Artículo I

Referencia:

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Título: Prevalencia de trastornos psiquiátricos en adultos con Trastorno del Espectro Autista: una revisión sistemática y metaanálisis

Resumen

Introducción: las dificultades relacionadas con el Trastorno del Espectro Autista (TEA) en su intento de adaptación al entorno pueden provocar la aparición de sintomatología psiquiátrica concomitante. Esta concurrencia de trastornos psiquiátricos en personas con TEA se hace especialmente evidente en la etapa adulta, cuando las exigencias del ambiente aumentan y la persona no puede responder a las mismas, estableciendo contacto con servicios de salud mental con el objetivo de reducir el malestar asociado. Sin embargo, la mayoría de los estudios se han centrado en explorar la frecuencia de los trastornos psiquiátricos concomitantes en la edad infanto-juvenil, dejando en un segundo plano el estudio de estos trastornos en la población adulta con TEA.

Objetivo: el objetivo del presente trabajo es llevar a cabo una revisión sistemática y metaanálisis de la evidencia disponible sobre la concurrencia de trastornos psiquiátricos en personas adultas con TEA.

Método: Se realizó una búsqueda electrónica en cuatro bases de datos (PubMed, PsycInfo, Web of Science y CINAHL), así como una búsqueda manual a través de listas de referencias y editoriales altamente susceptibles de contener trabajos sobre el tema de revisión (Science Direct, Wiley, Springer, Taylor & Francis, SAGE Publishing y BioMed Central). Se incluyeron estudios observacionales que reportaran datos de prevalencia de trastornos psiquiátricos en población adulta (18 años o más) con diagnóstico de TEA.

Resultados: Un total de 1288 y 24 referencias fueron detectadas en las búsquedas electrónica y manual, respectivamente. Los resultados mostraron una mayor prevalencia de trastornos del neurodesarrollo (Trastorno por déficit de atención e hiperactividad), afectivos (depresión, distimia), y ansiedad (fobia social, trastorno adaptativo y trastorno obsesivo-compulsivo). Los trastornos con menor prevalencia en esta población son los trastornos por consumo de sustancias y los trastornos de la conducta alimentaria.

Conclusiones: La prevalencia de trastornos psiquiátricos en adultos con TEA es superior a la reportada en población general, estableciéndose de este modo el TEA como un posible factor de vulnerabilidad para el desarrollo de un trastorno psiquiátrico concomitante. Son necesarios estudios longitudinales para establecer relaciones de causalidad, así como identificar factores de riesgo/protección frente al desarrollo de patología psiquiátrica. Igualmente, el solapamiento de las características relacionadas con los TEA con síntomas de otras entidades diagnósticas, especialmente los trastornos del espectro de la esquizofrenia), obligan a profundizar en la descripción de características discriminatorias que permitan realizar una buena aproximación diagnóstica en la edad adulta.

Palabras clave: Trastorno del Espectro Autista; Trastornos psiquiátricos; Adultos; Revisión Sistemática; Metaanálisis.

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Title: Prevalence of psychiatric disorders in adults with autism spectrum disorder: a systematic review and meta-analysis
Research in Autism Spectrum Disorders

Dear Professor Canal-Bedia,

Thank you for submitting your revised manuscript to Research in Autism Spectrum Disorders. I have reviewed your paper and believe that you have carefully addressed all of the reviewers' comments. I am therefore pleased to inform you that your paper is now ready for publication and will be passed to the production team.

Thank you for your valuable contribution to Research in Autism Spectrum Disorders.

Kind Regards

Grace Iarocci, Ph.D
Associate Editor
Research in Autism Spectrum Disorders

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

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, while 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.

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

Autism spectrum disorder (ASD) is a neurodevelopmental disorder of early onset, 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 with 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 adolescents 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 the interest that this issue is raising. 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. A scarce number of systematic studies apply a meta-analytical methodology 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 are focused on depression and anxiety disorders, which are generally considered to be the most frequent comorbidity (Howlin, 2000) 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 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 those 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. 112 references were selected for full-text screening. 65 references were considered for inclusion in the review. In the quality assessment stage, 4 studies were excluded. During the 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

From all 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 I2 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 (I2 = 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%) (I2 = 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 (I2 = 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%) (I2 = 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 (I2 = 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%) (I2 = 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 (I2 = 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 lessprevalent 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%) (I2 = 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 (I2 = 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%) (I2 = 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 (I2 = 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%) (I2 = 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 ($I2 = 98\%$, 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%) ($I2 = 91\%$, $p = 0.01$).

[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 ($I2 = 93\%$, 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%) ($I2 = 93\%$, $p = 0.01$).

[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, including ADHD, depression and anxiety disorders as the most prevalent. 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.

Conflict of interest.

None of the authors have any conflict of interest.

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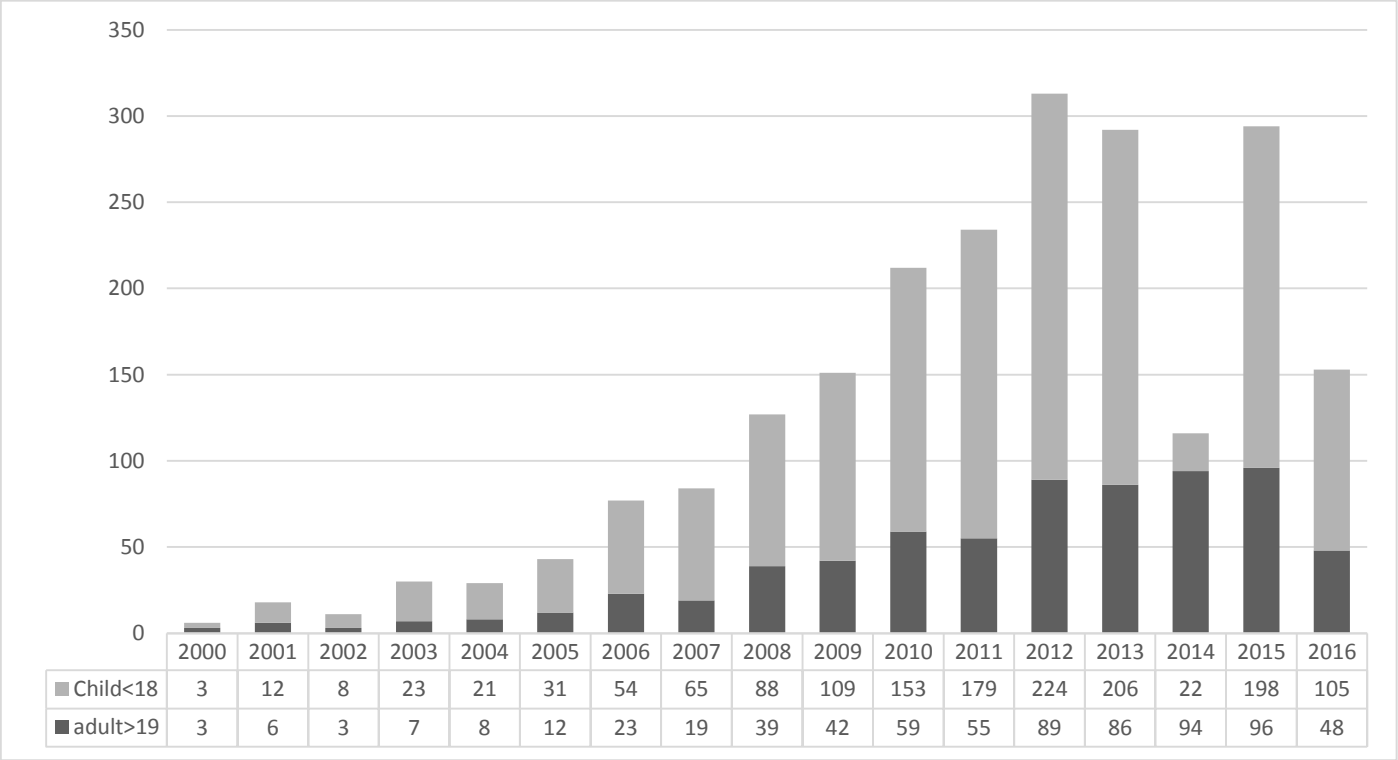
Figure 1. Published studies regarding psychiatric disorders on ASD infants vs. adults.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Child<18	3	12	8	23	21	31	54	65	88	109	153	179	224	206	22	198	105
adult>19	3	6	3	7	8	12	23	19	39	42	59	55	89	86	94	96	48

Figure 2. PRISMA flow diagram

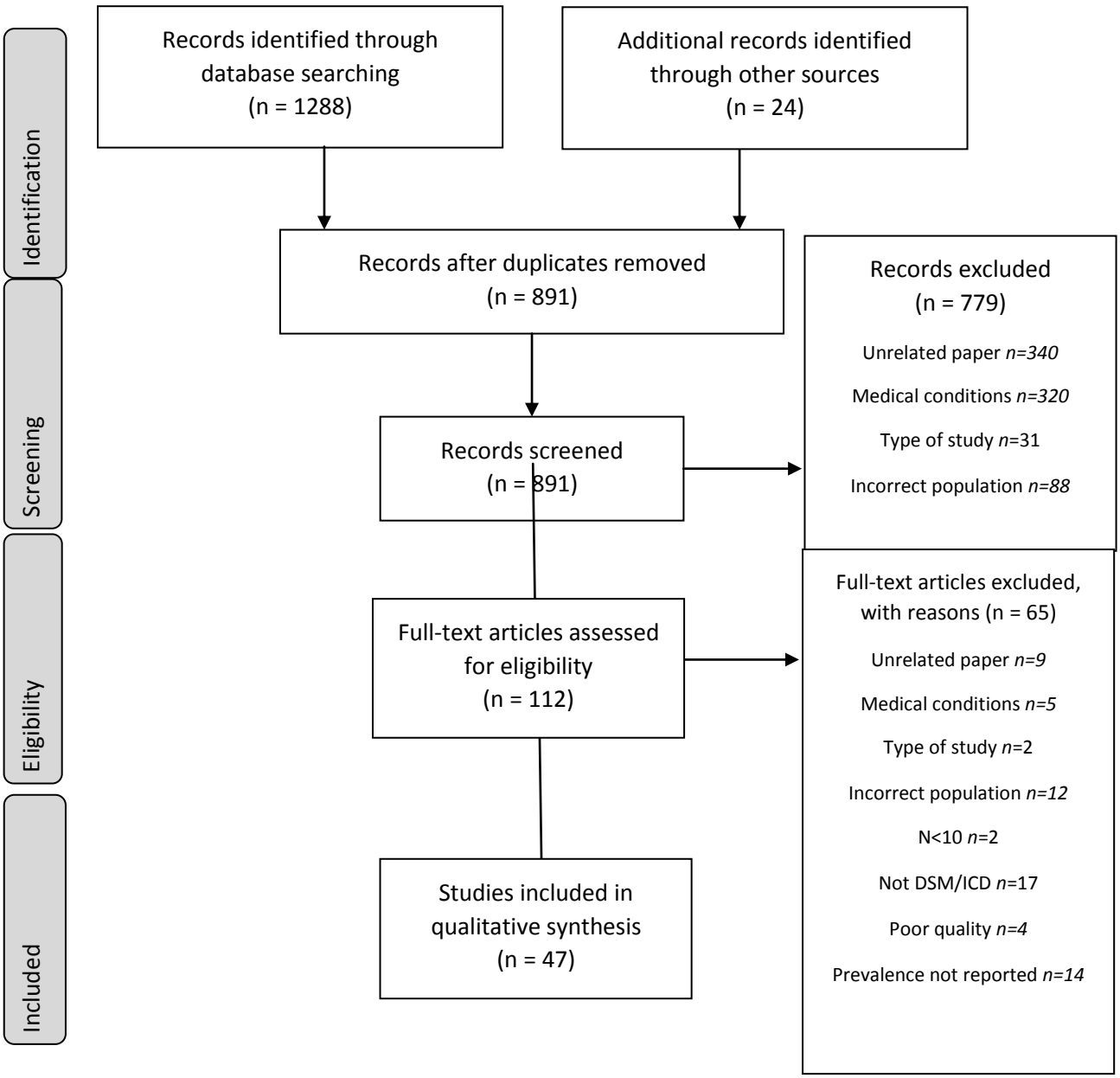


Figure 3. Forest plot of the pooled prevalence of SUD in adults with ASD.

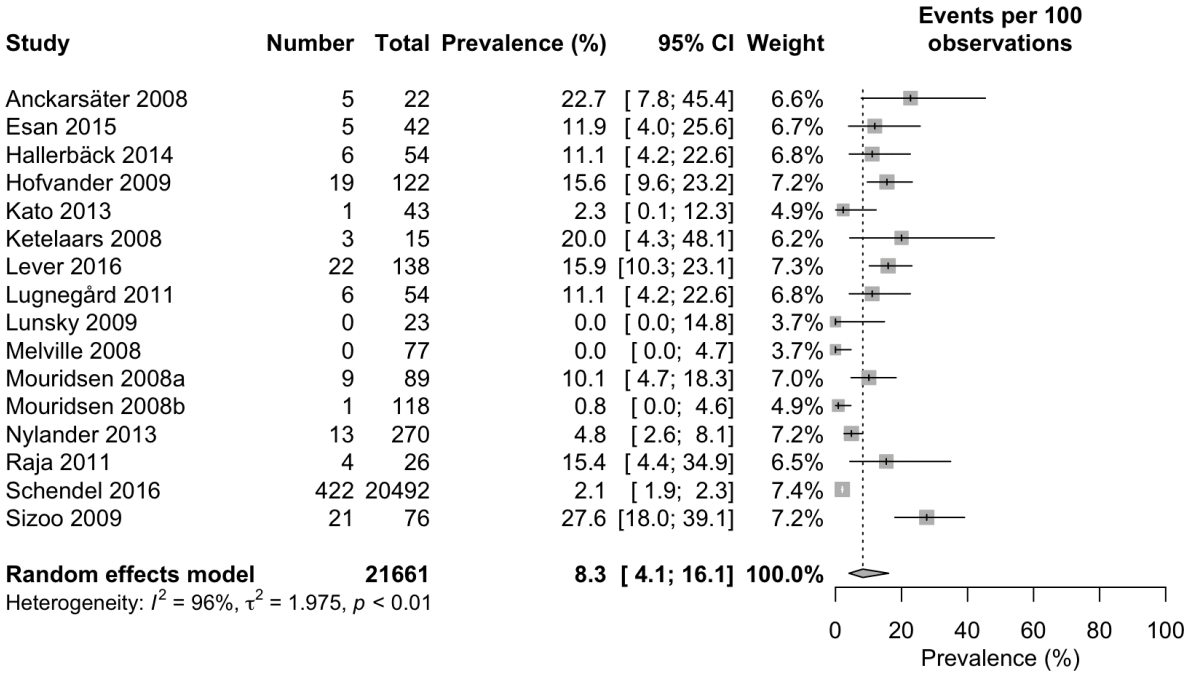


Figure 4. Forest plot of the pooled prevalence of SSD in adults with ASD.

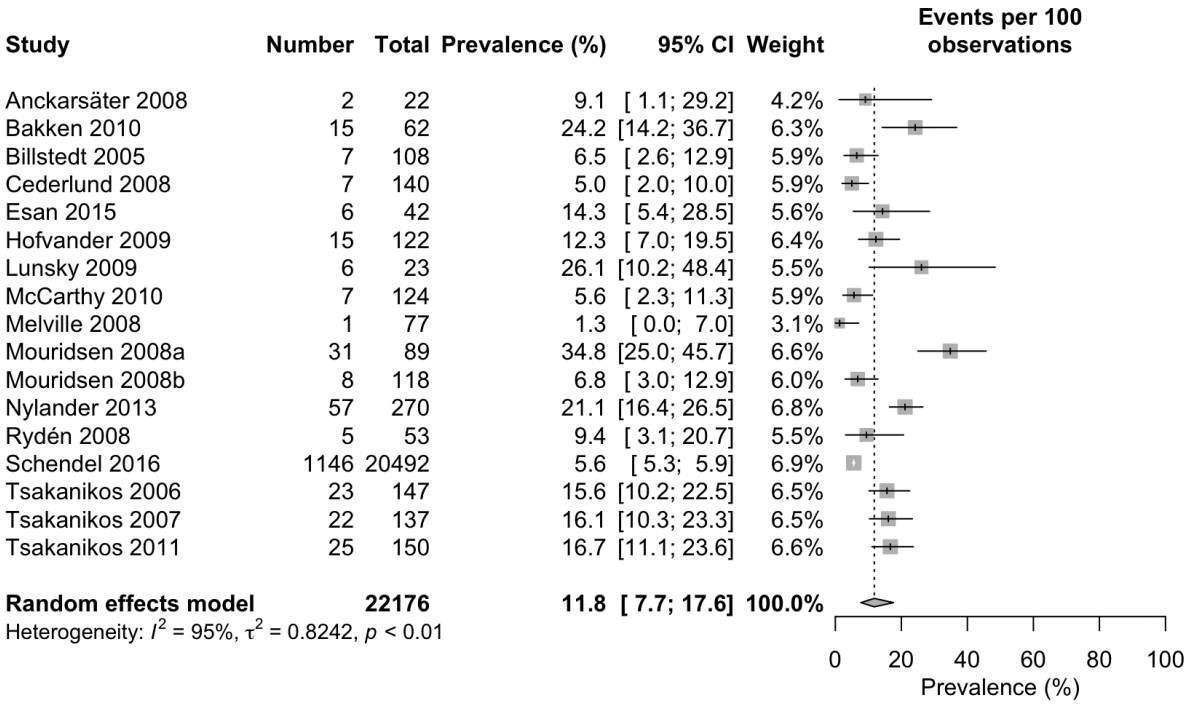


Figure 5. Forest plot of the pooled prevalence of MD in adults with ASD.

