Prevalence of psychiatric disorders in adults with autism spectrum disorder: a systematic review and meta-analysis.

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Abstract

Some challenges faced by people with autism spectrum disorder (ASD) when adapting to a neurotypical environment are related with the risk of suffering a psychiatric disorder. The aim of the present study is to conduct a systematic review on the prevalence of psychiatric disorders in adults with ASD (PROSPERO's reference number CRD42016041948). Four databases (PubMed, PsycINFO, Web of Science and CINAHL) were used for the electronic search, and six editorials (Science Direct, Wiley, Springer, Taylor & Francis, SAGE Publishing and BioMed Central) were manually searched for studies not previously identified. Study eligibility criteria were observational studies on psychiatric comorbidity in adults (18 years or older) with ASD, based on standard diagnostic classifications (DSM/ICD), reported in English peer-reviewed journals. A total of 1288 and 24 references were identified by electronic and manual searches, respectively. Results showed that attention deficit and hyperactivity disorder is the most prevalent psychiatric disorder in adults with ASD. Mood and anxiety disorders are also very frequent among this population. The lowest comorbidity prevalence rates of all diagnostic categories are the ones related to substance use and eating disorders. These results show a need for a greater production of studies in this field, especially follow-up studies that focus on risk and protective factors for the emergence of psychiatric problems in adults with ASD. For this reason, it is imperative to create specific diagnostic tools that allow the assessment of mental pathology, attending to the particularities of its manifestation in people with ASD.

Keywords: Autism Spectrum Disorder; Psychiatric Disorders; Adults; Systematic Review; Meta-Analysis.

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Autism spectrum disorder (ASD) is a early onset neurodevelopmental disorder, characterized by persistent difficulties in social communication along with restrictive and repetitive patterns of behaviour and interests that have a significant effect on daily routines. About 70% of people with ASD may have a comorbid psychiatric disorder and about 40% have two or more comorbid psychiatric disorders (American Psychiatric Association, 2013). The fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) describes a psychiatric disorder as a "syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning" (American Psychiatric Association, 2013 p.20). Furthermore, the International Classification of Diseases (ICD-10) states that a mental disorder "implies the existence of a clinically recognizable set of symptoms or behaviors associated, in most cases, with distress and interference with personal functions" (World Health Organization, 1992, page 11).

Initial studies that reported data on psychiatric comorbidity made more references to specific symptoms and not so many to diagnostic categories. For example, papers published by Rutter, Greenfield & Lockyer (1967) Simons, (1974), Ando & Yoshimura, (1979) and Rumsey, Rapoport & Sceery (1985), highlighted compulsive behaviour, self-injury, or anxiety. The most important debate was focused on whether the observed psychiatric symptoms represent true comorbid psychiatric disorders or are isolated symptoms (Frazier et al., 2001). Most of these published studies were based on children and adolescent clinical samples, contributing to better describe the difficulties that clinicians had to distinguish ASD from other comorbid mental disorders (Clarke, Littlejohns, Corbett, & Joseph, 1989; Ghaziuddin, Tsai, & Ghaziuddin, 1992;

Kobayashi & Murata, 1998; Volkmar & Cohen, 1991). These studies, as a whole, highlight that psychiatric comorbidity significantly increases the adaptive difficulties of these persons in daily life, interfering with activities such as eating or sleeping, accentuating problems such as passivity, social isolation, restlessness, irritability, aggressiveness, or self-injury. The general conclusion from the studies was that the presence of these concurrent behavioural alterations leads to an increase in ASD severity (Lainhart, 1999), as well as leading to confusion for clinicians when differentiating ASD from other psychiatric disorders.

However, there have been very few studies published addressing adults with ASD, to the point that there is a huge disproportion in the number of publications focused on children with respect to those focused on adults. Figure 1 shows the result of a PubMed search on studies about psychiatric problems in people with ASD. The considerable discrepancy in number of publications between children and adults reflects the lack of knowledge about psychiatric problems in adulthood.

[Insert Figure 1 about here]

During the last 10 years there has been a notable increase in the number of publications about comorbid psychiatric disorders in ASD. This indicates that interest in this issue is increasing. The studies are mainly focused on investigating the comorbidity of ASD with a specific psychiatric disorder. However, there are not many that have made efforts to systematically analyze and synthesize information with meta-analyses techniques. Few systematic studies that apply a meta-analytical methodology appeared in the results found. Nevertheless, numerous reviews focus on specific psychiatric disorders (Hollocks, Lerh, Magiati, Meiser-Stedman, & Brugha, 2018; Huke, Turk, Saeidi, Kent, & Morgan, 2013; Kalyva, Kyriazi, Vargiami, & Zafeiriou, 2016; Marín et al., 2018; Skokauskas & Gallagher, 2010; Stewart, Barnard, Pearson, Hasan, & O'Brien, 2006; van Steensel, Bögels, & Perrin, 2011; Vannucchi et al., 2014). The largest number of studies focused on depression and anxiety disorders, which are generally

considered to be the most frequent comorbidity (Howlin, 2000) and which can be associated with other problems such as maladaptive behaviors, self-injurious aggression and oppositional behaviour (Stewart et al., 2006). A recent meta-analysis (Hollocks et al., 2018) estimates a combined prevalence of 27% to 42% for any anxiety disorder, and from 23% to 37% for depressive disorders. This study reveals a high degree of heterogeneity in the methodology used in different studies and excessive dependence on clinical samples, highlighting the need to conduct studies with well characterized samples. Methodological heterogeneity and limitations in the process of sample selection are aspects mentioned in most of the reviews that address comorbid psychopathology (Gillberg and & Billstedt, 2000; Mannion & Leader, 2013; Matson & Cervantes, 2014; Matson & Goldin, 2013; Underwood, McCarthy, & Tsakanikos, 2010). The reviews provide a wide range of prevalence rates for the different disorders and behavioral problems analyzed. To the knowledge of the authors, there are no reviews that integrate meta-analyses results from systematic reviews analyzing the prevalence of different comorbid mental disorders in adults with ASD. For this reason, there is a need for an integrative effort that could bring a better understanding of mental comorbidity in adults with ASD.

The purpose of this work is to systematically collect all the information available on comorbidity of psychiatric disorders in adults with ASD and to provide relevant information to improve clinical practice in terms of diagnosis and treatment.

METHODS

The review was registered at PROSPERO (reference number CRD42016041948, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=41948) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009) was used as a guideline.

Search of studies

An electronic search was conducted from 01/01/2000 to 05/31/2016 in four databases: PsycINFO, PubMed, CINAHL Full-Text and Web of Science. The search strategy included terms relating to all psychiatric disorders as they are classified in the standard classifications (DSM-5 and/or ICD-10). The same strategy was used in all databases (see Appendix A's Table 1). In order to find studies not detected by the electronic search, a manual search was performed reviewing references lists of eligible studies, as well as searching in the "most-likely to publish" editorial webs (Science Direct, Wiley, Springer, Taylor & Francis, SAGE Publishing and BioMed Central).

Inclusion and exclusion criteria

The inclusion criteria were: 1) observational studies focusing on psychiatric comorbidity in ASD; 2) clinical diagnoses which had been established on the basis of diagnostic classifications in DSM (any version) and/or ICD-10; 3) english-written studies; 4) peer reviewed articles. Exclusion criteria were: 1) studies related to genetic / medical conditions; 2) studies based on children and youth population samples (<18 years); 3) small samples (N <10). See Appendix A's Table 2 for rationale on some of the inclusion/exclusion criteria.

References screening

 Title, abstract and full text screenings were conducted by three independent reviewers. The selection strategy was the following: 1) One of the raters reviewed all references and the other two reviewed one half of the studies, randomly assigned to each one; 2) When a discrepancy occurred, a fourth independent rater was consulted. To assess the interrater agreement between reviewers, Kappa coefficient (k) was applied. Regarding discrepancies, age criterion raised some doubts, as several of the selected studies included participants both under and above 18 years old. In these cases, it was agreed to include those studies where the average age of the whole sample was equal or greater than 18 years.

