REVIEW

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

Objective: To derive the first systematically calculated estimate of the relative proportion of boys and girls with autism spectrum disorder (ASD) through a meta-analysis of prevalence studies conducted since the introduction of the *DSM-IV* and the *International Classification of Diseases, Tenth Revision*.

Method: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. The Medline, Embase, and PsycINFO databases were searched, and study quality was rated using a risk-of-bias tool. Random-effects meta-analysis was used. The pooled outcome measurement was the male-to-female odds ratio (MFOR), namely the odds of being male in the group with ASD compared with 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 analyzed, with 13,784,284 participants, of whom 53,712 had ASD (43,972 boys and 9,740 girls). 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: Of children meeting criteria for ASD, the true male-to-female ratio is not 4:1, as is often assumed; rather, it is closer to 3:1. 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

J Am Acad Child Adolesc Psychiatry 2017;56(6):466–474.

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impairments in social reciprocity and social communication and restricted, repetitive patterns of behavior.[1] It is highly heritable, persists across the lifespan, and affects approximately 1% of the population.[2,3] One striking and consistent feature of ASD is that it is more commonly diagnosed in boys than in girls.[1] This has motivated influential ideas about the nature and etiology 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 boys 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 in part on their gender.[7] As such, it is important to have a systematically derived, precise estimate of the male-to-female ratio in ASD 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 4:1 gender ratio is widely cited and comes from work that calculated the mean male-to-female ratio from population prevalence studies of ASD.[8] Although such estimates are useful as a rough guide to the male-to-female ratio in ASD, they do not use meta-analysis to synthesize 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 epidemiologic studies that implemented similar inclusion criteria and recruitment methods, ASD male-to-female ratios show striking variability, ranging from 8:1[9] to 2:1.[10] This heterogeneity is currently little studied and therefore poorly understood. Its investigation will be instructive about the true ratio of boys to girls with ASD and can elucidate whether there are, as is often suggested, diagnostic biases against girls 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, then particular weight should be given to studies with the greatest methodologic

Supplemental material cited in this article is available online.

merit, because 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. In contrast, passive case-finding studies review existing databases (e.g., medical or special educational records) or contact parents by mass-telephone surveys to discover who within a given population has received an ASD diagnosis.[11] Such approaches are considered passive because they pick up only those who have already been officially identified. We argue that active methods will yield more valid estimates of the male-to-female ratio, because 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 girls 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 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 larger among people with higher IQ.[13] However, to date, this has not been formally tested using meta-analysis.
5. Participant age. Girls with ASD tend to receive their diagnosis later than boys,[14] so the male-to-female ratio could be higher in younger samples.

In summary, the present systematic review sought to investigate the relative proportion of boys and girls on the autism spectrum by a meta-analysis of published prevalence studies. The initial aim was to ascertain the first systematically derived, weighted, pooled estimate of the male-to-female ratio of ASD. The second aim was to enhance understanding of the true ASD male-to-female ratio by investigating the effects of study quality, active versus passive case ascertainment, date of study, participant IQ, and 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, Tenth Revision* (*ICD-10*) criteria. This was designed to maximize generalizability to current practice.
3. Information provided on numbers of girls and boys with ASD and overall size of population studied to enable calculation of the primary outcome measurement for this meta-analysis.
4. Year(s) of data collection reported.
5. Age range of sample from 0 to 18 years. It was decided to exclude studies of prevalence in adults with ASD because such research is currently rare, and ASD gender ratios for adults could be different from those in child and adolescent populations.[15]

Information Sources and Search

Figure 1 shows the process by which articles were identified. A systematic search was conducted on September 23, 2015 using the Medline, Embase, and PsycINFO databases. These searches combined keywords, Medical Subject Heading 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 blinded 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 the inclusion criteria. There was perfect (i.e., 100%) agreement between the initial and second (blinded) raters about which of these articles met the inclusion criteria for this review.

Data Extraction

The first (R.L.) and second (L.H.) authors independently extracted data from all articles identified as meeting the study criteria using a coding sheet designed for the present 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 methodologic features of prevalence studies, which consists of 10 items plus a summary assessment. Items 1 to 4 assess external validity, and items 5 to 10 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 blindly double-rated by the first and second authors. Inter-rater reliability for the total RoBT score, calculated using Case 2A intraclass correlations, to assess levels of absolute agreement[17] was high (intraclass correlation 0.93; 95% CI 0.89–0.96). 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, then the senior author (W.P.L.M.) was consulted.

Data Analysis

The outcome measurement summarized in this meta-analysis was the odds ratio (OR) describing the odds of being male in the group with ASD compared with the odds of being male in the group without ASD. This was termed the "male-to-female odds ratio" (MFOR). In effect, this presents the male-to-female ratio among those with ASD, controlling for the male-to-female ratio among participants without ASD. This MFOR is a purer measurement of the ASD gender ratio than simply calculating a male-to-female