Accepted Manuscript

What is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis

Rachel Loomes, DClinPsy, Laura Hull, MSc, William Polmear Locke Mandy, DClinPsy, PhD

Please cite this article as: Loomes R, Hull L, Mandy WPL, What is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis, *Journal of the American Academy of Child & Adolescent Psychiatry* (2017), doi: 10.1016/j.jaac.2017.03.013.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
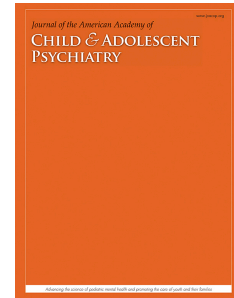
What is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis

RH: Male-to-Female Ratio in ASD

Rachel Loomes, DClinPsy, Laura Hull, MSc, William Polmear Locke Mandy, DClinPsy, PhD

Supplemental material cited in this article is available online.

Drs. Loomes, Mandy, and Ms. Hull are with University College London, UK.

Correspondence to Will Mandy, PhD, Research Department of Clinical, Educational and Health Psychology, UCL, Gower Street, London, UK, WC1E 6BT; email: w.mandy@ucl.ac.uk

ABSTRACT

Objective: To derive the first systematically-calculated estimate of the relative proportion of males and females with autism spectrum disorder (ASD), via a meta-analysis of prevalence studies conducted since the introduction of the *DSM-IV/International Classification of Diseases–10th Revision* (*ICD-10*).

Method: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. We searched MEDLINE, Embase, and PsycINFO databases, and study quality was rated using a risk of bias tool. Random effects meta-analysis was used. The outcome measure that we pooled was the male-to-female odds ratio (MFOR), namely the odds of being male in the group with ASD compared to in the non-ASD group. In effect this is the ASD male-to-female ratio, controlling for the male-to-female ratio among participants without ASD.

Results: Fifty-four studies were analysed, with 13,784,284 participants, of whom 53,712 had ASD (43,972 males and 9,740 females). The overall pooled MFOR was 4.20 (95% CI 3.84, 4.60), but there was very substantial between-study variability (I^2=90.9%). High-quality studies had a lower MFOR = 3.32 (95% CI [2.88, 3.84]). Studies that screened the general population to identify participants regardless of whether they already had an ASD diagnosis showed a lower MFOR = 3.25 (95% CI [2.93, 3.62]) than studies that only ascertained participants with a pre-existing ASD diagnosis (MFOR = 4.56, 95% CI [4.10, 5.07]).

Conclusion: Among children meeting criteria for ASD, the true male-to-female ratio is not four to one, as is often assumed; rather, it is closer to three to one. There appears to be a diagnostic gender bias, meaning that girls who meet criteria for ASD are at disproportionate risk of not receiving a clinical diagnosis.

Key words: Autism spectrum disorder; male-to-female ratio; sex difference; meta-analysis; epidemiology

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterised by impairments in social reciprocity and social communication, as well as restricted, repetitive patterns of behaviour.[1] It is highly heritable, persists across the lifespan, and affects approximately one percent of the population.[2,3] One striking and consistent feature of ASD is that it is more commonly diagnosed in males than in females.[1] This has motivated influential ideas about the nature and aetiology of ASD, such as the Extreme Male Brain,[4] Female Protective Effect,[5] and Female Autism Phenotype[6] theories. Further, the widely acknowledged excess of males on the autism spectrum influences day-to-day clinical and educational practice, for example when clinicians and teachers make decisions about whether a child has autistic symptoms based partly on their gender.[7] As such, it is important to have a systematically derived, precise estimate of the male-to-female ratio in ASD in order to guide research and practice.

The *DSM-5* states that "autism spectrum disorder is diagnosed four times more often in males than in females."[1(p57)] This four-to-one gender ratio is widely cited and comes from work that calculated the mean male-to-female ratio from population prevalence studies of ASD.[8] Whilst such estimates are useful as a rough guide to the male-to-female ratio in ASD, they do not use meta-analysis to synthesise findings. As such they do not take account of important factors such as sample size and case ascertainment method, and so give equal weight to all reviewed studies irrespective of their size, design, and quality.

Further, simple averages of gender ratios do not capture a key feature of the ASD gender ratio; namely, its substantial variability across studies. Even among epidemiological studies that implemented similar inclusion criteria and recruitment methods, ASD male-to-female ratios show striking variability, ranging between eight-to-one[9] and two-to-one.[10] This heterogeneity is currently little studied and therefore poorly understood. Its investigation will

be instructive about the true ratio of males to females with ASD, and can elucidate whether there are, as is often suggested, diagnostic biases against females with ASD. Specifically, it will be valuable to examine formally between-study variability in the ASD male-to-female ratio to discover whether it is influenced by the following:

1. Study quality. If study quality is associated with variability in the ASD male-to-female ratio, particular weight should be given to studies with the greatest methodological merit, as these are likely to give the most precise, valid estimates.

2. Case-ascertainment method. Active case-finding methods involve screening a population-based sample in an attempt to identify all cases regardless of whether they have already come to clinical attention. By contrast, passive case-finding studies review existing databases (e.g. medical or special educational records), or contact parents via mass-telephone surveys, to discover who within a given population has received an ASD diagnosis.[11] Such approaches are considered passive because they only pick up those who have already been officially identified. We argue that active methods will yield more valid estimates of the male-to-female ratio, as they are more likely to identify individuals with ASD, even if they have been missed by services. Further, comparisons of estimates from active and passive studies will be instructive about whether females who would meet criteria for ASD are at disproportionate risk of missing out on a clinical diagnosis.