Quality assessment and data extraction

The quality assessment was conducted for the five first authors, who independently assessed risk of bias on the included studies. For this, a specific instrument based on standard criteria was used (Berra, Elorza-Ricart, Estrada, & Sánchez, 2008). Disagreements between authors were solved by discussion. An external judge was involved when necessary.

A standardized form was used to extract data from the eligible studies. The collected variables were: first author, year of study, country, context (clinical or community), total of ASD participants, male-to-female ratio, age mean, intellectual quotient (IQ) mean score, intellectual disability (ID) percentage, DSM/ICD version, ASD diagnostic measures, ASD subtype, psychiatric disorders diagnostic measures and main outcomes. When an inter-group comparison was made, the diagnostic nature of this comparison group was recorded, as well as the number of included subjects and the main outcomes.

Statistical analysis

The extraction of selected variables was made with Microsoft Excel 2013. Analyses were conducted with Meta, an R package for meta-analysis (Schwarzer, 2007).

RESULTS

The electronic and manual searches identified 1,288 and 24 studies, respectively. A total of 891 studies remained after duplicates were removed. Of these, 112 were selected for full-text screening leaving 65 for further review. In the quality assessment stage, 4 studies were excluded. During data extraction, 14 studies were also excluded because they did not report

quantitative data. Thus, a total of 47 studies were included in the review. Figure 2 shows the PRISMA Flow-diagram of the conducted search.

[Insert Figure 2 about here]

Qualitative synthesis

Of the included studies, 26% were conducted in Sweden, while 18% and 13% took place in England and USA, respectively. A total of 87% of the studies were performed in a clinical context. The whole sample was comprised of 26,679 adults with ASD, 74.35% of whom were male, ranging from 16 to 84 years old. IQ scores, when reported, ranged from 46 to 143. When regarding ASD measures, Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview (ADI-R) were found to be chosen as diagnostic instruments in only 17% and 15% of the studies, respectively. DSM diagnostic criteria were the most frequent among the included studies (55%), while ICD criteria were 34%. Both diagnostic criteria were taken into account in 11% of the included studies. A qualitative synthesis of the results on the prevalence for each psychiatric disorder category can be found in Appendix B. A summary of the quality assessment results for the included studies is described in Appendix C.

Quantitative synthesis (meta-analysis)

We conducted a meta-analysis for each general psychiatric category (substance use disorders, schizophrenia spectrum disorders, mood disorders, anxiety disorders, eating disorders, personality disorders and ADHD). In addition, a general meta-analysis was performed with those studies reporting prevalence for any psychiatric disorder. Only studies reporting prevalence in the main diagnosis category were considered. Consequently, a total of 8 random effects model meta-analyses were conducted. In all analyses, an overall prevalence rate from studies reporting a single proportion was calculated using an inverse variance method, with Clopper-Pearson confidence interval for individual studies and continuity correction of 0.5 in

studies with zero cell frequencies. Cochran's Q and I^2 were used to assess heterogeneity. Publication bias was explored by way of visual inspection of funnel plots (Appendix D).

Substance use disorders (SUD)

A total of 16 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 360.05, $p < 0.001$), pointing to a high heterogeneity in the included studies ($I^2 = 96\%$, 95% CI [94.4-96.9]). The pooled prevalence of SUD in ASD adults was 8.3% (4.1-16.1, CI 95%). When considering the specific categories, alcohol abuse/dependence disorder was the most frequent SUD reported throughout the studies. Cannabis use is also prevalent among adults with ASD. Other drugs, such as cocaine, heroin or stimulants, were not found as prevalent in these samples. Figure 3 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 12.9% (8.9 – 18.4, CI95%) ($I^2 = 43\%$, $p = 0.08$).

[Insert Figure 3 about here]

Schizophrenia spectrum disorders (SSD)

A total of 17 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 306.76, $p < 0.001$), pointing to a high heterogeneity in the included studies ($I^2 = 95\%$, 95% CI [92.9-96.1]). The pooled prevalence of SSD in ASD adults was 11.8% (95% CI [7.7-17.6]). When considering the specific categories, Schizophrenia was the most frequent SSD reported throughout all the studies. Other categories, such as delusional disorder, schizoaffective disorder and brief psychotic disorder, were not diagnosed as often among these samples. Figure 4 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 10.5% (5.8 – 18.5, CI95%) ($I^2 = 76\%$, $p = 0.01$).

[Insert Figure 4 about here]

Mood disorders (MD)

A total of 14 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 565.98, p = 0.00), pointing to a high heterogeneity in the included studies (I^2 = 98%, CI 95% [97-98.2]). The pooled prevalence of MD in ASD adults was 18.8% (95% CI [10.6-31.1]). Depression spectrum disorders were the most frequent MD described throughout the studies when considering the specific categories. Bipolar disorder was also relatively frequent among adults with ASD. Single manic episodes were not so prevalent in these samples. Figure 5 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 21.2% (9.7 – 40.3, CI95%) (I^2 = 98%, p = 0.01).

[Insert Figure 5 about here]

Anxiety disorders (ANX)

A total of 17 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 451.13, p < 0.001), pointing to a high heterogeneity in the included studies (I^2 = 96%, 95% CI [95.4-97.3]). The pooled prevalence of ANX in ASD adults was 17.8% (95% CI [12.3-25.2]). Social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), and adjustment disorder (ADJ), were the most frequent ANX reported in all the studies when considering the specific categories. Agoraphobia (AGO), panic disorder (PAN) and generalized anxiety disorder (GAD) were also prevalent among adults with ASD. Other categories, such as post-traumatic stress disorder (PTSD), dissociative disorder (DIS) and somatoform disorder (SMF), were found to be less prevalent in these samples. Figure 6 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 27.2% (17.2 – 40.2, CI95%) (I^2 = 91%, p = 0.01).

[Insert Figure 6 about here]

Eating disorders (ED)

A total of 8 studies were included for quantitative synthesis. The Q analysis showed non-significant results (Chi square = 8.23, *p* = 0.23), pointing to a low heterogeneity in the included studies (I^2 = 21.6%, 95% CI [0.0-63.7]). The pooled prevalence of ED in ASD adults was 3.6% (95% CI [2.1-6.1]). When considering the specific categories, anorexia nervosa (AN) seems to be slightly more prevalent than bulimia nervosa (BM) among these samples. Figure 7 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 3.6% (2.1 – 6.1, CI95%) (I^2 = 22%, *p* = 0.26).

[Insert Figure 7 about here]

Personality disorders (PD)

A total of 13 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 858.83, *p* < 0.001), pointing to a high heterogeneity in the included studies (I^2 = 99% 95% CI [98.2-98.9]). The pooled prevalence of PD in ASD adults was 12.6% (95% CI [4.8-29.3]). When considering the specific categories, schizoid (SCHZ), antisocial (ANT) and obsessive-compulsive (OBS) were the most frequent PD reported throughout the studies. Avoidant (AVD), paranoid (PAR), borderline (BOR) and schizotypal (SCHZT) personality disorders, were also prevalent among adults with ASD. Other PD categories, such as narcissistic (NAR), dependent (DEP) and histrionic (HIS), were found to be less common in these samples. Figure 8 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 20.8% (7.3 – 46.7, CI95%) (I^2 = 93%, *p* = 0.01).

[Insert Figure 8 about here]

Attention deficit and hyperactivity disorder (ADHD)

A total of 18 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 769.07, $p < 0.001$), pointing to a high heterogeneity in the included studies ($I^2 = 98\%$, 95% CI [97.2-98.2]). The pooled prevalence of ADHD in ASD adults was 25.7% (95% CI, [18.6-34.3]). Figure 9 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 27.4% (19.3 – 37.2, CI95%) ($I^2 = 91\%$, $p = 0.01$).

