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

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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.

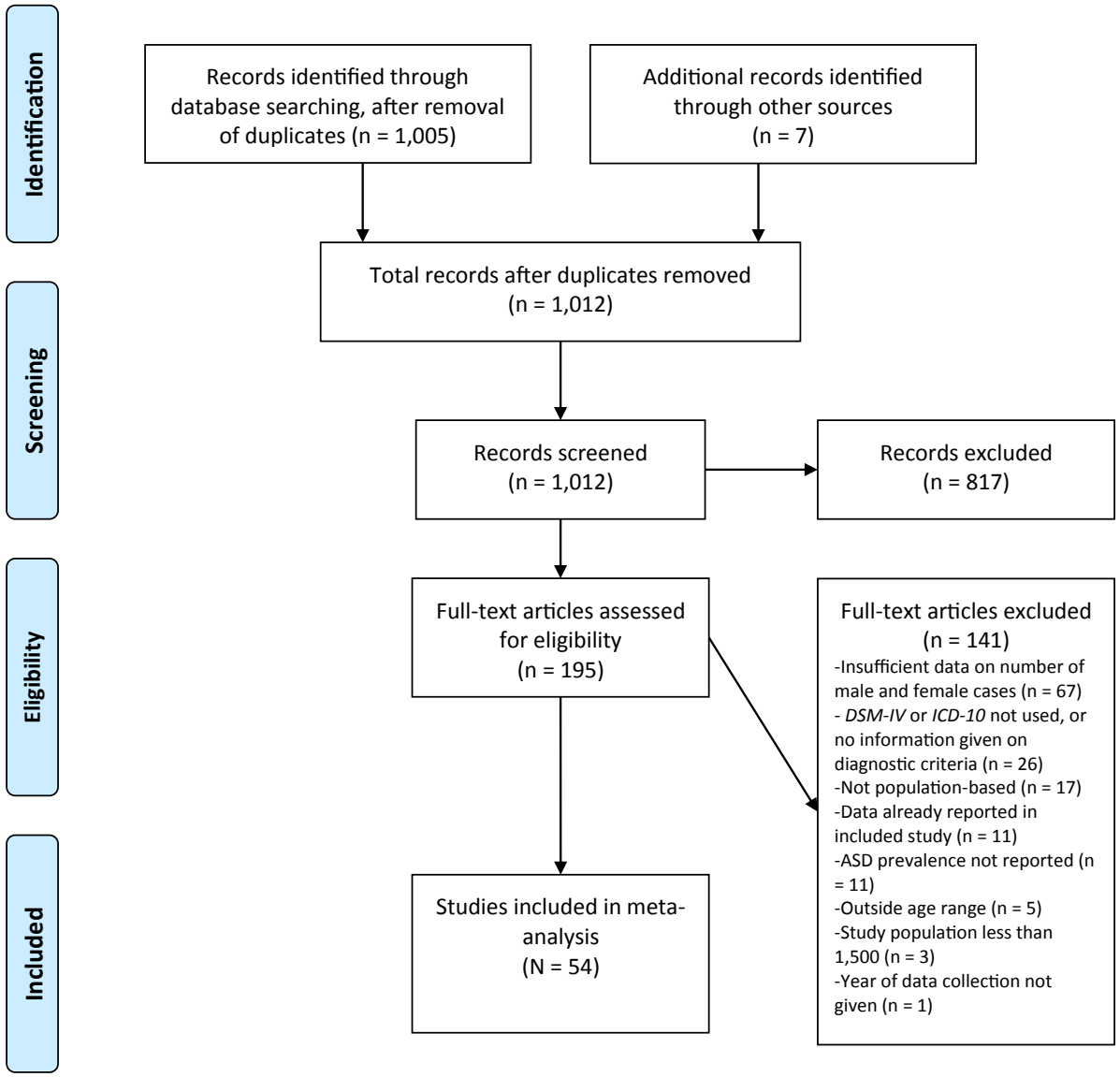
Assessing Risk of Bias

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

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



ratio for diagnosed cases, because 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 (STATA Corp., College Station, TX) command "metan" was used to conduct a random-effects meta-analysis using the DerSimonian-Laird procedure to derive a pooled MFOR and 95% CIs. The I^2 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 indicate 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, and age of sample) were regressed separately against the log of the MFOR. Where a significant association was found, we checked for potential confounds (i.e., other study characteristic variables that were significantly associated with 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: low versus medium to higher risk of bias; passive versus active case ascertainment; older (1992–2001) versus more recent (2002–2011) studies; lower IQ (>50% of those with ASD had intellectual disability) versus higher IQ (≤50% of those with ASD had intellectual disability); and younger (0–6 years) versus older (6–18 years) participants.