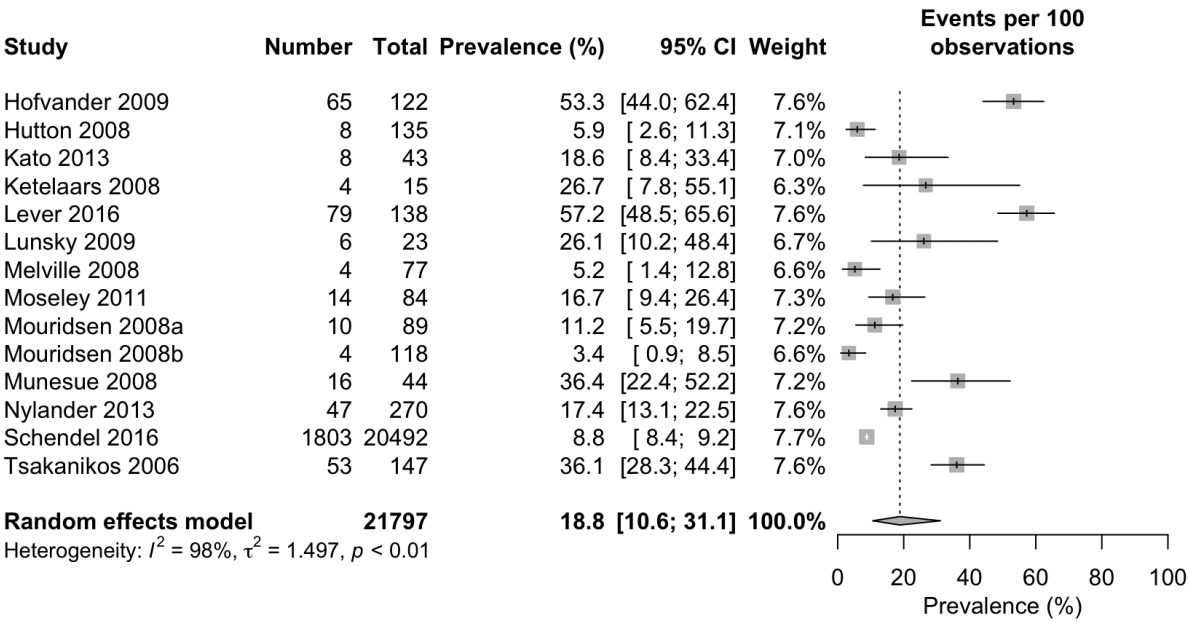


Figure 6. Forest plot of the pooled prevalence of ANX in adults with ASD.

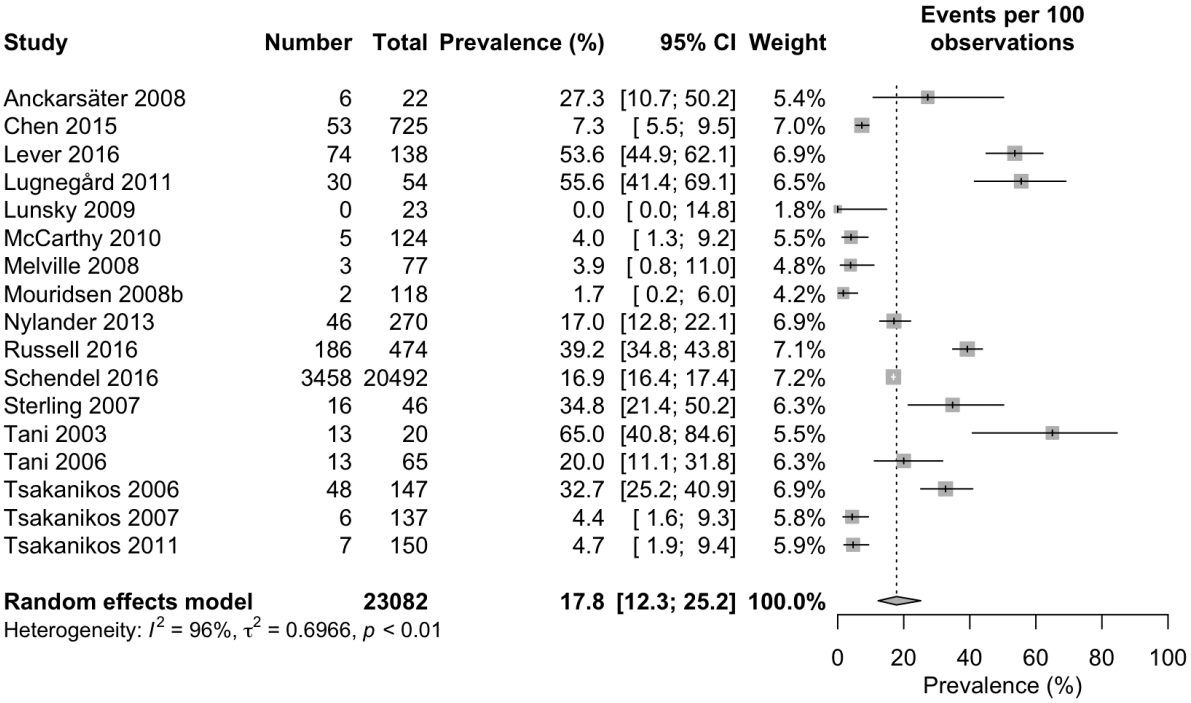


Figure 7. Forest plot of the pooled prevalence of ED in adults with ASD.

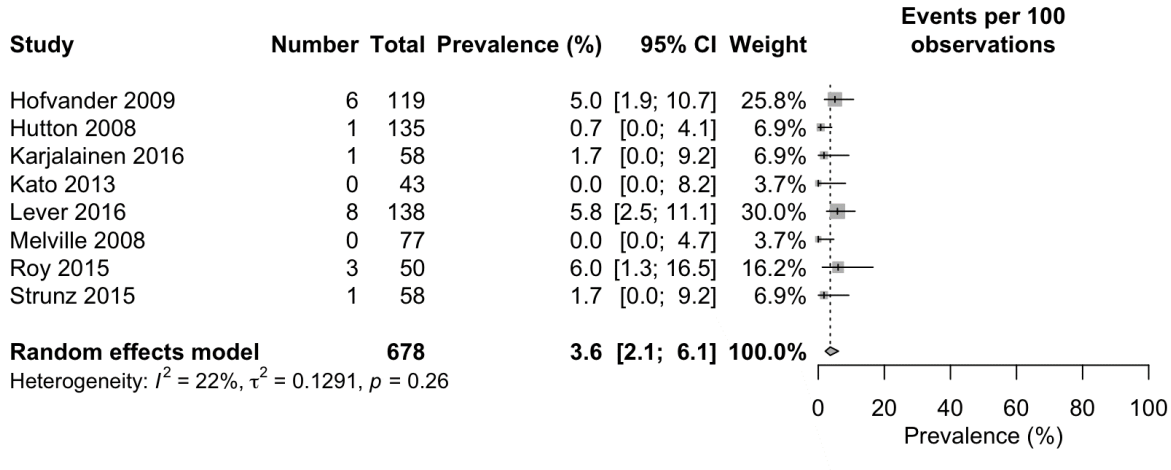


Figure 8. Forest plot of the pooled prevalence of PD in adults with ASD.

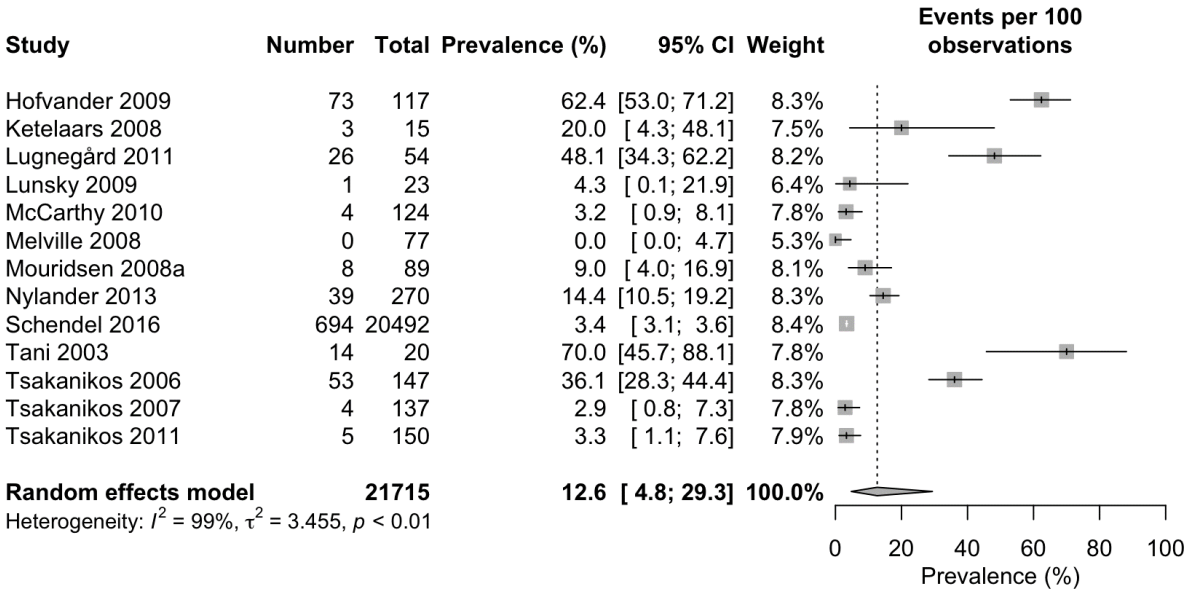


Figure 9. Forest plot of the pooled prevalence of ADHD in adults with ASD.

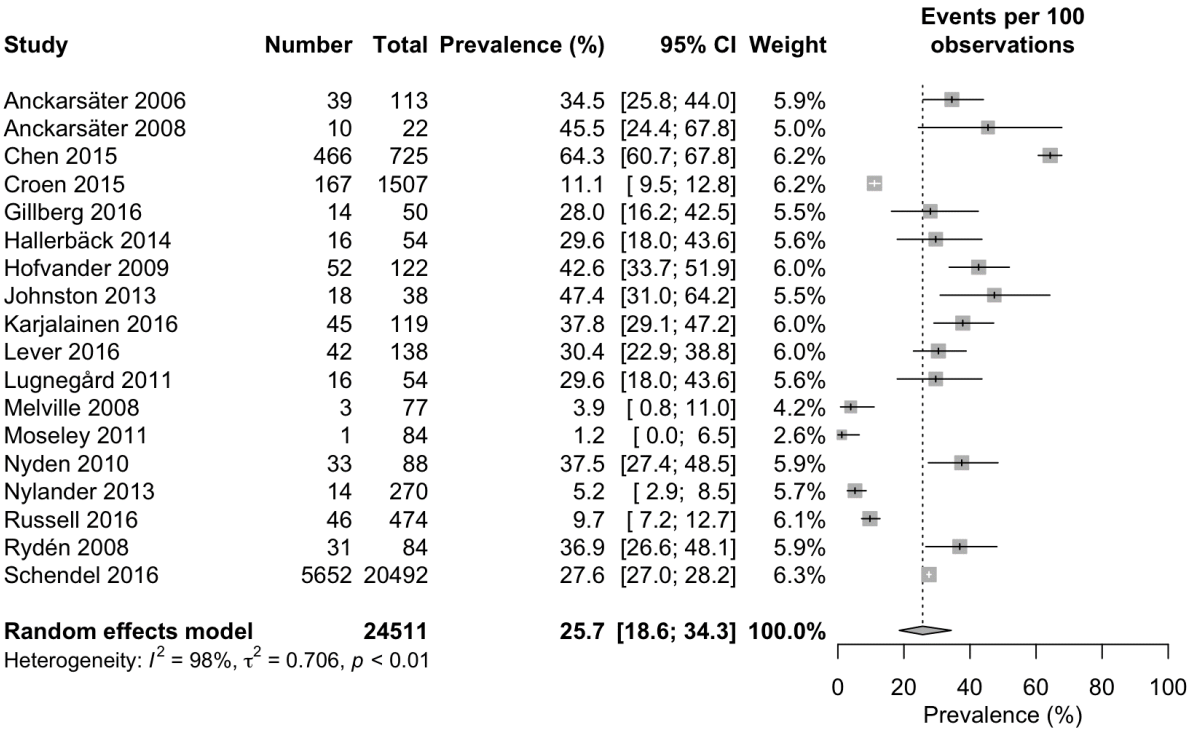
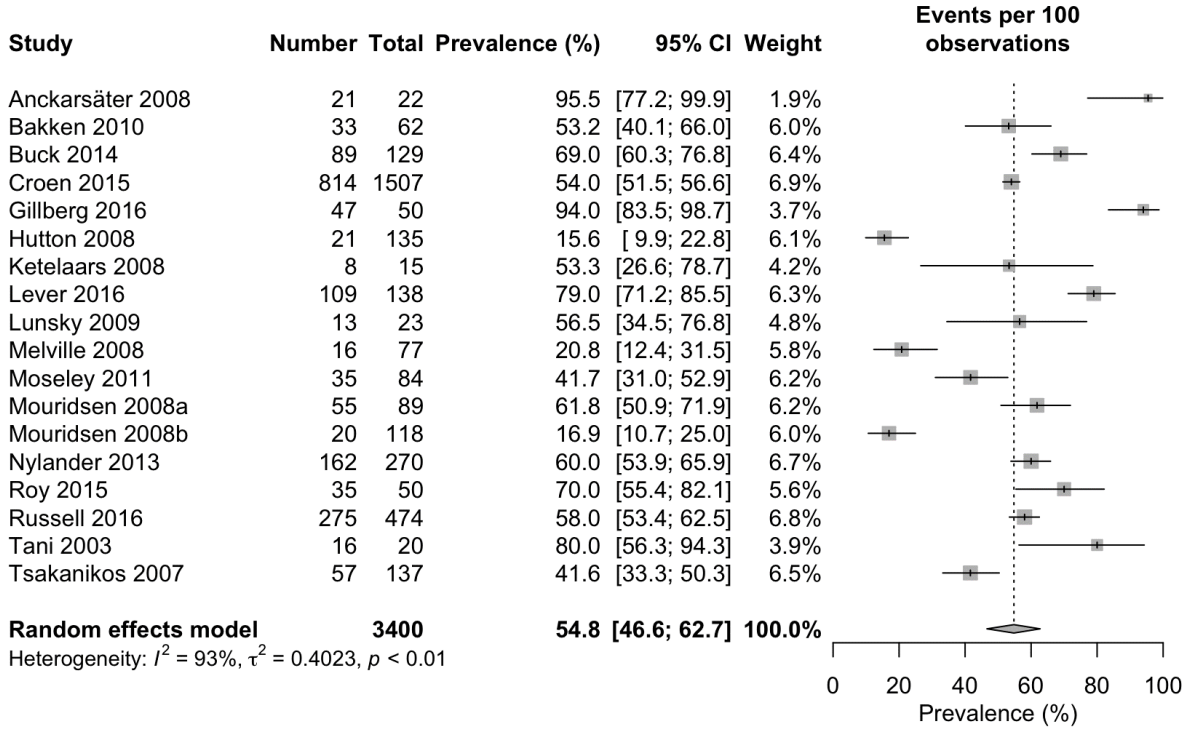


Figure 10. Forest plot of the pooled prevalence of APD in adults with ASD.



