Anxiety and Depression in Adults with Autism Spectrum Disorder: A Systematic Review and Meta-analysis

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Abstract

Adults with autism spectrum disorder (ASD) are thought to be at disproportionate risk of developing mental health comorbidities, with anxiety and depression being considered most prominent amongst these. Yet, no systematic review has been carried out to date to examine rates of both anxiety and depression focusing specifically on adults with ASD. This systematic review and meta-analysis examined the rates of anxiety and depression in adults with ASD and the impact of factors such as assessment methods and presence of comorbid intellectual disability (ID) diagnosis on estimated prevalence rates. Electronic database searches for studies published between January 2000 and September 2017 identified a total of 35 studies, including 30 studies measuring anxiety (n = 26,070; mean age = 30.9, SD=6.2 years) and 29 studies measuring depression (n = 26,117; mean age = 31.1, SD=6.8 years). The pooled estimation of current and lifetime prevalence for adults with ASD were 27% and 42% for any anxiety disorder, and 23% and 37% for depressive disorder. Further analyses revealed that the use of questionnaire measures and the presence of ID may significantly influence estimates of prevalence. The current literature suffers from a high degree of heterogeneity in study method and an overreliance on clinical samples. These results highlight the importance of community based studies and the identification and inclusion of well characterised samples to reduce heterogeneity and bias in estimates of prevalence for comorbidity in adults with ASD and other populations with complex psychiatric presentations.

Key words: Affective Disorders; Autism; Comorbidity; Epidemiology; Prevalence.

Introduction

Our understanding of the social and mental health needs of individuals with an autism spectrum disorder (ASD) across the lifespan has increased in recent years (Baxter *et al.* 2015), and there has been increased emphasis on better understanding these in adults (Taylor & Seltzer 2011; Howlin 2013; Moss *et al.* 2015, 2017). Adults with ASD are thought to be at heightened risk for several co-occurring mental health conditions, with anxiety and depressive disorders being the most prominent (Joshi *et al.* 2013). However, estimates of the rates of these co-occurring disorders in adults with ASD vary considerably, with some studies reporting rates of anxiety or depression as high as 70% (Charlot et al. 2008; Mazefsky et al. 2008), and others reporting rates as low as <1% for depression (Buck et al. 2014) and 5% for anxiety (Tsakanikos et al. 2011).

Given that ASD was, until recently, primarily considered a diagnosis of childhood, most research to date has focused on the child and adolescent years. van Steensel and colleagues published a meta-analysis of the prevalence of anxiety in young people with ASD aged <18 years of age (van Steensel *et al.* 2011). Their results indicated that 39.6% of young people with ASD had at least one anxiety disorder diagnosis, with specific phobias, obsessive compulsive disorder (OCD) and social anxiety being most commonly reported. Co-occurring depression in young people with ASD has so far received less attention than anxiety, possibly due to lower prevalence estimates in some studies. For instance, evidence from a population derived sample of children and adolescents with ASD reported a 3-month point prevalence of any depressive disorder to be 1.4% compared to 41.9% for any anxiety disorder (Simonoff *et al.* 2008). In contrast, clinical studies based on treatment seeking adults suggest that depression may indeed be common in adults with ASD, with reported rates

ranging from 20-35% (Gotham et al. 2015; Mazefsky et al. 2008). In contrast, rates in the general population are reported to be around 7% for depression, and between 1% and 12% for anxiety, depending on the specific diagnostic category (Kessler et al. 2003; 2012).

There are several challenges to the use of meta-analytic methods with studies on the prevalence of anxiety and depression in adults with ASD. Prominent amongst these are the lack of measures available to assess mental health comorbidities in those with ASD, particularly in adulthood, which are validated in ASD and non-ASD populations. This, along with variability in the diagnostic assessment of ASD itself and a lack of community-based studies focusing on co-occurring mental health presentations in individuals with ASD in adulthood means that there is substantial heterogeneity in both the populations being assessed and the study designs and methods/tools used to measure anxiety and depression. This is a potential caveat in the use of meta-analytic techniques as it becomes very challenging to integrate and synthesize the literature currently available. Nonetheless, describing these measurement differences enables us to quantify the degree of heterogeneity in a robust way.

One important issue to consider when reviewing the available literature on mental health comorbidities in those with ASD is the problem of diagnostic over-shadowing (Wood & Gadow 2010). This phenomenon has most often been discussed in relation to social phobia and OCD, which are also the most commonly reported anxiety disorders in ASD (Ozsivadjian *et al.* 2012; Kerns *et al.* 2014; Magiati *et al.* 2017). In the case of social phobia, it has been suggested that the reduced social motivation or difficulties in social situations commonly observed in ASD can appear behaviourally similar to the anxious avoidance of social situations which is

characteristic of social phobia. In addition, compulsive behaviours in OCD can appear similar in presentation to restrictive and repetitive behaviours as observed in ASD, and indeed recent evidence has suggested some neurobiological overlap (Carlisi *et al.* 2017). Similarly, social disinterest and/ or atypical social communication may be difficult to distinguish from psychomotor symptoms of depression in those with ASD (Chandrasekhar & Sikich 2015; Stewart et al. 2006).

Another factor that adds to the complexity of determining the rates of anxiety and depressive disorders in adults with ASD is the wide range of intellectual, verbal and adaptive functioning. With regards to intellectual functioning, for example, it has been suggested that in clinical samples approximately one third of people with ASD have intellectual functioning in the impaired range (Kim *et al.* 2011). Therefore, it is important to consider individuals' functioning when considering and interpreting findings from different studies of individuals with ASD with and without intellectual disability (ID).

The aim of the current systematic review and meta-analysis was to examine the rates of anxiety and depression in adults with ASD based on the literature currently available. To our knowledge, previous systematic reviews have focused solely on depression rates, have considered both children and adults together, or have included only a limited range of studies (i.e. Wigham et al. 2017; Stewart et al. 2006). Therefore, a systematic review is now required that focuses on adults, and examines both rates of depression and anxiety. Given our *a-priori* knowledge of a lack of community based prevalence studies in this area, we have opted to be inclusive in our selection criteria. As discussed above, the current literature has been affected by a high degree of between study heterogeneity, both in terms of the clinical populations assessed, as well as the study methodology and measures used to assess anxiety and depression.

Therefore, as well as providing the first, to our knowledge, meta-analysis of rates of anxiety and depression in adults with ASD, we aimed to explore the potential impact of ASD diagnostic measures, measures of comorbidity (i.e. clinical interviews vs questionnaire measures) and the role of intellectual disability on the estimates reported.

Methods

Definition/ operationalization of key constructs

In the current systematic review and meta-analysis, anxiety was defined as either clinically significant/ elevated symptoms of anxiety (defined as scores above clinical cut-offs on questionnaires) or a clinical diagnosis of any specific anxiety disorder (including generalized anxiety disorder; social phobia/social anxiety; specific phobia; separation anxiety; panic/agoraphobia; post-traumatic stress disorder (PTSD); or obsessive-compulsive disorder (OCD)[1]). Most studies present panic disorder and agoraphobia as a single estimate, but in cases where they are presented separately the highest rate of the two was included. This was to reduce the chances of them being double coded due to high comorbidity, given that most articles did not specify levels of multiple comorbidity in their samples (Kessler *et al.* 2006).

For depression, we only included cases which were above recommended clinical cut-off scores on validated questionnaires or where a professional/ clinical diagnosis of major depression was given. As an example, for the most commonly used questionnaire, the Beck Depression Inventory (BDI; Beck 1978), a cut-off score of “20” or “24”, depending on the version, or at least depression in the moderate range would

[1] We have included PTSD and OCD as they have a strong anxiety component and were previously organized and conceptualized under anxiety disorders in DSM-IV-TR, when many of the included studies took place.

be required. For all other questionnaires used, their specific published cut-offs as applied by the original authors were used.

