; questions on previous ADHD diagnosis; questions on previous ADHD treatment	self-reported	132	n=32, 24.2%°	

* complete names of the tools are provided in the list of abbreviations.
** adult ADHD sample here provided was restricted to enrolled subjects with data on cocaine use or cocaine use disorder.
° lifetime
^ last month
^^ at the time of ADHD diagnosis

Table 2. Risk of bias of included studies

Study	Biederman 1995	De Alwis 2014	Faraone 2007	Groβ-Lesch 2016	Huntley 2014	Liebrenz 2015	Murphy 1996	Ohlmeier 2011	Piñeiro-Diéguez 2016	Scully 2014	Sizoo 2009	Vingilis 2015
Was the sample frame appropriate to address the target population?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were study participants sampled in an appropriate way?	yes	yes	yes	yes	yes	no	yes	yes	yes	no	yes	yes
Was the sample size adequate?*	no	yes	no	yes	no	yes	no	no	yes	no	no	no
Were the study subjects and the setting described in detail?	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
Was the data analysis conducted with sufficient coverage of the identified sample?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were valid methods used for the identification of the condition?	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Was the condition measured in a standard, reliable way for all participants?	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Was there appropriate statistical analysis?	yes	yes	no	no	no	no	no	no	no	no	no	Yes
Was the response rate adequate, and if not, was the low response rate managed appropriately?	yes	unclear	yes	yes	yes	yes	unclear	yes	yes	yes	yes	yes
Overall risk of bias	**low**	**moderate**	**low**	**low**	**low**	**low**	**moderate**	**low**	**low**	**moderate**	**low**	**low**

* Assuming a prevalence of 20%, with 95% CI and alpha=0.05, the sample size needed for the estimation of prevalence of cocaine use was 245 subjects; assuming a prevalence of 10%, with 95% CI and alpha=0.05, the sample size needed for the estimation of prevalence of cocaine use disorder was of 138 subjects.