[Insert Figure 9 about here]

Any psychiatric disorder

A total of 18 studies were included for quantitative synthesis. The Q analysis showed significant results (Chi square = 241.62, $p < 0.001$), pointing to a high heterogeneity in the included studies ($I^2 = 93\%$, 95% CI [90.3-94.9]). The pooled prevalence of any psychiatric disorder in ASD adults was 54.8% (95 CI, [46.6-62.7]). Figure 10 shows the results derived from the meta-analysis. When including only studies with diagnosis based on clinical interviews, the result was 60.5% (47.3 – 72.4, CI95%) ($I^2 = 93\%$, $p = 0.01$).

[Insert Figure 10 about here]

DISCUSSION

To the extent of our knowledge, this is the first systematic review and meta-analysis conducted on the prevalence of psychiatric disorders in adults with ASD. The results suggest a very high prevalence of several psychiatric conditions in adults with ASD, the most prevalent being ADHD, depression and anxiety disorders. Results suggest that adults with autism are more likely to have a psychiatric disorder than the general population.

SUD is one of the psychiatric categories less frequently diagnosed in adults with ASD. However, looking closely at the specific categories, a high prevalence in the abuse/dependence

of two specific substances, alcohol and cannabis, was found (Kronenberg, Goossens, van Busschbach, van Achterberg, & van den Brink, 2015; Sizoo et al., 2009). The anxiolytic effect derived from the abuse/dependence of both substances is quite well-known, especially with alcohol; these are also easily accessible, without often requiring highly-demanding social skills for their purchase. This could explain their use in this population, while typically recreational and social-consumed substances (cocaine, amphetamines and hallucinogens) have a lower prevalence.

The SSD prevalence in general population is approximately 1% (NIMH, 2018). Results found in this review are much higher than this number. This is not surprising as both SSD and ASD have been related since the beginning of modern psychiatry. Regarding research evidence, numerous studies have found similarities between SSD and ASD symptomatology (Konstantareas & Hewitt, 2001; Lugnegård, Hallerbäck, & Gillberg, 2015; Spek & Wouters, 2010) and biological shared structures (Burbach & van der Zwaag, 2009; Crespi, Stead, & Elliot, 2010). In the studies included in this review, schizophrenia is postulated as the most prevalent SSD in adults with ASD, showing a much higher prevalence than that found in the general population (Rössler, Salize, van Os, & Riecher-Rössler, 2005). A possible explanation for this result can be found in the ease of confusing both diagnoses (Nylander, 2014; Raja & Azzoni, 2010). Also, the late inclusion of less severe forms of autism may have led to misdiagnosis of people with ASD who have psychosis-like symptoms. As a matter of fact, follow-up studies with children with ASD have not found a similar outcome (Howlin, 2000; Volkmar & Cohen, 1991). It is the opinion of the authors that, indeed the ASD population seems more vulnerable to suffer from psychotic symptoms at any given time, although this does not necessarily have to mean the first manifestations of schizophrenia.

The one-year and lifetime prevalence of MD in general population have been observed at 9.7% and 21.4%, respectively (NIMH, 2018). The results found in this study suggest a greater than average prevalence of MD in ASD adult population. Two of the most frequent psychiatric categories in the adult population with ASD are mood and anxiety disorders. Regarding the

first, people with ASD show a high prevalence of depressive disorders. The occurrence of depressive disorders could be related to the awareness of the core social difficulties of ASD. The person would be aware of their difficulties in the social environment, which would lead to a loss of self-esteem. After several unsuccessful attempts to fit into the social world, the person with ASD would suffer the rejection of their peers, precipitating the onset of depressive disorder and, in some cases, suicide attempts (Kato et al., 2013; Raja, Azzoni, & Frustaci, 2011).

Regarding anxiety, an estimated of 19.1% of adults in a general population have experienced ANX in the last year, and approximately 31.1% have experienced ANX in their lives (NIMH, 2018). When comparing with ASD participants, the prevalence rate seems greater in the general population. Three specific categories can be found as the most frequently diagnosed ANX in adults with ASD. Firstly, social phobia presents a high prevalence in adults with ASD, although this is not a direct outcome from adult transition (Kuusikko et al., 2008). The explanation for this result seems clear, as people with ASD present difficulties in social communication that may precipitate the emergence of a phobic disorder. Secondly, OCD is one of the most typically anxiety diagnoses found in adults with ASD. There seems to be a relation between the repetitive behaviors and the compulsive rituals. Due to the overlap in the manifestation of symptoms, it is a challenge to establish a differential diagnosis between both behaviors. A differentiating factor that seems to discriminate well between both diagnoses is the cognitive component. The repetitive behaviors of a person with ASD are not performed as a response to the presence of an obsessive thought, whereas in OCD a person performs the ritual in order to neutralize an obsessive thought. Also, the egodystonic nature of the rituals in OCD is not reflected in the repetitive behaviors of the person with ASD. It is for this reason that the results found here should be taken with caution, since it could be a confusion between diagnoses. Finally, adjustment disorder is the diagnostic category that presents the highest dispersion in its results, with only one study yielding results of high prevalence (Kato et al., 2013). The remaining diagnostic categories of the spectrum of anxiety, although elevated, do not present a frequency as striking as those mentioned above.

ED are, along with substance use disorders, those with the lowest prevalence in people with ASD. General population prevalence of ED is observed at around 1% (NIMH, 2018). In this study, the results found in the ASD group suggest a greater risk of developing ED in this population. The most striking case may be that of anorexia, with some studies finding prevalence rates of up to 13% in the population with ASD (Rydén & Bejerot, 2008). There are some studies on the prevalence of eating disorders in childhood and adolescence (Huke et al., 2013; Oldershaw, Treasure, Hambrook, Tchanturia, & Schmidt, 2011; Zucker et al., 2007), which have found similar results. Among the possible explanations for this phenomenon may be the low cognitive flexibility in anorexia, or the repetitive behaviors of people with bulimia. In any case, there does not seem to be a direct relation between the two conditions.

When it comes to PER, general population prevalence is 9.1% (NIMH, 2018), slightly lower than the results found in this study. When it comes to ASD adult population, three specific personality disorders stand out over the rest. It is not surprising to see the high prevalence of the schizoid personality disorder in adult population with ASD. Although some of its characteristics coincide with those shown by people with ASD (preference for solitary activities, low emotionality, few friends), others do not seem to be explained solely by the presence of ASD (little enjoyment in social relations, indifference to the praises or criticism from others, little interest in having sex). Furthermore, obsessive personality disorder is also frequently found as axis-II disorder in adults with ASD. An explanation can be easily found for this result, because people with ASD have a high need for control and structuring of the environment, with low flexibility to change and frustration with interruptions of their routine. Finally, having a look at the defining characteristics of the antisocial personality disorder, it is not surprising to find a high prevalence of this diagnosis in ASD adults. This result could be explained by a diagnostic overlap, since the difficulties in social communication characteristic of ASD predispose the emergence of antisocial behaviors, without being associated with the intention to carry out these behaviors. This issue will be addressed by the authors in greater depth in the "Limitations" section.

ADHD is the most frequent psychiatric diagnosis found in adults with ASD. The prevalence in children that have ever been diagnosed with ADHD is 11% (NIMH, 2018), suggesting a greater risk of having an ADHD diagnosis in ASD population. They are neurodevelopmental disorders that have been closely linked in the scientific literature ever since their definition. Regarding this issue, Gillberg (2010) has proposed a multidimensional diagnostic category, which reflects this relation between both conditions, but also as a part of a cluster of syndromes with a high co-occurrence in early developmental stages. In any case, a risk of symptom overlapping should be taken into consideration. ADHD symptoms may well be explained by the existence of an ASD. Attention deficit could be a result of the executive-dysfunction frequently observed in ASD. Another possible explanation is related to the preference for focusing on detail in people with ASD. This could be a deficit in sustained attention, concerning problems with keeping focused and avoiding distractions. Furthermore, hyperactivity can be triggered by sensory overstimulation, which is often described in people with ASD. The challenge here is to correctly describe both conditions, not only at a behavioral, but also at a neurological level.