Information Sources & Search approach

We conducted a search of three electronic literature databases (PsycINFO, PubMed, and Web of Science) selected to provide good coverage of both medical and psychology literature. The search included publications from the start of the year 2000 and ran up until 30th of September 2017. The start date was selected based on the publication of the text revision of the DSM-IV, to reduce the challenge of combining definitions from multiple diagnostic systems.

The search terms used were "autis*" OR "Asperger*" OR "Pervasive Developmental Disorder"); AND ("anxi*" OR "anxiety disorder" OR "anxious") OR ("comorbid* OR "psychiatric disorder" OR "mental health") OR ("depress*" OR "mood disorder" OR "low mood") AND ("adults" NOT "animal").

Two earlier systematic reviews (Stewart et al. 2006; Wigham et al. 2017) and a narrative review (Chandrasekhar & Sikich 2015) on depression in adults with ASD were also examined; and one additional citation (Crane *et al.* 2013) met our inclusion criteria and was included. We identified no systematic reviews or meta-analyses focusing on the prevalence of anxiety in adults with ASD. One review of comorbid Bipolar disorder was reviewed for depression related literature, but no additional citations were identified (Vannucchi *et al.* 2014). A Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart (Figure 1) is displayed as a summary of our search and review process (see Table 1 for inclusion and exclusion criteria).

INSERT FIGURE 1 ABOUT HERE

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Selecting studies for inclusion in the review

One author (MJH) initially screened titles and abstracts for eligibility and excluded those that clearly did not meet criteria; following this, two authors (MJH & J-WL) reviewed all remaining full-texts for eligibility. Disagreements were discussed and resolved on a case-by-case basis (see Reliability).

Data extraction

We extracted the following information from each study: a) sampling strategy; b) descriptive variables (e.g., age, gender); c) tools used to diagnose ASD; d) number of participants with an ID in the sample; e) tools used to assess anxiety/depression; f) whether diagnostic overshadowing/symptom overlap was considered in the study; and g) current and lifetime estimates of anxiety and depression.

As the primary interest of this meta-analysis is on current prevalence, all sensitivity analyses were conducted on current estimates only. Three studies included both current and lifetime estimates and both were used in their respective analyses (Joshi et al. 2013; Buck et al. 2014; Gillberg et al. 2016).

Reliability

Selecting studies. There was good inter-rater reliability in study selection for inclusion in the review/ meta-analysis (intra-class correlation = 0.72) and all disputes were resolved by referring to the inclusion/exclusion criteria. On three occasions, the same dataset was used in data analyses in three different publications, with different subsamples from the same study being analysed (Tsakanikos *et al.* 2006, 2007, 2011). In this case, we included the most recent citation which had the most participants.

Reasons for exclusion included: no clinical cut-off/diagnostic algorithm for anxiety/depression applied (*n=28);* study did not measure anxiety/depression (*n=25);* minimum age of participants was <16 years (n=11); non-ASD sample (n=9); no English translation was available (n=8); not peer reviewed (n=3), intervention study (n=1), review article (n=1).

Data extraction. All data was extracted by the first author (MJH) and then a randomly selected sample of 25% of the studies were checked for accuracy (J-WL), resulting in no disagreement.

Study Sample

The final sample included 35 studies across both anxiety and depression, with 27 studies measuring anxiety, 29 measuring depression, and 21 measuring both. Studies measuring anxiety included a total of 26,070 participants (mean age = 30.9 years, SD=6.2), and for depression there were in total of 26,117 participants (mean age = 31.1 years, SD=6.8; see Tables 2 & 3 for study characteristics and summary of main findings).

INSERT TABLE 2 ABOUT HERE

For three studies where the age of the sub-sample of interest was not reported, the mean was estimated based on the age of the overall sample (Morgan *et al.* 2003; Hermans *et al.* 2011; Houghton *et al.* 2017). Seven of the 36 studies included in the meta-analysis included adolescents in the sample (≥16 years old). Nine of the studies included had a sample that included at least 50% of people with an ID and were included in the sub-analysis described below (Buck et al. 2014; Charlot et al. 2008; Helverschou et al. 2009; Hermans et al. 2012; Mazefsky et al. 2008; McDermott et al. 2005; Morgan et al. 2003; Moss et al. 2015; Tsakanikos, et al. 2011).

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Meta-analytic method

A random-effects meta-analysis with arcsine transformation was used to account for issues with study weightings when estimating prevalence (Barendregt *et al.* 2013). Study heterogeneity was assessed using the I^2 statistic, whereby a score of more than 50% indicates moderate, and a score of 75% high levels of heterogeneity, respectively (Higgins & Thompson 2002).

Subgroup analyses were conducted to investigate differences in rates reported in studies where ≥50% of the sample had ID as compared to studies of participants without ID or with small number of individuals with ID in the sample; assessment of ASD diagnoses (i.e., using Autism Diagnostic Observation Schedule (ADOS)/ Autism Diagnostic Interview (ADI)/ other standardized diagnostic assessment for ASD versus studies not reporting standardized diagnostic procedures to confirm ASD diagnosis); and measurement of comorbidity (i.e., questionnaire versus clinical interview). A table showing the range of measures used to assess anxiety and depression and their psychometric properties can be seen in the Supplementary Materials (see Supplementary Materials 2). It was also of interest to investigate the impact of sample type (e.g., clinical versus community sampling). However, as there were few studies that could clearly be defined as non-clinical, sampling was considered under study quality.

The significance of differences in pooled estimates between subgroups was assessed via meta-regression analyses. Study quality was assessed on two domains, selection bias and detection bias, which were adapted for this meta-analysis from the Effective Public Health Practice Project Quality Assessment Tool (Armijo-Olivo et al.

2012 ; see Suppementary Material). OpenMeta, a tool for running *metafor* package in R (Viechtbauer 2010), was used to conduct the meta-analysis (Wallace *et al.* 2012).

Results

Prevalence of anxiety disorders in adults with ASD

Any anxiety disorder. Meta-analytic pooling of the estimates yielded the prevalence of any *current* anxiety disorder as 27% (95% CI 17% – 37%; *k (number of studies)= 13, n = 431/1444*). Assessment of heterogeneity indicated high levels of variance between studies included in the analysis (I^2 = 96%). A subsequent analysis of the eight studies which were classified as measuring *lifetime* prevalence indicated a prevalence of 42% (95% CI 35% – 50%; *k = 8, n = 6634/25714,* I^2 = 96%; see Table 4).

Social Anxiety. Overall 12 studies reported on rates of social anxiety, together reporting an estimated *current* prevalence of 29% and *lifetime* prevalence of 20% (*current*: 95% CI 18% – 40%, *k = 9*, *n = 200/1009,* I^2 = 91%; *lifetime*: 95% CI 7% – 38%, *k = 5, n = 75/322,* I^2 = 91%).

OCD. Fifteen studies in total measured the rates of OCD with *current* prevalence estimate of 24% and a *lifetime* prevalence of 22% (*current*: 95% CI = 15% – 33%, *k = 10, n = 265/1147,* I^2 = 93%; *lifetime*: 95% CI = 10% – 27%, *n = 247/2063, k = 7,* I^2 = 93%).

GAD. Seven studies reported *current* GAD prevalence of 18% and *lifetime* prevalence of 26% (*current*: 95% CI 10% – 26%, *k* = 4, *n* = 138/847, I^2 = 86%; *lifetime*: 95% CI 15% – 28%, *k* = 4, *n* = 63/272, I^2 = 74%).

Panic/ Agoraphobia. Eight studies in total reported an estimated *current* and *lifetime* prevalence of 15% and 18%, respectively (*current*: 95% CI 8% – 23%, *k = 4, n* = 62/388, I^2 = 62%; *lifetime*: 95% CI 10% - 27%, *k = 4, n* = 66/322, I^2 = 75%).

PTSD. Post-traumatic stress disorder was reported in five studies with a *current* prevalence of 1% and *lifetime* prevalence of 5% was found (current: 95% CI 0% – 5%, *k = 3, n* = 5/587, I^2 = 63%; *lifetime*: 95% C.I. 1% – 10%, *n studies = 3, n* = 12/251, I^2 = 67%).