3. Date of study. Prevalence rates of ASD have increased over time, but it is unclear whether or not the male-to-female ratio of diagnosed cases is also changing.[12]

4. Participant IQ. It is commonly suggested that IQ affects the ASD male-to-female ratio, with the proportion of males often observed to be higher amongst people with higher IQ.[13] However, to date, this has not been formally tested using meta-analysis.

5. Participant age. Females with ASD tend to receive their diagnosis later than males,[14] so it is possible that the male-to-female ratio will be higher in younger samples.

In summary, the present systematic review seeks to investigate the relative proportion of males and females on the autism spectrum via a meta-analysis of published prevalence studies. The initial aim is to ascertain the first systematically-derived, weighted, pooled estimate of the male-to-female ratio of ASD. The second aim is to enhance understanding of the true ASD male-to-female ratio by investigating the effects of: (1) study quality; (2) active versus passive case ascertainment; (3) date of study; (4) participant IQ; (5) participant age.

METHOD

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.

Eligibility Criteria

Studies with the following characteristics were eligible for this systematic review:

1. Investigation of ASD prevalence within a general population sample of at least 1,500.

2. Diagnosis of ASD based on *DSM-5*, *DSM-IV-TR*, *DSM-IV* or *International Classification of Diseases–10th Revision (ICD-10)* criteria. This was designed to maximise generalizability to current practice.

3. Information provided on number of females and males with ASD, as well as overall size of population studied, to enable calculation of the primary outcome measure for this meta-analysis.

4. Year(s) of data collection reported.

5. Age range of sample falls between 0 and 18 years. It was decided to exclude studies of prevalence in adults with ASD, as such research is currently rare; and ASD gender ratios for adults may be different from those in child and adolescent populations[15].

Information Sources and Search

Figure 1 shows the process by which papers were identified. A systematic search was conducted on 23/09/2015 using the MEDLINE, Embase and PsychINFO databases. These searches combined keywords, MeSH terms, and text words "autism" OR "pervasive developmental disorde*" OR "Asperger*" AND "epidemiology" OR "prevalence." Also, the reference lists of relevant articles and previous reviews of ASD prevalence were obtained and screened for any additional studies missed by the database search. Next, titles and abstracts of the articles identified were screened against inclusion criteria. For articles passing this screening stage, the full journal articles were read to determine whether they met study inclusion criteria. This process was conducted by the first author. To check its reliability, a second, blind rater (L.H.) was given a random sample of 200 of the 1,012 articles identified in the initial search stage, and evaluated these against our inclusion criteria. There was perfect (i.e., 100%) agreement between the initial and second (blind) rater about which of these articles met inclusion criteria for this review.

Data Extraction

The first (R.L.) and second authors (L.H.) independently extracted data from all articles identified as meeting study criteria, using a coding sheet designed for the current meta-analysis (available on request from the corresponding author). Disagreements about data points were discussed and resolved within the study team.

Assessing Risk of Bias

We used the Hoy Risk of Bias Tool (RoBT)[16] for assessing methodological features of prevalence studies, which consists of ten items plus a summary assessment. Items one to four assess external validity, and items five to ten assess internal validity. Each item is scored "0" (risk of bias absent) or "1" (risk of bias present), so that the scale has an overall maximum of 10, with higher scores reflecting a greater risk of bias. To assess reliability of the RoBT, all studies were blind double-rated by the first and second authors. Inter-rater

reliability for the total RoBT score, calculated using Case 2A intra-class correlations (ICCs) to assess levels of absolute agreement[17] was high (ICC=.93, 95% CI [.89. .96]). In order to derive a consensus RoBT score, any disagreements on individual items were discussed between the first and second authors, and if these could not be resolved in this way, the senior author (W.M.) was consulted.

Data Analysis

The outcome measure summarised in this meta-analysis was the odds ratio describing the odds of being male in the group with ASD compared to the odds of being male in the group without ASD. We call this the "male-to-female odds ratio." In effect, this presents the male-to-female ratio amongst those with ASD, controlling for the male-to-female ratio amongst participants without ASD. This male-to-female odds ratio is a purer measure of the ASD gender ratio than simply calculating a male-to-female ratio for diagnosed cases, as it takes account of any gender imbalance in a study's overall sample that could artificially inflate or depress the ASD male-to-female ratio. The STATA command 'metan' was used to conduct a random-effects meta-analysis using the DerSimonian and Laird procedure to derive a pooled male-to-female odds ratio and 95% CIs. The I^2 squared statistic was used to measure between-study heterogeneity.[18] An I^2 value of 0% indicates no observed heterogeneity beyond that expected from sampling error, and larger values show increasing heterogeneity,[19] with I^2 above 75% indicative of substantial heterogeneity. A Harbord Test, implemented using the STATA 'metabias' command, was used to evaluate publication bias.[20]

Meta-regressions, using the STATA 'metareg' command, were conducted to investigate influences on the ASD male-to-female ratio. Study characteristic variables (risk of bias, case ascertainment method, date of study, IQ of those with ASD, age of sample) were regressed separately against the log of the male-to-female odds ratio. Where a significant association was found, we checked for potential confounds (i.e., other study characteristic

variables that were significantly associated with both the predictor and the outcome) and controlled for these by adding them to the model. We also present subgroup meta-analyses comparing studies grouped according to predictors of interest, as follows: (1) low versus medium/higher risk of bias; (2) passive versus active case ascertainment; (3) older (1992 to 2001) versus more recent (2002 to 2011) studies; (4) lower IQ (>50% of those with ASD had intellectual disability) versus higher IQ (≤50% of those with ASD had intellectual disability); (5) younger (0 to 6 years) versus older (6 to 18 years) participants.