Limitations

There are some limitations that could engage the validity of the results. Only a small percentage of the studies used gold standard diagnostic instruments for ASD (ADOS, ADI-R). Also, few studies used self-developed interviews or screening instruments to establish the diagnosis (Munesue et al., 2008; Roy, Prox-Vagedes, Ohlmeier, & Dillo, 2015), thus increasing the likelihood of including false positives in the ASD group. Furthermore, most of the selected studies have recruited the ASD sample in clinical settings (hospitals, health centers). This may bias the results, as these samples may be more vulnerable to develop mental disorders. More studies are needed in ecological contexts to be able to discern the real prevalence of psychiatric problems and the factors that prevent the development of mental pathology in this population.

Regarding the diagnostic approach, two limitations can be considered. Firstly, a great proportion of the included studies reported diagnosis as being based on medical records and/or clinical judgement. These were considered relevant as they reflected a more ecological approach on how the diagnosis was made in real clinical practice. That is, the results found in this review reflect the probability of being diagnosed with a mental disorder when ASD is present. The concept of prevalence should be considered here as a reflection of this probability. Secondly, when systematically assessed, the diagnostic tools chosen to assess the presence of mental disorders in the ASD population may not be sensitive to the particularities in the expression of mental disorders in people with ASD. Although specific instruments have been developed for people with ASD (Bolton & Rutter, 1994; Helverschou, Bakken, & Martinsen, 2009), these tools are unfortunately not widely known in clinical practice. In fact, only a small percentage of the studies included in this review, have used them for the psychiatric evaluation of the ASD sample (Bakken et al., 2010; Hutton, Goode, Murphy, Le Couteur, & Rutter, 2008). Likewise, the development of specific tests implies rethinking about the diagnostic categories as they are currently described. Moreover, most disorders are described in behavioral terms, which eliminates the possibility of assessing the etiology of that behavior. One good example is the category "antisocial personality disorder". In the included studies, this disorder has one of the highest prevalence, which in some cases may reach 33% (Esan, Chester, Gunaratna, Hoare, & Alexander, 2015). This is not surprising, as antisocial personality disorder (APD) is described as a pattern of violation of social norms, aggression, lack of repentance, irresponsibility, inability to plan and inattention. All these behaviors can easily be found when assessing an ASD adult's personality. However, if these behaviors are compared with those of a person with a APD, it would be agreed that this person is aware of the damage that can be caused, being unlike for the person with ASD to realize the final consequences of their actions. Even so, both would meet criteria for antisocial personality disorder.

Another issue that should be addressed is related to the characteristics of the sample. Approximately 75% of the sample were male. This is consistent with the typical higher

prevalence of ASD in men. However, several studies have found differences in the manifestation of ASD characteristics in relation to gender (Rivet & Matson, 2011; Van Wijngaarden-Cremers et al., 2014). This suggests the need to carry out comparative studies that describe gender differences concerning psychiatric pathology in ASD. Similarly, a high percentage of the ASD sample presented ID. People with ID present a potential risk to develop mental disorders (Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011), so it is logical to think this factor has increased the prevalence of psychiatric disorders in adults with ASD.

A final limitation is the high heterogeneity found in the meta-analysis results. This could be explained by the variables mentioned above (e.g. gender, IQ, diagnostic measures). Nevertheless, the data reported for the included studies was inconsistent and often did not report the specific data needed to carry out meta-regression analyses. Also, as mean age was available in most of the studies, a set of meta-regression analyses were conducted to explore the heterogeneity explained by the age of the sample. Results showed a meaningful amount of variance (although small and not reaching significance) in the case of eating disorders (44.03%), anxiety disorders (21.43%) and ADHD (19.62%), pointing to the possible relevance of age when estimating the prevalence of these psychiatric disorders.

In addition, an extra pool of meta-analysis was performed with those studies reporting a systematic psychiatric assessment, based on a clinical interview and/or standardized measures. These analyses showed no differences in the heterogeneity when compared with the prior meta-analysis, except in the cases of SUD and SSD, thus suggesting an effect of diagnostic methodology on the prevalence results of these two categories.

Clinical implications

More research is needed on the factors that predispose people to the development of mental disorders, as well as those that protect against their emergence. For this, follow-up studies including psychiatric disorders among their variables, should be conducted. Also, diagnostic tools that present a high discriminative capacity between mental disorders and the core ASD

features are necessary. Finally, the approach to psychiatric pathology should be one of the fundamental pillars of intervention in adulthood. As this population deals with communication problems, psychiatric demands can remain masked. As a consequence, professionals should be familiarized with the manifestation of psychiatric disorders within this population.

Ultimately, the insight gathered by meta-analyses like these is imperative for future advances in diagnosis and treatment. The opportunity arises to develop specific diagnostic tools of mental pathology that cater for the distinctive patterns found in people with ASD. Future studies could identify risk and protective factors integral for the development of treatment options that could improve the quality of life of adults with ASD and comorbid psychiatric disorders.

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FIGURE LEGENDS

Figure 1. Published studies regarding psychiatric disorders on ASD infants vs. adults.