Specific Phobia. A total of four studies reported on rates of specific phobia yielding an estimated current prevalence of 6% and a *lifetime* prevalence of 31% (*current*: 95% CI 1% – 32%, *k = 2, n* = 13/537, I^2 = 97%; *lifetime*: 95% C.I. 10% – 66%, *k = 3, n* = 46/218, I^2 = 92%).

Separation Anxiety. *Current* separation anxiety was reported by only one study as present in 3% of the sample (*n*=2/62), with a *lifetime* prevalence of 21% (13/62) (Joshi, et al. 2013).

Sub-group analyses: the role of clinical interview versus questionnaire measures, ASD diagnostic tools and intellectual disability on current anxiety prevalence estimates

Use of clinical interview versus questionnaires to measure anxiety. When comparing studies which used a structured clinical interview versus questionnaires to assess *current* rates of any anxiety disorder, we found no significant differences in prevalence estimates (Clinical interview: *k* = 7; n = 275/786, estimated prevalence = 28%, 95% CI 19% – 39%, I^2 = 85%; questionnaires: *k* = 4, n = 103/238, estimated prevalence = 31%, 95% CI 12% – 54%, I^2 = 91%). However, all but one of the nine studies of *current* social anxiety used a structured diagnostic interview, with this one study employing a questionnaire indicating a prevalence of 51% (Spain *et al.* 2016) versus a pooled prevalence of 26% in the remaining studies (k = 8, n = 174/958, CI 16% – 37%, I^2 = 90%).

Eight studies which assessed *current* OCD used clinical interviews resulting in a significantly lower (β = 0.26, *p = 0.03)* estimated pooled prevalence of 19% versus 43% from the two studies which used questionnaire measures and a reduced level of between study heterogeneity (Clinical interview: *k* = 8, n = 215/1050, 95% CI 13% – 23%, I^2 = 79%; questionnaires: *k* = 2, n = 50/97, 95% CI 3% - 92%, I^2 = 97%).

Use of ASD diagnostic tools. Only 4/13 studies of *current* prevalence of any anxiety disorder used the ADOS and/or ADI to confirm ASD diagnosis for inclusion into studies. The use of ADOS/ADI assessment lead to slight, but non-significant, increases in the estimated pooled prevalence (ADOS/ADI studies: *k = 4, n = 223/603,* estimated prevalence = 28%, 95% CI 15% – 43%, I^2 = 86%; non-ADOS/ADI studies: *k = 9, n = 208/841,* estimated prevalence = 25%, 95% CI 13% – 37%, I^2 = 95%).

Similar results were found when looking at the 6/9 studies of *current* social anxiety (ADOS/ADI studies: *k = 6, n = 159/846,* estimated prevalence = 33%, 95% CI 19% – 46%, I^2 = 92%; non-ADOS/ADI studies: *k = 3, n = 41/163,* estimated prevalence = 21%, 95% CI 4% – 48%, I^2 = 93%) and 5/10 studies of *current* OCD (ADOS/ADI: *k = 5, n = 196/857,* estimated prevalence = 24%, 95% CI 12% – 41%, I^2 = 95%; non-ADOS/ADI: *k = 5, n = 69/290,* estimated prevalence = 19%, 95% CI 14% – 31%, I^2 = 65%).

Presence of intellectual disability. Subgroup analysis of studies of *current* prevalence of anxiety disorder or clinically elevated anxiety symptomatology of participants with or without associated ID revealed a somewhat lower, but non-significant, pooled estimate of any anxiety disorder in adults with ASD and associated ID (*k = 6, n = 79/394,* estimated prevalence = 20%, 95% CI 7% – 39%, I^2 = 93%) compared to samples including only individuals with ASD without ID (*k* =7, n = 352/1050, estimated prevalence = 24%, 95% CI 19% – 43%, I^2 = 93%).

All nine studies of *current* social anxiety included only participants with ASD without an intellectual disability, while only three of ten studies measuring OCD included primarily adults with ASD and ID, resulting in no significant difference in pooled prevalence estimates (ID: *k* = 3, n = 55/177, estimated prevalence = 24%, 95% CI 0.14 – 0.36, I^2 = 49%; non-ID: *k* = 7, n=210/970, estimated prevalence = 20%, 95% CI 0.10 – 0.34, I^2 = 93%).

Prevalence of depression in adults with ASD

Meta-analytic pooling of the estimates yielded a 23% prevalence of *current* co-morbid depression diagnoses or moderate to severe clinically elevated depressive symptoms in adults with ASD (k = 22, n = 400/1975; 95% CI 17% – 29%). Assessment of heterogeneity indicated high levels of variance between studies included in the analysis (I^2 = 90%).

A subsequent analysis of the seven studies which were classified as measuring *lifetime* prevalence of depression indicated a prevalence of 37% (k = 10, n = 4603/24384; 95% CI 27% – 47%; I^2 = 98%).

INSERT TABLE 4 ABOUT HERE

Sub-group analyses: the role of clinical interview versus questionnaire measures, ASD diagnostic tools and intellectual disability on current depression prevalence estimates

Use of clinical interview versus questionnaires to measure depression. When comparing studies which used a clinical interview versus questionnaires to assess depression, we found a small, but non-significant, increase in prevalence estimates for studies using a clinical interview rather than a questionnaire measure (Clinical interview: *k* = 11, n = 237/1182, estimated prevalence = 27%, 95% CI 18% –

37%, I^2 = 92%; questionnaire: *k* = 8, n = 106/429, estimated prevalence = 20%, 95% CI 11% – 33%, I^2 = 87%).

Use of ASD diagnostic measures. Only 6/19 studies of current prevalence used the ADOS and/or ADI to assess or confirm ASD in their participants. This made little difference to prevalence estimates, but resulted in a considerable drop in heterogeneity between studies (ADOS/ADI studies: *k = 6, n = 170/878,* estimated prevalence = 22%, 95% CI 16% – 28%, I^2 = 66%; non-ADOS/ADI: *k = 15, n = 214/1047,* estimated prevalence = 23%, 95% CI 14% – 34%, I^2 = 93%; *p* =.09).

Presence of ID. Subgroup analysis of studies of current prevalence of depression based on whether the sample included participants with or without an ID revealed a significantly lower pooled estimate of depression in those with ASD and ID (meta-regression: β = .12, *p* = .03), compared to samples including only those without ID (ID: *k* = 6, n = 58/512, estimated prevalence = 14%, 95% CI 5% – 28%, I^2 = 92%; non-ID: *k* = 16, n=326/1413, estimated prevalence = 26%, 95% CI 20% – 32%, I^2 = 83%).

Evaluating the quality of included studies

Our analysis of study quality revealed overall poor quality. Most prominent with regards to prevalence is the reliance on clinic samples and little data available on how representative study participants are of adults with ASD more generally. These results can be seen in Supplementary Materials 1 and indicate that there are few studies which have clearly taken measures to reduce selection and detection bias.

Discussion

Summary of main findings

While it is widely accepted that adults with a diagnosis of ASD are at higher risk of experiencing comorbid anxiety and depressive disorders, there has yet to be a systematic review and meta-analysis to summarise the range of estimates of prevalence available in the literature (see also Wigham et al., 2017). We found a pooled estimate of *any current* anxiety and depression of 27% and 23% respectively in clinical studies, considerably higher than would be expected based on estimates of 1-12% in the general population (Kessler et al. 2003; 2012). The rate of current depression was consistent with the estimate of >20% reported by Wigham et al. (2017), which examined a subset of the studies included in the present meta-analysis. The finding of somewhat higher rates of anxiety compared to depression was also similar for pooled *lifetime* estimates of any anxiety (42%) and depression (37%). Consistent with estimates from childhood (van Steensel et al. 2011), we found that specific anxiety disorders, particularly social phobia and OCD, were more commonly present in adults with ASD. However, our analyses of both heterogeneity and study quality indicated high level of variance between studies, a wide range of study methodologies and sample selection, all of which increase the likelihood of biases and reduce our ability to make more firm estimates of prevalence from the studies currently available.