Appendix A. Table 1. Electronic search strategy

1. Autism OR "Autism Spectrum Disorder*" OR ASD OR "Autistic Disorder*" OR "Pervasive Developmental Disorder*" OR PDD OR "PDD-NOS" OR "High Functioning Autism" OR "Asperger*" OR "Asperger Syndrome"
2. Comorbidity OR "Co morbidity" OR Comorbidities OR "Secondary pathology" OR Coexistence OR Multimorbidity OR "Dual diagnosis"
3. Adult* OR "Young Adult" OR "Middle Aged" OR Aged OR Elderly
4. ((Descriptive OR Prevalence OR Cross-Sectional OR Cohort OR Longitudinal OR Follow-up OR Prospective OR Incidence OR "Case Control" OR Retrospective) Study) OR Epidemiology
5. "Minimal Brain Dysfunction" OR "Intellectual Disabilit*" OR (Mental (Retard* OR Deficienc*)) OR "Attention Deficit Hyperactivity Disorder*" OR "Hyperkinetic Syndrome" OR ADDH OR ADHD OR "Substance-Related Disorders" OR Paranoia* OR ((Schizophren* OR Psychotic OR Schizoaffective OR Schizophreniform OR Delusional OR Paranoid) Disorder*) OR (("Brief Reactive" OR Paranoid) Psychos*) OR "Paranoid Schizophrenia*" OR ((Mood OR Affective OR Cyclothym* OR Bipolar OR Manic OR Depressive OR "Mixed anxiety-depressive") Disorder* OR Neurosis OR Syndrome) OR Mania OR Depression OR ((Bipolar OR Unipolar) Depression) OR ((Anxiety OR Neurotic OR Panic OR Phobic) Disorder* OR Neuros*s OR Attack) OR Phobia* OR Claustrophobia* OR Social Phobia* OR "Anankastic Personalit*" OR "Obsessive Compulsive Disorder*" OR OCD OR Neuros*s OR (("Post-Traumatic Stress" OR Adaptive) Disorder*) OR PTSD OR (Dissociati* OR Conversion (Disorder* OR Reaction OR Hysteria)) OR Fugue OR Globus Hystericus OR Hypochondriacal Neuros*s OR ((Somatoform OR Somatization OR Pain) Disorder*) OR ((Bulimia OR Anorexia) Nervosa*) OR ((Eating OR Feeding OR Appetite OR "Binge Eating") Disorder*) OR ((Sleep Walking OR Hypersomnolence OR "Sleep Terror*") Disorder*) OR Insomnia OR Hypersomnia OR Nightmares OR Sleepwalking OR Nocturnal Wandering OR Frigidity OR (("Psychological Sexual" OR Psychosexual OR "Hypoactive Sexual Desire" "Sexual Aversion" OR Orgasmic OR "Sexual Arousal") Dysfunction* OR Disorder*) OR "Gender dysphoria" OR Transsexualisms OR Transgender OR Trichotillomanias OR (("Impulse Control" OR "Intermittent Explosive") Disorder*) OR Kleptomania OR "Firesetting Behaviors" OR Pyromania OR Arson OR Gambling* OR "Pathological Gambling" OR ((Avoidant OR Narcissistic OR Antisocial OR Sociopathic OR Psychopathic OR Dyssocial OR Borderline OR "Obsessive Compulsive" OR Dependent OR Hysterical OR Histrionic OR Paranoid OR Negativistic OR "Passive Agressive" OR Schizoid OR Schizotypal) Personality Disorder*) OR Voyeurisms OR Paraphili* Disorder* OR Sex Deviations OR Exhibitionisms OR Fetishisms OR "Sexual Masochisms" OR Pedophilias OR "Sexual Sadisms" OR Transvestisms
6. #1 AND #2 AND #3 AND #4 AND #5
7. Search range: 01/01/2000 – 05/31/2016
8. Lenguage: English
9. Academic Journals (Peer Reviewed)
10. Age range: adults (>18 years)
11. #6 AND #7 AND #8 AND #9 AND #10

Table 2. Summary of inclusion and exclusion criteria and rationale

Inclusion Criteria
Observational studies focusing on psychiatric comorbidity in ASD
Clinical diagnoses which had been established on the basis of diagnostic classifications in DSM (any version) and/or ICD-10[a]
English-written studies
Peer reviewed articles
Exclusion Criteria
Studies related to genetic / medical conditions[b]
Studies based on children and youth population samples (<18 years)[c]
Small samples (N <10)[d]

[a] Rationale is to include results from studies that use two of the most commonly used standards for stablishing clinical diagnoses

[b] Rationale is to remove the influence of specific confounding variables

[c] Rationale is that because ASD are conceptualized as developmental disorders, research regarding co-occurrent psychiatric disorders has been focused in the first years of life and there are a lack of knowledge about psychiatric problems in adulthood

[d] Rationale is that random effects model will be used to conduct meta-analysis and substantial heterogeneity is expected. In this situation, weights tend to become more equal and even even a small study may have almost the same weight as a large one. We assume that studies with small samples are of poorer quality and they are not likely to be a random sample of all the small studies population.

Table 1. Characteristics of included studies

				ASD GROUP						
Author (Year)	**Country**	**Context**	**Recruitment source**	**N (% Male)**	**Mean Age (SD) (Range)**	**Mean IQ (SD) (Range)**	**% ID**	**Diagnostic Criteria**	**Diagnostic Measures**	**Diagnostic Subtypes**
Anckarsäter (2006)	Sweden	Clinical	Child Neuropsychiatric Clinic	113 (NR)	NR (NR) (19-60)	NR	NR	DSM-IV	ASSQ, ASDI, DSM-IV Checklist	AD: 6 AS: 46 AA: 61
Anckarsäter (2008)	Sweden	Clinical	Forensic Psychiatric Hospital	22 (77.3)	NR (NR) (18-47)	NR	27.3	DSM-IV	ASSQ, ASDI	AD: 7 AS: 5 AA: 10
Bakken (2010)	Norway	Clinical	Autism Team	62 (27.4)	23.9 (NR) (14-57)	NR	100	ICD-10	Clinical examination	AD: 62
Billstedt (2005)	Sweden	Clinical	Child Neuropsychiatric Clinic	108 (NR)	NR (NR) (17-40)	NR	96.3	DSM-IV/ICD-10	DISCO-10	AD: 73 AS: 35
Buck (2014)	USA	Community	UCLA University of Utah	129 (75.2)	36.4 (5.9) (26.1-54.4)	NR	72.8	DSM-III/DSMIV-TR	NR	NR
Cederlund (2008)	Sweden	Clinical	Child Neuropsychiatric Clinic	AS 70 (100) AD 70 (100)	21.5 (4.4) (16-33.9) 24.5 (5.4) (16.1-36.1)	103 (14.8) (66-143) 59.6 (17.9) (NR)	1.4 93	DSM-IV/ICD-10	DISCO-10	AD: 70 AS: 70
Chen (2015)	Taiwan	Clinical	National Health Insurance Research Database	725 (77.2)	18.3 (13.4) (NR)	NR	NR	ICD9-CM	NR	NR
Croen (2015)	USA	Clinical	Kaiser Permanente in Northern California	1507 (73.1)	29 (12.2) (NR)	NR	19.2	ICD-9-CM	NR	NR
Esan (2015)	England	Clinical	Specialized Forensic Inpatient Service	42 (85.7)	30.1 (9.14) (NR)	NR	100	ICD-10	NR	NR
Gillberg (2016)	Sweden	Clinical	Child Neuropsychiatric Clinic	50 (100)	30.2 (5) (23-43)	107.6 (NR) (NR)	0	DSM-IV/ICD10	ASSQ, ASDI, DISCO-11	NR
Hallerbäck (2014)	Sweden	Clinical	Two Outpatient Clinics	54 (48.2)	27 (3.9) (NRNR)	NR	NR	DSM-IV	DISCO-11	AS: 54
Hofvander (2009)	France/Sweden	Clinical	Albert Chevalier Hospital Child Neuropsychiatric Clinic Psychiatric Outpatient Clinic	122 (67.2)	NR (NR) (16-60)	NR	0	DSM-IV	ASDI	AD: 5 AS: 67 PDD-NOS: 50
Hutton (2008)	England	Clinical	Maudsley Hospital Outpatient Clinic	135 (77)	34.9 (NR) (21-57)	>30	NR	DSM-IV	ADI-R, ADOS	NR
Johnston (2013)	England	Clinical	Tertiary level assessment Clinic	48 (85.4)	25.6 (12.09) (19-62)	NR	0	ICD-10	ADOS, ADI-R	AS: 1 HFA: 23 PDD-NOS: 7
Joshi (2013)	USA	Clinical	University Hospital	63 (65.1)	29.2 (11) (18-63)	104.4 (17.3) (55-136)	3	DSM-IV	NR	AD: 41 AS: 16 PDD-NOS: 6
Karjalainen (2016)	Sweden	Clinical	Child Neuropsychiatric Clinic	119 (NR)	>18	NR	NR	DSM-IV	ASDI, DSM-IV Checklist	NR
Kato (2013)	Japan	Clinical	Advanced Critical Care Center Tokai University Hospital	43 (81.4)	33.7 (12.6) (NR)	NR	NR	DSM-IV	AQ	NR
Ketelaars (2008)	Netherlands	Clinical	Outpatient Psychiatric Center Outpatient Psychiatric Clinic	15 (80)	22 (5) (18-24)	104 (10) (NR)	0	DSM-IV	AQ, ADOS-G, ADI-R, Self-developed Interview	AS: 4 HFA:1 PDD-NOS:10
Kronenberg (2015)	Netherlands	Clinical	The Dual Diagnosis Dept. of Dimence Victas Centre for addiction care	31 (94)	40 (NR) (NR)	>80	0	DSM-IV	NR	NR
Lever (2016)	Netherlands	Mixed	Mental Health Institutions, Websites	138 (30.4)	46.5 (NR) (NR)	113.8 (NR)	0	DSM-IV	ADOS	AD: 21 AS:69 PDD-NOS: 43
Lugnegård (2011)	Sweden	Clinical	Two Outpatient Clinics	54 (48.2)	27 (3.9) (NR)	102 (12) (NR)		DSM-IV	DISCO-11	AS: 54
Lugnegård (2012)	Sweden	Clinical	Two Outpatient Clinics (DAH, NCCA)	54 (48.2)	27 (3.9) (NR)	102 (12) (73-143)	0	DSM-IV	DISCO-11	AS: 54
Lunsky (2009)	Canada	Clinical	Three psychiatric hospitals	23 (74)	35.4 (9.12) (NR)	NR	100	ICD-9	CCAR	NR
Maddox (2015)	USA	Mixed	University Center for Autism University Autism Clinic ASD Support groups for adults	28 (53.6)	23.9 (6.9) (16.4)	106.7 (16.6) (80-141)	0	DSM-IV	AQ, ADOS-2, SRS-2-A	NR
McCarthy (2010)	England	Clinical	Specialist Mental Health Service	124 (69.3)	NR (NR) (18-65)	NR	100	ICD-10	NR	NR
McDermott (2005)	USA	Clinical	Family medicine physicians	51 (78.4)	26.7 (NR) (NR)	NR	100	ICD-9	NR	NR
Melville (2008)	Scotland	Mixed	Greater Glasgow Health Board	T1 77 (76.6) T2 50 (NR)	T1 37.8 (14.1) (NR) T2 NR	T1 NR T2 NR	100	DSM-IV/ICD-10	PAS-ADD Checklist, Clinical Interview	NR
Moseley (2011)	Australia	Community	Community Developmental Assessment Services	84 (82.1)	19.5 (4.6) (NR)	NR	79	DSM-IV/ICD-10	Clinical Interview and Observations	AD: 84
Mouridsen (2008a)	Denmark	Clinical	University Hospital	89 (65.2)	45.3 (7.2) (27-60)	NR	39	ICD-10	NR	AA: 89
Mouridsen (2008b)	Denmark	Clinical	University Hospital	118 (72)	40.6 (7.7) (25-55)	NR	70	ICD-10	NR	AD: 118
Munesue (2008)	Japan	Clinical	Outpatient Clinic	44 (63.6)	NR (NR) (13-39)	NR	0	DSM-IV	TABS, AQ, ASSQ	AD: 9 AS: 27 PDD-NOS: 8
Nydén (2010)	Sweden	Clinical	Child Neuropsychiatric Clinic	88 (65.9)	32 (10) (NR)	> 71	0	DSM-IV	ASSQ, ASDI, DSM-IV Checklist	AD: 3 AS: 44 PDD-NOS: 41
Nylander (2013)	Sweden	Clinical	University Hospital	270 (69)	30.7 (11.5) (16-63)	NR	0	ICD-9/ICD-10	NR	NR
Raja (2011)	Italy	Clinical	Psychiatric Intensive Care Unit of a General Hospital	26 (96.15)	30.2 (9.8) (16-56)	83.5 (18.2) (46-121)	15.4	DSM-IV-TR	Medical charts, Interview with relatives	AD: 5 AS: 16 PDD-NOS: 5
Roy (2015)	Germany	Clinical	Psychiatric Intensive Care Unit of a General Hospital	50 (68)	36.4 (NR) (20.62)	NR	NR	DSM-IV	AQ, EQ, Self-developed Interview	AS: 50
Russell (2016)	England	Clinical	National Specialist Clinic	474 (78.4)	30.6 (11.18) (NR)	NR	NR	ICD-10R	AQ, ADOS-G, ADI-R	AD: 115 AS: 212 AA: 100
Rydén (2008)	Sweden	Clinical	Tertiary Psychiatric Clinic	84 (53.6)	30 (10) (NR)	>70	0	DSM-IV	FTF, ASSQ, ASDI	AD: 5 AS: 51 PDD-NOS: 28
Schendel (2016)	Denmark	Clinical	Danish Psychiatric Central Research Register	20492 (77.6)	NR	NR	16	ICD-8/ICD-10	Medical records	NR
Sizoo (2009)	Netherlands	Clinical	Two specialized clinics	76 (81.6)	34.1 (11.9) (NR)	103 (13.6)	0	DSM-IV	ADI-R, DSM-IV Checklist	AD: 10 AS:32 PDD-NOS: 34
Stahlberg (2004)	Sweden	Clinical	Child Neuropsychiatric Clinic	129 (61.2)	30.6 (9.7)	NR	NR	DSM-IV	ASSQ, ASDI, DSM-IV Checklist	AD: 13 AS:49 AA:67
Sterling (2008)	USA	Community	University Of Washington Autism Center	46 (91.3)	23.7 (7.21) (18-44)	NR (NR) (57-139)	NR	DSM-IV	ADOS-WPS/ADOS-G, ADI-R	NR
Strunz (2015)	Germany	Clinical	Charité University Medicine Berlin	58 (45.8)	32.7 (10.9)	>70	0	DSM-IV	ADOS, ADI-R	AS: 49 HFA: 10
Tani (2003)	Finland	Community	Helsinki Asperger Centre	20 (70)	27.2 (7.3)	111.6 (11.9)	NR	DSM-IV	ASSQ	AS: 20
Tani (2006)	Finland	Community	Helsinki Asperger Center	20 (70)	27.2 (7.3) (NR)	111.6 (11.9) (NR)	NR	DSM-IV	ASSQ	AS: 20
Tsakanikos (2006)	England	Clinical	Specialist Mental Health Service	147 (67.3)	NR (NR) (16-84)	NR	100	ICD-10	NR	NR
Tsakanikos (2007)	England	Clinical	Specialist Mental Health Service	137 (67.2)	28.4 (NR) (NR)	NR	100	ICD-10	NR	NR
Tsakanikos (2011)	England	Clinical	Specialist Mental Health Service	150 (66.7)	28.5 (10.6) (16-84)	NR	100	ICD-10	NR	NR

ASD – Autism Spectrum Disorders; NR – Non-reported; SD – Standard deviation; IQ – Intelligence quotient; ID – Intellectual disability; ASSQ – Asperger Syndrome Screening Questionnaire; ASDI – Asperger Syndrome Diagnostic Interview; DISCO – Diagnostic Interview for Social and Communication Problems; ADI-R – Autism Diagnostic Interview Revised; ADOS – Autism Diagnostic Observational Schedule; AQ – Autism Quotient; CCAR – Colorado Client Assessment Record; SRS – Social Responsiveness Scale; PAS-ADD - Psychiatric Assessment Schedule for Adults with Developmental Disabilities; TABS – Tokyo Autistic Behavior Scale; EQ – Empathy Quotient; FTF-Q – Five-to-Fifteen Questionnaire; AD – Autistic Disorder; AS – Asperger Syndrome; AA – Atypical Autism; PDD-NOS – Pervasive Developmental Disorder Not Otherwise Specified; HFA – High-Functioning Autism.