RESULTS

Overview

Figure 1 depicts the process by which studies were identified. A total of 54 met inclusion criteria, comprising 13,784,284 participants, 53,712 of whom were diagnosed with ASD (43,972 males and 9,740 females). Details of each study, including total risk of bias score, are provided in Table S1, available online. Fourteen studies were conducted in North America, with 11 taking place in the United States of America[21-31] and three in Canada.[32-34] Twenty-four were European, with 12 carried out in the United Kingdom,[3,35-45] and the other 13 being in Sweden,[46-49] Denmark,[50-52] Norway,[53-55] France,[10] Iceland,[56] and Portugal.[57] There were 11 Asian studies, in Japan,[58-60] China,[61-62] Israel,[63-64] Iran,[65] Oman,[66] South Korea,[67] and Taiwan.[68] There were two studies from South America, conducted in Aruba[69] and Venezuela,[70] and two from Australia.[9,52] The studies spanned a period of 19 years, conducted between 1992 and 2011. The average estimated ASD prevalence across all studies was 61.9 per 10,000 (SD=48.5, 95% CI [48.6, 75.1]).

[Figure 1 here]

Risk of Bias and Case Ascertainment

Overall, the methodological quality of the reviewed studies was high. The RoBT used to evaluate study quality ranges from 0 to 10, with higher scores being indicative of greater

risk of bias (i.e., lower quality). The most common risk of bias detected was that 40 studies failed to demonstrate explicitly that the study's target population was a close representation of the national population (RoBT Item 1). Also, a majority of studies (n=37) did not use an assessment instrument with well-established psychometric properties to identify ASD cases (Item 7). None of the studies scored above five on the RoBT (median = 3, mean = 3.15, SD=1.29). For the risk of bias subgroup meta-analysis, we grouped 17 studies as having a low risk of bias (scoring 0-2, i.e., below the average score), and 37 studies as having a medium or higher risk of bias (scoring 3-5). Twenty studies used active case ascertainment, with the remaining 34 employing passive case ascertainment.

Age and IQ of Young People With ASD

Only half (n=27/54) of studies reported the average age of the participants with ASD they identified (mean=7.45 years, SD=2.91). All studies reported an age range for their sample. To avoid missing data, we estimated the average age for each study by taking a midpoint between the minimum and maximum of this age range. For the 27 studies for which precise age data were available, this method provided an excellent estimate of the individuals with ASDs' reported average age (r=.98, p<.001). There were 24 studies that provided sufficient information for the proportion of participants with an intellectual disability (i.e., IQ 70 or below) to be derived. Amongst these, the mean percentage of people with ASD who did not have an intellectual disability was 51.75% (SD = 19.80). For the subgroup meta-analyses, we categorised studies into higher IQ (at least 50% of individuals with ASD had IQ above 70, n=14) and lower IQ (less than 50% had IQ above 70, n=10) groups.

ASD Male-to-Female Odds Ratio in ASD

Inspection of a funnel plot and the Harbor test did not suggest evidence of publication bias (p=.458). As shown in Table 1, the overall pooled male-to-female odds ratio was 4.20

(95% CI [3.84, 4.60]). The I^2 statistic was 90.9%, indicating a large amount of between-study heterogeneity.

[Table 1 here]

Influences on the ASD Male-to-Female Odds Ratio

Table 2 shows the results of meta-regressions investigating which study characteristics were associated with variability in the ASD male-to-female ratio. Risk of bias, case ascertainment method (active v. passive), proportion of participants with ASD with intellectual disability and date of study were each individually associated with the male-to-female odds ratio. However, as is shown in Table 2, once we identified and controlled for confounds, only IQ and case ascertainment method (active v. passive) remained significant predictors of the ASD male-to-female ratio.

The subgroup meta-analyses presented in Table 2 demonstrate the nature of these effects. Studies that identified a higher proportion of ASD cases with a co-occurring intellectual disability showed a lower male-to-female odds ratio. Active case ascertainment studies showed a lower male-to-female ratio than those relying on passive case ascertainment, an effect that is depicted in Figure 2. For the studies employing passive case ascertainment, the I^2 statistic indicated substantial and significant heterogeneity. By contrast, no significant heterogeneity was observed for the active case ascertainment studies.

[Table 2 here]

[Figure 2 – here]

We sought to explore whether the lower male-to-female ratio in active studies was driven by the ascertainment of more females than in passive studies. We did this by examining, post hoc, the raw numbers of female and male participants with ASD identified by active and passive studies. Overall, active studies identified, on average, 65.6 cases per 10,000 (SD=63.8, 95% CI [35.7, 95.4], compared to 59.7 [SD=37.8, 46.5, 72.9]) for passive

9

studies. Active studies identified, on average, 24.1 females per 10,000 females (SD=22.5, 95% CI [13.6, 34.6]), whereas passive studies identified 20.3 (SD=14.9, 95% CI [15.1, 25.5]). The opposite pattern was observed for males: active studies (M=81.1, SD=62.2, 95% CI [51.9, 110.2]) tended to identify fewer males per 10,000 males than did passive ones (M=95.4, SD=59.3, 95% CI [74.7, 116.1]).

DISCUSSION

We conducted the first meta-analysis of the ASD male-to-female ratio based on a systematic review of epidemiological prevalence studies, reported according to PRISMA guidelines. The overall weighted male-to-female odds ratio (4.20, 95% CI [3.84, 4.60]), derived from 54 prevalence studies, was consistent with *DSM-5*'s assertion that amongst diagnosed cases, there are four males for every female on the autism spectrum.[1] However, there was significant and very substantial variability amongst the 54 studies, which calls into question the validity of this overall estimate of the male-to-female ratio in ASD.