Figure 2. PRISMA flow diagram
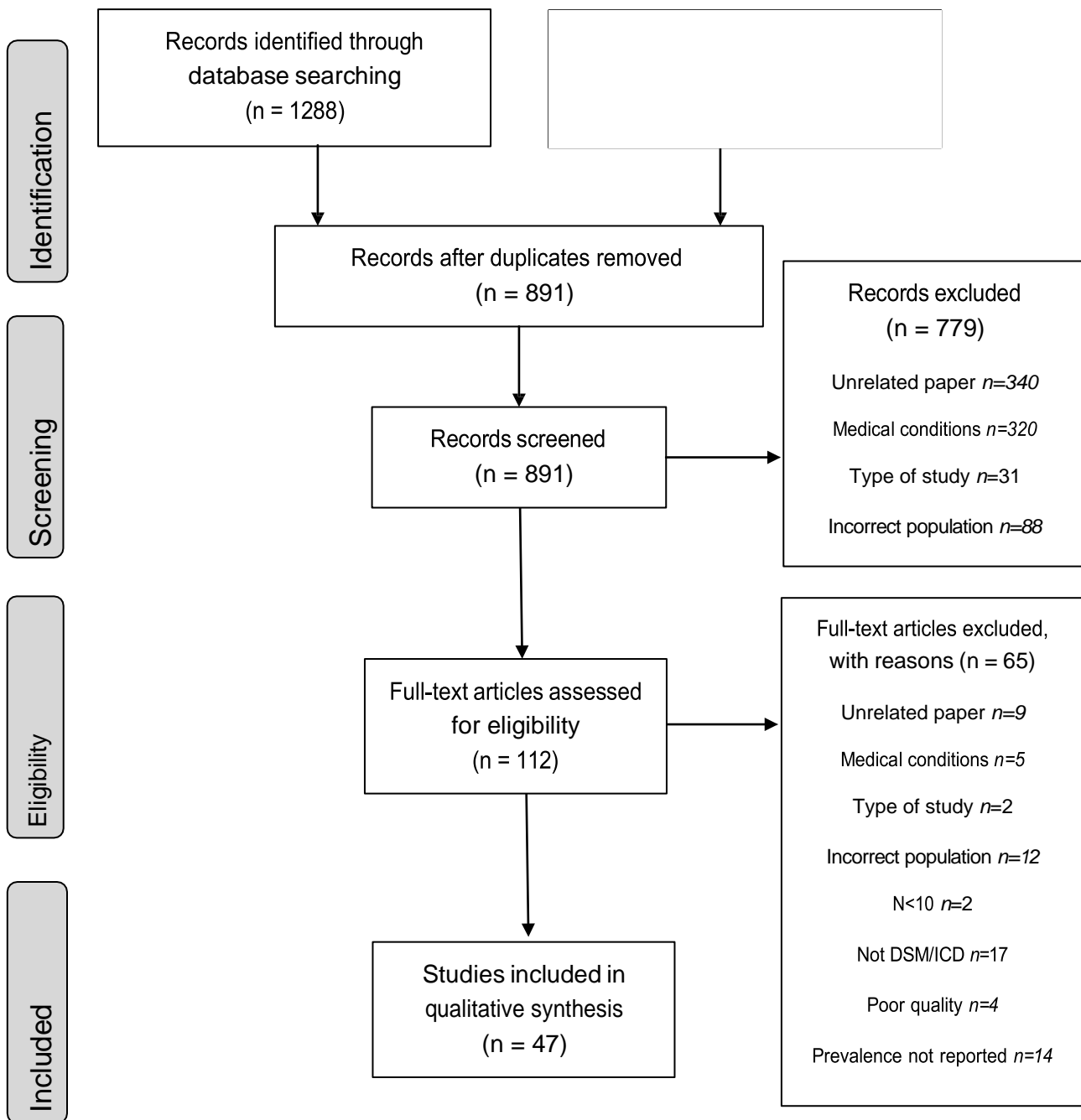
Figure 3. Forest plot of the pooled prevalence of SUD in adults with ASD.
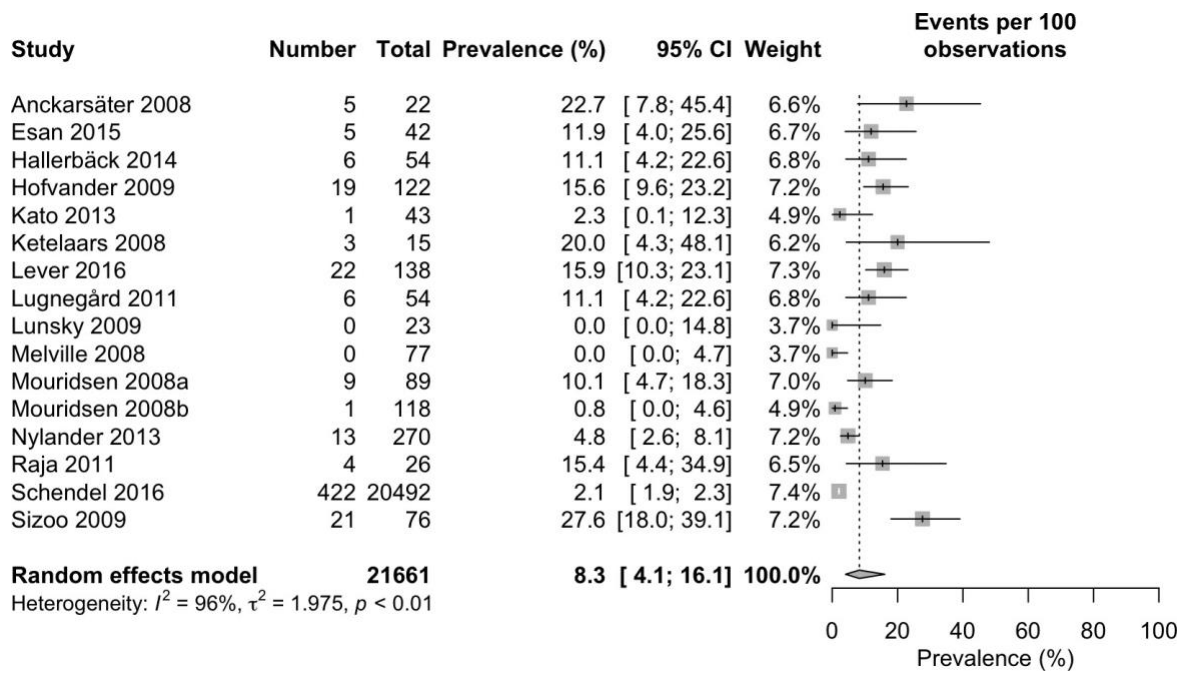
Figure 4. Forest plot of the pooled prevalence of SSD in adults with ASD.
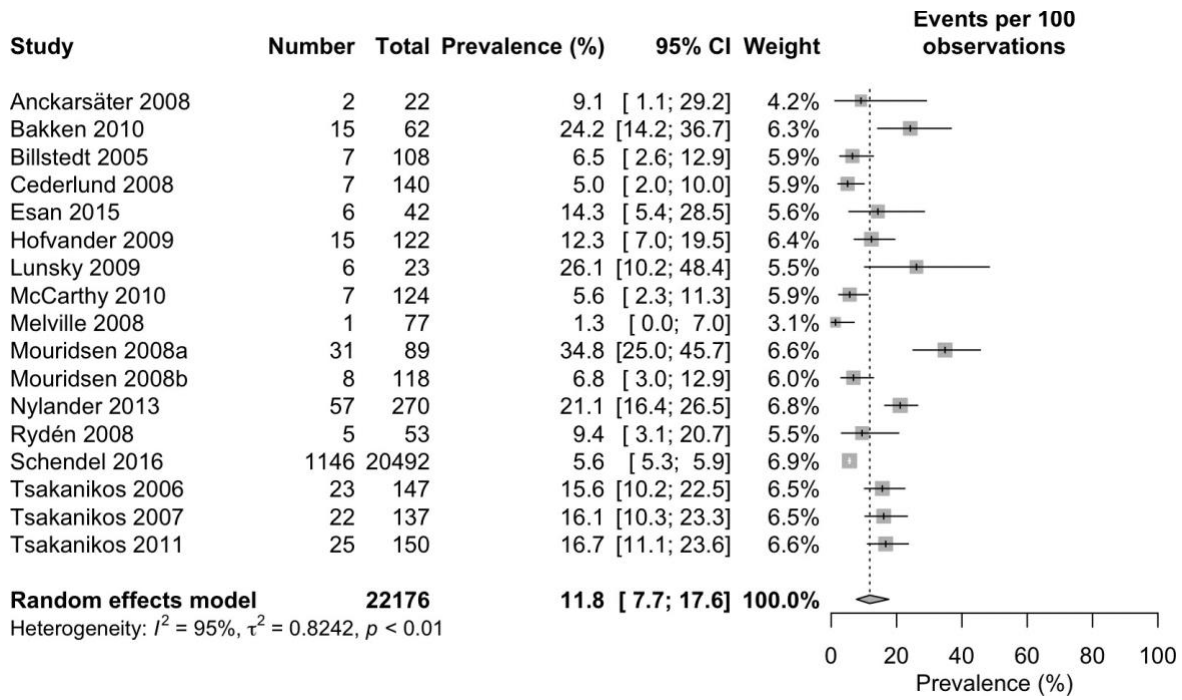
Figure 5. Forest plot of the pooled prevalence of MD in adults with ASD.
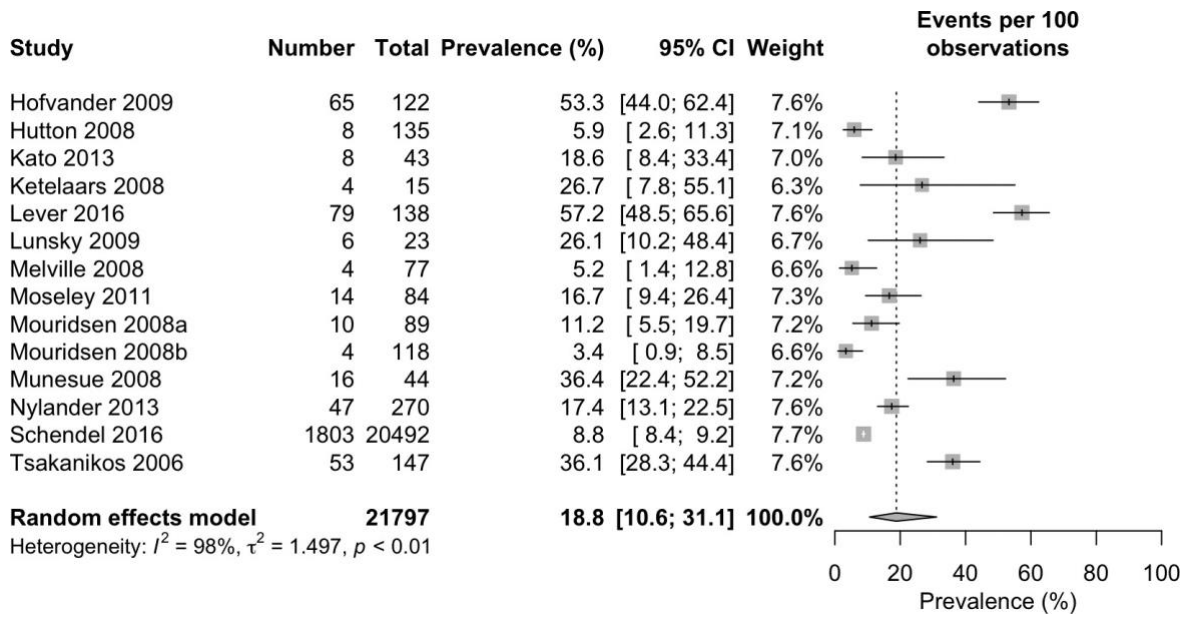