Table 2. Disorders due to psychoactive substance use (SUD)

Author (Year)	N ASD	N CG	Psychiatric disorders measures	Outcome
Anckarsäter (2008)	22	-	Medical files Structured Interviews	2 (9.1%), 1 (4.5%) and 2 (9.1%) had a SUD, OH and Mixed SUD diagnose, respectively.
Croen (2015)	1507	15,070	Medical records	**ASD:** OH abuse 33 (2.2%) OH dependence 16 (1.1%) Drug abuse 39 (2.3%) Drug dependence 27 (1.8%) **Non-ASD:** OH abuse 591 (4%) OH dependence 296 (2%) Drug abuse 418 (2.8%) Drug dependence 325 (2.5%)
Esan (2015)	42	96	Medical records	5 (11.9%) and 34 (35.4%) individuals had a harmful use or dependence on substances in the ASD and ID groups, respectively.
Gillberg (2016)	50	-	ASRS	2 (4%) reported current alcohol dependency. None reported current drug dependency.
Hallerbäck (2014)	54	41	SCID-I	**ASD:** SUD 6 (11.1%) OH 4 (7.4%) CAN 2 (3.7%) STI 4 (7.4%) Other drugs 2 (3.7%) **SQZ:** SUD 13 (31.1%) OH 6 (14.6%) CAN 4 (9.8%) STI 7 (17.1%) Other drugs 0
Hofvander (2009)	122	-	SCID-I DSM-IV Checklist Interview	19 (16%) individuals had a lifetime SUD. The majority of diagnoses were related to alcohol (n = 15, 12%), 4 (3.3%) subjects met criteria for cannabis use disorder, 3 (2.5%) for amphetamine use disorder, 2 (1.6%) had a history of taking non-prescribed opiates or analgetics, and 1 (0.8) had used anabolic steroids. Another subject, a 27-year-old man with Autistic Disorder, had a history of inhaling solvents.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** Any SUD 21 (33%) 7 (11%) OH abuse 18 (29%) 4 (6%) OH dependence 8 (13%) 2 (3%) Drug abuse 9 (14%) 2 (3%) Drug dependence 3 (5%) 1 (2%) **Non-ASD:** Any SUD 28 (44%) 5 (8%) OH abuse 5 (8%) 3 (5%) OH dependence 17 (27%) 2 (3%) Drug abuse 12 (20%) 0 Drug dependence 11 (18%) 2 (3%)
Kato (2013)	43	544	MINI	1 (2.3%) and 42 (7.7%) participants fulfilled diagnostic criteria for a substance abuse disorder in the ASD and Non-ASD groups, respectively.
Ketelaars (2008)	15	21	SCAN-2.1	3 (20%) and 2 (10%) reported a current SUD in the ASD and Non-ASD groups, respectively.
Kronenberg (2015)	31	50	NR	**ASD**: OH 71 % CAN 13% HER 0% COC 7% STI 3% **SUD**: OH 66% CAN 18% HER 4% COC 8% STI 0% **SUD+ADHD**: OH 39% CAN 24% HER 2% COC 7% STI 15%
Lever (2016)	138	170	MINI	22 (15.9%) and 43 (25.3%) had a substance abuse disorder in the ASD and Non-ASD, respectively.
Lugnegard (2011)	54	-	SCID-I	6 participants (11%) had had a previous SUD (one woman and one man with a combination of alcohol and drug dependence, two men with alcohol dependence and two men with drug dependence).
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	0 (0%), 3 (13%) and 8 (34.8%) participants fulfilled diagnostic criteria for a substance abuse disorder in the ASD group, ID group and non-ID group, respectively.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	0 participants fulfilled Alcohol/substance disorder diagnostic criteria at T1
Mouridsen (2008a)	89	258	Medical records	9 (10.1%) and 2 (0.8) individuals had a SUD during the follow-up period in the ASD and Non-ASD groups, respectively.
Mouridsen (2008b)	118	336	Medical records	1 (0.8%) and 8 (2.4%) individuals had a SUD during the follow-up period in the ASD and Non-ASD groups, respectively.
Nylander (2013)	270	437	NR	13 (4.8%) and 93 (21.3%) had a SUD diagnosis in the ASD and ADHD groups, respectively.
Raja (2011)	26	-	Record charts	4 (15.4%) had a SUD diagnosis.
Roy (2015)	50	-	SCID-I	6 adults (12%) were cannabis abusers; and 5 (10%) and 4 adults (8%) were diagnosed with alcohol abuse or dependence, respectively
Russell (2016)	474	385	Neuropsychiatric Asesssment	**ASD:** OH dependence 3 (0.6%) Drug dependence 1 (0.2%) **Non-ASD:** OH dependence 10 (2.5%) Drug dependence 5 (1.2%)
Schendel (2016)	20,492	1,892,412	Medical records	422 (2.1%) and 15,835 (0.8%) had a SUD diagnosis in the ASD and Non-ASD groups, respectively.
Sizoo (2009)	76	53	NR	**ASD:** any SUD 21 (28%) OH 10 (47%) CAN 6 (29%) Other drugs or gambling 5 (24%) **ADHD:** any SUD 32 (60%) OH 8 (25%) CAN 9 (28%) Other drugs or gambling 15 (47%)
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	MINI SCID-I	**ASD**: OH dependence 0, OH abuse 0, Drug dependence 0, Drug abuse 0 **BOR**: OH dependence 14 (18.2), OH abuse 20 (26), Drug dependence 14 (18.2), Drug abuse 9 (11.7) **NAR**: OH dependence 7 (11.3), OH abuse 10 (16.1), Drug dependence 7 (11.3), Drug abuse 2 (3.2) **NCC**: OH dependence 0, OH abuse 0, Drug dependence 0, Drug abuse 0

ASD – Autism Spectrum Disorders; CG – Comparison group;; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; ADHD – Attention deficit and hyperactivity disorder; NCC – Non-clinical Controls; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; MINI – MINI International Neuropsychiatric Interview; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; CCAR – Colorado Client Assessment Record; SUD – Substance use disorders; OH – Alcohol; CAN – Cannabis; HER – Heroine; COC – Cocaine; STI – Stimulants; SQZ – Schizophrenia.

Table 3. Schizophrenia, schizotypal, or delusional disorders (SSD)

Author (Year)	N ASD	N CG	Psychiatric disorders measures	Outcome
Anckarsäter (2008)	22	-	Medical files Structured Interviews	2 (9.1%) had a SSD diagnose, one a psychotic disorder and the other SQAFF.
Bakken (2010)	62	132	PAC	15 (25.1%) and 12 (9.1) participants had a diagnosis of Psychosis in the ASD and ID groups, respectively.
Billstedt (2005)	108	-	Observation, a semi-structured interview and a brief psychiatric examination	7 individuals (5 males, 3 females) had been diagnosed as suffering from psychosis. Only in one individual (male) had the psychotic condition been labelled Schizophrenia.
Buck (2014)	129	-	Mini PAS-ADD Clinical Interview	Six participants (5 %) endorsed current and 13 (10 %) endorsed lifetime symptoms meeting psychosis criteria.
Cederlund (2008)	AD 70 AS 70	-	NR	3 (4.3%) and 4 (5.7%) participants have been diagnosed as suffering from psychosis in the AS and AD groups, respectively. No individuals have been diagnosed with schizophrenia in either both groups.
Chen (2015)	725	-	Medical charts	81 (11.2%) had a Schizophrenia diagnosis
Croen (2015)	1507	15,070	Medical records	118 (7.8%) and 56 (0.4%) individuals had Schizophrenic disorders (295.xx) in the ASD and Non-ASD group, respectively. 95 (6.3%) and 83 (0.6%) individuals had Other psychoses (297.1x; 297.3x; 298.8x; 298.9x; 301.22) in the ASD and Non-ASD group, respectively.
Esan (2015)	42	96	Medical records	6 (14.3%) and 21 (21.9%) individuals had a Psychosis diagnosis in the ASD and ID groups, respectively.
Gillberg (2016)	50	-	ASRS	1 (2%) had reported Schizophrenic psychosis ever.
Hofvander (2009)	122	-	SCID-I DSM-IV Checklist and Interview	15 (12%) individuals had a lifetime Psychotic disorder. 4 (3.3%) patients met criteria for a schizophreniform disorder, 3 (2.5%) for brief psychotic disorder, and 1 (0.8%) for a delusional disorder. No subject met criteria for schizoaffective disorder.
Hutton (2008)	135	41	SAPPA	There were no cases of schizophrenia
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** 8 (13%) and 5 (8%) had lifetime and current psychosis, respectively. **Non-ASD:** None individual had lifetime neither current psychosis.
Ketelaars (2008)	15	21	SCAN-2.1	4 (19%) reported a Psychotic disorder NOS in the Non-ASD group. None individual in either group had current Schizophrenia diagnosis.
Lugnegard (2011)	54	-	SCID-I	2 (3.7%) met criteria for psychosis (one brief psychotic episode, and one psychotic syndrome NOS). 7 participants (13%) had experienced recurrent (primarily auditory) hallucinations without other signs of psychosis. No participant met criteria for SQZ, SQZAFF or substance induced psychotic disorder.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	6 (26.1%), 18 (78.3%) and 19 (82.6%) participants fulfilled diagnostic criteria for a psychotic disorder in the ASD group, ID group and non-ID group, respectively.
McCarthy (2010)	124	562	Medical records Clinical interview	7 (5.6%) and 102 (18.1%) had a SSD in the ASD and ID groups, respectively.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	1 (1.3%) participants fulfilled psychotic disorder diagnostic criteria at T1 Incidence at two years follow-up was 0 for psychotic disorder.
Mouridsen (2008a)	89	258	Medical records	**ASD:** Any SSD 31 (34.8%) SQZ 25 (28.1%) DD 2 (2.3%) Acute Psychotic Disorder 1 (1.1%) SQZAFF 0 Psychotic disorder NOS 3 (3.4%) **Non-ASD:** Any SSD 8 (3.1%) SQZ 5 (1.9%) DD 0 Acute Psychotic Disorder 2 (0.8%) SQZAFF 1 (0.4%) Psychotic disorder NOS 0
Mouridsen (2008b)	118	336	Medical records	**ASD:** Any SSD 8 (6.8%) SQZ 4 (3.4%) DD 1 (0.8%) Acute Psychotic Disorder 1 (0.8%) Psychotic disorder NOS 2 (1.6%) **Non-ASD:** Any SSD 3 (0.9%) SQZ 3 (0.9%) DD 0 Acute Psychotic Disorder 0 Psychotic disorder NOS 0
Nylander (2013)	270	437	NR	57 (21.1%) and 30 (6.9%) had a psychotic disorder in the ASD and ADHD groups, respectively.
Raja (2011)	26	-	Record charts	16 (61.5%) were diagnosed with Schizophrenia.
Roy (2015)	50	-	SCID-I	1 (2%) individual were diagnosed with Paranoid Schizophrenia.
Russell (2016)	474	385	Neuropsychiatric Assessment	6 (1.2%) and 9 (3.2%) individuals had SQZ in the ASD and Non-ASD groups, respectively.
Rydén (2008)	53	37	Medical records	5 (9.4%) and 5 (15.5%) had a psychosis disorder in the ASD and Non-ASD groups, respectively.
Schendel (2016)	20,492	1,892,412	Medical records	1146 (5.6%) and 1263 (0.7%) had a SSD diagnosis in the ASD and Non-ASD groups, respectively.
Tsakanikos (2006)	147	605	Medical records	23 (16.4%) and 109 (18.5%) individuals had a SSD in the ASD and ID groups, respectively.
Tsakanikos (2007)	137	-	Medical records	22 (16.1%) individuals had a SSD.
Tsakanikos (2011)	150	-	Medical records	25 (17.2%) had a SSD.

ASD – Autism Spectrum Disorders; CG – Comparison group; AD – Autistic disorder; AS – Asperger Syndrome; ID – Intellectual Disability; ADHD – Attention Deficit and Hyperactivity Disorder; T1 – First-time measure; T2 – Second-time measure; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; CCAR – Colorado Client Assessment Record; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; SSD – Schizophrenia Spectrum disorders; SQZ – Schizophrenia; DD – Delusional Disorder; SQZAFF – Schizoaffective Disorder; NOS – Not otherwise specified.

Table 4. Mood disorders (MD)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2008)	22	-	Medical files, Structured Interviews	2 (9.1) and 7 (31.8%) had DEP and BPD, respectively.
Bakken (2010)	62	132	PAC	23 (37.1%) and 20 (15.2%) participants had a diagnosis of Depression in the ASD and ID groups, respectively.
Billstedt (2005)	108	-	Observation a semi-structured interview and a brief psychiatric examination	1 individual had been diagnosed with BPD. 1 individual had recurrent unipolar depressive episodes.
Buck (2014)	129	-	Mini PAS-ADD Clinical Interview	Depression rate from lifetime Mini PAS-ADD was 13 % (n = 17). Two (2 %) participants met current criteria for expansive mood (hypomania/mania) and 8 (6 %) met lifetime criteria.
Cederlund (2008)	AD 70 AS 70	-	NR	1 (1.4%) participant have been diagnosed with BPD in the AS.
Chen (2015)	725	-	Medical charts	29 (4%) and 56 (7.7%) had a BPD and Depressive disorder diagnosis
Croen (2015)	1507	15,070	Medical records	159 (10.6%) and 251 (1.7%) individuals had a BPD in the ASD and Non-ASD groups, respectively. 388 (25.8%) and 1490 (9.9%) individuals had a Depression in the ASD and Non-ASD groups, respectively.
Esan (2015)	42	96	Medical records	4 (9.5%) and 11 (11.5%) individuals had a BPD in the ASD and ID groups, respectively. 3 (7.1%) and 19 (19.8%) individuals had a Depressive disorder in the ASD and ID groups, respectively.
Gillberg (2016)	50	-	ASRS	29 (58%) and 14 (28%) had depressive disorders ever and current, respectively. From this groups, 16 (32%) and 2 (4%) had MDD ever and current, respectively. None individual had DYS ever. 2 (4%) had BPD, one of them with psychotic-manic episodes.
Hofvander (2009)	122	-	SCID-I DSM-IV Checklist and Interview	65 (53%) individuals had a MD. Criteria for a BPD were met by 10 (8.2%) subjects.
Hutton (2008)	135	41	SAPPA	8 (6%) participants developed an affective disorder with marked obsessional features; 3 (2.2%) complex affective disorders; 4 (3%) more straightforward affective disorders; 1 (0.7%) a bipolar disorder.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** 48 (77%) and 19 (31%) had lifetime and current MDD, respectively. 16 (25%) and 4 (6%) had lifetime and current BPD, respectively. **Non-ASD:** 29 (46%) and 14 (23%) had lifetime and current MDD, respectively. 8 (13%) and 3 (5%) had lifetime and current BPD, respectively.
Kato (2013)	43	544	MINI	8 (18.6%) and 186 (34.2%) participants fulfilled diagnostic criteria for a mood disorder in the ASD and Non-ASD groups, respectively.
Ketelaars (2008)	15	21	SCAN-2.1	4 (26.7%) had a MD in the ASD group, two of them with psychotic symptoms. 3 (14%) individuals had MD without psychotic symptoms in the Non-ASD group.
Lever (2016)	138	70	MINI	**ASD:** MD 79 (57.2), DEP 74 (53.6), and DYS 25 (18.1) **Non-ASD:** MD 31 (18.2), DEP 28 (16.5), and DYS 5 (2.9)
Lugnegard (2011)	54	-	SCID-I	38 participants (70%) had experienced at least one episode of major depression, and 27 (50% of the total group) had had recurrent major depressions. 5 participants (9% of the total group) met criteria for bipolar II disorder, whereas none met criteria for bipolar I disorder.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	6 (26.1%), 3 (13%) and 1 (4.3%) participants fulfilled diagnostic criteria for a mood disorder in the ASD group, ID group and non-ID group, respectively.
McCarthy (2010)	124	562	Medical records Clinical Interview	9 (7.3%) and 69 (12.3%) had a depressive disorder in the ASD and ID groups, respectively.
McDermott (2005)	51	-	Medical records Clinical Interview	3 (5.9) had Depression (ICD-9 300.4, 311, 296.2, 296.3 or 309.1)
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	4 (5.2%) participants fulfilled affective disorder diagnostic criteria at T1. Incidence at two years follow-up was 4 for affective disorder. Three of the affective disorders were depressive episodes, and one was a mixed affective disorder. Incidence at two years follow-up was 0 for mania.
Moseley (2011)	84	-	Clinical Assessment Protocol, Developmental Behavior Checklist	9 (11%), 1 (1%), 3 (4%) and 1 (1%) participants have developed MDD, Dysthymia and BPD and MDD not otherwise specified, respectively.
Mouridsen (2008a)	89	258	Medical records	10 (11.2%) and 10 (3.9%) individuals had any MD in the ASD and Non-ASD groups, respectively.
Mouridsen (2008b)	118	336	Medical records	4 (3.4%) and 4 (1.2%) individuals had any MD in the ASD and Non-ASD groups, respectively.
Munesue (2008)	44	-	Clinical interview	16 (36.4%) individuals had a MD: 4 (9.1%) MDD and 12 (27.3%) BPD
Nylander (2013)	270	437	NR	47 (17.4%) and 119 (27.3%) had a MD diagnosis in the ASD and ADHD groups, respectively.
Raja (2011)	26	-	Record charts	3 (11.5%) and 1 (3.8%) were diagnosed with Depression and Mania with psychotic signs, respectively. Other 3 (11.5%) participants were diagnosed with MD with psychotic signs.
Roy (2015)	50	-	SCID-I	24 (48%) and 12 (24%) had a MDD and DYS, respectively. In 7 participants (14%) a combination of MDD and DYS was observed (double depression). MAN and BPD were not noted in the adults with AS.
Russell (2016)	474	385	HADS	95 (20%) and 86 (22.3%) individuals had any MD in the ASD and Non-ASD groups, respectively. 75 (15.8%) and 49 (12.7%) individuals had a Depressive episode in the ASD and Non-ASD groups, respectively. 4 (0.8%) and 5 (1.2%) individuals had BPD in the ASD and Non-ASD groups, respectively.
Rydén (2008)	53	37	Medical records	26 (49%) and 23 (68%) had a MDD in the ASD and Non-ASD groups, respectively. 2 (3.7%) and 1 (2.9%) had a BPD in the ASD and Non-ASD groups, respectively.
Schendel (2016)	20,492	1,892,412	Medical records	1803 (8.8%) and 33063 (1.8%) had a MD diagnosis in the ASD and Non-ASD groups, respectively.
Sterling (2007)	46	-	FHI-RDC	20 (43.5%) were depressed.
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	MINI, SCID-I	**ASD:** MDD 9 (15.5) DYS 5 (8.6) **BOR:** MDD 24 (31.2) DYS 17 (22.1) **NAR:** MDD 23 (37.1) DYS 12 (19.4) **NCC:** MDD 0 DYS 0
Tani (2003)	20	-	SCID-I	5 (25%) AS subjects had mild to moderate depressive disorder and none of them had severe MDD.
Tsakanikos (2006)	147	605	Medical records	53 (9%) and 9 (6.4%) individuals had a Depressive disorder in the ASD and ID groups, respectively.
Tsakanikos (2007)	137	-	Medical records	9 (6.6%) individuals had a Depressive disorder
Tsakanikos (2011)	150	-	Medical records	9 (6.9%) had a depressive disorder.