A different picture emerged when we only looked at studies likely to yield the most valid estimates of the male-to-female odds ratio, namely those with the highest methodological quality (3.32, 95% CI [2.88, 3.84]) and those that used active case-ascertainment methods (3.25, 95% CI [2.92, 3.61]). In these subgroups, male-to-female odds ratios were lower, and there was consistency between studies, with no significant heterogeneity observed. Accordingly, we argue that the current consensus that in ASD there is a 4-to-1 male-to-female ratio is inaccurate: the true male-to-female ratio for ASD is lower, below 3.5-to-1.

The contrast between active and passive case ascertainment studies is especially instructive. In studies that actively sought cases of ASD, regardless of whether they had already been identified by clinical or educational services, there were on average 24 girls per 100 cases of ASD (calculated from the male-to-female odds ratio of 3.25). By contrast, in

passive studies, which only identify cases if they have already been diagnosed by services, there were 18 females per 100 ASD cases. This could arise because there are girls in the general population who, if assessed, would meet criteria for ASD, but who do not in practice receive a clinical diagnosis. Consistent with this interpretation is our observation that active studies tended to identify more female ASD cases than did passive studies. Our findings compliment and extend evidence elsewhere that suggests girls with autism are at greater risk than boys of having their ASD overlooked,[71] misdiagnosed,[7,72] or identified late.[14] It is also notable that the lower male-to-female ratio in active studies was partially driven by a lower prevalence of male ASD cases, compared to passive case ascertainment studies. One possible interpretation of this is that active studies were more liable to miss male cases. An alternative interpretation is that passive studies, which rely on pre-existing diagnoses, over-estimate the prevalence of ASD in males.

There is a need to formulate and counter the gender bias that leads to some girls with autism missing out on a timely diagnosis and the accompanying support. One likely influence is the female autism phenotype, a female-specific autism presentation that is subtly distinct from conventional conceptualisations of the disorder.[12] In particular, compared to males, females with autism are less likely to show overt restricted interests, which would reduce the chances of their autism being identified.[73] Further, there is some emerging evidence that females are more likely to mask their autistic difficulties, via a process known as camouflaging, making timely, accurate diagnosis more challenging.[7,12] Another factor potentially contributing to the diagnostic bias could be key professionals (teachers, family doctors, paediatricians, psychiatrists, psychologists, etc.) holding gender stereotypes that ASD is a male disorder, reducing their sensitivity to autistic symptoms when they occur in females.[7] Future research should address whether the diagnostic bias against females can be

11

reduced by increasing knowledge of the female autism phenotype, and conveying this information to diverse professionals involved in case identification.

We found evidence for a diagnostic bias against girls who meet criteria for ASD. It has been proposed that an additional, nosological bias exists, whereby some females who have severe autistic traits (i.e. social, communication, sensory, and flexibility difficulties) fail to meet diagnostic criteria for ASD because these lack sensitivity to the female phenotype.[12] Evidence for this idea comes from the contrast between the male-to-female ratio we observed for diagnosable cases (a little over three-to-one) and the male-to-female ratio for people who score high for autistic traits on parent-report measures, which is commonly observed to be two-to-one or lower.[74,75] Thus there are a disproportionate number of females who score high on measures of autistic traits, but who do not, even if carefully assessed, have ASD according to current diagnostic criteria. It is important to study such individuals, to discover if they really do have ASD that is being missed by male-centric diagnostic criteria, or whether instead their high scores on measures of autistic traits actually reflect different, non-autistic difficulties, such as anxiety, depression, or low IQ.[76]

We found that lower IQ was associated with a lower male-to-female ratio.[13] This result should be treated with caution, given that it is based on only the subgroup of studies (24/54) that provided sufficient IQ information. Further, this systematic review was not designed to engage fully with the challenges of measuring IQ amongst people with autism, and of assessing autism amongst people with intellectual disability. Nevertheless, our finding of there being proportionally more females in lower-IQ ASD samples does accord with other observations in clinical samples.[13] It could arise because IQ is more protective against ASD in females than in males, thus making females with normal-range IQ and diagnosable ASD relatively rare.[76] An alternative explanation is that high-functioning females with ASD are "flying under the radar," their difficulties especially likely to be missed by current diagnostic

rubric and methods, due to them having a subtler, female-specific phenotype; and a greater capacity to camouflage their difficulties.[77,78]

It is important to acknowledge that our findings are exclusively based on studies using *DSM-IV*, *DSM-IV-TR,* and *ICD-10* criteria, as there are not yet *DSM-5* ASD prevalence studies in the literature. Some have expressed concern that the changes to ASD diagnostic criteria ushered in by the publication of *DSM-5* may have reduced their sensitivity to females with the condition, thus further inflating the male-to-female ratio of diagnosed cases.[79] However, empirical work has tended to contradict this idea by showing a similar male-to-female ratio for cases identified by *DSM-IV* and *DSM-5* criteria.[80,81] Therefore, it is likely that our findings generalise to samples diagnosed according to *DSM-5* rules, but it will be important to continue to monitor the gender ratio as *DSM-5*-based epidemiological studies are published. We only included studies of childhood and adolescence. As the literature on adult autism prevalence grows, it will be valuable to include this in future reviews. One possibility is that the male–female ratio diminishes in adulthood, as women with ASD who were missed in childhood refer themselves for assessment and self-report symptoms.[15]

Whilst we have argued that the male-to-female ratio in ASD is lower than previously assumed, it is worth stating that our findings clearly confirm the basic fact that males are more vulnerable to ASD than are females. This underlines the value of research that seeks to explain greater male vulnerability, for example by considering the role of sex hormones[4] and sex effects on genetic risk.[5] Nevertheless, this meta-analysis supports the view, expressed by members of the autism community[82] and by clinicians,[83] that there is a need to improve systems for the timely detection of ASD in females.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual, Fifth Edition (DSM-5). Arlington, VA: American Psychiatric Association: 2013.

