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Autistic Spectrum Disorder symptoms in children and adolescents with Attention-deficit/hyperactivity disorder: a meta-analytical review

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Autistic Spectrum Disorder symptoms in children and adolescents with Attention-deficit/hyperactivity disorder: a meta-analytical review.

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Abstract

Background: Research identifies highly variable prevalence estimates for Autism Spectrum Disorder (ASD) in children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD), particularly between community and clinical samples, warranting quantitative meta-analyses to investigate the true prevalence of ASD in children and adolescents with ADHD.

Methods: Studies were identified through a systematic literature search of PsycINFO, MEDLINE and Web of Science through January 2018. Twenty-two publications met inclusion criteria (Total N=61,985). Two random effects meta-analyses were conducted: (1) to identify the proportion of children and adolescents with ADHD that met criteria for ASD; and (2) to compare the severity of dimensionally-measured ASD symptomology in children and adolescents with and without ADHD.

Results: The overall pooled effect for children and adolescents with ADHD who met threshold for ASD was 21%. There was no significant difference between community samples (19%) and clinical samples (24%) or between US studies versus those from other countries. Children and adolescents with ADHD had substantially more dimensionally-measured ASD traits compared with those who did not have ADHD (d=1.23).

Conclusion: The findings provide further evidence that ADHD and ASD are associated in nature. Clinical and research implications are discussed.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a neurodevelopmental disorder, characterised by attentional and/or hyperactive/impulsive traits (American Psychiatric Association (APA), 2013). The worldwide-pooled prevalence rate of ADHD in children is 5-7% (Polanczyk, Lima, Horta, Biederman & Rohde, 2007; Thomas, Sanders, Doust, Beller & Glasziou, 2015) making it one of the most common childhood disorders. Despite variability between countries, including higher rates identified within the US, the prevalence of ADHD is relatively comparable across US and non-US countries (Faraone, Sergeant, Gillberg & Biederman, 2003).

Childhood ADHD is associated with impaired function across a range of domains (Shaw et al., 2012) including poorer academic and educational outcomes (Loe & Feldman, 2007), and difficulties establishing and maintaining peer relationships (Hoza, 2007). Symptoms of ADHD are associated with impaired social problem-solving (Matthys, Cuperus, & van Engeland, 1999), social immaturity and peer rejection (Carpenter Rich, Loo, Yang, Dang & Smalley, 2009), social cognitive impairments, including emotional face and prosody perception (Uekermann, et al., 2010), emotional dysregulation, including more aggressive and negative behaviour (Wheeler-Maedgen & Carlson, 2000; DuPaul, McGoey, Eckert & VanBrakle, 2001), poorer social and communicational skills (Klimkeit et al., 2006), language impairment, specifically communication and language comprehension (Bruce, Thernlund & Nettelbladt, 2006), and deficits in working memory and

executive functioning (Kofler et al., 2011). Although the majority of studies have examined the functional impairments experienced by males with ADHD, deficits in interpersonal functioning are also present in females with the condition (Greene, et al., 2001).

High rates of co-occurring conditions have been identified for children and adolescents diagnosed with ADHD including mood, anxiety and conduct disorders (Cantwell, 1996; Spencer, 2006). Disruptive behaviour (which includes substance abuse), neurological, learning and cognitive difficulties, obsessive-compulsive and tic disorders have also been found to co-occur with ADHD at rates substantially above chance (Pliszka, Carlson, & Swanson, 1999; Kessler et al., 2006). Furthermore, high rates of neurodevelopmental conditions such as intellectual disability, tic disorder and social communication disorders, such as autistic spectrum disorder (ASD), are frequently found to co-occur with ADHD (Larson, Russ, Kahn, & Halfon, 2011; Cantwell, 1996; Jensen & Steinhausen, 2015; Young et al., 2018).

Autistic Spectrum Disorders (ASD)

The estimated prevalence of ASD, worldwide, is between 0.6 and 1% (Elsabbagh et al., 2012; Baird et al., 2006). ASD is a highly heritable neurodevelopmental condition characterised by persistent deficits in social communication and social interaction and restricted, repetitive patterns of behaviour, interests or activities (APA, 2013). Previous diagnostic systems (Diagnostic and Statistical Manual of Mental Disorders 4th Edition and International Classification of Diseases 10th Revision) distinguished between different subtypes of ASD, namely autistic disorder, Asperger's disorder, pervasive developmental disorder – not otherwise specified (PDD-NOS).

However, it was not possible to reliably distinguish between them (Lord et al., 2012; Berument, Rutter, Lord, Pickles & Bailey, 1999; Hattori et al., 2006). These conditions share common genetic aetiologies (Frazier et al., 2012; Mahjouri & Lord, 2012) and symptoms of ASD can change over time, leading to potential movement between diagnostic categories (Lord et al., 2006). As a result, DSM-5 subsumed all autistic subtypes under one overall diagnostic category of ASD (APA, 2013). Further, ASD is increasingly understood as a dimensional condition, representing the extreme of a trait dimension of autistic symptoms that extends throughout the general population, with no natural boundary between autism and non-autism (Constantino & Todd, 2003). Similar considerations have been raised for ADHD subtypes (Willcutt et al., 2012).

ADHD and ASD

Following social anxiety disorder, ADHD is the second most common co-occurring mental disorder in individuals diagnosed with ASD (Simonoff et al., 2008). There is significant variability between identified rates, ranging from 28.2% to 31% in community samples (Simonoff et al., 2008; Leyfer et al., 2006) and higher rates of 53% and 78% in clinical samples (Sinzig, Walter, Doepfner, 2009; Lee & Ousley, 2006).

Conversely, elevated levels of ASD symptoms have been identified in children and adolescents with ADHD. Studies examining the proportion of children with ADHD that also met criteria for ASD, have found rates between 4.68% - 32% (Riersen et al., 2007; Grzadzinski et al., 2011; Grzadzinski, Dick, Lord, & Bishop, 2016; Kochhar et al., 2011; Kotte et al., 2013; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008; Russell, Rodgers, Ukoumunne, & Ford, 2014) across clinical

and community samples, leading to considerable uncertainty as to the true rates. Variability in the frequency of reported ASD in child and adolescent ADHD populations is likely to be due to methodological differences including sampling, measures and thresholds (Reiersen, Constantino, Volk & Todd, 2007; Grzadzinski et al., 2011). This can impede the accurate assessment and identification of prevalence rates (Boyle, 1998; Hoy et al., 2012). Gender differences have been identified, with evidence suggesting that boys with ADHD experience more ASD symptoms than girls (Green et al., 2015; Mulligan et al., 2009). However, it is important to recognise that such findings may partly reflect difficulties with identifying ASD in girls (Lai, Lombardo, Auyeung, Chakrabarti & Baron-Cohen, 2015; Mandy et al., 2012).