ASD – Autism Spectrum Disorders; CG – Comparison group; AD – Autistic disorder; AS – Asperger Syndrome; ID – Intellectual Disability; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; NCC – Non-clinical Controls; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; MINI – MINI International Neuropsychiatric Interview; CCAR – Colorado Client Assessment Record; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; HADS – Hamilton Anxiety and Depression Scale; FHI-RDC – Family History Interview with Research Diagnostic Criteria; MD – Mood Disorders; DEP – Depressive episode; BPD – Bipolar Disorder; MDD – Major Depressive Disorder; DYS – Dysthymia.

Table 5. Neurotic, stress-related, somatoform disorders (ANX)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2008)	22	-	Medical files Structured interviews	6 (27.3%) had anxiety disorders. One of them had OCD, another had AGO and another one had DIS
Bakken (2010)	62	132	PAC	21 (33.9%) and 12 (9.1%) participants had a diagnosis of anxiety in the ASD and ID groups, respectively. 8 (12.9%) and 4 (3.3%) participants had a diagnosis of OCD in the ASD and ID groups, respectively.
Buck (2014)	129	-	Mini PAS-ADD Clinical Interview	The most common current and lifetime psychiatric disorder identified by the Mini PAS-ADD was anxiety [40 % (n = 51) and 53 % (n = 68), respectively], followed by OCD [33 % (n = 43) and 36 % (n = 47), respectively].
Chen (2015)	725	-	Medical charts	53 (7.3%) had an anxiety disorder diagnosis
Croen (2015)	1507	15,070	Medical records	439 (29.1%) and 1371 (9.1%) individuals had an ANX in the ASD and Non-ASD groups, respectively. 115 (7.6%) and 74 (0.5%) individuals had an OCD in the ASD and Non-ASD groups, respectively.
Gillberg (2016)	50	-	ASRS	5 (10%) met criteria for current GAD, 4 (8%) men had a diagnosis of current OCD, 3 (6%) reported current AGO, 2 (4%) individuals reported current SAD, and 1 (2%) individual had a current PAN. None reported PTSD.
Hofvander (2009)	122 (119)	-	SCID-I DSM-IV Checklist and Interview	29 (24%) out of 122 individuals had an OCD. 59 (50%) and 6 (5%) out of 119 individuals had a lifetime ANX and SMF, respectively. GAD was common (n = 18, 15%) as was SAD (n = 16, 13%). 13 subjects (11%) met criteria for PAN and/or AGO and 7 (6%) met criteria for a specific phobia. 2 (1.7%) patients suffered from PTSD, and one had an ANX-NOS.
Hutton (2008)	135	41	SAPPA	5 (3.7%) individuals developed an obsessive-compulsive disorder and/or catatonia. 1 individual experienced an acute anxiety state complicated by alcohol excess.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** >=2 ANX 37 (59%) and 24 (38%) AGO 22 (35%) 15 (24%) GAD 22 (35%) 18 (29%) SAD 35 (56%) 25 (40%) OCD 15 (24%) 10 (16) PAN 5 (15%) 2 (3%) PTSD 7 (11%) 3 (5%) **Non-ASD:** >=2 ANX 11 (17%) and 7 (11%) AGO 4 (6%) 2 (3%) GAD 11 (17%) 9 (16%) SAD 12 (19%) 10 (16%) OCD 0 0 PAN 6 (18%) 1 (2%) PTSD 1 (2%) 0
Kato (2013)	43	544	MINI	7 (16.3%) and 107 (19.7%) participants fulfilled diagnostic criteria for anxiety disorders in the ASD and Non-ASD groups, resp. 30 (70%) and 226 (41.5%) participants fulfilled diagnostic criteria for adjustment disorders in the ASD and Non-ASD groups, resp. 0 (0%) and 14 (2.6%) participants fulfilled diagnostic criteria for dissociative disorders in the ASD and Non-ASD groups, resp. 0 (0%) and 8 (1.5%) participants fulfilled diagnostic criteria for somatoform disorders in the ASD and Non-ASD groups, resp.
Ketelaars (2008)	15	21	SCAN-2.1	**ASD:** PAN/AGO 2 (13%) OCD 1 (7%) Other ANX 1 (7%) SAD 3 (20%) **Non-ASD:** PAN/AGO 1 (5%) OCD 1 (5%) Other ANX 0 SAD 4 (19%)
Lever (2016)	138	170	MINI	**ASD:** ANX 74 (53.6%), PAN 21 (15.2%), AGO 29 (21%), SAD 21 (15.2%), PTSD 4 (2.9%), OCD 30 (21.7%), GAD 22 (15.9%), and SMF 8 (5.8%) **Non-ASD:** ANX 25 (14.7%), PAN 6 (3.5%), AGO 6 (3.5%), SAD 8 (4.7%), PTSD 1 (0.6%), OCD 1 (0.6%), GAD 5 (2.9%), and SMF 3 (1.8%)
Lugnegard (2011)	54	-	SCID-I	Thirty individuals (56%) met criteria for at least one ANX, and 11 of these fulfilled diagnostic criteria for two or more ANX. 12 (22%) had SAD, 12 (22%) had generalized GAD, 7 (13%) had PAN, 8 (15%) had AGO and 4 participants (7%) had OCD.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	0 (0%), 2 (8.7%) and 0 (0%) participants fulfilled diagnostic criteria for a substance abuse disorder in the ASD group, ID group and non-ID group, respectively.
Maddox (2015)	28	-	ADIS-IV	14 (50%) individuals had SAD.
McCarthy (2010)	124	562	Medical recrods Clinical Interview	5 (4%) and 44 (7.8%) had an ANX in the ASD and ID groups, respectively. 3 (2.4%) and 26 (4.6%) had an Adjustment reaction in the ASD and ID groups, respectively.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	4 (5.2%) and 0 participants fulfilled anxiety disorder and OCD diagnostic criteria at T1, respectively. Incidence at two years follow-up was 1 for anxiety disorder and 0 for OCD.
Moseley (2011)	84	-	Clinical Assessment Protocol, Developmental Behavior Checklist	7 (8.3%), 3 (3.5%), 3 (3.5%), 2 (2.4%), 1 (1.2%) and 1 (1.2%) participants have developed GAD, specific phobia, separation anxiety disorder, PAN, and anxiety not otherwise specified, respectively.
Mouridsen (2008a)	89	258	Medical records	7 (7.9%) and 8 (3.1%) individuals had any ANX in the ASD and Non-ASD groups, respectively.
Mouridsen (2008b)	118	336	Medical records	2 (1.7%) and 6 (1.8%) individuals had any ANX in the ASD and Non-ASD groups, respectively.
Nylander (2013)	270	437	NR	46 (17%) and 80 (18.3%) had an ANX diagnosis in the ASD and ADHD groups, respectively.
Raja (2011)	26	-	Record charts	2 (7.7%) were diagnosed with OCD.
Roy (2015)	50	-	SCID-I	Anxiety disorders, such as panic disorder (7, 14%), agoraphobia (7, 14%), and social phobia (6, 12%), as well as OCD (7, 14%) with obsessive thoughts (4, 8%) and behavior (4, 6%), were also frequent comorbidities. 3 (6%) individuals had SMF.
Russell (2016)	474	385	Neuropsychiatric Assessment, OCD Inventory Revised	**ASD:** Any ANX 186 (39.2%) PAN 1 (0.2%) AGO 19 (4%) OCD 85 (17.9%) SAD 59 (12.4%) GAD 56 (11.8%) PTSD 2 (0.4%) **Non-ASD:** Any ANX 127 (32.9%) PAN 0 AGO 7 (1.8%) OCD 51 (13.2%) SAD 47 (12.2%) GAD 46 (11.9%) PTSD 0
Rydén (2008)	53	37	Medical records	**ASD:** SAD 9 (17%) OCD 12 (23%) PAN 5 (9.4%) GAD 3 (5.7) PTSD 1 (1.9%) **Non-ASD:** SAD 3 (9%) OCD 5 (16%) PAN 3 (9.1%) GAD 1 (3%) PTSD 0
Schendel (2016)	20,492	1,892,412	Medical records	3458 (16.9%) and 64362 (3.4%) had an ANX diagnosis in the ASD and Non-ASD groups, respectively.
Sterling (2007)	46	-	FHI-RDC	16 (80%) and 11 (55%) had ANX and OCD, respectively.
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	MINI SCID-I	**ASD:** PAN 0 AGO+PAN 0 AGO-PAN 0 SAD 8 (13.8) ADJ 0 OCD 1 (1.7) PTSD 4 (6.9) **BOR:** PAN 3 (3.9) AGO+PAN 5 (6.5) AGO-PAN 3 (3.9) SAD 4 (5.2) AD 3 (3.9) OCD 3 (3.9) PTSD 21 (5.2) **NAR:** PAN 5 (8.1) AGO+PAN 2 (3.2) AGO-PAN 3 (4.8) SAD 5 (8.1) AD 4 (6.5) OCD 1 (1.6) PTSD 4 (6.5) **NCC:** PAN 0 AGO+PAN 0 AGO-PAN 0 SAD 0 ADJ 0 OCD 0 PTSD 0
Tani (2003)	20	-	SCID-I	13 (65%) AS subjects met the diagnostic criteria of one or more anxiety disorders, the most prevalent being social phobia (n = 8).
Tani (2006)	20	-	SCID-I	13 (65%) had an ANX and 7 (35%) had showed some clinical anxiety symptoms, though not reaching the threshold of a specific anxiety disorder.
Tsakanikos (2006)	147	605	Medical records	48 (8.1%) and 6 (4.3%) individuals had an ANX in the ASD and ID groups, respectively. 38 (6.5) and 7 (5%) individuals had an Adjustment reaction in the ASD and ID groups, respectively.
Tsakanikos (2007)	137	-	Medical records	6 (4.4%) and 7 (5.1%) individuals had an ANX and an Adjustment reaction, respectively.
Tsakanikos (2011)	150	-	Medical records	7 (4.8%) had an ANX. 7 (4.8%) had an adjustment reaction

ASD – Autism Spectrum Disorders; CG – Comparison group; ID – Intellectual Disability; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; NCC – Non-clinical Controls; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; MINI – MINI International Neuropsychiatric Interview; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; CCAR – Colorado Client Assessment Record; ADIS-IV – Anxiety Disorders Interview Schedule for DSM-IV; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; FHI-RDC – Family History Interview with Research Diagnostic Criteria; ANX – Anxiety disorders; AGO – Agoraphobia; SAD – Social Anxiety Disorder; PAN – Panic Disorder; GAD – Generalized Anxiety Disorder; OCD – Obsessive-Compulsive Disorder; PTSD – Post-Traumatic Stress Disorder; ADJ – Adjustment Disorder; DIS – Dissociative Disorder; SMF – Somatoform Disorder.

Table 6. Behavioral syndromes associated with physiological disturbances and physical factors (BEH)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Hofvander (2009)	119	-	SCID-I DSM-IV Checklist and Interview	6 (5%) out of 119 individuals had an ED.
Hutton (2008)	135	-	SAPPA	1 (0.7) woman also had a severe eating disorder.
Karjalainen (2016)	119	109	SCID	**ASD:** ED 9 (7.6%) AN 6 (5%) BN 2 (1.7%) Binge eating disorder 1 (0.8%) **ADHD:** ED 9 (8.3%) AN 2 (1.8%) BN 0 Binge eating disorder 7 (6.4%)
Kato (2013)	43	544	MINI	0 (0%) and 14 (2.6%) participants fulfilled diagnostic criteria for eating disorders in the ASD and Non-ASD groups, respectively.
Ketelaars (2008)	15	21	SCAN-2.1	4 (27%) and 6 (29%) had a current SLE in the ASD and Non-ASD groups, respectively.
Lever (2016)	138	170	MINI	8 (5.8) and 1 (0.6) had an Eating disorder diagnosis in ASD and Non-ASD groups, resp.
Lugnegard (2011)	54	-	SCID-I	Two participants (4%) had bulimia nervosa, and none had anorexia nervosa.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	0 participants fulfilled ED diagnostic criteria at T1. Incidence at two years follow-up was 0 for ED.
Nylander (2013)	270	437	NR	1 (0.4%) woman had anorexia nervosa in the ASD group and 7 (1.6%) participants had an ED in the **ADHD** group.
Roy (2015)	50	-	SCID-I	2 (4%) and 1 (2%) had Binge-eating disorder and BN, respectively. No adult had AN.
Russell (2016)	474	385	Neuropsychiatric Assessment	1 (0.2%) and 0 individuals had an ED in the ASD and Non-ASD groups, respectively.
Rydén (2008)	53	37	Medical records	**ASD:** AN 7 (13.2) BN 0 **Non-ASD:** AN 0 BN 1 (3.3)
Schendel (2016)	20,492	1,892,412	Medical records	511 (2.5%) and 12795 (0.7%) had a BEH diagnosis in the ASD and Non-ASD groups, resp.
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	MINI SCID-I	**ASD:** AN 0 BN 0 **BOR:** AN 2 (2.6) BN 15 (19.5) **NAR:** AN 4 (6.5) BN 2 (3.2) **NCC:** AN 0 BN 0

ASD – Autism Spectrum Disorders; CG – Comparison group; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; ADHD – Attention Deficit and Hyperactivity Disorder; NCC – Non-clinical Controls; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; MINI – MINI International Neuropsychiatric Interview; SCAN-2.1 – Schedules for Clinical Assessment in Neuropsychiatry; CCAR – Colorado Client Assessment Record; ADIS-IV – Anxiety Disorders Interview Schedule for DSM-IV; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; FHI-RDC – Family History Interview with Research Diagnostic Criteria; BEH – Behavioral syndromes associated with physiological disturbances and physical factors; ED – Eating Disorders; AN – Anorexia Nervosa; BN – Bulimia Nervosa; SLE – Sleep Disorders.