Rates/ prevalence of anxiety and depression in adults with ASD

The findings of the current study are consistent with meta-analyses of the prevalence of anxiety in people with ASD aged 18 years and under (van Steensel *et*

al. 2011; van Steensel & Heeman, 2017). However, while the 2011 meta-analytic study suggested a current rate of any anxiety disorder of around 39%, our pooled estimate of anxiety in adulthood appears lower at 27%. This may be explained by lower rates (when measured) of anxiety disorders more typically associated with the childhood period such as separation anxiety (Bögels *et al.* 2013), and a reduction in the estimated prevalence of specific phobias. It is notable, however, that compared to the estimates by van Steensel and colleagues, we found a near 10% higher rate of both social anxiety and OCD in adults. This could in part be accounted for by the fact that these anxiety subtypes were assessed/reported more often in the literature included in the current meta-analysis. It is also possible that these high rates could be at least partially due to diagnostic overshadowing, which is a challenge with OCD and social anxiety as discussed earlier. In fact, this was evident in our sub-group analysis comparing structured interviews and questionnaires, with the later resulting in higher estimates of both OCD and social anxiety. This may suggest that the process of eliciting a detailed description of the target behaviour, as is often the case when conducting a diagnostic or a semi-structured interview and making a clinical judgement on this may reduce the impact of diagnostic overshadowing. Similarly, this may account for the higher heterogeneity of prevalence rates based on questionnaire measures vs. structured interviews. However, it is important to note that in both methods the heterogeneity remains high.

One *a-priori* aim of this systematic review and meta-analysis was to consider the possible impact of diagnostic overshadowing on the estimated reported prevalence of anxiety and depression in adults with ASD. Unfortunately, only four of the total of 36 studies included in this meta-analysis considered diagnostic over-shadowing: two relied on clinical experience or trained research staff who conducted the interviews in

differentiating symptoms of anxiety and ASD (Capriola et al. 2016; Maddox & White 2015); one used a measure specifically designed to assess comorbidity in ASD (Helverschou *et al.* 2008), and one removed all symptoms of OCD which potentially overlapped with those of ASD from their diagnostic coding (Buck et al. 2014). In the latter study, this resulted in the lifetime prevalence dropping from 36% to 22%, suggesting that overlap between ASD and anxiety symptomatology and presentation does to some extent impact the estimated reported prevalence and that caution should be exercised when interpreting the results of the other studies and of this meta-analysis. From a clinical perspective, this finding suggests that at the current time an overreliance on informant-based or self-report questionnaire measures to assess mental health in ASD without the use of more detailed in depth structured clinical interviews is not recommended. Rather, a detailed assessment focusing explicitly on follow-up questions to clarify the nature of symptoms and to differentiate between ASD and mental health symptomatology may be warranted in clinical settings, with checklists used as supplementary or preliminary information. However, in research this must be performed in a transparently reproducible way, which so called 'clinical consensus' methods often make difficult.

In contrast to studies in children & adolescents with ASD (Simonoff *et al.* 2008; Salazar *et al.* 2015) which report relatively low rates of depression, our current study found a high estimated pooled prevalence of 22% in adults with ASD. This suggests that mood related issues likely pose significant difficulties for many adults with ASD. Moreover, these findings may also suggest a developmental progression with depression becoming more prominent in adulthood. Interestingly, our findings suggest the prevalence of depression was 10% lower in those with compared to those without ID, suggests that current self-report measures may not be adequately assessing

symptoms of depression. This may be because of difficulties with identifying and describing low mood, which may be further exacerbated by ID or difficulties with the verbal articulation of the physiological, emotional, cognitive and behavioural experiences of depression (Hassiotis & Turk 2012).

Limitations

The results presented here must be considered in the context of several limitations. Due to the high heterogeneity between the studies included, it is difficult to be certain how much our current estimates reflect the true prevalence of anxiety and depression in adults with identified ASD. The high heterogeneity, while making firm conclusions regarding prevalence difficult, is a realistic presentation of the current literature on mental health comorbidities in ASD. Due to several factors, including missing data from studies, we were unable to look at other factors that may influence prevalence rates, such as age or gender ratio. For example, to explore whether rates of depression increase with age or, as suggested in the non-ASD literature, that prevalence of anxiety is higher in females than males (McLean *et al.* 2011). Future meta-analyses can investigate the influence of these factors when more data from empirical studies become available. Furthermore, there were several studies which we were unable to include due to not being able to extrapolate a prevalence rate which may have influenced the accuracy of our current estimates. In addition, due to the lack of studies which used information from multiple informants we were unable to evaluate the inter-rater reliability of diagnoses and reported prevalence rates and the rates from studies using questionnaires mostly relied on self-report data. Nevertheless, studies which did use measures completed by different informants (i.e. caregivers versus self-report) suggested a reasonable overall level of agreement (Gotham et al. 2015; Maddox & White 2015), although degree of agreement did vary between studies (Buck

et al. 2014). Furthermore, there were no community studies that included adults whose ASD had not been recognised or who had not been in contact with clinical services, and therefore the samples included in the current analysis may not fully represent adults with ASD in the whole population. Accordingly, our *findings* should be of value in clinical practice settings but may be of more limited value to our understanding of the relationship of ASD to other forms of mental health disorders in the wider community.

Implications and recommendations for future research

The current analysis has identified several gaps in the literature. Future studies of prevalence should use well defined and validated diagnostic assessments to both confirm the diagnosis of ASD and to assess psychiatric comorbidity. We found no studies examining comorbidity in non-clinical (i.e. community or general population) samples of adults with ASD. The development and implementation of such studies should be a priority. In addition, the current literature does not consider difficulties with alexithymia (*difficulties with labelling emotions*) which are common in ASD (Bird *et al.* 2011). Variability in symptoms of alexithymia may influence the reported levels of emotional symptoms and this should be considered in future studies. The use of standardised and validated semi-structured, investigator rated ASD diagnostic tools, such as the ADOS and ADI-R, in future prevalence studies may also help to reduce heterogeneity and strengthen the characterization of participants included in such studies. Despite the recognition of possible diagnostic overshadowing, there is a dearth of research on validated assessments of depression and anxiety in adults with ASD (Brugha *et al.* 2015). While across both child and adult populations there have been efforts to validate some existing questionnaires (i.e. Zainal *et al.* 2014; Magiati *et al.* 2017; Uljarevic *et al.* 2018) and to develop population specific tools (Bearss *et*

al. 2016; Rodgers *et al.* 2016), more research in this area is still required concerning assessment issues.

Conclusion and clinical implications

In conclusion, adults with a diagnosis of ASD experience high rates of comorbid anxiety and depression. The exact prevalence is difficult to estimate precisely, given high levels of heterogeneity between studies, but our results suggest rates significantly higher than one would expect. Although it is possible that depression is underestimated, especially in the context of ASD with ID, both anxiety and depression are prominent and common in adults with a diagnosis of ASD. This suggests that in clinical settings a thorough assessment of the mental health of individuals with ASD involving different methodologies and self-, in addition to other-informant, measures is warranted. Provision for access to evidence-based psychological interventions specifically adapted for this population is also important clinically (Rodgers et al, 2018; Russell et al, 2017). As is to consider that due to the high rates of anxiety and depression in this population, as yet unidentified and undiagnosed, individuals with ASD may be over represented in mental health services.

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Conflicts of interest

None.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart.