Despite variation, the higher rates of co-occurrence identified in young people with ASD and ADHD dwarf rates identified in the general population for either condition independently, thus precluding that these co-occurrence rates happen by chance. A number of models of comorbidity have been proposed to explain these high rates of co-occurrence. For example, whether the presence of one condition increases the risk of the other (multiformity), that specific risk factors for both conditions are correlated, or that the two conditions share genetic risk factors but are different phenotypic expressions (pleiotropy). These models go some way in helping us understand the shared difficulties between the two conditions (Taurines et al., 2012).

Diagnostic Overlap

Children with ADHD share a number of difficulties with children with ASD, including social impairments (Santosh & Mijovic, 2004), language difficulties (Bishop & Baird, 2001), behavioural difficulties (Clark, Feehan, Tinline, & Vostanis, 1999; Gadow, DeVincent, Pomeroy & Azizian, 2005), attentional and overactivity problems (APA, 2013; Rao and Landa, 2014). Shared difficulties with communicative and stereotyped and repetitive behaviours have also been identified (Clark et al., 1999; Santosh & Mijovic, 2004). Distinguishing between similar presentations often relies on clinical judgement and an in depth understanding of both conditions. For example, a child who is hyperactive may be talkative to the extent that it is inappropriate. They may be aware that this is inappropriate but find it difficult to stop themselves. A child with ASD speaking in a monologue may also present as overly talkative, but is less likely to have the social awareness to realise that this is inappropriate. Therefore, the same observable behaviour may be the result of symptoms of ADHD, ASD or a combination of both.

There are behavioural parallels and diagnostic similarities between ADHD and ASD. (Gadow, et al., 2005; Holtmann, Bölte, & Poustka, 2007; Simonoff et al., 2008). This can lead to difficulties distinguishing the conditions from one another (Buitelaar, van der Wees, Swaab-Barneveld, & van der Gaag, 1999; Grzadzinski, Dick, Lord, & Bishop, 2016) and misdiagnosis (Sikora, Hartley, McCoy, Gerrard-Morris & Dill, 2008), which impacts upon clinical care. The domain of restricted, repetitive and stereotyped patterns of behaviour, rather than social communication difficulties, supports diagnostic discrimination between the two disorders (Hartley & Sikora, 2009).

Prior to the publication of the DSM-5 (APA, 2013), comorbidity between the two disorders was not permitted, despite recognition that symptoms overlap. The DSM-IV (APA, 2000) identified that children often receive a diagnosis of ADHD prior to a diagnosis of ASD. It also prohibited the diagnosis of ADHD if symptoms of inattention and hyperactivity occurred during the course of a pervasive developmental disorder. Therefore, despite the overlapping symptomology, diagnostic similarities and whether an individual met the diagnostic criteria for both ADHD and ASD, a dual diagnosis could not be given. The DSM-5 takes more recent research into account and allows for a dual diagnosis of ADHD and ASD.

Current Study

Now that a dual diagnosis of ADHD and ASD is accepted, there is a need to develop understanding as to prevalence rates and clinical implications of co-morbid ADHD and ASD. To date only a few studies have attempted to identify the prevalence rate of ASD in children and adolescents with ADHD. These studies have utilised varying methodologies and assessments of ASD, resulting in discrepancies between the findings. Therefore, combining the findings from these studies may provide a more accurate reflection of the true proportion of children and adolescents with ADHD who also experience ASD symptoms, irrespective of diagnostic category. More specifically, it will identify the frequency of ASD symptoms found in children and adolescents with ADHD.

Research Questions:

- What proportion of children and adolescents with ADHD meet diagnostic criteria for ASD?

- What is the mean difference of dimensionally-measured ASD symptoms in children with ADHD and children without ADHD?

Methods

Locating studies

The 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines were followed (Moher, Liberati, Tetzlaff & Altman, 2009; Liberati et al., 2009). The literature search was conducted in January 2018. Terms for ADHD ("attention deficit hyperactivity disorder" OR ADHD OR ADD OR "hyperkinetic disorder") and ASD (ASD OR "Autism" OR "Asperger's" OR PDD OR PDD-NOS) were searched independently within the titles and abstracts of articles within the following databases; PsycINFO, MEDLINE and Web of Science. These independent searches were then combined to identify articles who reported both terms for ADHD and terms for ASD within their titles and abstracts.

Identified abstracts were reviewed for their suitability in accordance with the eligibility criteria described below. The reference lists of included studies were searched to identify papers that met inclusion criteria, but were not identified in the electronic database search.

Study Selection

In the first instance, duplicate articles were removed and the inclusion and exclusion screening process was conducted. The screening process, risk of bias and data extraction were completed

independently by two researchers (JH and AF), who compared their results and sought a consensus when there was disagreement. Any dilemmas that could not be resolved between the two raters were raised with the supervising author (WM). Based on risk of bias criteria by Hoy and colleagues (2012), only one study was identified to have no risk of bias (Jensen et al., 2015). All other studies were identified to hold the same risk of bias. Due to a lack of variability of risk of bias between studies no bias comparison analysis was warranted. Studies were included if they were peer reviewed articles written in English, had samples aged between 2-19 years, used either clinical or community populations, and reported the appropriate statistical data for meta-analyses, specifically means, standard deviations and percentages. Studies were not excluded based on their country of origin, sample size or publication date.

In some instances, studies utilised the same population sample, therefore, in order to reduce bias the study with the highest N was included (Green et al., 2015; Reiersen, et al., 2007; Tye et al., 2014) and the smaller study removed (Reiersen, Constantino & Todd, 2008; Green et al., 2016, Green et al., 2017; Tye et al., 2016). One study did not use a validated measure of ASD (Santosh & Mijovic, 2004) and therefore was excluded from the analysis. Five studies failed to report the required statistical data and were contacted directly (Clark et al., 1999; Clark et al., 2011; Hattori et al., 2006; Mohiuddin et al., 2010; Mulligan, Butler, Sorohan, Fitzgerald & Gill, 2005). The requests yielded no response and therefore these papers were omitted from further analysis. In two cases, having a pre-existing diagnosis of ASD was an exclusion criterion and therefore these articles were omitted (Carpenter Rich et al., 2009; Mayes et al., 2009).

For studies where the data was split by ADHD presentation or gender, pooled means and standard deviations were calculated (Reiersen et al., 2007; Ayaz, Gökçe, Gümüştaş, & Ayaz, 2014; Mayes, Calhoun, Mayes, & Molitoris, 2012). In studies that utilised multiple measures to identify social communication difficulties (Ayaz et al., 2014; Luteijnet al., 2000; Kochhar et al., 2010; van Steijn et al., 2014), only data from the most reliable and valid measure of autistic symptoms was used.