Table 7. Disorders of adult personality and behavior (PD)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2006)	74	81	SCID-II	**ASD:** PAR (19, 25.7%) SCHZT (14, 19%) SCHZ (21, 28.4%) HIS (0) NAR (4, 5.4%) BOR (9, 12.2%) ANT (5, 6.8%) AVO (19, 25.7%) DEP (10, 13.5%) OBS (28, 37.8%). **ADHD:** PAR (18, 22.2%) SCHZT (4, 4.9%) SCHZ (10, 12.3%) HIS (0) NAR (3, 3.7%) BOR (30, 37%) ANT (25, 30.9%) AVO (18, 22.2%) DEP (21, 25.9%) OBS (11, 13.6%).
Anckarsäter (2008)	22	-	Medical files Structured Interviews	3 (13.6%) had IMP. One of them had Kleptomania, another had Pyromania and another one had gambling 2 (9.1%) had SEX diagnosis (Paedophilia).
Esan (2015)	42	96	Medical records	**ASD:** Cluster A PD 15 (35.7%) ANT 14 (33.3%) BOR 6 (14.3) **ID:** Cluster A PD 62 (64.6%) ANT 54 (56.3%) BOR 32 (33.3)
Gillberg (2016)	50	-	ASRS	6 (12%) men showed clear signs of antisocial personality disorder.
Hofvander (2009)	122 (117)	-	SCID-I SCID-II DSM-IV Checklist and Interview	73 (62%) out of 117 individuals had at least one PD. PAR (22, 19%) SCHZT (15, 13%) SCHZ (25, 2%) HIS (0) NAR (3, 3%) BOR (10, 9%) ANT (4, 3%) AVO (29, 3%) DEP (6, 5%) OBS (37, 3%). 11 (9%) out of 122 individuals had an IMP. Among patients affected with IMP, intermittent explosive disorder was the most common diagnosis (n = 7, 6%), followed by kleptomania, pyromania, pathological gambling, trichotillomania, and impulse control disorder NOS, all affecting one patient each.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	6 (10%) and 3 (5%) had lifetime and current ANT in the ASD group, respectively. 5 (8%) and 1 (2%) had lifetime and current ANT in the Non-ASD group, respectively.
Ketelaars (2008)	15	21	IPDE	**ASD:** Any PD 3 (20%) PAR 0 SCHZ 1 (7%) SCHZT 0 ANT 0 BOR 1 (7%) AVO 1 (7%) OBS 0 **Non-ASD:** Any PD 3 (20%) PAR 0 SCHZ 1 (5%) SCHZT 0 ANT 0 BOR 0 AVO 2 (10%) OBS 3 (14%)
Lugnegård (2012)	54	-	SCID-II Medical records	Twenty-six participants (48%; 9 women and 17 men) did meet criteria for at least 1 Axis II disorder. Fourteen participants (26% of the whole AS group; 5 women and 9 men) met criteria for schizoid PD, 7 (13%; 3 women and 4 men) met criteria for avoidant PD, and 10 (19%; 3 women and 7 men) met criteria for obsessive-compulsive PD. One individual (a woman) met criteria for schizotypal PD. None met criteria for paranoid PD, antisocial PD, histrionic PD, borderline PD, narcissistic PD, or dependent PD.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	1 (4.3%), 6 (26.1%) and 7 (30.4%) participants fulfilled diagnostic criteria for a personality disorder in the ASD group, ID group and non-ID group, respectively.
McCarthy (2010)	124	562	Medical records Clinical Interview	4 (3.2%) and 27 (4.8%) had a PD in the ASD and ID groups, respectively.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	0 participants fulfilled any PD diagnostic criteria at T1.
Mouridsen (2008a)	89	258	Medical records	8 (9%) and 7 (2.9%) individuals had any PD in the ASD and Non-ASD groups, respectively.
Nylander (2013)	270	437	NR	39 (14.5%) and 71 (16.2%) had a PD diagnosis in the ASD and ADHD groups, respectively. 3 (1.1%) and 0 were diagnosed with schizotypy (F21.0) in the ASD and ADHD groups, respectively. None participant in either both groups were diagnosed with a disorder of impulse control.
Russell (2016)	474	385	Neuropsychiatric Assessment	4 (0.8%) and 8 (2%) individuals had a PD in the ASD and Non-ASD groups, respectively. 4 (0.8%) and 7 (1.8%) had a SCHZT in the ASD and Non-ASD groups, respectively.
Rydén (2008)	53	37	Medical records	7 (13.5%) and 3 (9.1%) had a BOR diagnosis in the ASD and Non-ASD groups, respectively.
Schendel (2016)	20,492	1,892,412	Medical records	694 (3.4%) and 23524 (1.2%) had a PD diagnosis in the ASD and Non-ASD groups, respectively.
Strunz (2015)	58	BOR 77/73 NAR 62/57 NCC 105/106	SCID-II	**ASD**: AVO 1 (1.7) OBS 10 (17.2) PAR 1 (1.7) SCHZT 0 SCHZD 21 (36.2) HIS 0 ANT 0 **BOR**: AVO 28 (38.4) OBS 1 (1.4) PAR 9 (12.3) SCHZT 0 SCHZD 0 HIS 5 (6.8) ANT 12 (16.4) **NAR:** AVO 7 (12.3) OBS 5 (8.7) PAR 14 (24.6) SCHZT 0 SCHZD 3 (5.3) HIS 7 (12.3) ANT 10 (17.5) **NCC**: AVO 0 OBS 0 PAR 0 SCHZT 0 SCHZD 0 HIS 0 ANT 0
Tani (2003)	20	-	SCID-II	14 (70%) subjects met the full diagnostic criteria of any axis-II disorders. 5 AS subjects had Cluster A (paranoid, schizoid, schizotypal) personality disorder, and 3 subjects had cluster B (antisocial, borderline, histrionic, narcissistic) disorder. 13 subjects presented Cluster C (avoidant, dependent, obsessive-compulsive, passive-aggressive) personality disorder. 5 subjects had both cluster A and cluster C personality disorder. Obsessive-compulsive personality disorder (12 subjects) or traits of it (7 subjects) were the most common axis-II disorders.
Tsakanikos (2006)	147	605	Medical records	53 (9%) and 4 (2.9%) individuals had a PD in the ASD and ID groups, respectively.
Tsakanikos (2007)	137	-	Medical records	4 (2.9%) individuals had a PD.
Tsakanikos (2011)	150	-	Medical records	5 (3.4%) had a PD diagnosis.

ASD – Autism Spectrum Disorders; CG – Comparison group; ID – Intellectual Disability; ADHD – Attention deficit and hyperactivity disorder; T1 – First-time measure; T2 – Second-time measure; BOR – Borderline Personality Disorder; NAR – Narcissistic Personality Disorder; NCC – Non-clinical Controls; SCID-II – Structured Clinical Interview for DSM – Axis II disorders; ASRS – Autism Spectrum Rating Scales; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; IPDE – International Personality Disorder Examination; CCAR – Colorado Client Assessment Record; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; PD – Personality Disorders; PAR – Paranoid Personality Disorder; SCHZ – Schizoid Personality Disorder; SCHZT – Schizotypal Personality Disorder; ANT – Antisocial Personality Disorder; BOR – Borderline Personality Disorder; HIS – Histrionic Personality Disorder; OBS – Obsessive-Compulsive Personality Disorder; AVO – Avoidant Personality Disorder; DEP – Dependent Personality Disorder; NAR – Narcissistic Personality Disorder; IMP – Impulse control Disorders; SEX – Sexual disorders.

Table 8. Behavioral and emotional disorders with juvenile onset (INF)

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2006)	113	-	DSM-IV Checklist for ADHD	39 (34.5%) individuals had an ADHD.
Anckarsäter (2008)	22	-	Medical files Structured Interviews	10 (45.5%) had ADHD, 2 (9.1%) had TOU and 11 (50%) had TICS.
Billstedt (2005)	108	-	Observation, a semi-structured interview and a brief psychiatric examination	1 woman had a severe case of Tourette Syndrome. 25 individuals were reported to have periods of substantial tics without fulfilling the criteria of Tourette Syndrome.
Chen (2015)	725	-	Medical charts	26 (3.6%) had a tics disorder diagnosis. Out of the whole ASD group (n=1,191), 466 (39.1%) had ADHD.
Croen (2015)	1507	15,070	Medical records	167 (11.1%) and 294 (2%) individuals had an ADHD in the ASD and Non-ASD groups, respectively.
Gillberg (2016)	50	-	ASRS DISCO-11	22 (50%) out of 44 individuals reported tic disorder in childhood/adolescence (6 individuals met criteria for TOU and 16 had either vocal or motor tics). 14 men (28 %) had clear signs of a current diagnosis of ADHD.
Hallerbäck (2014)	54	41	WRAADS SNAP	Eight men and eight women in the AS group (16/54, 30%) had an ADHD diagnosis. Two men and two women in the SP group (4/41, 10%) had an ADHD diagnosis.
Hofvander (2009)	122	-	SCID-I DSM Checklist and Interview A-TAC Semi-structured collateral interview based on the ASDI, ADHD-RS, FTF-Q and WURS	52 (43%) and 25 (20%) individuals had an ADHD and TICS diagnosis, respectively.
Johnston (2013)	38	-	BAARS	18 (47.4%) of 38 participants that fulfilled the BAARS had any type of ADHD.
Joshi (2013)	63	63	SCID-I (Lifetime and Current)	**ASD:** ADHD 42 (68%) 26 (42%) OPD 33 (53%) 17 (27%) TICS 7 (11%) 4 (6%) TOU 3 (5%) 3 (5%) **Non-ASD:** ADHD 44 (70%) 36 (57%) OPD 9 (20%) 5 (11%) TICS 7 (11%) 3 (5%) TOU 0 0
Karjalainen (2016)	119	-	DSM-IV Checklist for ADHD	45 (%) individuals had ADHD diagnosis.
Lever (2016)	138	170	ADHD Rating Scale	42 (30.4%) and 9 (5.3%) had an ADHD diagnosis in ASD and Non-ASD groups, respectively.
Lugnegard (2011)	54	-	Medical records	Sixteen participants (30%) had been given a diagnosis of AD/HD before the study. One individual (2%) had been diagnosed with Tourette syndrome.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	3 (3.9%) and 4 (5.2%) participants fulfilled ADHD and Pica diagnostic criteria at T1.
Moseley (2011)	84	-	Clinical Assessment Protocol, Developmental Behavior Checklist	1 (1.2%) participant have developed ADHD.
Nyden (2010)	88	-	DSM-IV Checklist	33 ASD participants fulfilled ADHD diagnostic criteria
Nylander (2013)	270	437	NR	14 (5.2%) had an ADHD diagnosis in the ASD group. 4 (1.5%) and 7 (1.6%) had a diagnosis of Tourette Syndrome in the ASD and ADHD groups, respectively.
Russell (2016)	474	385	Neuropsychiatric Assessment	46 (9.7%) and 39 (10.1%) individuals had an ADHD in the ASD and Non-ASD groups, respectively. 7 (1.4%) and 1 (0.3%) had a TICS in the ASD and Non-ASD groups, respectively.
Rydén (2008)	84	-	WRAADS Adult ADHD Self-report Scale	31 (37%) had an ADHD diagnosis in the ASD group.
Schendel (2016)	20,492	1,892,412	Medical records	8074 (39.4%) and 45761 (2.4%) had an INF diagnosis in the ASD and Non-ASD groups, respectively. 5652 (27.6%) and 28191 (1.5%) had an ADHD diagnosis in the ASD and Non-ASD groups, respectively.

ASD – Autism Spectrum Disorders; CG – Comparison Group; T1 – First-time measure; T2 – Second-time measure; ASRS – Autism Spectrum Rating Scale; DISCO-11 – Diagnostic Interview for Social and Communication Disorders; WRAADS – The Wender-Reimherr Adult Attention Deficit Rating Scale; SNAP – The Swanson, Nolan and Pelham Questionnaire; SCID-I – Structured Clinical Interview for DSM – Axis 1 disorders; ASDI – Asperger Syndrome Diagnostic Interview; ADHD-RS – Attention Deficit and Hyperactivity Disorder Rating Scale; FTF-Q – Five-to-Fifteen Questionnaire; WURS – Wender-Utah Rating Scale; A-TAC – Autism-Tics, ADHD and other Comorbidities; BAARS – The Barley Adult ADHD Rating Scale; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; INF – Behavioral and Emotional Disorders with juvenile onset; ADHD – Attention Deficit and Hyperactivity Disorder; TOU – Tourette Syndrome; TICS – Tics Disorders; OPD – Oppositional Defiant Disorder.

Table 9. Any psychiatric disorder

Author (Year)	N ASD	N CG	Psychiatric disorder measures	Outcome
Anckarsäter (2008)	22	-	Medical files Structured Interviews	21 (95.5%) had at least one psychiatric disorder.
Bakken (2010)	62	132	PAC	33 (53.2%) and 23 (17.4%) had at least one psychiatric disorder in the ASD and Non-ASD groups, respectively.
Buck (2014)	129	-	Mini PAS-ADD Clinical Interview	57 % (n = 73) of the participants met Mini PAS-ADD criteria for at least one current psychiatric disorder and an additional 12.4 % (n = 16) met criteria for experiencing at least one lifetime psychiatric disorder. Thus, a total of 89 (69 %) participants met Mini PAS-ADD criteria for a psychiatric disorder at any point during their lifetime.
Croen (2015)	1507	15,070	Medical records	More than half (54%) of adults with ASD were diagnosed with a psychiatric condition
Gillberg (2016)	50	-	ASRS	47 (94%) and 27 (54%) reported any psychiatric disorder ever and currently, respectively.
Hutton (2008)	135	41	SAPPA	21 (16%) participants had a definite new-onset psychiatric Disorder. There were also another 8 individuals (6%) with a dubious or uncertain new psychiatric disorder.
Ketelaars (2008)	15	21	SCAN-2.1 IPDE	8 (53%) and 14 (67%) had at least one psychiatric disorder currently in the ASD and Non-ASD groups, resp.
Lever (2016)	138	170	MINI ADHD-RS	109 (79%) and 83 (48.8%) had at least one psychiatric disorder in the ASD and Non-ASD, resp.
Lunsky (2009)	23	ID 23 Non-ID 23	CCAR	13 (56.5%) participants fulfilled diagnostic criteria for at least one psychiatric disorder in the ASD group.
Melville (2008)	T1 77 T2 50	T1 154 T2 82	C21st Health Check PPS-LD	16 (20.8%) 36 (23.4%) participants had mental-ill health of any type, excluding problem behaviors, in the ASD and ID groups, resp. Incidence at two years follow-up for mental-ill health of any type, excluding problem behaviors, was 6 and 14 in the ASD and ID groups, resp.
Moseley (2011)	84	-	Clinical Assessment Protocol, Developmental Behavior Checklist	35 (41.7%) participants have developed at least one psychiatric disorder.
Mouridsen (2008a)	89	258	Medical records	Fifty-five persons (61.8%) from the case group were given a psychiatric diagnosis other than PDD during the observation period.
Mouridsen (2008b)	118	336	Medical records	During the observation period, 20 subjects (17%) in the case group were given a psychiatric diagnosis other than PDD or mental retardation compared with 9 individuals (2.7%) in the CG.
Nylander (2013)	270	437	NR	162 (60%) and 268 (38.7%) had at least one psychiatric disorder in the ASD and ADHD groups, respectively.
Roy (2015)	50	-	SCID-I	35 (70%) had at least one comorbid psychiatric disorder in their lifetime.
Russell (2016)	474	385	Neuropsychiatric Assessment HADS OCD-Inventory-R	275 (58%) received one or more co-morbid psychiatric diagnoses.
Tani (2003)	20	-	SCID-I SCID-II	16 (80%) individuals had at least one psychiatric disorder.
Tsakanikos (2007)	137	-	Medical records	57 participants (41.6%) had at least one psychiatric disorder.