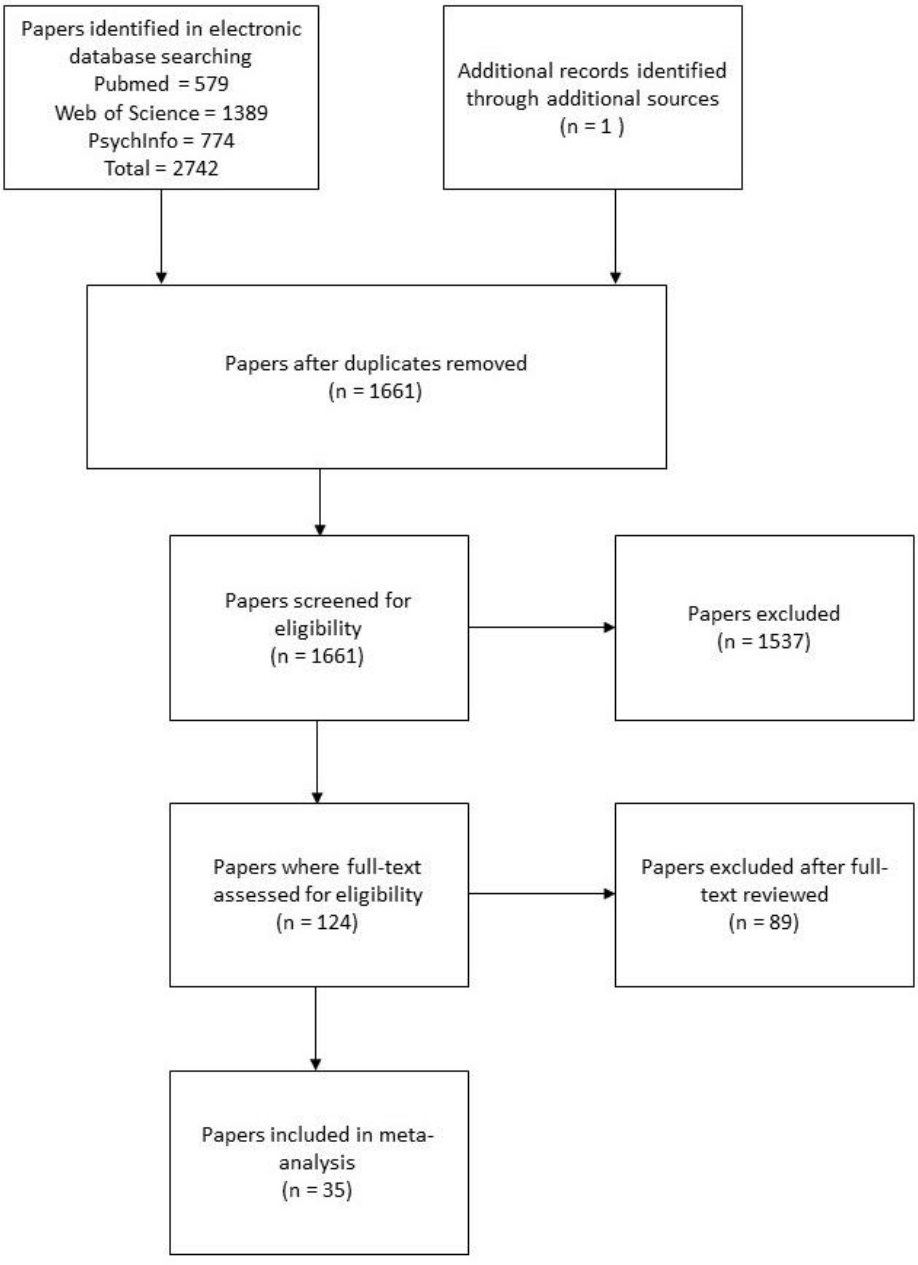

Table 1. Inclusion and exclusion criteria to be eligible for inclusion in the current systematic review

Inclusion criteria	Exclusion criteria
(i) include participants with a diagnosis of ASD based on either DSM or ICD criteria. Where the ASD diagnosis was not carried out using an ADOS or/ an ADI-R, we took an inclusive approach with the aim to explore the impact of ASD diagnostic tools on prevalence estimate in a sensitivity analysis; (ii) study participants, or an identifiable sub-group, with mean group age ≥ 18 years with the youngest participant being no younger than 16; (iii) include an assessment of comorbid anxiety or depression using either a diagnostic interview, or a validated questionnaire measure with cut-off scores for clinical caseness or a clinical diagnosis based on either DSM or ICD criteria; (iv) be published in English or have an English translation available.	(i) Studies which had not undergone peer review. (ii) Other systematic reviews which do not provide new data on rates of anxiety or depression in adults with ASD. (iii) Single case studies or case series methodologies. (iv) Treatment trial studies looking specifically at interventions for co-occurring psychiatric conditions in people with ASD, as these constituted clinical samples; (v) Studies which focused on genetic syndromes associated with ASD (e.g., Fragile X Syndrome, Rett Syndrome). (vi) Studies of dysthymia or bipolar disorder, as we focused on depression.

1 **Table 2.** Included studies assessing anxiety, study characteristics and prevalence rates of anxiety

First Author (year)	N	Mean age	Age range	Male (%)	ID (%)	Source	Ethnicity	Country	Meth-od	Respondent	Current /Lifetime	Rates of Anxiety %							
												ANY ANX	SOC	OCD	GAD	PAN/ AGO	SPH	SEP.	PTSD
Ashwood (2016)	260	32	18-70	NR	0	Clin	NR	London, UK	I	Self-report	Current	NR	18	24	23	16	NR	NR	NR
Bejerot (2014)	50	30	28-36	52	0	Clin	NR	Sweden	I	Self-report	Current	NR	28	NR	NR	NR	NR	NR	NR
Buck (2014)	129	36	26-54	75	73	Com	NR	Utah, USA	I	Self-report	Current / Lifetime	40/53	NR	33/36	NR	NR	NR	NR	NR
Capriola (2016)	18	25	18-44	56	0	NT	16 Caucasian 2 Others (multi, Asian)	Virginia, Philadelphia, USA	I	Self-report	Current	NR	61	NR	NR	NR	NR	NR	NR
Charlot (2008)	13	39	NR	62	100	Clin	NR	Massac-husetts, USA	I	Informant	Current	NR	NR	46	NR	NR	NR	NR	NR
Croen (2015)	1507	29	18-65+	73	19	Clin	988 White, non-Hispanic 59 White, Hispanic 460 Others [Black 115 Asian 168 Other 177]	California, USA	C	Clinical records	Lifetime	29	NR	8	NR	NR	NR	NR	NR
Ghaziuddin (2008)	28	27	18-57	64	7	Clin	NR	Michigan, USA	I	Self-report	Current	21	NR	NR	NR	NR	NR	NR	NR
Gillberg (2016)	50	30	23-43	100	0	Clin	NR	Gothenburg, Sweden	I	Self-report	Current	22	4	8	10	6	NR	NR	0
Helverschou (2009)	35	35	17-56	74	100	Clin	NR	Oslo, Norway	Q	Informant	Current	17	NR	17	NR	NR	NR	NR	NR
Hermans (2012)	46	NR	NR	NR	100	Clin	NR	The Netherlands	I	Self-report	Current	11	NR	NR	NR	NR	NR	NR	NR
Hofvander (2009)	122	27	16-60	67	0	Clin	NR	Paris, France	I	Self-report	Lifetime	48	NR	24	NR	NR	NR	NR	NR