RESULTS

Overview

Figure 1 depicts the process by which studies were identified. Fifty-four met the inclusion criteria, consisting of 13,784,284 participants, 53,712 of whom were diagnosed with ASD (43,972 boys and 9,740 girls). Details of each study, including total risk-of-bias score, are presented in Table S1 (available online). Fourteen studies were conducted in North America, with 11 taking place in the United States[21-31] and 3 in Canada.[32-34] Twenty-four were European, with 12 carried out in the United Kingdom,[3,35-45] and the other 13 being carried out in Sweden,[46-49] Denmark,[50-52] Norway,[53-55] France,[10] Iceland,[56] and Portugal.[57] There were 11 Asian studies from Japan,[58-60] China,[61-62] Israel,[63-64] Iran,[65] Oman,[66] South Korea,[67] and Taiwan.[68] There were 2 studies from South America, conducted in Aruba[69] and Venezuela,[70] and 2 from Australia.[9,52] The studies spanned a period of 19 years (1992–2011). The average estimated ASD prevalence across all studies was 61.9 per 10,000 (standard deviation [SD] 48.5; 95% CI 48.6–75.1).

Risk of Bias and Case Ascertainment

Overall, the methodologic 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, most 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 5 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 (score 0–2, i.e., below the average score) and 37 studies as having a medium or higher risk of bias (score 35). Twenty studies used active case ascertainment, with the remaining 34 using passive case ascertainment.

Age and IQ of Young People With ASD

Only half the studies (n = 27 of 54) reported the average age of the participants with ASD they identified (mean 7.45 years, SD 2.91 years). 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 reported average age of individuals with ASD ($r = 0.98$, $p < .001$). There were 24 studies that provided sufficient information for the proportion of participants with an intellectual disability (i.e., IQ ≤70) to be derived. Among 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 categorized studies into higher IQ (≥50% of individuals with ASD had an IQ >70, n = 14) and lower IQ (<50% had an IQ >70, n = 10) groups.

MFOR in ASD

Inspection of a funnel plot and the Harbor test did not suggest evidence of publication bias ($p = .458$). As presented in Table 1, the overall pooled MFOR 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 Subgroup Meta-Analyses of Male-to-Female Odds Ratio (OR) in Autism Spectrum Disorder

				Heterogeneity		
Analysis	**Studies, n**	**Pooled OR**	**95% CI**	χ^2	*p*	I^2 (%)
All studies	54	4.20	3.84–4.60	585.19	<.001	90.9
Risk of bias						
Low	17	3.32	2.88–3.84	19.14	.260	16.4
Higher	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						
0–6 y	14	4.04	3.56–4.59	22.35	.050	41.8
>6–18 y	40	4.26	3.83–4.74	562.47	<.001	93.1
Intellectual disability						
At least half with IQ ≤70	10	3.10	2.50–3.85	23.12	.006	61.1
Less than half with IQ ≤70	14	4.25	3.33–5.43	68.62	<.001	81.1
Date of study						
1992–2001	17	3.51	2.90–4.26	56.90	<.001	71.5
2002–2011	37	4.45	4.01–4.94	506.56	<.001	92.9

Influences on the ASD MFOR

Table 2 presents the results of meta-regressions investigating which study characteristics were associated with variability in the ASD MFOR. Risk of bias, case-ascertainment method (active versus passive), proportion of participants with ASD with intellectual disability, and date of study were each individually associated with the MFOR. However, as presented in Table 2, once we identified and controlled for confounds, only IQ and case-ascertainment method (active versus 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 larger proportion of ASD cases with a co-occurring intellectual disability showed a lower MFOR. 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 studies using passive case ascertainment, the I^2 statistic indicated substantial and significant heterogeneity. In contrast, no significant heterogeneity was observed for the active case-ascertainment studies.