Data Analysis

Meta-analyses were conducted using STATA Version 14 (Statacorp, 2015). For both analyses, homogeneity was not assumed due to the methodological variability between studies and therefore a random-effect model was fitted to the data to allow for variation in the true effect size (Brockwell & Gordon, 2001). Heterogeneity was assessed using the χ^2 and I^2 statistics.

To address the first research question (what proportion of children and adolescents with ADHD also meet diagnostic criteria for ASD?), a proportional meta-analysis using the STATA 'metaprop' command was conducted on studies that reported estimated prevalence rates of ASD within children and adolescents diagnosed with ADHD. Along with ASD diagnostic tools, including the Autism Diagnostic Observation Schedule - Version 2 (ADOS-2) (Lord, Luyster, Gotham, & Guthrie, 2012; Lord et al., 2012), Autism Diagnostic Interview-Revised (ADI-R) (Rutter, Le Couteur, Lord, 2003), International Classification of Diseases – 10 (ICD-10) (World Health Organization, 1994), the Development and Well-being assessment (DAWBA) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000), and parents who had been informed by a mental health professional that their

child had ASD, ASD screening tools (ASD-Tics, ADHD and other Comorbidities Inventory (A-TAC) (Hasson et al., 2005), Social Communication Questionnaire (SCQ) (Rutter, Bailey & Lord, 2003), Social Responsiveness Scale (SRS) (Constantino & Gruber, 2012) and Child Behaviour Checklist's (CBCL) (Withdrawal, Social Problems and Thought problems *T*-scores) (Achenbach & Edelbrock, 1991) were also included due to their clinical validity, specifically their sensitivity and specificity of identifying ASD (Bölte, Westerwald, Holtmann, Freitag, & Poustka, 2011; Charman et al., 2007; Hansson et al., 2005; Larson et al., 2010; Biederman et al., 2010). Individuals meeting clinical threshold for ASD on screening tools were considered appropriate to include within the study.

A second meta-analysis was conducted using the STATA 'metan' command to address the second research question (what is the mean difference of dimensionally-measured ASD symptoms in children with ADHD and children without ADHD?). A pooled standardised mean difference was calculated.

For both meta-analyses, further exploratory subgroup meta-analysis was conducted when significant heterogeneity was identified between studies. Subgroups were defined according to variables identified by the study team as plausible influences of estimated prevalence rates. Firstly, due to there being higher rates of comorbidity in clinically referred populations, we compared papers drawing on clinical and community samples (Low, Cui, & Merikangas, 2008). Secondly, the type of measure used to identify ASD caseness can affect the number of symptoms identified and diagnostic outcome (Boyle, 1998; Hoy et al., 2012) so papers were compared depending on whether they had used a screening questionnaire or a more comprehensive

diagnostic test. Thirdly, due to the variability in prevalence rates between US and non-US countries (Faraone et al., 2003) samples were divided by country (US vs Non-US).

Results

A flow diagram of the search strategy is presented in Figure 1. A total of 22 studies met inclusion criteria for the two meta-analyses and were included in study. After the screening and evaluation of papers, 13 studies were included within the final proportion meta-analysis, with a total sample size of 57,058 participants from six countries. A description of the studies is provided in Table 1. After further evaluation, 15 studies were also included within the mean difference meta-analysis, whose final samples comprised of 4,927 participants. A description of the studies is provided in Table 2.

[Figure 1]

[Table 1]

[Table 2]

Proportional Meta-analysis

The results of the meta-analyses are summarised in Table 3. The overall pooled effect size was 0.21 [0.18-0.24], indicating that 21% of children and adolescents with ADHD also meet respective thresholds for ASD. The Forest Plot is presented in Figure 2.

The I^2 statistic was 87.25%, $p<.01$ indicating that there was a high amount of heterogeneity between the studies (Higgins, Thompson, Deeks, & Altman, 2003), therefore further analysis was conducted in order to investigate influences on variability of the pool prevalence estimate.

Clinical versus Community ADHD samples

Studies that used a clinical sample (Craig et al., 2015, Grzadzinski et al., 2016, Grzadzinski et al., 2011, Kochhar et al., 2010, Kotte et al., 2013, Salley et al., 2015) tended to find a higher prevalence of ASD (see Table 3) compared to those that used a community sample (Green et al., 2015, Jensen et al., 2015, Lichtenstein et al., 2010, Reiersen et al., 2007, Ronald et al., 2008, Russell et al., 2014, Zablotsky et al., 2017) (0.19 ; 95% CI, 0.16-0.22). However, as is shown in Table 3, there was no evidence that this difference is significant as the confidence intervals for these pooled estimates overlapped. There was a significantly high level of heterogeneity among the studies that used both clinical samples and community samples.

Screening Tools versus Diagnostic Tools

Studies were divided into those that used screening tools (Craig et al., 2015, Green et al., 2015, Grzadzinski et al., 2011, Kochhar et al., 2010, Kotte et al., 2013, Lichtenstein et al., 2010, Reiersen

et al., 2007, Ronald et al., 2008, Zablotsky et al., 2017) and those that used more comprehensive diagnostic tests (Grzadzinski et al., 2016, Jensen et al., 2015, Russell et al., 2014, Salley et al., 2015). As is shown in Table 3, studies that used screening tools as their primary outcome measure of ASD symptoms identified a similar random pooled effect size compared to studies that used diagnostic instruments to evaluate the presence of ASD symptoms. There were also similar rates of heterogeneity between those studies that used screening tools (80.10%) and those that used diagnostic tools (86.52%).

US versus Non-US Studies

Variations in ADHD prevalence rates have been identified between US and non-US studies (Faraone et al., 2003). As shown in Table 3, US studies (Grzadzinski et al., 2011, Grzadzinski et al., 2016, Kotte et al., 2013, Reiersen et al., 2007, Salley et al., 2015, Zablotsky et al., 2017) were identified to have a similar random pooled effect size to non-US studies (Craig et al., 2015, Green et al., 2015, Jensen et al., 2015, Kochhar et al., 2010, Lichtenstein et al., 2010, Ronald et al., 2008, Russell et al., 2014). High levels of heterogeneity were identified in both US studies (78.61%) and non-US studies (89.86%), with US studies contributing to more of the heterogeneity.

[Figure 2]

[Table 3]

Mean Difference Meta-analysis

The overall pooled standardised mean difference of ASD symptoms between children and adolescents with ADHD and those without ADHD was 1.23, 95% CI [0.94– 1.51], illustrated in the Forest Plot in Figure 3. There was a high level of heterogeneity between the studies (I^2 = 93.4%),therefore further subgroup analyses were conducted as a preliminary exploration of this variability (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). A more detailed investigation into the identified variability was restricted due to the small number of studies included within the study.