								& Gothenburg, Sweden											
Houghton (2017)	22253	NR	18-50+	80	26	Clin	Only available for medicaid dataset 46,696 White 23,404 (50.12) Black 8,792 (18.83) Hispanic 1,909 (4.09) Other 12,591 (26.96)	USA	C	Clinical records	Lifetime	25	NR	NR	NR	NR	NR	NR	NR
Jones (2014)	120	39	18-76	58	0	NT	NR	London, UK	Q	Self-report	Current	57	NR	NR	NR	NR	NR	NR	NR
Joshi (2013)	63	29	18-63	65	0	Clin	55 Caucasian	Massachusetts, USA	I	Self/Informant	Current/Lifetime	NR	40/56	16/24	29/35	24/35	18/32	3/21	5/11
Ketelaars (2008)	15	22	18-24	80	0	Clin	NR	The Netherlands	I	Self-report	Current	NR	20	7	NR	13	NR	NR	NR
Lai (2011)	62	27	18-45	53	0	NT	NR	England and Wales	Q	Self-report	Current	44	NR	71	NR	NR	NR	NR	NR
Lever (2016)	138	47	19-79	70	0	Clin	NR	The Netherlands	I	Self-report	Lifetime	54	15	22	16	21	12	NR	3
Lugnegard (2011)	54	27	NR	48	0	Clin	NR	Karlstad, Sweden	I	Self-report	Lifetime	56	22	7	22	15	NR	NR	NR
Maddox (2015)	28	24	16-42	54	0	NT	Caucasian 22 Hispanic/Latino: 1 Others: 5	Virginia USA	I	Self-report	Current	NR	50	NR	NR	NR	NR	NR	NR
Mazefsky (2008)	16	25	18-32	94	70	Com	NR	Maryland USA	I	Informant	Lifetime	77	0	NR	41	0	59	NR	NR
Moss (2015)	21	43	29-64	83	0	Clin	NR	London UK	Q	Self-report	Current	10	NR	29	NR	NR	NR	NR	NR

Nylander (2013)	270	27	16-63	69	12	Clin	NR	Sweden	C	Clinical records	Current	17	NR	NR	NR	NR	NR	NR
Roy (2015)	50	37	20-62	68	0	Clin	NR	Germany	I	Self-report	Lifetime	NR	12	14	NR	14	NR	NR	2
Russell (2016)	474	31	18+	78	0	Clin	NR	London, UK	I	Self-report	Current	39	12	18	12	4	0.4	NR	0.4
Spain (2016)	50	26	18+	100	0	Clin	Majority 'White European'.	South-east England, UK	Q	Self-report	Current	NR	52	NR	NR	NR	NR	NR	NR
Sterling (2008)	46	24	18-44	91	0	Clin	44 Non-Hispanic or White, 2 Others: (1 African American, 1 more than one race)	Washington, USA	I	Self-report	Current	17	NR	9	NR	NR	NR	NR	NR
Tsakanikos (2011)	150	29	16-84	67	100	Clin	NR	South East London, UK	C	Clinical records	Current	5	NR	NR	NR	NR	NR	NR	NR

Note. ID= Intellectual Disability Disorder; Com= Recruited from a whole community or community sampling strategy was used; Clin= Recruited through a clinical service; NT= Non-treatment seeking and recruited through notices or databases, but not due to clinical contact; I= Structured Interview, Q= Standardised Questionnaire, C= Clinical Records or not reported; ANY ANX= Any Anxiety Disorder; SOC= Social Anxiety Disorder; OCD= Obsessive-compulsive Disorder; GAD= Generalised Anxiety Disorder; PAN/AGO= Panic Disorder/ Agoraphobia; SPH= Specific Phobia; SEP= Separation Anxiety Disorder; PTSD = Post-traumatic Stress Disorder, NR = not reported.

1 **Table 3.** Included studies assessing depression, study characteristics and prevalence rates of depression

Author (year)	N	Mean age	Age range	Male (%)	ID (%)	Source	Ethnicity	Country	Method	Respondent	Current/ Lifetime	Rates of Depression (%)
Ashwood (2016)	260	32	18-70	NR	0	Clin	NR	London, UK	I	Self-report	Current	20
Berthoz (2013)	38	36	28-36	63	0	NT	NR	UK	Q	Self-report	Current	32
Buck (2014)	129	36	26-54	75	73	Com	NR	Utah, USA	I	Self-report	Current / Lifetime	<1/13
Cederlund (2010)	76	22	16-37	100	NR	Clin	NR	Goteborg, Sweden	Q	Self-report	Current	4
Charlot (2008)	13	39	NR	62	100	Clin	NR	Massachusetts, USA	I	Informant	Current	69
Crane (2013)	28	42	NR	50	0	NT	NR	London, UK	Q	Self-report	Current	36
Croen (2015)	1507	29	18-65+	73	19	Clin	988 White, non-Hispanic 59 White, Hispanic 460 Others [Black 115 Asian 168 Other 177]	California, USA	C	Clinical records	Lifetime	26
Ghaziuddin (2008)	28	27	18-57	64	7	Clin	NR	Michigan, USA	I	Self-report	Current	50
Gillberg (2016)	50	30	23-43	100	0	Clin	NR	Gothenburg, Sweden	I	Self-report	Current / Lifetime	4/32
Gotham (2015)	50	21	16-31	90	0	Clin	82% / 41 Caucasian (n = 41),	North Carolina, Chicago, Michigan, USA	Q	Self-report	Current	20

							9 Others (12% / 6 African American, 1 Asian/Pacific Islander, 1 American Indian, 1 “two or more racial affiliations					
Hedley (2017)	76	25	17-56	91	10	NT	66 (86.8%) Australian 8 (10.5%) Other 2 (2.6%) Prefer not to answer	Australia	Q	Self-report	Current	25
Helverschou (2009)	35	35	17-56	74	100	Clin	NR	Oslo, Norway	Q	Informant	Current	14
Hill (2004)	27	35	16-63	56	0	NT	NR	UK	Q	Self-report	Current	22
Hofvander (2009)	122	27	16-60	67	0	Clin	NR	Paris, France & Gothenburg, Sweden	I	Self-report	Lifetime	53
Houghton (2017	22253	NR	18-50+	80	25	Clin	Only available for medicaid dataset 46,696	USA	C	Clinical records	Lifetime	18

							White 23,404 (50.12) Black 8,792 (18.83) Hispanic 1,909 (4.09) Other 12,591 (26.96)					
Jones (2014)	120	39	18-76	58	0	NT	-	London, UK	Q	Self-report	Current	42
Joshi (2013)	63	29	18-63	65	0	Clin	55 Caucasian	Massachusetts, USA	I	Self/Informant	Current/Lifetime	31/77
Ketelaars (2008)	15	22	18-24	80	NR	Clin	NR	The Netherlands	I	Self-report	Current	26
Lai (2011)	62	27	18-45	53	0	NT	NR	England and Wales	Q	Self-report	Current	27
Lever (2016)	138	47	19-79	70	0	Clin	NR	The Netherlands	I	Self-report	Lifetime	53
Lugnegard (2011)	54	27	NR	48	0	Clin	NR	Karlstad, Sweden	I	Self-report	Lifetime	70
Mazefsky (2008)	16	25	18-32	94	70	Com	NR	Maryland USA	I	Informant	Lifetime	24
McDermot (2005)	51	27	NR	78	0	Clin	29.4 African American, Rest are Spanish spaeaking/Asian / Caucasian	Carolina, USA	C	Clinical records	Lifetime	6
Morgan (2003)	164	NR	NR	56	100	Com	NR	Birmingham, UK	C	Clinical records	Current	20

Moss (2015)	21	43	29-64	83	0	Clin	NR	London UK	Q	Self-report	Current	10
Roy (2015)	50	37	20-62	68	0	Clin	NR	Germany	I	Self-report	Lifetime	48
Russell (2016)	474	31	18+	78	0	Clin	NR	London, UK	I	Self-report	Current	16
Sterling (2008)	46	24	18-44	91	0	Clin	44 Non-Hispanic or White, 2 Others: (1 African American, 1 more than one race)	Washington, USA	I	Self-report	Current	33
Tsakanikos (2011)	150	29	16-84	67	100	Clin	NR	South-East London, UK	C	Clinical records	Current	7

Note. ID= Intellectual Disability Disorder; Com= Recruited from a whole community or community sampling strategy was used; Clin= Recruited through a clinical service; NT= Non-treatment seeking and recruited through notices or databases, but not due to clinical contact; I= Structured Interview, Q= Standardised Questionnaire, C= Clinical Records or not reported. NR = not reported.