2. Mandy W, Lai M-C. Annual Research Review: The role of the environment in the developmental psychopathology of autism spectrum condition. J Child Psychol Psychiatry. 2016;57:271-92.

3. Baird G, Simonoff E, Pickles A, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet. 2006;368:210-5.

4. Baron-Cohen S. The extreme male brain theory of autism. Trends in Cogn Sci. 2002;6:248-54.

5. Jacquemont S, Coe BP, Hersch M, et al. A Higher Mutational Burden in Females Supports a "Female Protective Model" in Neurodevelopmental Disorders. Am J Hum Genet. 2014;94:415-25.

6. Kopp S, Gillberg C. Girls with social deficits and learning problems: Autism, atypical Asperger syndrome or a variant of these conditions. Eur Child and Adolesc Psychiatry. 1992;1:89–99.

7. Bargiela S, Steward R, Mandy W. The Experiences of Late-diagnosed Women with Autism Spectrum Conditions: An Investigation of the Female Autism Phenotype. J Autism Dev Disord. 2016;46:3281-94.

8. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res. 2009;65:591-8.

9. Icasiano F, Hewson PH, Machet P, Cooper C, Marshall A. Childhood autism spectrum disorder in the Barwon region: A community based study. J Paediatr Child Health. 2004;40:696-701.

10. Fombonne E, Du Mazaubrun C, Cans C, Grandjean H. Autism and associated medical disorders in a French epidemiological survey. J Am Acad Child Adolesc Psychiatry. 1997;36:1561-9.

11. Medical Research Council. *MRC review of autism research: Epidemiology and causes*. London: Author; 2001.

12. Lai M-C, Lombardo MV, Auyeung B, Chakrabarti B, Baron-Cohen S. Sex/Gender Differences and Autism: Setting the Scene for Future Research. J Am Acad Child Adolesc Psychiatry. 2015;54:11-24.

13. Volkmar FR, Szatmari P, Sparrow SS. Sex-differences in Pervasive Developmental Disorders. J Autism Dev Disord. 1993;23:579-91.

14. Giarelli E, Wiggins LD, Rice CE, et al. Sex differences in the evaluation and diagnosis of autism spectrum disorders among children. Disabil Health J. 2010;3:107-16.

15. Rutherford M, McKenzie K, Johnson T, et al. Gender ratio in a clinical population sample, age of diagnosis and duration of assessment in children and adults with autism spectrum disorder. Autism. 2016;20:628-34.

16. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65:934-9.

17. McGraw KO, Wong SP. Forming inferences about some intraclass correlations coefficients. Psych Method. 1996;1:30–46.

18. Lipsey M, Wilson D. Practical Meta-analysis. Thousand Oaks, CA: Sage Publications; 2001.

19. Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Series a-Stat Soc. 2009;172:137-59.

20. Harbord RM, Egge M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med. 2006;25:3443-57.

21. Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. The incidence of autism in Olmsted County, Minnesota, 1976-1997 Results from a population-based study. Arch Pediatr Adolesc Med. 2005;159:37-44.

22. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P. Prevalence of autism in a United States population: The Brick Township, New Jersey, investigation. Pediatrics. 2001;108:1155-61.

23. Center for Disease Control. Prevalence of autism spectrum disorders–autism and developmental disabilities monitoring network, six sites, United States 2000. MMWR Surveill Summ. 2007;56:1–11.

24. Center for Disease Control. Prevalence of autism spectrum disorders-autism and developmental disabilities monitoring network, 14 sites, United States 2002. MMWR Surveill Summ. 2007;56:12–28.

25. Center for Disease Control. Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring network, United States, 2006. MMWR Surveill Summ. 2009;58:1–14.

26. Center for Disease Control. Prevalence of autism spectrum disorders – autism and developmental disabilities monitoring network, 14 sites, United States, 2008. MMWR Surveill Summ. 2012;61:1–19.

27. Center for Disease Control. Prevalence of autism spectrum disorders – autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveill Summ 2014;63:1–20.

28. Kogan MD, Blumberg SJ, Schieve LA, et al. Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007. Pediatrics. 2009;124:1395-403.

29. Nicholas JS, Carpenter LA, King LB, Jenner W, Charles JM. Autism Spectrum Disorders in Preschool-Aged Children: Prevalence and Comparison to a School-Aged Population. Ann Epidemiol. 2009;19:808-14.

30. Windham GC, Anderson MC, Croen LA, Smith KS, Collins J, Grether JK. Birth prevalence of autism spectrum disorders in the San Francisco Bay area by demographic and ascertainment source characteristics. J Autism Dev Disord. 2011;41:1362-72.

31. Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. J Am Med Assoc. 2003;289:49-55.

32. Fombonne E, Zakarian R, Bennett A, Meng L, McLean-Heywood D. Pervasive developmental disorders in Montreal, Quebec, Canada: Prevalence and links with immunizations. Pediatrics. 2006;118:e139-e50.

33. Lazoff T, Zhong L, Piperni T, Fombonne E. Prevalence of pervasive developmental disorders among children at the English Montreal school board. Can J Psychiatry. 2010;55:715-20.

34. Ouellette-Kuntz H, Coo H, Lloyd JE, Kasmara L, Holden JJ, Lewis ME. Trends in special education code assignment for autism: implications for prevalence estimates. J Autism Dev Disord. 2007;37:1941-8.

35. Baird G, Charman T, Baron-Cohen S, et al. A screening instrument for autism at 18 months of age: A 6-year follow-up study. J Am Acad Child Adolesc Psychiatry. 2000;39:694-702.

36. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children. J Am Med Assoc. 2001;285:3093-9.

37. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children: Confirmation of high prevalence. Am J Psychiatry. 2005;162:1133-41.

38. Fombonne E, Simmons H, Ford T, Meltzer H, Goodman R. Prevalence of pervasive developmental disorders in the British nationwide survey of child mental health. J Am Acad Child Psychiatry. 2001;40:820-7.

39. Harrison MJ, O'Hare AE, Campbell H, Adamson A, McNeillage J. Prevalence of autistic spectrum disorders in Lothian, Scotland: An estimate using the "capture-recapture" technique. Arch Dis Child. 2006;91:16-9.

40. Russell G, Rodgers LR, Ukoumunne OC, Ford T. Prevalence of parent-reported ASD and ADHD in the UK: Findings from the Millennium Cohort Study. J Autism Dev Disord. 2014;44:31-40.

41. Sun X, Allison C, Auyeung B, Baron-Cohen S, Brayne C. Parental concerns, socioeconomic status, and the risk of autism spectrum conditions in a population-based study. Res Dev Disabil. 2014;35:3678-88.

42. Taylor B, Jick H, MacLaughlin D. Prevalence and incidence rates of autism in the UK: Time trend from 2004-2010 in children aged 8 years. BMJ Open. 2013;3:e003219.

43. Tebruegge M, Nandini V, Ritchie J. Does routine child health surveillance contribute to the early detection of children with pervasive developmental disorders? - An epidemiological fstudy in Kent, U.K. BMC Pediatr. 2004;4:4-10.

44. Totsika V, Hastings RP, Emerson E, Lancaster GA, Berridge DM. A population-based investigation of behavioural and emotional problems and maternal mental health: associations with autism spectrum disorder and intellectual disability. J Child Psychol Psychiatry. 2011;52:91-9.

45. Williams E, Thomas K, Sidebotham H, Emond A. Prevalence and characteristics of autistic spectrum disorders in the ALSPAC cohort. Dev Med Child Neurol. 2008;50:672-7.

46. Arvidsson T, Danielsson B, Forsberg P, Gillberg C, Johansson M, Kjellgren G. Autism in 3-6 year old children in a suburb of Goteborg, Sweden. Autism. 1997;1:163-173.

47. Idring S, Rai D, Dal H, et al. Autism spectrum disorders in the Stockholm youth cohort: Design, prevalence and validity. PLoS ONE. 2012;7(7):e41280.

48. Fernell E, Gillberg C. Autism spectrum disorder diagnoses in Stockholm preschoolers. Res Dev Disabil. 2010;31:680-5.

49. Nygren G, Cederlund M, Sandberg E, et al. The prevalence of autism spectrum disorders in toddlers: a population study of 2-year-old Swedish children. J Autism Dev Disord. 2012;42:1491-7.

50. Ellefsen A, Kampmann H, Billstedt E, Gillberg I, Gillberg C. Autism in the Faroe Islands. An epidemiological study. J Autism Dev Disord. 2007;37:437-44.

51. Nordenbaek C, Jorgensen M, Kyvik KO, Bilenberg N. A Danish population-based twin study on autism spectrum disorders. Eur Child and Adolesc Psychiatry. 2014;23:35-43.

52. Parner ET, Thorsen P, Dixon G, et al. A comparison of autism prevalence trends in Denmark and Western Australia. J Autism Dev Disord. 2011;41:1601-8.

53. Isaksen J, Diseth TH, Schjolberg S, Skjeldal OH. Observed prevalence of autism spectrum disorders in two Norwegian counties. Eur J Paediatr Neurol. 2012;16:592-8.

54. Sponheim E, Skjeldal O. Autism and related disorders: Epidemiological findings in a Norwegian study using ICD-10 diagnostic criteria. J Autism Dev Disord. 1998;28:217-27.

55. Suren P, Bakken IJ, Aase H, et al. Autism Spectrum Disorder, ADHD, Epilepsy, and Cerebral Palsy in Norwegian Children. Pediatrics. 2012;130(1):E152-E8.

56. Saemundsen E, Magnusson P, Georgsdottir I, Egilsson E, Rafnsson V. Prevalence of autism spectrum disorders in an Icelandic birth cohort. BMJ Open. 2013;3(6):e002748.

57. Oliveira G, Ataide A, Marques C, et al. Epidemiology of autism spectrum disorder in Portugal: prevalence, clinical characterization, and medical conditions. Dev Med Child

Neurol. 2007;49:726-33.

58. Honda H, Shimizn Y, Imai M, Nitto Y. Cumulative incidence of childhood autism: a total population study of better accuracy and precision. Dev Med Child Neurol. 2005;47:10-8.

59. Honda H, Shimizu Y, Misumi K, Niimi M. Cumulative incidence and prevalence of childhood autism in children in Japan. Br J Psychiatry. 1996;169:228-35.

60. Kawamura Y, Takahashi O, Ishii T. Reevaluating the incidence of pervasive developmental disorders: Impact of elevated rates of detection through implementation of an integrated system of screening in Toyota, Japan. Psychiatry Clin Neurosci. 2008;62:152-9.

61. Huang JP, Cui SS, Han Y, Irva HP, Qi LH, Zhang X. Prevalence and early signs of autism spectrum disorder (ASD) among 18-36 month old children in Tianjin of China. Biomed Environ Sci. 2014;27:453-61.

62. Zhang X, Ji CY. Autism and mental retardation of young children in China. Biomed Environ Sci. 2005;18:334-40.

63. Davidovitch M, Hemo B, Manning-Courtney P, Fombonne E. Prevalence and incidence of autism spectrum disorder in an Israeli population. J Autism Dev Disord. 2013;43:785-93.