[Figure 3]

Clinical versus Community ADHD samples

Due to known differences, clinical and community samples studies were separated by sample type (Low, Cui, & Merikangas, 2008). As seen in Table 3, studies that used a clinical sample (Ayaz et al., 2014; Craig et al., 2015, Kochhar et al., 2010, Kotte et al., 2013, Kopp et al., 2011, Lutejin et al., 2000; Mayes et al., 2012; Mulligan et al., 2009, Nijmeijer et al., 2009, Salley et al., 2015, Tye et al., 2014) were identified to have a higher pooled mean difference than studies that used a community sample (Green et al., 2015, Grzadzinski et al., 2011, Reiersen et al., 2007, van der Meer et al., 2012, van Steijn et al., 2014). Confidence intervals indicate that the pooled mean difference between the two groups was not significant. There was a significantly high level of heterogeneity between both clinical and community samples. Greater variation was identified within clinical samples than community (see Figure 4).

[Figure 4]

Discussion

To the authors knowledge these are the first meta-analyses to consolidate the literature on rates of ASD and ASD symptoms in children and adolescents with ADHD. High levels of heterogeneity were identified between both the proportional studies and mean difference studies, therefore further subgroup analysis was conducted to better understand this variability. Although it has been identified that five or more studies are sufficient to achieve adequate power to detect effects within random effects meta-analyses (Jackson & Turner, 2017), the current meta-analyses, with small numbers of studies is subject to low power.

The proportional meta-analysis identified that 21% of the children and adolescents with ADHD also met criteria for ASD. This is comparable with Ronald and colleagues' (2008) findings using a robust diagnostic measure, and only slightly higher than the 15% identified by Grzadzinski and colleagues (2016) who utilised the "gold standard" diagnostic tools. Thus, both ASD and traits of ASD can be considered as a common occurrence in children and adolescents with ADHD.

To put this in context, a number of co-occurring conditions have been identified to coexist with ADHD (Patel, Patel & Patel, 2012). For example, intellectual disability has been identified to co-occur in up to 46% of young people with ADHD (Larson et al., 2011). Depression and depressive symptomology have been found within 10-40% (Spencer, Biederman & Wilens, 1999) of children and adolescents with ADHD. Prevalence rates of ADHD and comorbid anxiety disorders have been identified, ranging between 5-50% (Pliszka et al., 1999; Mancini,

Van Ameringen, Oakman, & Figueiredo, 1999) with a large proportion having multiple anxiety disorders (Spencer, Biederman & Wilens; 1999). Conduct Disorder and Oppositional Defiant Disorder are two of the most commonly identified comorbid disorders, with rates ranging between 15% and 59% respectively in school-aged children (Wilens et al., 2002). Therefore, ASD symptoms form part of the wider complexity of the multimorbid conditions associated with ADHD.

Due to the high levels of heterogeneity, studies were divided by their sample type (clinical vs. community), ASD measurement type (screening vs diagnostic) and country of origin (USA vs. non-US) as can be seen in Table 1. Moderate to high heterogeneity was identified within all subgroups. Due to the small number of studies included within the meta-analysis and subsequent subgroup analyses, there are limited conclusions that can be drawn to accurately explain the variability between studies. Nevertheless, it is interesting to note that studies using screening instruments identified a similar ASD prevalence (22%) as those using more comprehensive diagnostic assessments (20%). One interpretation of this is that screening measures are useful tools for identifying ASD in ADHD populations. However, it should be acknowledged that individuals identified as having ASD via screening questionnaires may not fully overlap with those identified as having ASD via diagnostic assessment. This should be empirically tested to understand more about the accuracy of ASD screening measures when used in those with a primary diagnosis of ADHD.

The results from the second meta-analysis identified an overall pooled standardised mean difference of ASD symptoms, between children and adolescents with ADHD and those

without, of 1.23, representing a large effect. There was a high level of heterogeneity between the studies and therefore further subgroup analysis (clinical vs. non-clinical) was conducted as a preliminary attempt to explore this variability. High heterogeneity was identified between the studies in both sub-groups. Despite different methodologies and variability between studies, higher rates of ASD symptomology were identified within the ADHD groups compared with their non-ADHD groups in all cases.

Two possible explanations could be proposed to explain the current findings. Firstly, it is likely that measures used to identify ASD symptomology found characteristics of ADHD that diagnostically overlap, such as social impairment (Santosh & Mijovic, 2004). These overlaps may have impacted on the rates of comorbidity identified. However, ASD diagnostic tools such as the ADI-R, ADOS-2 and DAWBA would have identified the presence of restrictive, repetitive and stereotyped patterns of behaviour which are not understood to be diagnostic features of ADHD (Hartley & Sikora, 2009). Screening measures such as the SCQ and SRS identified comparable rates of ASD within children and adolescents with ADHD, indicating these were also effective in distinguishing between the two disorders (Kochhar et al., 2011; Kotte et al., 2013). Thus, it is unlikely that the comorbidity rates were substantially inflated as a result of overlapping symptoms.

The second possible explanation is that other shared causal processes between the two conditions can account for the high rates of overlapping symptoms (Mayes et al., 2012) and behaviours (Ronald et al., 2008). As well as the shared diagnostic overlap (APA, 2000; APA, 2013), research has identified shared genetic origins for ADHD and ASD conditions (Taurines

et al., 2012; Reiersen, Constantino, Grimmer, Martin & Todd, 2008; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008; Rommelse, Franke, Geurts, Hartmann & Buitelaar, 2010), leading some to consider that they may in fact be two aspects of the same disorder (Lee et al., 2013, van de Meer et al., 2012). However, genetics alone cannot account for the rates of co-occurrence. Genome-wide association studies have only identified a moderate association between ADHD and ASD (r_G = 0.360) (Grove et al., 2017) and underlying genetic risk factors may differ between the two conditions (van Steijn et al., 2012). Therefore, it may be that the same genes, or combination of genes, in conjunction with environmental interactions are responsible for creating distinct ADHD and ASD phenotypes (Kiser, Rivero & Lesch, 2015).

ADHD and ASD can be dissociated across a range of cognitive domains on the basis of their neural responses. For example, differences in response time variability under slow and fast incentive conditions (Tye et al., 2015), neurophysiological responses to faces and gaze direction (Tye et al., 2013) and emotional faces (Tye et al., 2014), and in attentional orientating and inhibitory control (Tye et al., 2014). Overall, the work from Tye and colleagues identifies distinct cognitive functioning between the two conditions. However, children with both ASD+ADHD have the unique profiles of the 'pure' disorders, acting like an additive condition.

Overall, the findings from this study support our understanding of the extent to which these two conditions are associated in nature. Based on the current study it is not possible to determine causal mechanisms, however assumptions can be made in regard to shared genetic effects, supporting previous research (Stergiakouli et al., 2012).