Figure 6. Forest plot of the pooled prevalence of ANX in adults with ASD.
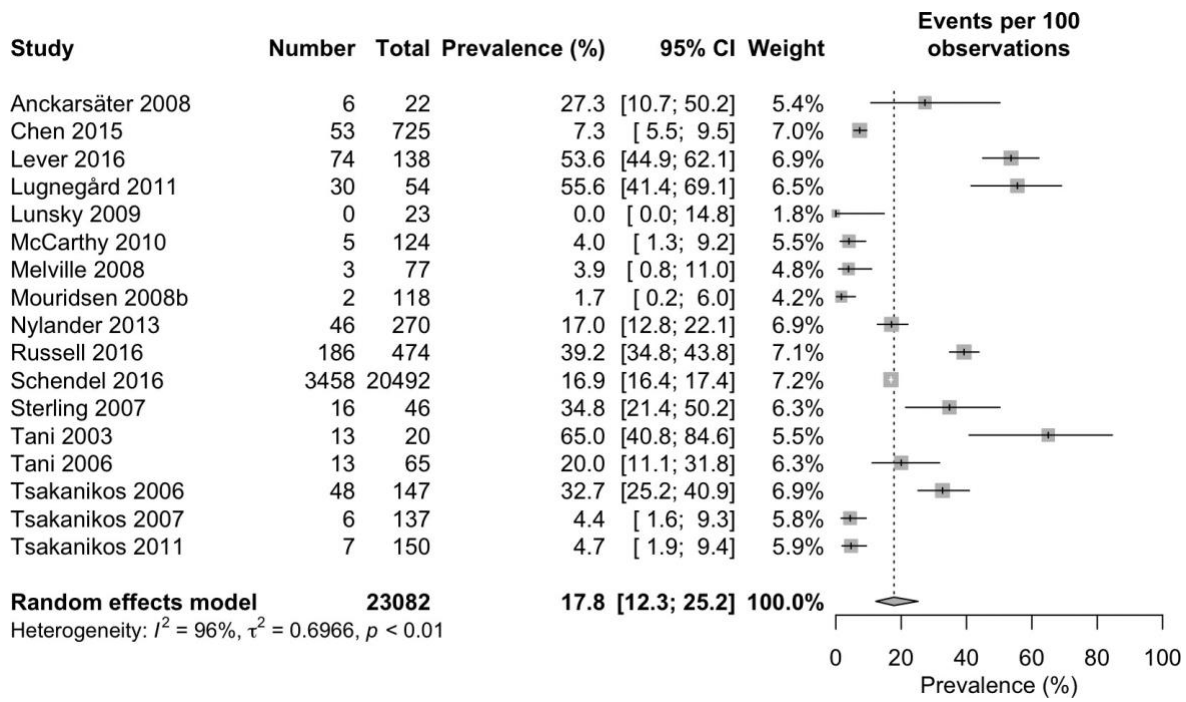
Figure 7. Forest plot of the pooled prevalence of ED in adults with ASD.
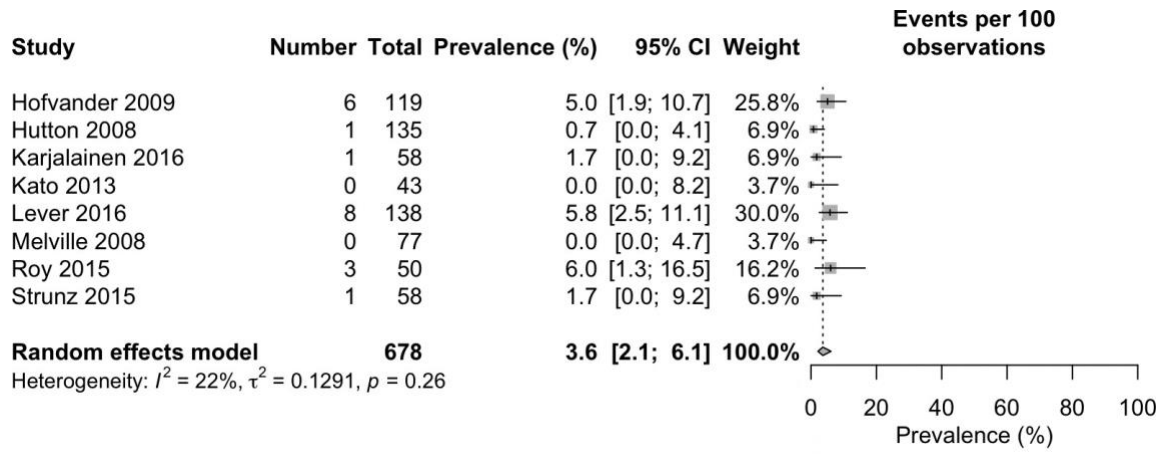
Figure 8. Forest plot of the pooled prevalence of PD in adults with ASD.
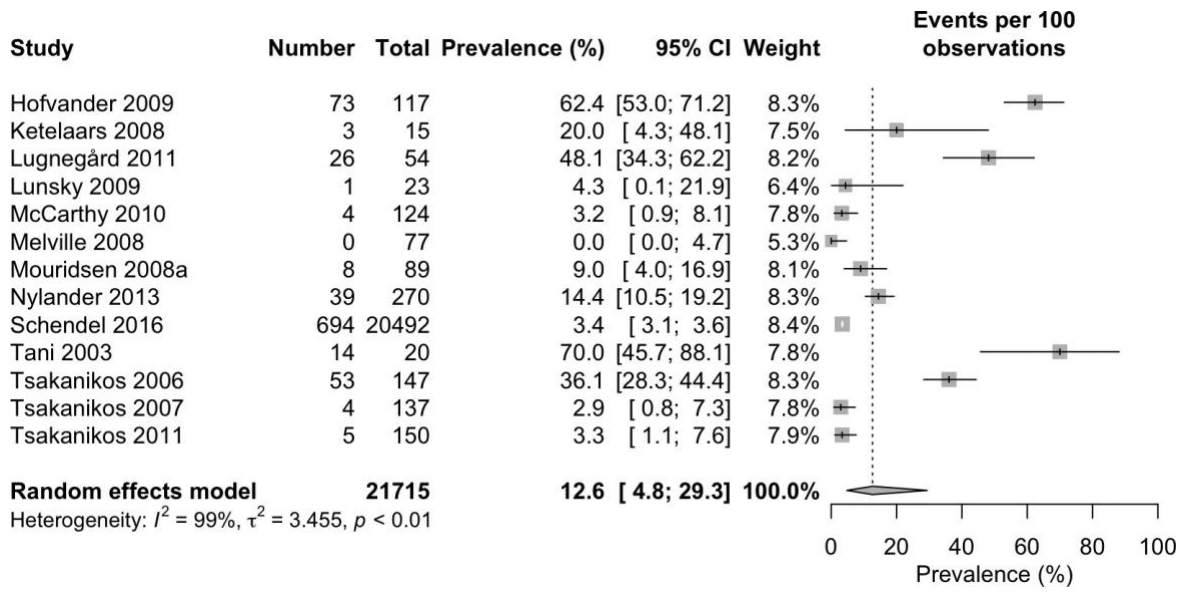
Figure 9. Forest plot of the pooled prevalence of ADHD in adults with ASD.