64. Raz R, Weisskopf MG, Davidovitch M, Pinto O, Levine H. Differences in autism spectrum disorders incidence by sub-populations in Israel 1992-2009: A total population study. J Autism Dev Disord. 2015;45:1062-9.

65. Samadi SA, Mahmoodizadeh A, McConkey R. A national study of the prevalence of autism among five-year-old children in Iran. Autism. 2012;16:5-14.

66. Al-Farsi YM, Al-Sharbati MM, Al-Farsi OA, Al-Shafaee MS, Brooks DR, Waly MI. Brief Report: Prevalence of Autistic Spectrum Disorders in the Sultanate of Oman. J Autism Dev Disord. 2011;41:821-5.

67. Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, Cheon KA, et al. Prevalence of autism spectrum disorders in a total population sample. Am J Psychiatry. 2011;168:904-12.

68. Lai DC, Tseng YC, Hou YM, Guo HR. Gender and geographic differences in the prevalence of autism spectrum disorders in children: Analysis of data from the national disability registry of Taiwan. Res Dev Disabil. 2012;33:909-15.

69. van Balkom ID, Bresnahan M, Vogtlander MF, et al. Prevalence of treated autism spectrum disorders in Aruba. J Neurodev Disord. 2009;1:197-204.

70. Montiel-Nava C, Pena JA. Epidemiological findings of pervasive developmental disorders in a Venezuelan study. Autism. 2008;12:191-202.

71. Russell G, Steer C, Golding J. Social and demographic factors that influence the diagnosis of autistic spectrum disorders. Soc Psychiatry Psychiatr Epidemiol. 2011;46:1283-93.

72. Mandy W, Tchanturia K. Do women with eating disorders who have social and flexibility difficulties really have autism? A case series. Mol Autism. 2015;6:6-16.

73. Frazier TW, Georgiades S, Bishop SL, Hardan AY. Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. J Am Acad Child Adolesc Psychiatry. 2014;53:329-40.e1-3.

74. Constantino JN, Todd RD. Autistic traits in the general population: A twin study. Arch Gen Psychiatry. 2003;60:524-30.

75. Constantino JN, Zhang Y, Frazier T, Abbacchi AM, Law P. Sibling recurrence and the genetic epidemiology of autism. Am J Psychiatry. 2010;167:1349-56.

76. Skuse DH, Mandy W, Steer C, et al. Social communication competence and functional adaptation in a general population of children: Preliminary evidence for sex-by-verbal IQ differential risk. J Am Acad Child Adolesc Psychiatry. 2009;48:128-37.

77. Dworzynski K, Ronald A, Bolton P, Happe F. How Different Are Girls and Boys Above and Below the Diagnostic Threshold for Autism Spectrum Disorders? J Am Acad Child Adolesc Psychiatry. 2012;51:788-97.

78. Mandy W, Chilvers R, Chowdhury U, Salter G, Seigal A, Skuse D. Sex Differences in Autism Spectrum Disorder: Evidence from a Large Sample of Children and Adolescents. J Autism Dev Disord. 2012;42:1304-13.

79. Mandy W, Charman T, Gilmour J, Skuse D. Toward Specifying Pervasive Developmental Disorder-Not Otherwise Specified. Autism Res. 2011;4:121-31.

80. Huerta M, Bishop SL, Duncan A, Hus V, Lord C. Application of DSM-5 Criteria for Autism Spectrum Disorder to Three Samples of Children With DSM-IV Diagnoses of Pervasive Developmental Disorders. Am J Psychiatry. 2012;169:1056-64.

81. McPartland JC, Reichow B, Volkmar FR. Sensitivity and Specificity of Proposed DSM-5 Diagnostic Criteria for Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry. 2012;51(4):368-83.

82. Pellicano E, Dinsmore A, Charman T. What should autism research focus upon? Community views and priorities from the United Kingdom. Autism. 2014;18:756-70.

83. Attwood T. The Complete Guide to Asperger's Syndrome. London: Jessica Kingsley Publishers; 2006.

Figure Captions

Figure 1. Flow diagram of study selection, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Note: ASD = autism spectrum disorder; *ICD-10 = International Classification of Diseases–10th Revision.*

Figure 2. Male-to-female odds ratio in autism spectrum disorder for active versus passive case ascertainment. Note: weights are from random effects analysis. OR = odds ratio.

Table 1 –Subgroup Meta-Analyses of Male-to-Female Odds Ratio (OR) in Autism Spectrum Disorder

Analysis	N of studies	Pooled OR	95% CIs	χ^2	Heterogeneity p	I^2
All studies	54	4.20	3.84 – 4.60	585.19	<.001	90.9%
Risk of bias						
Low risk of bias	17	3.32	2.88 – 3.84	19.14	.260	16.4%
Higher risk of bias	37	4.41	3.99 - 4.89	544.39	<.001	93.4%
Case ascertainment						
Active	20	3.25	2.93- 3.62	16.43	.628	0.0%
Passive	34	4.56	4.10 – 5.07	540.73	<.001	93.9%
Average age of participants						
0 to 6 years	14	4.04	3.56-4.59	22.35	0.050	41.8%
>6 years to 18 years	40	4.26	3.83 - 4.74	562.47	<.001	93.1%
Intellectual disability						
At least half with IQ 70 or below	10	3.10	2.50 - 3.85	23.12	0.006	61.1%
Less than half with IQ 70 or below	14	4.25	3.33 - 5.43	68.62	<.001	81.1%
Date of study						
1992 to 2001	17	3.51	2.90 - 4.26	56.90	<.001	71.5%
2002 to 2011	37	4.45	4.01 - 4.94	506.56	<.001	92.9%

23

Table 2 - Meta-Regressions Investigating Study Characteristics That Predict Variability in the Male-to-Female Odds Ratio (OR)