It is also important to note that only two of the included studies utilised DSM-5 criteria (Grzadzinski et al., 2016 and Salley et al., 2015) for ADHD and ASD. There was no obvious pattern from this very small sample of DSM-5 studies; the identified prevalence rates from these studies represent one of the lowest (15%) and highest (40%) rates found. In light of the changes within the DSM-5, and upcoming International Classification of Diseases - 11th revision, which have lowered the symptom threshold for ADHD but increased the requirements for a diagnosis of ASD, specifically the presence of restricted, repetitive and stereotyped behaviours (APA, 2013), it is not clear how the co-occurring prevalence rates of these conditions will be affected. It is possible that the prevalence of ADHD within child and adolescent populations will increase and consequently increase the number of children who may be identified to have co-occurring ASD symptomology. Alternatively, the requirement that restricted, repetitive and stereotyped behaviours be present for a diagnosis of ASD, which are not characteristics of ADHD, may reduce diagnostic comorbidity. The latter explanation may account for the relatively lower prevalence rates identified within Grzadzinski and colleagues 2016 study.

Limitations and Recommendations

A limitation of the current study is the relatively small number of papers (N=22, total sample=61,985 from both proportional and mean difference analyses) that were available to include within the meta-analysis. Methodologies between studies varied considerably and this may have affected the overall findings (Lipsey & Wilson, 2001). The limited number of available studies also had an impact on the ability of the authors to explore the observed heterogeneity between studies. More studies that utilise more robust methodologies are needed to investigate the rates of ASD within children and adolescents with ADHD.

The current study found that there was no significant difference between screeners and more robust diagnostic assessments when assessing for ASD symptomology in young people with ADHD. This suggests that overall the screeners used in this study demonstrate clinical utility comparable to that of the diagnostic measures used. However, it should be noted that the current ASD measures were developed under the previous categorical diagnostic understanding of ASD and may not be the most effective tools for measuring a continuum of symptoms, in accordance with our current understandings of ASD. For example, the SCQ was developed to distinguish between different ASDs and therefore may not be as effective at identifying milder cases on the spectrum (Fernandopulle, 2011). Current tools to measure ASD should be validated (against clinical diagnoses) in order to ascertain their suitability at identifying a continuum of ASD symptoms. New ASD measurement tools may be required moving forward.

Consideration should also be given to the population sample being used. Five of the studies included within the mean difference analysis utilised comparisons between general population and clinical samples (Ayaz et al., 2014; Grzadzinski et al., 2011; Kochhar et al., 2011; Mulligan et al., 2009; Nijmeijer et al., 2009). Sensitivity and specificity of the SCQ, in particular, has been found to differ between clinical (Allen, Silove, Williams & Hutchins, 2007) and community samples (Chandler et al., 2007) which may have contributed to the observed variability and impacted on the identified rates.

Clinical and Research Implications

The high rates of comorbidity between the two disorders indicate the necessity to consider the presence of ASD symptomology when working clinically with children and adolescents with ADHD. Future research attempting to better understand the underlying pathophysiology of ADHD or ASD should remain mindful of the high rates of co-occurring symptoms.

Specifically, when working with children and adolescents with ADHD, psychological interventions should consider restrictive thinking styles commonly associated with ASD such as detailed-focus processing style (Happé & Frith, 2006) and a limited Theory of Mind (Happé & Frith, 1995). Furthermore, therapeutic interventions that require children with ADHD to generalise learnt strategies or skills within multiple contexts may be particularly difficult for children who also experience symptoms of ASD (Rogers, 2000). Further research into the efficacy of pharmacological and psychosocial interventions for ADHD should be reviewed in order to accommodate for the potential presence of ASD symptomology.

As more research papers utilising the DSM-5 criteria for both ADHD and ASD are published, a further meta-analysis should be repeated to determine whether rates of ASD in young people with ADHD are comparable with rates identified in the current paper.

Treatment Implications

Due to high comorbidity between the two disorders it would be appropriate for specialist services to expand their service provision to accommodate for these two comorbid conditions. These findings lend support for a move away from specialist ADHD and ASD services to wider neurodevelopmental specialist services that can address the common co-occurring difficulties identified within children and adolescents with ADHD. Future research

could expand on the findings of the current study and the potential benefits of developing neurodevelopmental specialist services.

Currently, for young people there are recommended pharmacological treatments for severe ADHD (NICE, 2018), but there are no recommended medications that tackle the core features of ASD. As the co-occurrence of ADHD and ASD results in greater functional impairments than each condition individually (Guttmann-Steinmetz, Gadow & DeVincent, 2009; Gadow, DeVincent & Schneider, 2009; Jang et al., 2013), treatment is then reliant on effective psycho-social interventions for young people with both conditions. Unfortunately, there is limited evidence as to the effectiveness of psycho-social interventions for young people with both ADHD and ASD (Murray, 2010). Future non-pharmacological interventions should be adapted to attend to the higher rates of cognitive, behavioural and functional impairments.

Conclusion

This is the first meta-analysis to investigate the rates of ASD in young people with ADHD. Findings from the current study further our understanding of the relationship between ADHD and ASD. Acknowledging and addressing the presence of ASD symptomology when working with children and adolescents with ADHD will more accurately inform treatment interventions, educational strategies and service development.