ASD – Autism Spectrum Disorders; CG – Comparison Group; ID – Intellectual Disability; ADHD – Attention Deficit and Hyperactivity Disorder; PDD – Pervasive Developmental Disorder; T1 – First-Time measure; T2 – Second-Time measure; PAC – Psychopathology in Autism Checklist; PAS-ADD – Psychiatric Assessment Schedule for Adults with Developmental Disabilities; ASRS – Autism Spectrum Rating Scales; SAPPA – Schedule for Assessment of Psychiatric Problems in Autism; MINI – MINI International Neuropsychiatric Interview; IPDE – International Personality Disorder Examination; ADHD-RS – Attention Deficit and Hyperactivity Disorder Rating Scale; CCAR – Colorado Client Assessment Record; PPS-LD - Present Psychiatric State for Adults with Learning Disabilities; SCID-I – Structured Clinical Interview for DSM – Axis I disorders; HADS – Hamilton Anxiety and Depression Scale; SCID-II - Structured Clinical Interview for DSM – Axis II disorders.

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Appendix C. Quality assessment of the selected studies performed with Berra et al. (2008)

Study reference	Research question and objective	Participants	Groups comparison	Variables definition and measurement	Statistical analysis and bias risk	Internal validity	Results	Conclusions, external validity and aplicability	Conflict of interests	Global quality
Anckarsäter (2006)	Medium	Low	NA	Good	Good	Medium	Medium	Medium	Medium	Medium
Anckarsäter (2008)	Very good	NA	NA	Medium	Low	Low	Good	Good	Medium	Medium
Bakken (2010)	Very good	Medium	Good	Good	Low	Low	Medium	Medium	Good	Medium
Billstedt (2005)	Very good	Medium	NA	Good	Medium	Medium	Medium	Medium	NA	Medium
Buck (2014)	Very good	Good	NA	Good	Good	Good	Good	Good	Medium	High
Cederlund (2008)	Very good	Very good	NA	Good	Good	Good	Good	Good	Good	High
Chen (2015)	Very good	Good	Good	Very good	Good	Good	Very good	Good	Very good	High
Croen (2015)	Good	Medium	Good	Medium	Very good	Medium	Very good	Good	Very good	High
Esan (2015)	Good	Medium	NA	Medium	Medium	Medium	Good	Medium	NA	Medium
Gillberg (2016)	Very good	Good	NA	Good	Good	Good	Good	Good	Very good	High
Hallerbäck (2014)	Good	Low	NA	Good	Low	Low	Good	Good	NA	Medium
Hofvander (2009)	Very good	Medium	NA	Good	Very good	Good	Good	Good	Very good	High
Hutton (2008)	Very good	Good	NA	Good	NA	Medium	Good	Good	NA	Medium
Johnston (2013)	Very good	Medium	Medium	Good	Good	Medium	Medium	Medium	NA	Medium
Joshi (2013)	Very good	Good	Good	Good	Good	Good	Good	Good	Medium	High
Karjalainen (2016)	Very good	Medium	NA	Medium	Good	Medium	Medium	Medium	Good	Medium
Kato (2013)	Very good	Medium	NA	Medium	Medium	Medium	Medium	Medium	Good	Medium
Ketelaars (2008)	Very good	Medium	Medium	Medium	Medium	Medium	Medium	Medium	NA	Medium
Kronenberg (2015)	Very good	Medium	Very good	Good	Good	Good	Good	Good	Very good	High
Lever (2016)	Good	Very good	Very good	Very good	Very good	Very good	Very good	Very good	Very good	High
Lugnegård (2011)	Very good	Good	NA	Good	Medium	Medium	Medium	Good	Very good	High
Lugnegård (2012)	Good	Good	Good	Very good	Medium	Good	Good	Good	NA	Medium
Lunsky (2009)	Very good	Good	NA	Medium	Good	Medium	Good	Good	NA	Medium
Maddox (2015)	Very good	Good	Very good	Very good	Good	Good	Good	Very good	Very good	High
McCarthy (2010)	Very good	Low	Medium	Good	Good	Medium	Good	Good	NA	Medium
McDermott (2005)	Very good	Medium	Medium	Medium	Good	Medium	Very good	Good	Good	Medium
Melville (2008)	Very good	Good	Good	Good	Good	Good	Good	Very good	Very good	High
Moseley (2011)	Good	Good	NA	Good	Good	Medium	Good	Good	Good	Medium
Mouridsen (2008a)	Good	Medium	Medium	Medium	Good	Medium	Good	Medium	Medium	Medium
Mouridsen (2008b)	Very good	Medium	Medium	Good	Medium	Medium	Good	Good	Medium	Medium
Munesue (2008)	Medium	Low	NA	Low	Medium	Low	Medium	Medium	Very good	Medium
Nydén (2010)	Very good	Good	NA	Good	Medium	Medium	Good	Good	Good	High
Nylander (2013)	Good	Medium	NA	Good	Medium	Medium	Medium	Good	Medium	Medium
Raja (2011)	Very good	Medium	NA	Medium	Good	Medium	Good	Good	NA	Medium
Roy (2015)	Very good	Low	NA	Good	NA	Medium	Very good	Good	Very good	Medium
Russell (2016)	Very good	Medium	NA	Good	Low	Medium	Good	Good	Very good	Medium
Rydén (2008)	Very good	Medium	Very good	Good	Good	Good	Medium	Good	NA	High
Schendel (2016)	Good	Medium	Good	Good	Very good	Good	Very good	Good	Medium	High
Sizoo (2009)	Good	Very good	Good	Very good	Good	Good	Very good	Good	Good	High
Stahlberg (2004)	Very good	Good	NA	Good	Medium	Medium	Good	Good	NA	High
Sterling (2008)	Very good	Low	NA	Good	Medium	Medium	Medium	Good	Good	Medium
Strunz (2015)	Very good	Medium	Good	Very good	Good	Medium	Good	Good	NA	Medium
Tani (2003)	Very good	Medium	Good	Good	Good	Medium	Good	Good	Very good	High
Tani (2006)	Medium	Low	Good	Good	Very good	Medium	Medium	Medium	NA	Medium
Tsakanikos (2006)	Good	Medium	Medium	Good	Good	Medium	Good	Medium	NA	Medium
Tsakanikos (2007)	Good	Medium	NA	Medium	Good	Medium	Medium	Medium	NA	Medium
Tsakanikos (2011)	Good	Medium	Medium	Medium	Good	Medium	Medium	Medium	NA	Medium

NA *Not applicable*

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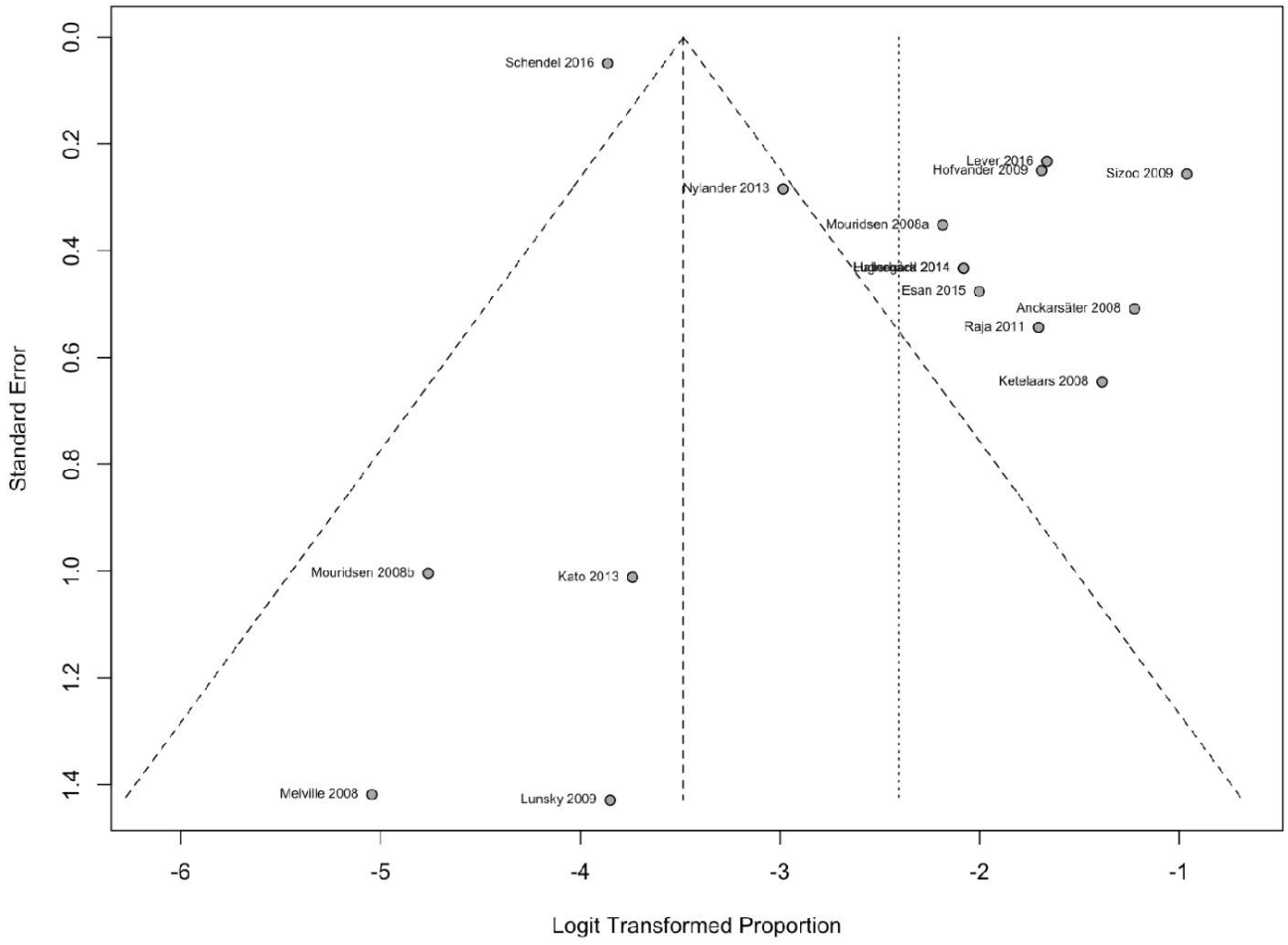
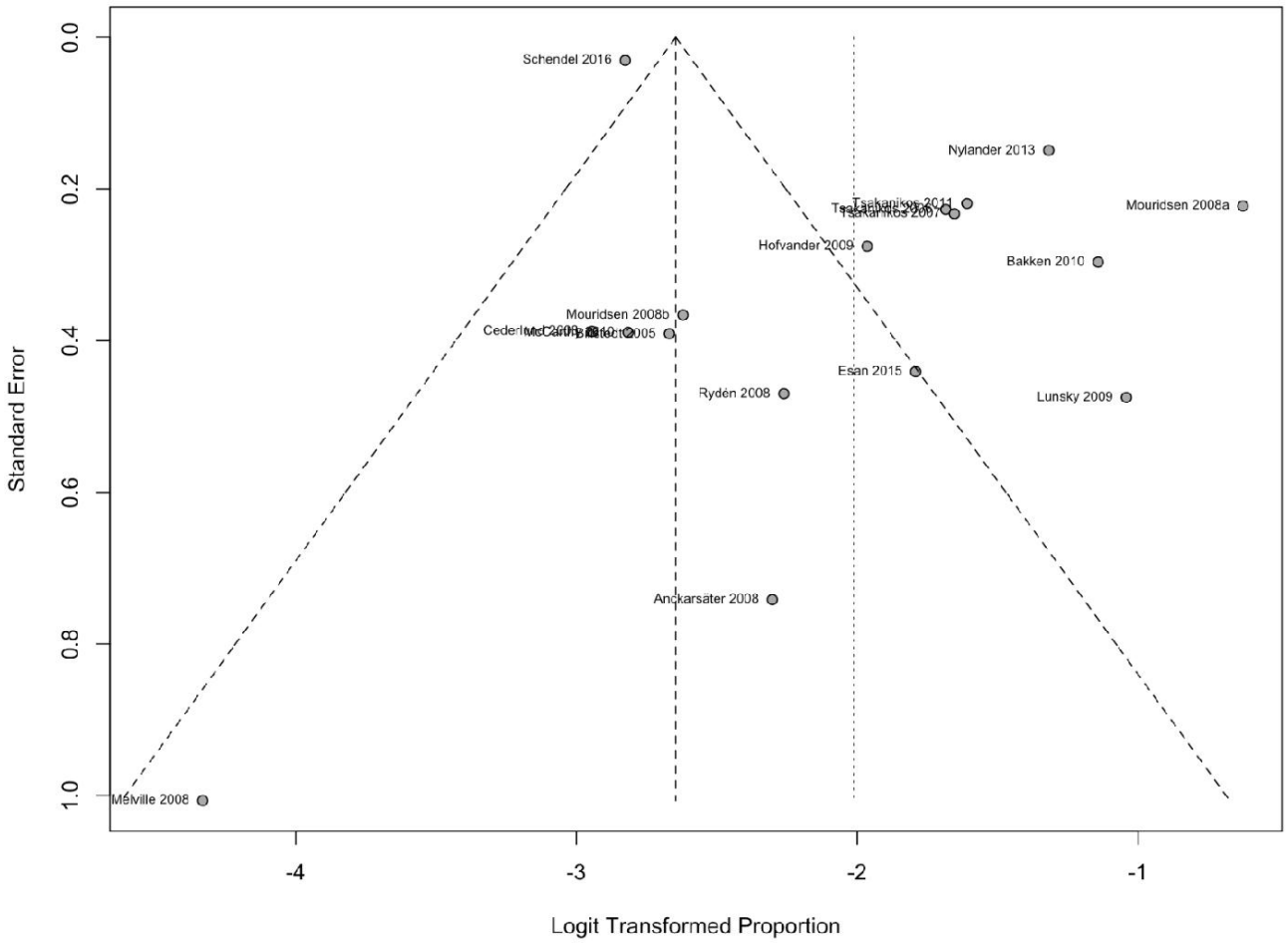
Appendix D. Publication risk of bias