Table 4. Pooled estimates of current and lifetime anxiety and depression in adults with ASD

Diagnosis	Current/ Lifetime	No. of Studies	Participants, *n*	Prevalence, %	95% C.I.	I^2, %
Any anxiety	Current	13	1444	27%	17% - 37%	96%
	Lifetime	8	25714	42%	35% - 50%	96%
Social phobia	Current	9	1009	29%	18% - 40%	91%
	Lifetime	5	322	20%	7% - 38%	91%
OCD	Current	10	1147	24%	15% - 33%	93%
	Lifetime	7	2063	22%	10% - 27%	93%
GAD	Current	4	847	18%	10% - 26%	86%
	Lifetime	4	272	26%	15% - 28%	74%
Panic/agoraphobia	Current	4	388	15%	8% - 23%	62%
	Lifetime	4	322	18%	10% - 27%	75%
Specific phobia	Current	2	537	6%	1% - 32%	97%
	Lifetime	3	218	31%	10% - 66%	92%
PTSD	Current	3	587	1%	0% - 5%	63%
	Lifetime	3	251	5%	1% - 10%	67%
Separation Anxiety	Current	1	63	3%	-	-
	Lifetime	1	63	21%	-	-
Depression	Current	22	1975	23%	17% - 29%	90%
	Lifetime	10	24384	37%	27% - 47%	98%

Supplementary Materials 1. Quality assessment of studies included in meta-analysis

Methods

Our assessment of study quality was adapted from the Effective Public Health Practice Project Quality Assessment Tool (Armijo-Olivo et al. 2012) and included an assessment of both selection and detection bias, two factors particularly relevant to studies of prevalence. Specific adaptation to the criteria where made to address the specific research question and target population. There was an emphasis placed on the tools used to assess and diagnose ASD and the target comorbidities. To assess the quality of studies, selection criteria were developed to evaluate studies on their use and reporting of standardised diagnostic assessments of ASD. The use of a standardised structured diagnostic assessment was rated as good, using other clinical assessments (i.e. questionnaire or screening measures) were rated as satisfactory; and a historical diagnosis (i.e., medical file review) or an unconfirmed historical self-reported diagnosis were rated as poor. An additional focus of the evaluation of detection bias was the quality of measures used to assess comorbid anxiety and depression. As with the ASD diagnosis, the use of a standardised structured assessment to measure psychiatric comorbidities was rated as good; the use of a questionnaire-based measure cut-off score was rated as satisfactory, and diagnosis based on medical records only (or self-report) as poor. The criteria used to assess quality are outlined below in Table SM1.

Table SM1. Criteria Quality Analysis Ratings of Study Selection and Detection Bias

	Selection Bias			Detection bias		
Key	Participant selection	Participant Representation	ASD assessment	Researcher blinding	Comorbidity assessment	Participant blinding
	How were participants selected?	What percentage of those approached / population participated?	How was ASD diagnosis assessed/ confirmed?	Were researches blinded to participant clinical history / research aims	What type of measure/assessment was used to assess anxiety or depression?	Were participants aware of research question?
Good	Community Sample	80 – 100%	ADOS/ADI (other structured assessment)	Yes	Structured interview / assessment	No
Satisfactory	Non-treatment seeking	60 – 79%	Clinical diagnosis / judgment	No	Questionnaire	Yes
Poor	Clinical	Less than 60% / cannot tell	Historic diagnosis / cannot tell	Cannot tell	Clinical records/ Cannot tell	Cannot tell

Each paper was reviewed by two authors (MJH & J-WL) and any disagreement were discussed and reviewed based on the criteria in Table SM1. There were four points of contention in total with all being resolved after discussion.

Results

As can be seen in Table SM2 below, studies were rated on six domains as either good (green), satisfactory (yellow) or poor (red). Most of the studies where rated as primarily poor in quality in the different domains assessed. Only ten of the 31 studies used a structured ASD assessment to confirm participants' ASD diagnoses. The domains in which most studies were scored as poor were participant selection and blinding. While these are important factors when considering estimates of prevalence, it is worth noting that most of the studies included in this meta-

analysis were limited by the fact that they were not originally designed as prevalence studies.

Table SM2. Results of Quality Analysis of Study Selection and Detection Bias

	Selection Bias			Detection bias		
First author (date)	Participant selection	Participant Represent-tation	ASD assessment	Researcher blinding	Comorbidity assessment	Participant blinding
Ashwood (2016)						
Bejerot (2014)						
Berthoz (2013)						
Buck (2014)						
Capriola (2016)						
Cederlund (2010)						
Charlot (2008)						
Crane (2011)						
Croen (2015)						
Ghaziuddin (2008)						
Gillberg (2016)						
Gotham (2015)						
Hedley (2017)						
Helversc. (2009)						
Hermans (2012)						
Hill (2004)						
Hofvander (2009)						
Houghton (2017)						
Jones (2014)						
Joshi (2013)						
Ketelaars (2008)						
Lai (2011)						
Lever (2016)						
Lugnegard (2011)						
Maddox (2015)						
Mazefsky (2008)						
McDermot (2005)						
Morgan (2003)						
Moss (2015)						
Nylander (2013)						
Roy (2015)						
Russell (2016)						
Spain (2017)						
Sterling (2008)						
Tsakanikos (2011)						

Supplementary Materials 2 – Table of measures used to assess anxiety and depression in studies included in the meta-analysis

Measure	Psychometrics properties	Studies
Structured/Semi-structured Interview measures		
The Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) This is a short structured diagnostic interview that evaluates whether the individual meets psychiatric disorders' criteria based on the DSM-IV and ICD-10	Not validated in ASD sample. <u>In typically developing adults:</u> Good inter-rater and test–retest reliability Adequate sensitivity and specificity across most diagnoses. (Lecrubier et al. 1997; Sheehan et al. 1997).	Bejerot (2014), Gillberg (2016), Lever (2016)
Psychiatric Assessment Schedule for Adults with a Developmental Disability (PAS-ADD) (Moss et al., 1993) This semi-structured interview is designed to be suitable for adults with intellectual disability and assesses for both current (preceding 4 weeks) and lifetime presence of common psychiatric disorders based on ICD-10.	Not validated in ASD sample. <u>In adults with intellectual developmental disorders:</u> Satisfactory inter–rater reliability of the lCD–10 version (Kappa≥ of 0.65 for individual item and clinical significance of the symptoms) Satisfactory validity for depressive disorder, but weak validity for anxiety disorder. (Costello et al. 1997; Moss et al., 1997)	Hermans 2012
Mini PAS-ADD[2] This shortened version is suitable for staff without a background in psychiatry or psychology.	Not validated in ASD sample. <u>In adults with intellectual developmental disorders:</u> Good internal consistency (.48–.95) and inter-rater reliability (.77–.91) Satisfactory sensitivity (62–100%) and specificity (71–100 %) (Devine et al. 2009; Prosser et al. 1998).	Buck (2014)
The Mood and Anxiety Semi-Structured (MASS) Interview (Charlot et al., 2007) It contains 29 questions relating to the presence of DSM-IV symptom criteria for mood and anxiety disorders and is designed for easy administration to individuals with intellectual disorder. Each symptom item is accompanied with a few behavioural examples, in which administer has to determine if a similar dysfunctional change is present.	Not validated in ASD sample. <u>In adults with intellectual developmental disorders:</u> Satisfactory agreement (Kappa = 0.42-0.78 with comprehensive clinical evaluation and Hamilton Depression Rating Scale cutoff) (Charlot et al., 2007)	Charlot (2008)