Figure 10. Forest plot of the pooled prevalence of APD in adults with ASD.

Figure 1. Published studies regarding psychiatric disorders on ASD infants vs. adults.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Child<18	5	12	8	23	21	31	54	65	88	109	133	179	224	206	22	198	105
adult>19	5	0	3	7	8	12	23	19	37	42	57	55	89	86	94	90	48

Figure 2. PRISMA flow diagram

Figure 3. Forest plot of the pooled prevalence of SUD in adults with ASD.

Study	Number	Total	Prevalence (%)	95% CI	Weight	Events per 100 observations
Anckarsäter 2008	5	22	22.7	[7.8; 45.4]	6.6%	
Esan 2015	5	42	11.9	[4.0; 25.6]	6.7%	
Hallerbäck 2014	6	54	11.1	[4.2; 22.6]	6.8%	
Hofvander 2009	19	122	15.6	[9.6; 23.2]	7.2%	
Kato 2013	1	43	2.3	[0.1; 12.3]	4.9%	
Ketelaars 2008	3	15	20.0	[4.3; 48.1]	6.2%	
Lever 2016	22	138	15.9	[10.3; 23.1]	7.3%	
Lugnegård 2011	6	54	11.1	[4.2; 22.6]	6.8%	
Lunsky 2009	0	23	0.0	[0.0; 14.8]	3.7%	
Melville 2008	0	77	0.0	[0.0; 4.7]	3.7%	
Mouridsen 2008a	9	89	10.1	[4.7; 18.3]	7.0%	
Mouridsen 2008b	1	118	0.8	[0.0; 4.6]	4.9%	
Nylander 2013	13	270	4.8	[2.6; 8.1]	7.2%	
Raja 2011	4	26	15.4	[4.4; 34.9]	6.5%	
Schendel 2016	422	20492	2.1	[1.9; 2.3]	7.4%	
Sizoo 2009	21	76	27.6	[18.0; 39.1]	7.2%	
Random effects model		**21661**	8.3	[4.1; 16.1]	100.0%	

Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.975$, $p < 0.01$

Prevalence (%)

Figure 4. Forest plot of the pooled prevalence of SSD in adults with ASD.

Study	Number	Total	Prevalence (%)	95% CI	Weight
Anckarsäter 2008	2	22	9.1	[1.1; 29.2]	4.2%
Bakken 2010	15	62	24.2	[14.2; 36.7]	6.3%
Billstedt 2005	7	108	6.5	[2.6; 12.9]	5.9%
Cederlund 2008	7	140	5.0	[2.0; 10.0]	5.9%
Esan 2015	6	42	14.3	[5.4; 28.5]	5.6%
Hofvander 2009	15	122	12.3	[7.0; 19.5]	6.4%
Lunsky 2009	6	23	26.1	[10.2; 48.4]	5.5%
McCarthy 2010	7	124	5.6	[2.3; 11.3]	5.9%
Melville 2008	1	77	1.3	[0.0; 7.0]	3.1%
Mouridsen 2008a	31	89	34.8	[25.0; 45.7]	6.6%
Mouridsen 2008b	8	118	6.8	[3.0; 12.9]	6.0%
Nylander 2013	57	270	21.1	[16.4; 26.5]	6.8%
Rydén 2008	5	53	9.4	[3.1; 20.7]	5.5%
Schendel 2016	1146	20492	5.6	[5.3; 5.9]	6.9%
Tsakanikos 2006	23	147	15.6	[10.2; 22.5]	6.5%
Tsakanikos 2007	22	137	16.1	[10.3; 23.3]	6.5%
Tsakanikos 2011	25	150	16.7	[11.1; 23.6]	6.6%
Random effects model		**22176**	**11.8**	**[7.7; 17.6]**	**100.0%**

Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.8242$, $p < 0.01$

Figure 5. Forest plot of the pooled prevalence of MD in adults with ASD.

Study	Number	Total	Prevalence (%)	95% CI	Weight	Events per 100 observations
Hofvander 2009	65	122	53.3	[44.0; 62.4]	7.6%	
Hutton 2008	8	135	5.9	[2.6; 11.3]	7.1%	
Kato 2013	8	43	18.6	[8.4; 33.4]	7.0%	
Ketelaars 2008	4	15	26.7	[7.8; 55.1]	6.3%	
Lever 2016	79	138	57.2	[48.5; 65.6]	7.6%	
Lunsky 2009	6	23	26.1	[10.2; 48.4]	6.7%	
Melville 2008	4	77	5.2	[1.4; 12.8]	6.6%	
Moseley 2011	14	84	16.7	[9.4; 26.4]	7.3%	
Mouridsen 2008a	10	89	11.2	[5.5; 19.7]	7.2%	
Mouridsen 2008b	4	118	3.4	[0.9; 8.5]	6.6%	
Munesue 2008	16	44	36.4	[22.4; 52.2]	7.2%	
Nylander 2013	47	270	17.4	[13.1; 22.5]	7.6%	
Schendel 2016	1803	20492	8.8	[8.4; 9.2]	7.7%	
Tsakanikos 2006	53	147	36.1	[28.3; 44.4]	7.6%	
Random effects model		**21797**	**18.8**	**[10.6; 31.1]**	**100.0%**	

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.497$, $p < 0.01$

Prevalence (%)
0   20   40   60   80   100

Figure 6. Forest plot of the pooled prevalence of ANX in adults with ASD.

Study	Number	Total	Prevalence (%)	95% CI	Weight
Anckarsäter 2008	6	22	27.3	[10.7; 50.2]	5.4%
Chen 2015	53	725	7.3	[5.5; 9.5]	7.0%
Lever 2016	74	138	53.6	[44.9; 62.1]	6.9%
Lugnegård 2011	30	54	55.6	[41.4; 69.1]	6.5%
Lunsky 2009	0	23	0.0	[0.0; 14.8]	1.8%
McCarthy 2010	5	124	4.0	[1.3; 9.2]	5.5%
Melville 2008	3	77	3.9	[0.8; 11.0]	4.8%
Mouridsen 2008b	2	118	1.7	[0.2; 6.0]	4.2%
Nylander 2013	46	270	17.0	[12.8; 22.1]	6.9%
Russell 2016	186	474	39.2	[34.8; 43.8]	7.1%
Schendel 2016	3458	20492	16.9	[16.4; 17.4]	7.2%
Sterling 2007	16	46	34.8	[21.4; 50.2]	6.3%
Tani 2003	13	20	65.0	[40.8; 84.6]	5.5%
Tani 2006	13	65	20.0	[11.1; 31.8]	6.3%
Tsakanikos 2006	48	147	32.7	[25.2; 40.9]	6.9%
Tsakanikos 2007	6	137	4.4	[1.6; 9.3]	5.8%
Tsakanikos 2011	7	150	4.7	[1.9; 9.4]	5.9%
Random effects model		**23082**	**17.8**	**[12.3; 25.2]**	**100.0%**

Heterogeneity: $I^2 = 96\%$, $\tau^2 = 0.6966$, $p < 0.01$

Figure 7. Forest plot of the pooled prevalence of ED in adults with ASD.

Study	Number	Total	Prevalence (%)	95% CI	Weight	Events per 100 observations
Hofvander 2009	6	119	5.0	[1.9; 10.7]	25.8%	
Hutton 2008	1	135	0.7	[0.0; 4.1]	6.9%	
Karjalainen 2016	1	58	1.7	[0.0; 9.2]	6.9%	
Kato 2013	0	43	0.0	[0.0; 8.2]	3.7%	
Lever 2016	8	138	5.8	[2.5; 11.1]	30.0%	
Melville 2008	0	77	0.0	[0.0; 4.7]	3.7%	
Roy 2015	3	50	6.0	[1.3; 16.5]	16.2%	
Strunz 2015	1	58	1.7	[0.0; 9.2]	6.9%	
Random effects model		**678**	**3.6**	**[2.1; 6.1]**	**100.0%**	

Heterogeneity: $I^2 = 22\%$, $\tau^2 = 0.1291$, $p = 0.26$

Prevalence (%): 0 20 40 60 80 100

Figure 8. Forest plot of the pooled prevalence of PD in adults with ASD.