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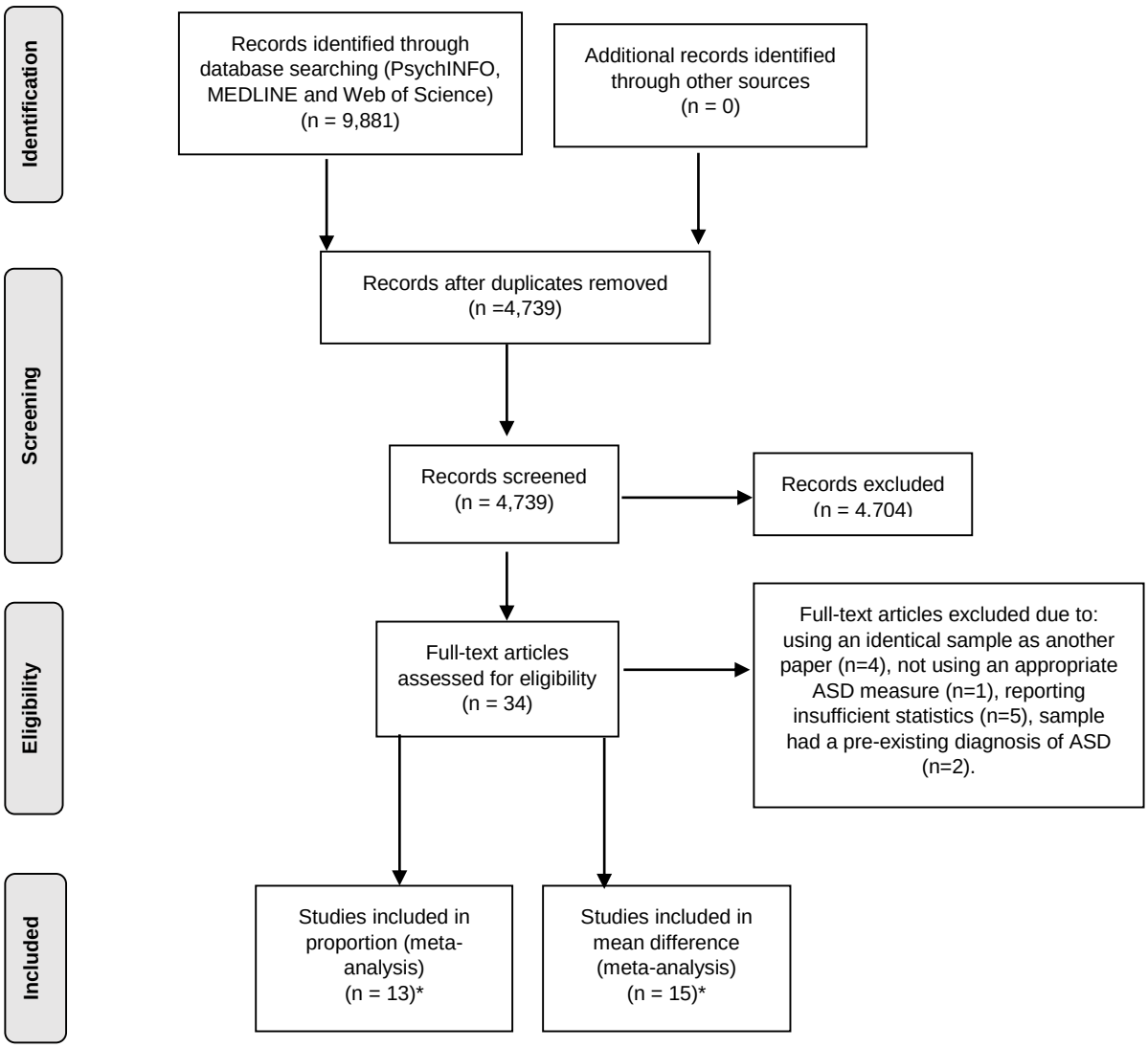
Figure 1. *Search strategy (Moher, Liberati, Tetzlaff & Altman, 2009)*



* A total of 22 studies were included within the two meta-analyses. Craig et al., 2015, Green et al., 2015, Grzadzinski et al., 2011, Kochhar et al., 2010, Reiersen et al., 2007 & Salley et al., 2015 were included within both meta-analyses.

Figure 2. *Forest Plot for the proportion of children and adolescents with ADHD that also met symptom threshold for ASD.*

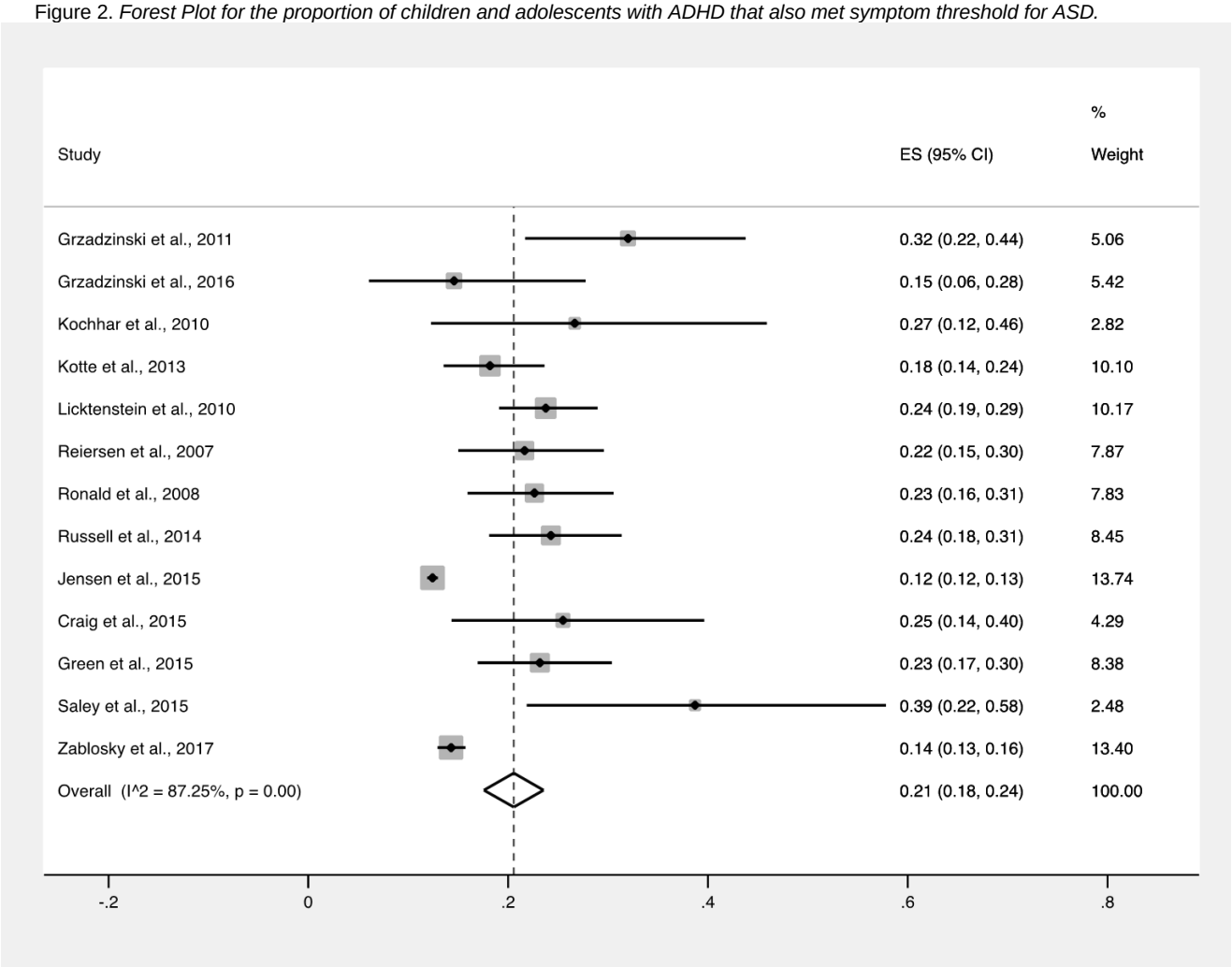


Figure 3. *Forest Plot of mean difference of ASD symptoms between children and adolescents with and without ADHD.*