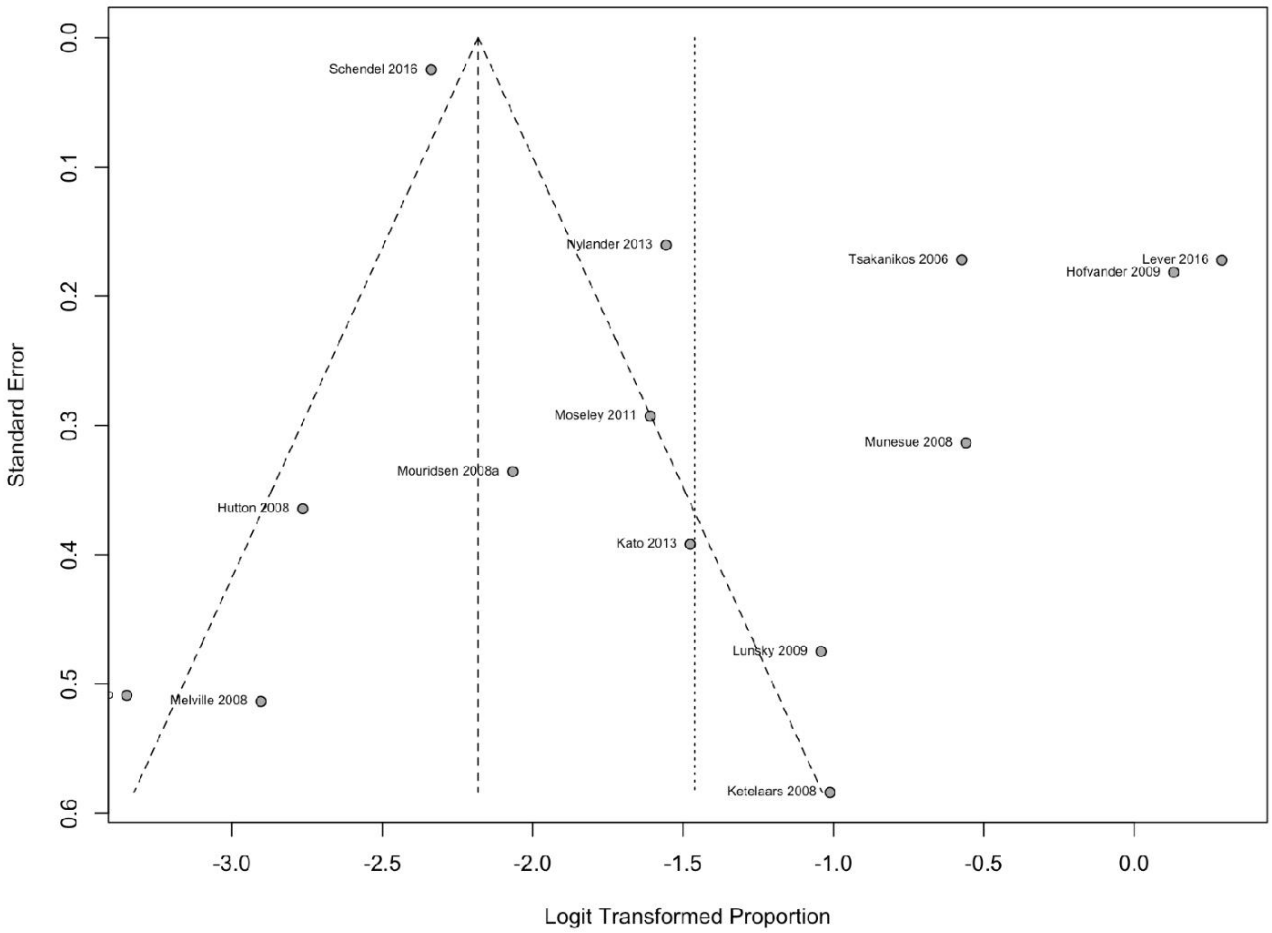
Substance Use Disorders



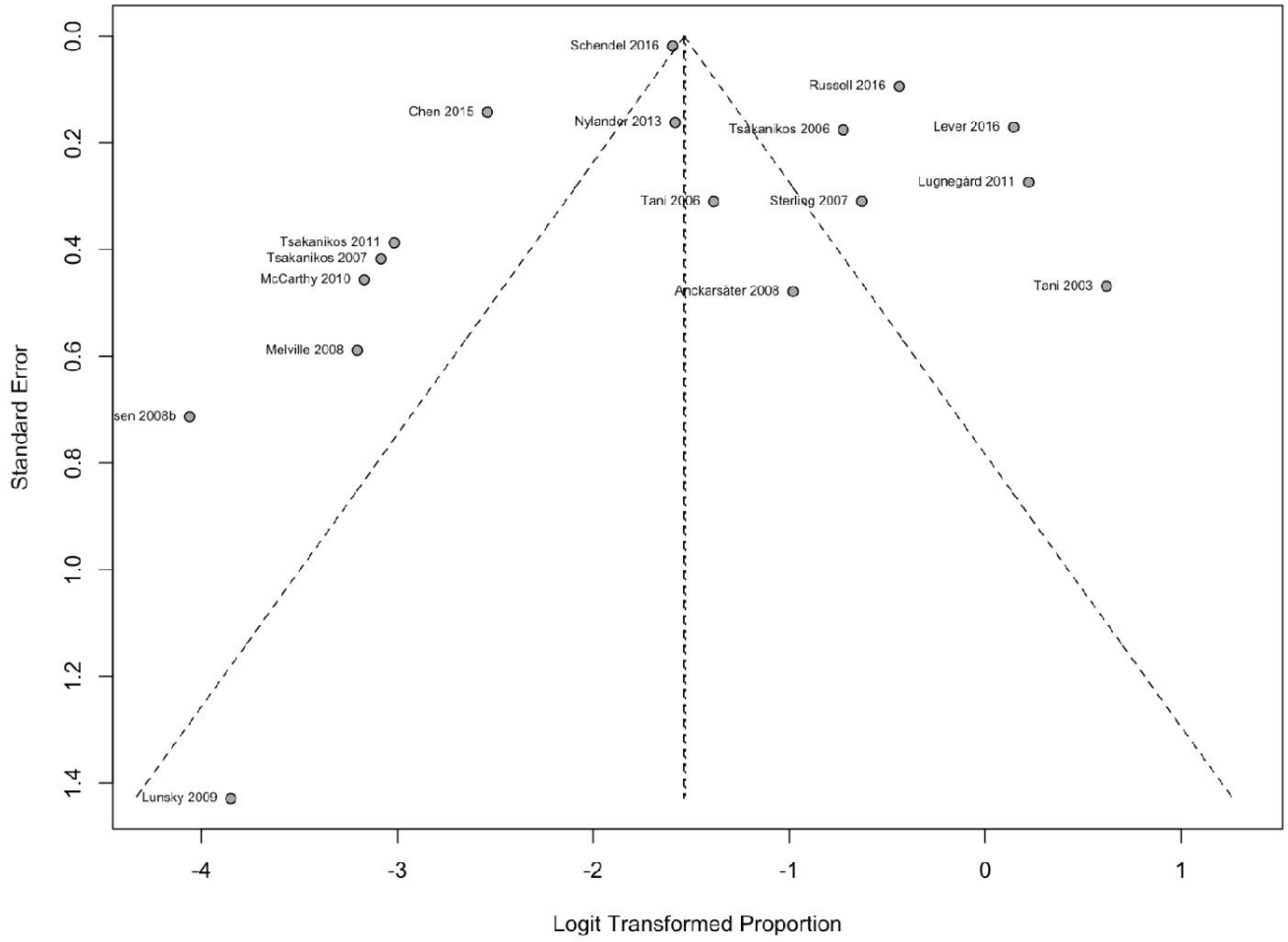
Schizophrenia Spectrum Disorders



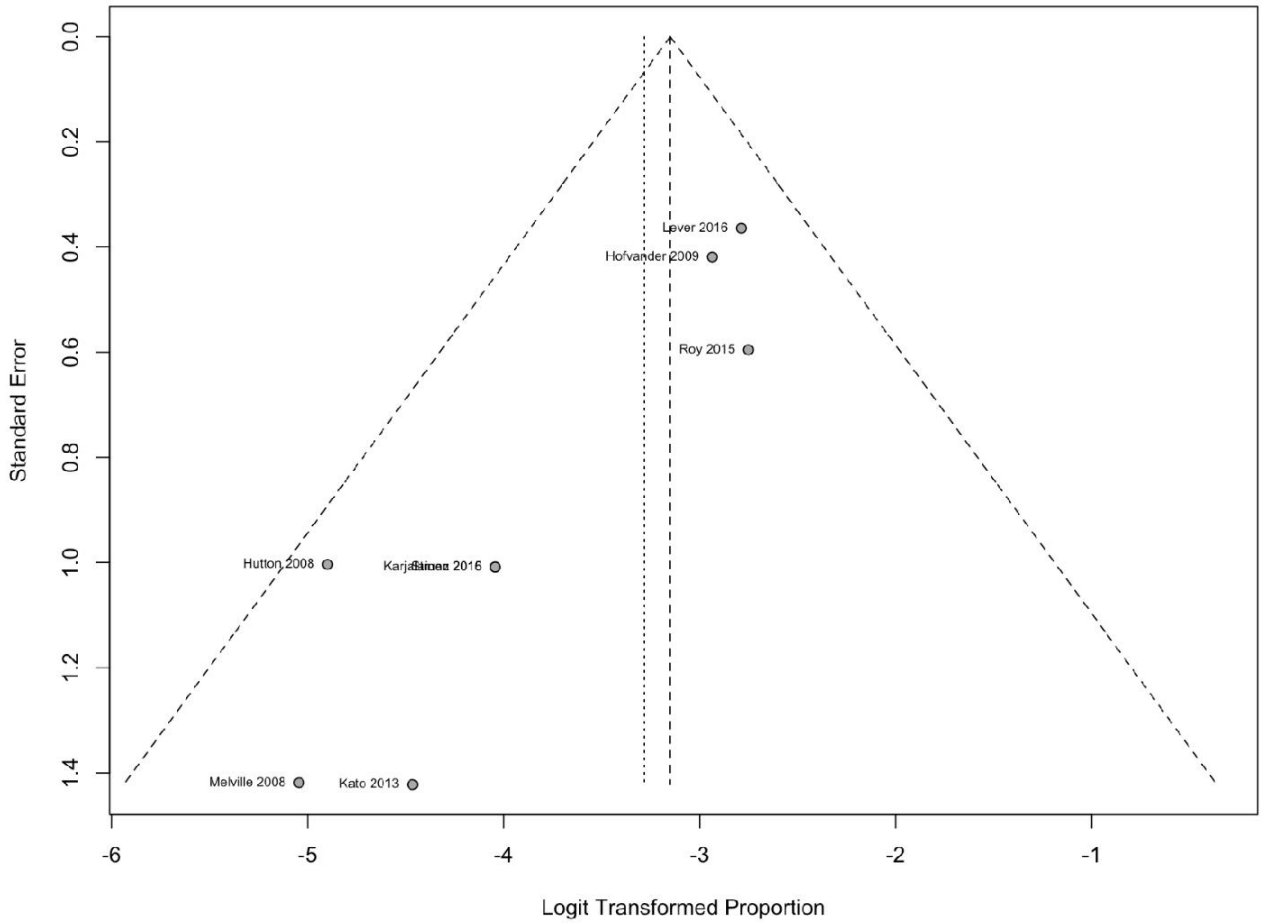
Mood Disorders



Anxiety Disorders



Eating Disorders



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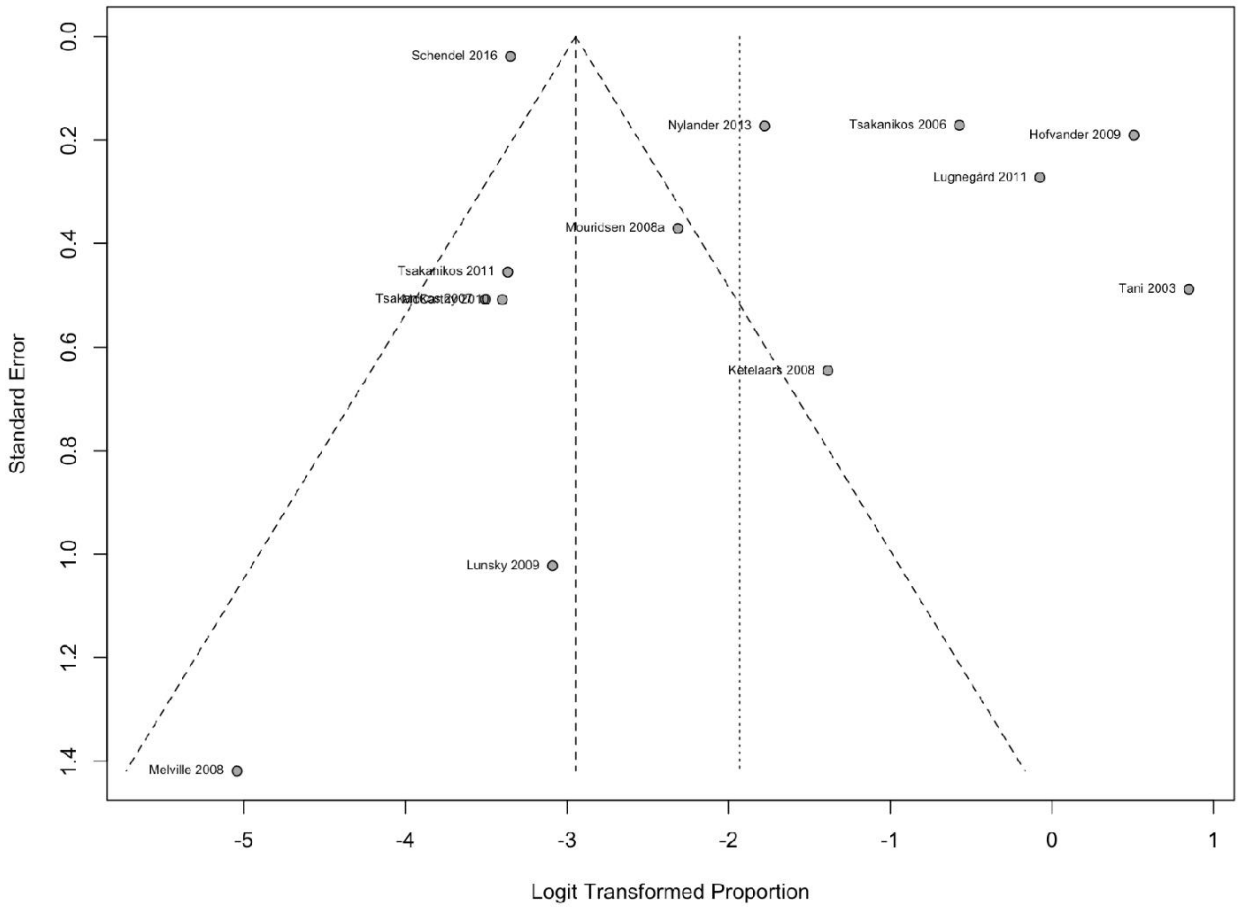
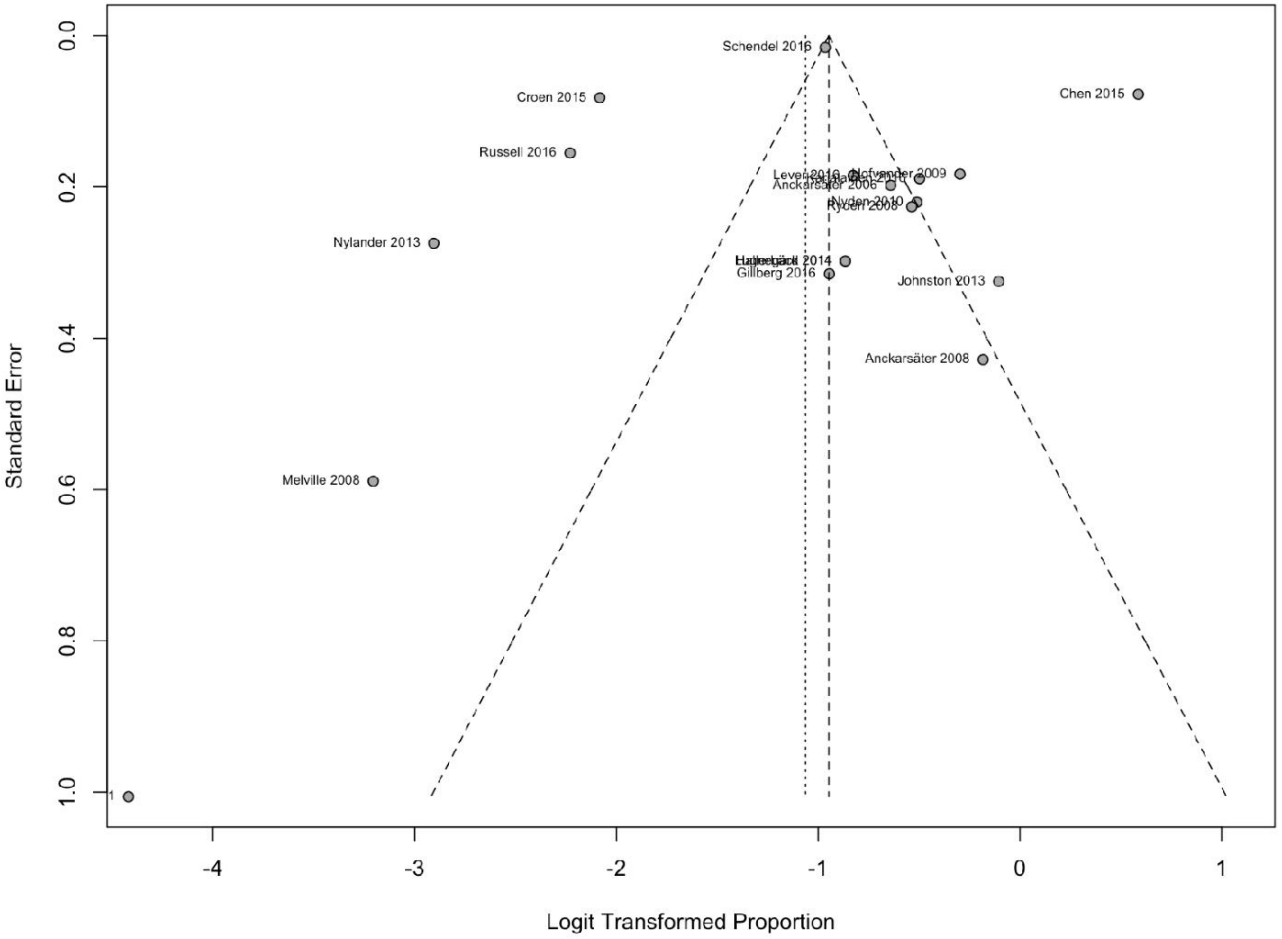


Attention Deficit and Hyperactivity Disorder



Any Psychiatric Disorder