We sought to explore whether the lower male-to-female ratio in active studies was driven by the ascertainment of more girls 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 with 59.7 (SD 37.8; 95% CI 46.5–72.9) for passive studies. Active studies identified, on average, 24.1 per 10,000 girls (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 boys: active studies (mean 81.1, SD 62.2; 95% CI 51.9–110.2) tended to identify fewer boys per 10,000 than did passive ones (mean 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 epidemiologic prevalence studies reported according to PRISMA guidelines. The overall weighted MFOR (4.20; 95% CI 3.84–4.60), derived from 54 prevalence studies, was consistent with *DSM-5*'s assertion that among diagnosed cases, there are 4 boys for every girl on the autism spectrum.[1] However, there was significant and very substantial variability among 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 looked only at studies likely to yield the most valid estimates of the MFOR, namely those with the highest methodologic 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, MFORs 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 4:1 male-to-female ratio is inaccurate: the true male-to-female ratio for ASD is lower, that is, lower than 3.5:1.

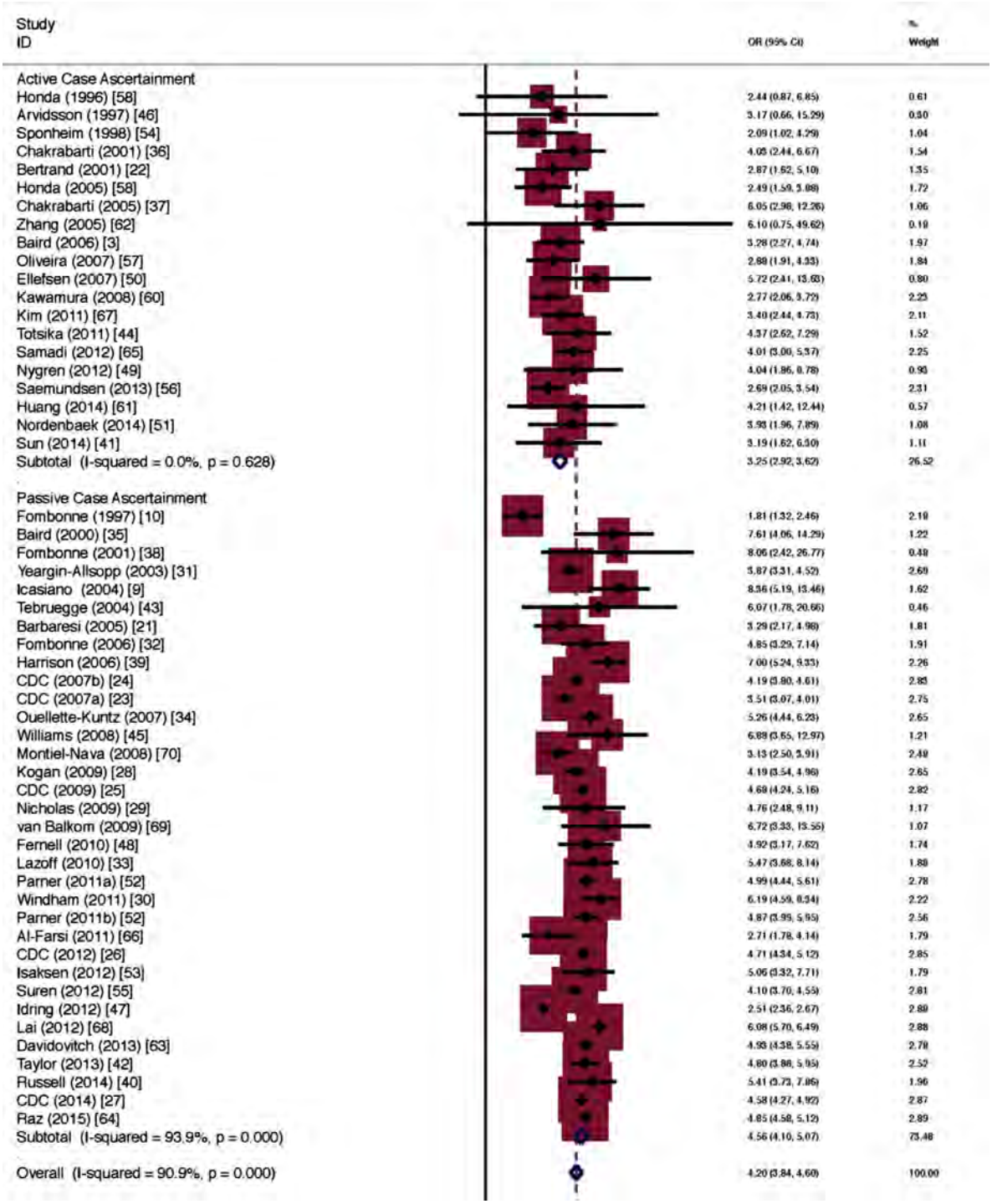
The contrast between active and passive case-ascertainment studies is especially instructive. In studies that actively sought cases of ASD, regardless of whether they had already been identified by clinical or educational services, there were on average 24 girls per 100 cases of ASD (calculated from the MFOR of 3.25). In contrast, in passive studies, which only identify cases if they have already been diagnosed by services, there were 18 girls 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 complement and extend evidence that suggests girls with autism are at greater risk than boys of having their ASD overlooked,[71]