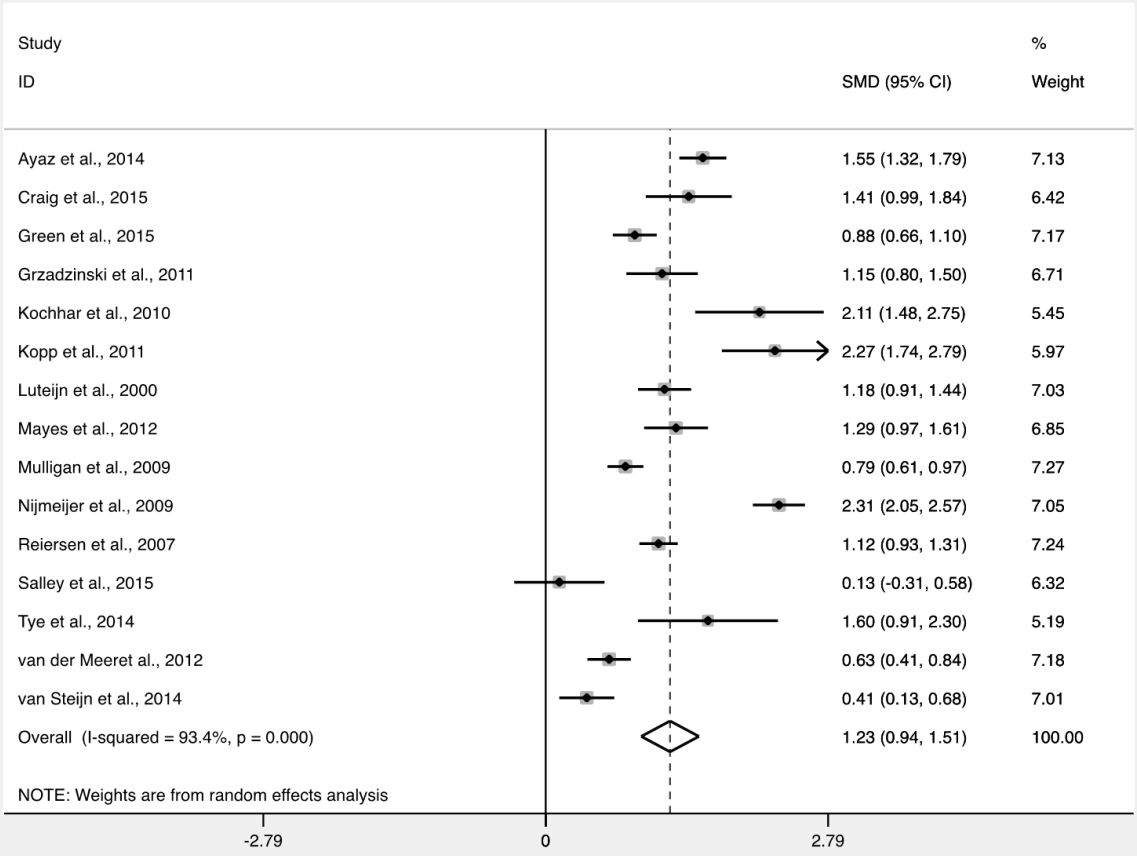


Figure 4. *Forest Plot of mean difference of ASD symptoms between clinical and community samples.*