Structured Interview for DSM (SCID) (First, Gibbon, Spitzer, & Williams, 1996, First & Gibbon, 2004; Wittchen et al. 1997) This semi-structured clinical interview assesses for the presence of major DSM-IV Axis I diagnoses.	Not validated in ASD. In typically developing adults: Satisfactory Test-retest reliability (Kappas≥.44) Good Inter-rater reliability (Kappas≥.63)	Hofvander (2009), Joshi (2013), Lugnegard (2011), German version: Roy (2015)
Schedule for Clinical Assessment in Neuropsychiatry (SCAN-2.1, Giel & Nienhuis, 1996; World Health Organisation, 1992) This is a structured interview that assesses for mental illness, which could be used to match the diagnostic criteria in either ICD-10 or DSM-IV.	Not validated in ASD. In typically developing adults: Test-retest κ = 0.62 94% agreement on caseness between interviewers (Rijnders et al, 2000).	Ketelaars (2008)
Schedule of Affective Disorders and Schizophrenia - Lifetime version (SADS-L; Endicott & Spitzer, 1978) This is a semi-structured diagnostic interview that involves questions regarding the peak severity of the current presentation, severity of various common psychological disorders in the preceding week, and psychosocial functioning history.	Used previously by Lainhart (2003) and shown to be effective in people with ASD. Psychometric properties not commonly reported for adult version.	Mazefsky (2008)
Family History - Research Diagnostic Criteria It is a Family History Interview (Rutter and Folstein, 1995) augmented with research diagnostic criteria (Andreasen et al. 1977). This interview inquiry the parents of participants about their and relatives' experiences of presenting psychiatric illnesses. The specific probes for each question and coding were based on DSM-IV (APA, 1994) definitions.	Not reported	Sterling (2008)
Anxiety Disorders Interview Schedule (ADIS) -Social anxiety section (Brown et al. 1994) A semi-structured diagnostic interview to assess for anxiety disorders in adults.	Validated for children with ASD (intraclass correlation = 0.85-0.98, κ = 0.67-0.91) but not adults (Kerns et al, 2016).	Maddox (2015)
Questionnaire Measures		
Beck Anxiety Inventory (Beck et al., 1988) This questionnaire contains 21 items on anxiety symptoms and measures the severity of the anxiety in the past week. Those who scored 26 and above were considered as possibly having severe anxiety.	Not validated in ASD population. In typically developing adults: Excellent Internal consistency (Cronbach's a=0.92)	Jones (2014), Kleinhans (2016), Lai (2011), Moss (2015)

	Satisfactory Test-retest reliability (1 week r= 0.75 Good convergent validity (Moderate correlation with Revised Hamilton Anxiety Rating Scale= .51), Good convergent validity (low correlation with Hamilton Depression Rating Scale=.25) (Beck et al., 1988)	
Beck Depression Inventory (BDI) (Beck et al., 1961). This 21 item questionnaire measures the degree of emotional, behavioural and physiological changes related to depression over the past week. A score of 20 indicated clinical caseness for typically developing adults.	Not validated in ASD population. <u>In typically developing adults:</u> Excellent internal consistency (mean Cronbach's α=0.86) High validity (high correlation ≥ .72with Hamilton Psychiatric Rating Scale for Depression) (Beck et al., 1988)	Berthoz (2013), Cederlund (2010, Hill (2004), Jones (2014), Lai (2011), Crane (2013)
BDI-II (Beck et al., 1996) This is a revised version of BDI which excluded items, such as body image, hypochondria, and extended the timeframe to 2 weeks to match the DSM-IV diagnostic criteria.	<u>In youths and adults with ASD:</u> High internal consistency (Cronbach's α =.87) High convergent validity (high correlation r= .62 to .82 with other self-reports; moderate correlaton with parent-rated Children's Depression Rating Scale) Good Divergent Validity (low correlation with age and verbal IQ=-.12 to .27) (Gotham et al., 2015) <u>In typically developing adults:</u> High internal consistency (Cronbach's α =0.92) High convergent validity (Dozois et al., 1998).	Gotham (2015), Kleinhans (2016), Moss (2015)
Liebowitz Social Anxiety Scale (Liebowitz, 1987) It contains 24 items that measures the level of fear and extent of avoidance in common social situations (13 items relating to performance anxiety and 11 items relating to social interaction anxiety). A total score of 60 or more suggested a possibility of generalised social anxiety disorder.	Not validated for ASD population. <u>In typically developing adults:</u> Good test-retest reliability and Internal consistency (Cronbach's α = 0.83 to 0.95) Good convergent validity	Spain (2016)

	(High correlation with other related measures >.60; high correlation with clinician-administered version = .85) Good divergent validity (low correlation with BDI & HRSD ≤.48) (Baker et al., 2001, Fresco et al., 2001)	
Brief Fear of Negative Evaluation Questionnaire (Leary, 1983) This is a shortened version of the FNE questionnaire (Watson and Friend 1969), which requires participants to rate the extent in which each of the 12 items on concerns about others' negative evaluation are representative of them.	Not validated in ASD population. In typically developing adults: The BFNE has high correlation with the original FNE (.96) Excellent internal consistency (Cronbach's α = .90) and 2-week Test-retest reliability (r=.94) Acceptable Convergent Validity (correlation with other self-reports = .35 to .56) Acceptable Divergent Validity (correlation with BDI and Anxiety Sensitivity scale = .27 to .47, but moderate correlation with .51 with Penn State Worry Questionnaire) (Collins et al., 2005; Weeks et al., 2005)	Capriola (2016)
Obsessive Compulsive Inventory – Revised (OCI-R; Foa et al., 2002) The OCI-R is a shortened version of the self-report OCI (Foa, Kozak, Salkovskis, Coles, & Amir, 1998). This 18-item inventory assesses for symptoms of Obsessive-Compulsive Disorder (OCD). The total score of 21 or more indicates the likely clinical severity of OCD.	Not validated in ASD population. In typically developing adults: The OCI-R correlates very strongly with the original version (r = .98), Excellent internal consistency (Cronbach's α =.81) Excellent two-week test–retest reliability (r=.82) Satisfactory convergent validity (moderate-to-high correlation with Y-BOCS .53, Maudsley Obsessive–Compulsive Inventory .85), and the PI-WSUR (.75) Poor divergent validity (moderate correlation with Hamilton Depression Rating Scale .58 and BDI .70)	Lai (2011)

	Satisfactory Sensitivity (65.6%) and specificity (63.9%) (Foa et al., 2002)	
Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) This is a 9-item self-report questionnaire that measures the severity of depression. It has a cut off of 10 for item1 to 8.	Not validated in ASD population. <u>In typically developing adults:</u> Good internal consistency (Cronbach's α =.86 and .89) Excellent Sensitivity (95%) and Specificity (70%) Good convergent validity (High correlation with BDI = .73) (Kroenke et al., 2009; Martin et al., 2006)	Hedley (2017)
Psychopathology in Autism Checklist (PAC) This 42-item checklist that are reviewed by a group of expert clinicians to facilitate the diagnosis discrimination between autism and four major psychiatric disorders (psychosis (10 items), depression (7 items), anxiety disorder (6 items) and OCD (7 items) based on DSM-IV and ICD-10.	<u>In adults with ASD:</u> **Anxiety:** Good degree of interrater agreement. Kappa = .58 between familiar staff or family member Good internal consistency: (Cronbach's a = .78) **Depression:** Good degree of interrater agreement. Kappa = .67 Good internal consistency: (Cronbach's a = .85)	Helverschou (2009)
Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989). This 10-item clinician-rated scale measures the severity of obsessive-compulsive behaviours. A cut off of total score between 16–23 represents a possible moderate OCD, 24–31 a severe disorder and >31 as an extreme severity).	Not validated in ASD population. <u>In typically developing adults:</u> Good internal consistency (Cronbach's a=.69-.89) and interrater reliability (ICC=.93-.96) Satisfactory convergent validity (Moderate correlation with Maudsley Obsessional-Compulsive Inventory, subjective ratings of fear and ritual composite r=.38-.64) Good divergent validity (Non-significant correlation with gender, age and socioeconomic status and low correlation with anxiety subscale of symptom checklist r=.23-.37, but moderately correlated with depression subscale .42-.51). (Goodman et al., 1989; Woody et al. 1995).	Moss (2015)

Note. Psychometric properties presented are based on typical adult population unless otherwise stated.

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