TABLE 2 Meta-Regressions Investigating Study Characteristics That Predict Variability in Male-to-Female Odds Ratio (MFOR)

		Unadjusted Association With Log of MFOR		Adjusted Association With Log of MFOR		
	n	B (SE) [95% CI]	p	B (SE) [95% CI]	p	Control Variable(s)
Risk of bias total score	54	0.068 (0.033) [0.001 to 0.135]	.046	−0.001 (0.043) [−0.090 to 0.086]	.965	case ascertainment
Case ascertainment (active = 1, passive = 0)	54	−0.306 (0.096) [−0.499 to −0.112]	.003	−0.310 (0.133) [−0.577 to −0.042]	.024	risk-of-bias total score
Age of individuals with ASD	54	0.001 (0.022) [−0.044 to 0.045]	.971	—	—	—
Proportion of individuals with ASD and ID	24	0.009 (0.004) [0.001 to 0.018]	.034	0.012 (0.005) [0.002 to 0.023]	.021	date of study
Date of study (1992–2011)	54	0.020 (0.009) [0.002 to 0.037]	.033	−0.022 (0.021) [−0.066 to 0.021]	.285	proportion of individuals with ID

Note: ASD = autism spectrum disorder; ID = intellectual disability; SE = standard error.

FIGURE 2 Male-to-female odds ratio (OR) in autism spectrum disorder for active versus passive case ascertainment. Note: Weights are from random-effects analysis.



misdiagnosed,[7,72] or identified late.[14] It also is notable that the lower male-to-female ratio in active studies was driven in part by a lower prevalence of male ASD cases compared with 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, overestimated the prevalence of ASD in boys.

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 conceptualizations of the disorder.[12] In particular, compared with boys, girls with autism are less likely to show overt restricted interests, which would lessen the chances of their autism being identified.[73] Further, there is some emerging evidence that girls are more likely to mask their autistic difficulties by 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, pediatricians, psychiatrists, psychologists, etc.) holding gender stereotypes that ASD is a male disorder, thus decreasing their sensitivity to autistic symptoms when they occur in girls.[7] Future research should address whether the diagnostic bias against girls could be decreased 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 nosologic bias exists, whereby some girls 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 (slightly higher than 3:1) and the male-to-female ratio for people who score high for autistic traits on parent-report measurements, which is commonly observed to be no higher than 2:1.[74,75] Thus, there is a disproportionate number of girls who score high on measurements 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 whether they really do have ASD that is being missed by male-centric diagnostic criteria or whether their high scores on measurements 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, because it is based on only the subgroup of studies (24 of 54) that provided sufficient IQ information. Further, this systematic review was not designed to engage fully with the challenges of measuring IQ among people with autism and of assessing autism among people with intellectual disability. Nevertheless, our finding of there being proportionally more girls 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 girls than in boys, making girls with normal-range IQ and diagnosable ASD relatively rare.[76] An alternative explanation is that high-functioning girls 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 based exclusively on studies using *DSM-IV*, *DSM-IV-TR*, and *ICD-10* criteria, because there are no *DSM-5* ASD prevalence studies in the literature. Some have expressed concern that the changes to ASD diagnostic criteria ushered in by publication of the *DSM-5* might have decreased their sensitivity to girls 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 generalize to samples diagnosed according to *DSM-5* rules, but it will be important to continue to monitor the gender ratio as *DSM-5*–based epidemiologic studies are published. We included only 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 decreases in adulthood, as women with ASD who were missed in childhood refer themselves for assessment and self-report symptoms.[15]

Although 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 boys are more vulnerable to ASD than girls. This emphasizes 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 girls. &

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

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

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