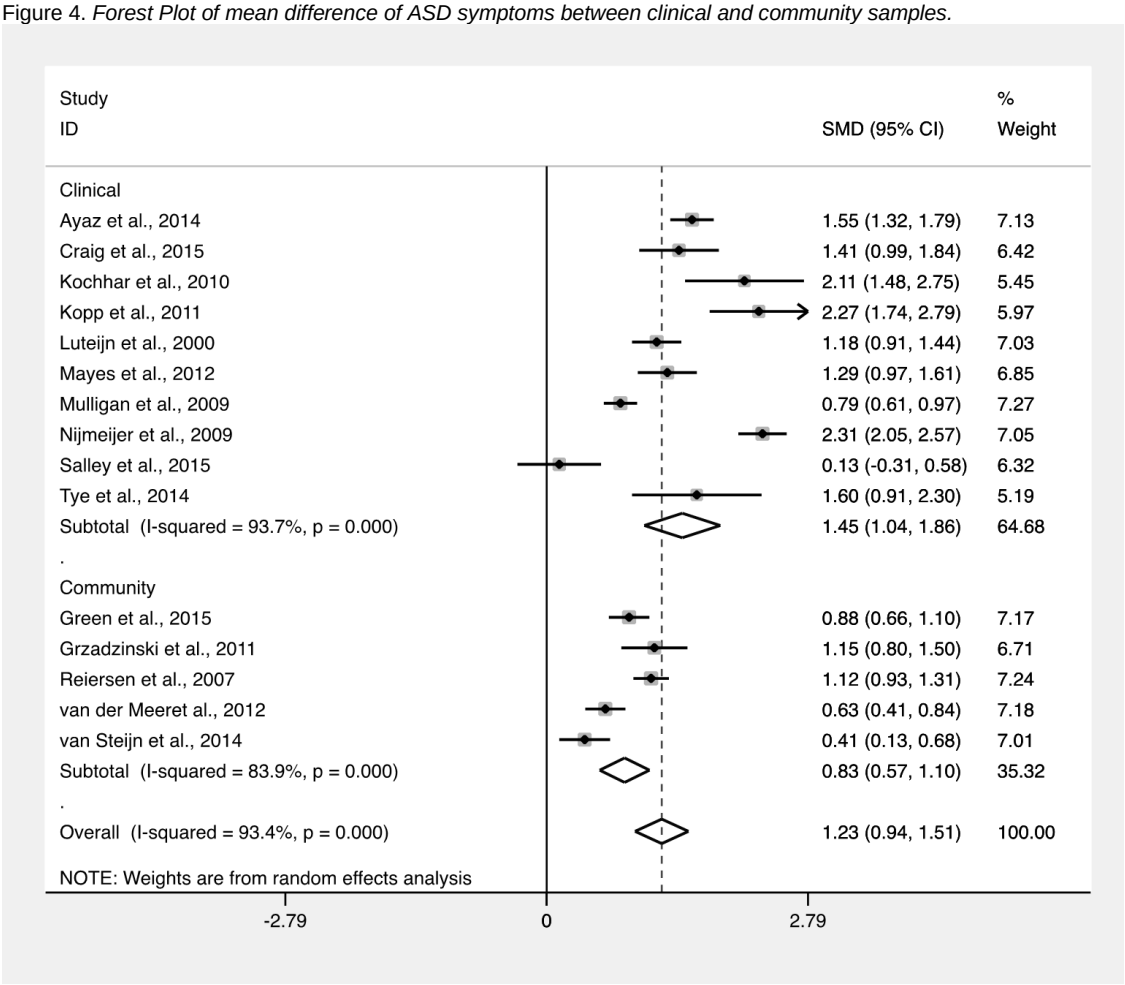


Table 1. *Summary of studies included in proportion meta-analysis*

Study	Country	Total Sample Size	Sample Source	Diagnostic manual used	Age of original sample in years	ASD outcome measure*	With ASD n/N (%)
Craig et al., 2015	Italy	181	Clinical	DSM-IV	7-9	SCQ	13/51 (25.7)
Green et al., 2015	Australia	362	Community	DISC-IV	6-10	SCQ	38/164 (33)
Grzadzinski et al., 2016	US	212	Clinical	DSM-5	4-18	ADOS + ADI-R	7/48 (15)
Grzadzinski et al., 2011	US	144	Clinical	DSM-IV TR	7-17	SRS	24/75 (32)
Jensen et al., 2015	Denmark	14,825	Community	ICD-10	4-18	ICD-10	1,842/14,825 (12.4)
Kochhar et al., 2010	UK	60	Clinical	DSM-IV	9-15	SCQ	8/30 (28)
Kotte et al., 2013	US	469	Clinical	DSM-III-R	6-18	CBCL	44/242 (18.2)
Lichtenstein et al., 2010	Sweden	17,036	Community	DSM-IV	9-12	A-TAC	72/303 (23.7)
Reiersen et al., 2007	US	946 twins	Community	DSM-IV	7-19	Pooled SRS	29/134 (21.6)
Ronald et al., 2008	UK	6107	Community	DSM-IV	7.88 (mean)	DAWBA	31/137 (22)
Russell et al., 2014	UK	14,043	Community	Diagnosis	6-8	Health Professional confirmation	42/173 (24.1)
Salley et al., 2015	US	209	Clinical	DSM-5	3-18	ADOS	12/31 (40)
Zablotsky et al., 2017	US	2464	Community	DSMIV	4-17	Health Professional confirmation	352/2464 (14)

* ADI-R= Autism Diagnostic Interview-Revised; ADOS-2 = Autism Diagnostic Observation Schedule- Version 2; A-TAC = ASD-Tics, ADHD and other Comorbidities Inventory; DAWBA = Development and Well-being assessment; SCQ = Social Communication Questionnaire; SRS = Social Responsiveness Scale.

Table 2. *Summary of studies included in mean difference meta-analysis.*

Study	Country	ADHD Group Sample	Control Group Sample	Diagnostic manual used	Age of original sample in years	ASD outcome measure	ADHD Group Mean (SD)	Control Group Mean (SD)
Ayaz et al., 2014	TUR	Clinical	Community	DSM-IV	6-17	SRS Total (Pooled)	83.12 (25.92) (n=238)	45.99 (20.22) (n=149)
Craig et al., 2015	ITA	Clinical	Clinical	DSM-IV	7-9	SCQ Total	11.4 (4.9) (n=51)	4.9 (4.3) (n=56)
Green et al., 2015	AUS	Community	Community	DSM-IV	6-10	SCQ Total	10.3 (7.2) (n=164)	5.3 (4.0) (n=198)
Grzadzinski et al., 2011	US	Clinical	Community	DSM-IV	7-17	SRS Total	50.9 (5.8) (n=75)	44 (6.2) (n=69)
Kochhar et al., 2010	UK	Clinical	Community	DSM-IV	9-15	SCQ Total	11.6 (5.5) (n=30)	2.8 (2.1) (n=30)
Kopp et al., 2011	SE	Clinical	Clinical	DSM-IV	6-16	ASSQ Total (females)	13 (6) (n=37)	3 (3) (n=58)
Luteijn et al., 2000	NL	Clinical	Clinical	DSM-IV	5-12	ABC Total	25.5 (19.8) (n=152)	6.5 (9.2) (n=113)
Mayes et al., 2012	USA	Clinical	Clinical	DSM-IV	2-16	CASD Total (Pooled)	4.77 (2.96) (n=158)	1.3 (1.8) (n=63)
Mulligan et al., 2009	8 European Countries	Clinical	Community	DSM-IV	5-17	SCQ Total	8.49 (6.23) (n=821)	3.89 (2.77) (n=149)
Nijmeijer et al., 2009	NL	Clinical	Community	DSM-IV	5-19	CSBQ Total	72 (13.1) (n=256)	46.4 (6.2) (n=147)
Reiersen et al., 2007	USA	Community	Community	DSM-IV	7-19	SRS Total (Pooled)	60.09 (30.88) (n=134)	33.0 (23.0) (n=812)
Salley et al., 2015	US	Clinical	Clinical	DSM-5	3-18	ADOS	5.45 (4.12) (n=31)	4.9 (4.07) (n=51)
Tye et al., 2014	UK	Clinical	Clinical	ICD-10	8-13	SCQ Total	10.89 (5.36) (n=18)	3.88 (3.54) (n=26)
van der Meer et al., 2012	US	Community	Community	DSM-IV	5-17	SCQ *t*-score	6.9 (4.7) (n=109)	4.1 (4.4) (n=418)
van Steijn et al., 2014	US	Community	Community	DSM-IV	5-19	SCQ Total	6.6 (3.2) (n=67)	4.7 (5.0) (n=247)

*SRS = Social Responsiveness Scale, SCQ = Social Communication Questionnaire, ASSQ = Autism Spectrum Screening Questionnaire, ABC = ASD Behavior Checklist, CASD = Checklist for ASD Spectrum Disorder, CSBQ = The Children's Social Behavior Questionnaire, ADOS = Autism Diagnostic Observation Schedule.

Table 3. *Random effect meta-analyses of ASD symptoms in children and adolescents with ADHD.*

Analysis		N of studies	Random Pooled Effect Size	95% Confidence Intervals	Heterogeneity χ^2	Heterogeneity p	Heterogeneity I^2 (%)
Proportion analysis							
All Studies		13	0.21	0.18-0.24	94.10	<0.001	87.25
Sample							
	Clinical	6	0.24	0.17-0.31	12.14	<0.05	58.81
	Community	7	0.19	0.16-0.22	61.86	<0.001	90.30
Measurement Tool							
	Screening	9	0.22	0.18-0.26	40.20	<0.001	80.01
	Diagnostic	4	0.20	0.11-0.29	22.25	<0.001	86.52
Country of Origin							
	USA	6	0.21	0.15-0.26	23.37	<0.001	78.61
	Non-USA	7	0.22	0.16-0.28	59.15	<0.001	89.86
		N of studies	**Pooled Std Mean Difference**	**95% Confidence Intervals**	**χ^2**	**p**	**I^2**
Mean Difference analysis							
All Studies		15	1.23	0.94-1.51	210.69	<0.001	93.4
Sample							
	Clinical	10	1.45	1.04-1.86	141.86	<0.001	93.7
	Community	5	0.83	0.57-1.10	24.84	<0.001	83.9