	N	Unadjusted association with log of male-to-female OR		Adjusted association with log of male-to-female OR		
		B (SE) [95% CIs]	P	B (SE) [95% CIs]	P	Control variable(s)
Risk of bias total score	54	.068 (.033) [.001, .135]	.046	-.001 (.043) [-.090, .086]	.965	Case ascertainment
Case ascertainment (active=1, passive=0)	54	-.306 (.096) [-.499, -.112]	.003	-.310 (.133) [-.577, -.042]	.024	Risk of bias total score
Age of individuals with ASD	54	.001 (.022) [-.044, .045]	.971	-	-	-
Proportion of individuals with ASD and ID	24	.009 (.004) [.001, .018]	.034	.012 (.005) [.002, .023]	.021	Date of study
Date of study (1992-2011)	54	.020 (.009) [.002, .037]	.033	-.022 (.021) [-.066, .021]	.285	Proportion individuals with ID

Note: ASD = autism spectrum disorder; ID = intellectual disability

Study ID	OR (95% CI)	% Weight
Active Case Ascertainment		
Honda (1996) [58]	2.44 (0.87, 6.85)	0.61
Arvidsson (1997) [46]	3.17 (0.66, 15.29)	0.30
Sponheim (1998) [54]	2.09 (1.02, 4.29)	1.04
Chakrabarti (2001) [36]	4.03 (2.44, 6.67)	1.54
Bertrand (2001) [22]	2.87 (1.62, 5.10)	1.35
Honda (2005) [58]	2.49 (1.59, 3.88)	1.72
Chakrabarti (2005) [37]	6.05 (2.98, 12.26)	1.06
Zhang (2005) [62]	6.10 (0.75, 49.62)	0.18
Baird (2006) [3]	3.28 (2.27, 4.74)	1.97
Oliveira (2007) [57]	2.88 (1.91, 4.33)	1.84
Ellefsen (2007) [50]	5.72 (2.41, 13.63)	0.80
Kawamura (2008) [60]	2.77 (2.06, 3.72)	2.23
Kim (2011) [67]	3.40 (2.44, 4.73)	2.11
Totsika (2011) [44]	4.37 (2.62, 7.29)	1.52
Samadi (2012) [65]	4.01 (3.00, 5.37)	2.25
Nygren (2012) [49]	4.04 (1.86, 8.78)	0.93
Saemundsen (2013) [56]	2.69 (2.05, 3.54)	2.31
Huang (2014) [61]	4.21 (1.42, 12.44)	0.57
Nordenbaek (2014) [51]	3.93 (1.96, 7.89)	1.08
Sun (2014) [41]	3.19 (1.62, 6.30)	1.11
Subtotal (I-squared = 0.0%, p = 0.628)	3.25 (2.92, 3.62)	26.52
.		
Passive Case Ascertainment		
Fombonne (1997) [10]	1.81 (1.32, 2.46)	2.18
Baird (2000) [35]	7.61 (4.06, 14.29)	1.22
Fombonne (2001) [38]	8.06 (2.42, 26.77)	0.48
Yeargin-Allsopp (2003) [31]	3.87 (3.31, 4.52)	2.69
Icasiano (2004) [9]	8.36 (5.19, 13.46)	1.62
Tebruegge (2004) [43]	6.07 (1.78, 20.66)	0.46
Barbaresi (2005) [21]	3.29 (2.17, 4.98)	1.81
Fombonne (2006) [32]	4.85 (3.29, 7.14)	1.91
Harrison (2006) [39]	7.00 (5.24, 9.33)	2.26
CDC (2007b) [24]	4.19 (3.80, 4.61)	2.83
CDC (2007a) [23]	3.51 (3.07, 4.01)	2.75
Ouellette-Kuntz (2007) [34]	5.26 (4.44, 6.23)	2.65
Williams (2008) [45]	6.88 (3.65, 12.97)	1.21
Montiel-Nava (2008) [70]	3.13 (2.50, 3.91)	2.48
Kogan (2009) [28]	4.19 (3.54, 4.96)	2.65
CDC (2009) [25]	4.68 (4.24, 5.16)	2.82
Nicholas (2009) [29]	4.76 (2.48, 9.11)	1.17
van Balkom (2009) [69]	6.72 (3.33, 13.55)	1.07
Fernell (2010) [48]	4.92 (3.17, 7.62)	1.74
Lazoff (2010) [33]	5.47 (3.68, 8.14)	1.88
Parner (2011a) [52]	4.99 (4.44, 5.61)	2.78
Windham (2011) [30]	6.19 (4.59, 8.34)	2.22
Parner (2011b) [52]	4.87 (3.99, 5.95)	2.56
Al-Farsi (2011) [66]	2.71 (1.78, 4.14)	1.79
CDC (2012) [26]	4.71 (4.34, 5.12)	2.85
Isaksen (2012) [53]	5.06 (3.32, 7.71)	1.79
Suren (2012) [55]	4.10 (3.70, 4.55)	2.81
Idring (2012) [47]	2.51 (2.36, 2.67)	2.88
Lai (2012) [68]	6.08 (5.70, 6.49)	2.88
Davidovitch (2013) [63]	4.93 (4.38, 5.55)	2.78
Taylor (2013) [42]	4.80 (3.88, 5.95)	2.52
Russell (2014) [40]	5.41 (3.73, 7.86)	1.96
CDC (2014) [27]	4.58 (4.27, 4.92)	2.87
Raz (2015) [64]	4.85 (4.58, 5.12)	2.89
Subtotal (I-squared = 93.9%, p = 0.000)	4.56 (4.10, 5.07)	73.48
.		
Overall (I-squared = 90.9%, p = 0.000)	4.20 (3.84, 4.60)	100.00