Study	Number	Total	Prevalence (%)	95% CI	Weight	Events per 100 observations
Hofvander 2009	73	117	62.4	[53.0; 71.2]	8.3%	
Ketelaars 2008	3	15	20.0	[4.3; 48.1]	7.5%	
Lugnegård 2011	26	54	48.1	[34.3; 62.2]	8.2%	
Lunsky 2009	1	23	4.3	[0.1; 21.9]	6.4%	
McCarthy 2010	4	124	3.2	[0.9; 8.1]	7.8%	
Melville 2008	0	77	0.0	[0.0; 4.7]	5.3%	
Mouridsen 2008a	8	89	9.0	[4.0; 16.9]	8.1%	
Nylander 2013	39	270	14.4	[10.5; 19.2]	8.3%	
Schendel 2016	694	20492	3.4	[3.1; 3.6]	8.4%	
Tani 2003	14	20	70.0	[45.7; 88.1]	7.8%	
Tsakanikos 2006	53	147	36.1	[28.3; 44.4]	8.3%	
Tsakanikos 2007	4	137	2.9	[0.8; 7.3]	7.8%	
Tsakanikos 2011	5	150	3.3	[1.1; 7.6]	7.9%	
Random effects model		21715	12.6	[4.8; 29.3]	100.0%	

Heterogeneity: $I^2 = 99\%$, $\tau^2 = 3.455$, $p < 0.01$

Figure 9. Forest plot of the pooled prevalence of ADHD in adults with ASD.

Study	Number	Total	Prevalence (%)	95% CI	Weight
Anckarsäter 2006	39	113	34.5	[25.8; 44.0]	5.9%
Anckarsäter 2008	10	22	45.5	[24.4; 67.8]	5.0%
Chen 2015	466	725	64.3	[60.7; 67.8]	6.2%
Croen 2015	167	1507	11.1	[9.5; 12.8]	6.2%
Gillberg 2016	14	50	28.0	[16.2; 42.5]	5.5%
Hallerbäck 2014	16	54	29.6	[18.0; 43.6]	5.6%
Hofvander 2009	52	122	42.6	[33.7; 51.9]	6.0%
Johnston 2013	18	38	47.4	[31.0; 64.2]	5.5%
Karjalainen 2016	45	119	37.8	[29.1; 47.2]	6.0%
Lever 2016	42	138	30.4	[22.9; 38.8]	6.0%
Lugnegård 2011	16	54	29.6	[18.0; 43.6]	5.6%
Melville 2008	3	77	3.9	[0.8; 11.0]	4.2%
Moseley 2011	1	84	1.2	[0.0; 6.5]	2.6%
Nyden 2010	33	88	37.5	[27.4; 48.5]	5.9%
Nylander 2013	14	270	5.2	[2.9; 8.5]	5.7%
Russell 2016	46	474	9.7	[7.2; 12.7]	6.1%
Rydén 2008	31	84	36.9	[26.6; 48.1]	5.9%
Schendel 2016	5652	20492	27.6	[27.0; 28.2]	6.3%
Random effects model		24511	25.7	[18.6; 34.3]	100.0%

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.706$, $p < 0.01$

Figure 10. Forest plot of the pooled prevalence of APD in adults with ASD.

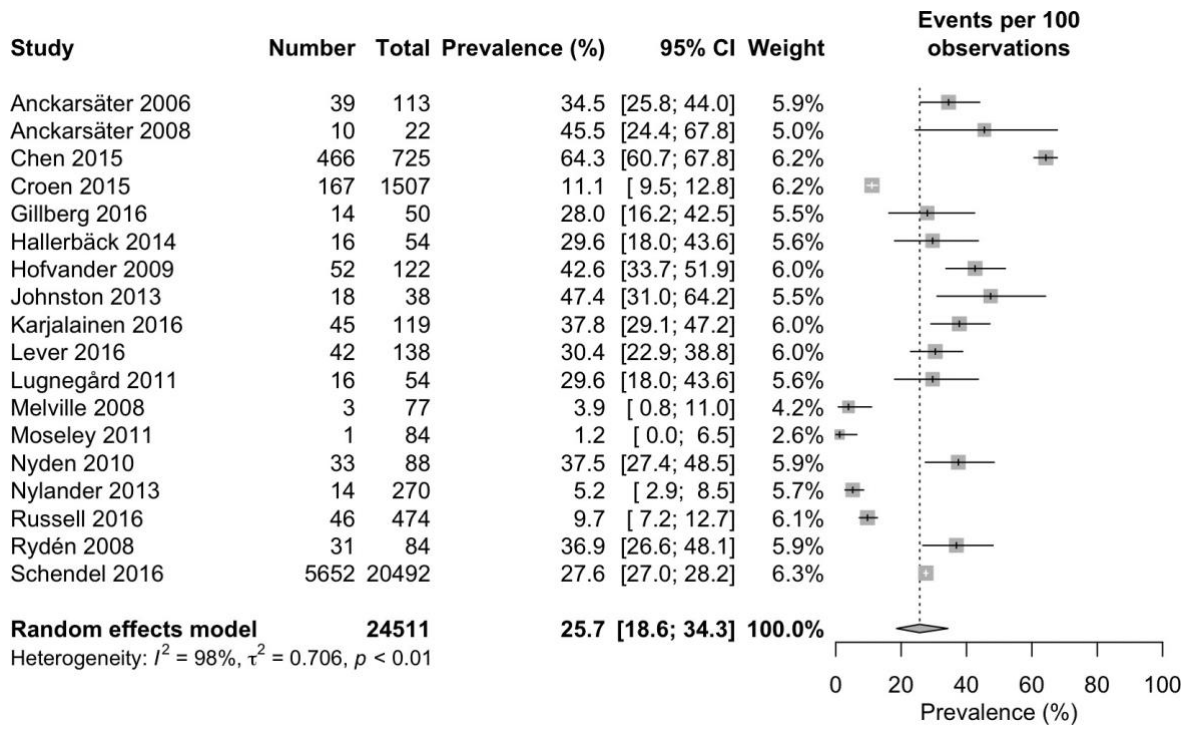| Study	Number	Total	Prevalence (%)	95% CI	Weight
Anckarsäter 2008	21	22	95.5	[77.2; 99.9]	1.9%
Bakken 2010	33	62	53.2	[40.1; 66.0]	6.0%
Buck 2014	89	129	69.0	[60.3; 76.8]	6.4%
Croen 2015	814	1507	54.0	[51.5; 56.6]	6.9%
Gillberg 2016	47	50	94.0	[83.5; 98.7]	3.7%
Hutton 2008	21	135	15.6	[9.9; 22.8]	6.1%
Ketelaars 2008	8	15	53.3	[26.6; 78.7]	4.2%
Lever 2016	109	138	79.0	[71.2; 85.5]	6.3%
Lunsky 2009	13	23	56.5	[34.5; 76.8]	4.8%
Melville 2008	16	77	20.8	[12.4; 31.5]	5.8%
Moseley 2011	35	84	41.7	[31.0; 52.9]	6.2%
Mouridsen 2008a	55	89	61.8	[50.9; 71.9]	6.2%
Mouridsen 2008b	20	118	16.9	[10.7; 25.0]	6.0%
Nylander 2013	162	270	60.0	[53.9; 65.9]	6.7%
Roy 2015	35	50	70.0	[55.4; 82.1]	5.6%
Russell 2016	275	474	58.0	[53.4; 62.5]	6.8%
Tani 2003	16	20	80.0	[56.3; 94.3]	3.9%
Tsakanikos 2007	57	137	41.6	[33.3; 50.3]	6.5%
Random effects model		**3400**	**54.8**	**[46.6; 62.7]**	**100.0%**

Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.4023$, $p < 0.01$

Events per 100 observations

Prevalence (%)