

REVIEW

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Autism spectrum disorder in females with fragile X syndrome: a systematic review and meta-analysis of prevalence

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Abstract

Background: Whilst up to 60% of males with fragile X syndrome (FXS) meet criteria for autism spectrum disorder (ASD), the prevalence and nature of ASD in females with FXS remains unclear.

Method: A systematic literature search identified papers reporting ASD prevalence and/or symptomatology in females with FXS.

Results and conclusion: Meta-analysis suggested that rates of ASD for females with FXS are reliably higher than for females in the general population (a random effects model estimated weighted average prevalence at 14%, 95% CI 13–18%). Whilst papers highlighted a number of social and repetitive difficulties for females with FXS, characteristic profiles of impairment are not clear. Possible associations between ASD traits and IQ, and between ASD and levels of fragile X mental retardation protein, are suggested, but data are equivocal.

Keywords: Fragile X syndrome, Female, Autistic spectrum disorder, Prevalence, Meta-analysis

Background

Fragile X syndrome (FXS) is the most common inherited single-gene cause of intellectual disability and autism spectrum disorder (ASD). It is caused by a mutation on the X chromosome in the *FMR1* gene, typically due to the expansion of the CGG triplet repeat, resulting in disruption to the fragile X mental retardation protein (FMRP). FXS occurs when a person has 200 or more repeats (the full mutation); a repeat size between 55 and 200 is classified as a premutation. Cognition and behaviour are more severely affected for those with a full mutation, whose prevalence is approximately 1.4 per 10,000 males and 0.9 per 10,000 females according to a recent meta-analysis [1]. Due to the X-linked nature of the condition, females are reported to be less affected than males [2]. The increased severity of presentation in

males and the lower prevalence in females has led to underrepresentation and often exclusion of females in research.

A prominent set of behavioural/psychological features associated with FXS are characteristics associated with ASD. The prevalence of ASD in the general population is approximately 1 in 68 [3], with boys being more commonly diagnosed (1 in 42) than girls (1 in 189). Rates of ASD in those with certain genetic neurodevelopmental syndromes are considerably higher, with the nature of ASD-related behaviours also reported to vary by syndrome group (e.g. [4–6]).

More than 90% of males with FXS are reported to display autistic-like characteristics and, when using gold standard diagnostic instruments, up to 60% of males meet diagnostic criteria [7–9]. Very few researchers have included females in their samples [10]. One review [4] found the prevalence of ASD for females with FXS was 1–3%; however, this was based on only two papers with female participants. Several studies have since been

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undertaken including female participants, necessitating further review.

For FXS, results across several studies suggest that children with comorbid ASD differ in their symptoms from children with FXS only, with the former being more similar to individuals with idiopathic autism than to individuals with FXS only [11–14]. However, given the low number of female participants, it is unclear whether these findings are also observed in females with FXS and ASD [10].

Two factors potentially associated with ASD in FXS are the level of intellectual disability and FMRP levels. There have been several studies which have reported that children diagnosed with FXS and ASD have significantly lower IQ scores than individuals with FXS without autism (e.g. [11, 14–17]). Less is known about any possible connection between IQ and ASD in females with FXS. Studies assessing the potential link between individuals' level of FMRP and ASD-related behaviours have reported mixed results. Hessel et al. [18] found that FMRP did not predict autistic behaviours in those with FXS, but Hatton et al. [19] reported that lower levels of FMRP did predict higher scores for autistic behaviours. Since levels of FMRP and IQ are also correlated with each other [20, 21], the potential relationships between ASD, IQ and FMRP may be complex. However, again, the vast majority of research has been conducted with males.

The current paper presents a review of existing literature on the prevalence and nature of ASD in females with FXS. Prevalence data were meta-analysed to give a weighted average prevalence. The reported severity and nature of behaviours associated with ASD are also assessed, and we consider factors potentially associated with ASD behaviours or diagnosis, including IQ and FMRP levels.

Method

Initial search

Following PRISMA-P guidelines for systematic reviews [22], a systematic literature search was conducted in July 2018 of three online databases: PsychINFO (1984 to July 2018), PubMed (1948 to July 2018) and SCOPUS (1966 to July 2018). This search was repeated in February 2020 for the time period July 2018 to February 2020, as an update. Search terms (see Table 1) were determined from an initial scoping of literature and journals and followed up by investigating MeSH (Medical Subject Heading) term browsers and researching key terms used by The Fragile X Society and The National Autistic Society.

Where databases allowed, MeSH terms were also included. To ensure comprehensiveness of the search, no terms were included to denote sex, with papers including only male subjects excluded at a later stage. Initial filters were used to include only peer-reviewed journals available in the English language and to exclude studies with non-human subjects.

Inclusion/exclusion criteria

Papers were selected for review if they reported behaviours related to ASD or prevalence of ASD in females with FXS. Papers were excluded if they (1) reported on FXS males only, (2) contained no analysis by sex, (3) focused solely on neurology, genetics, biology, a drug trial or development of a research measure, (4) did not report ASD behaviours or prevalence or (5) reported on FXS *within* samples of individuals with ASD.

Where it was not clear from the title/abstract whether a paper might meet the inclusion criteria, the full paper was read.

Table 1 Search terms

Fragile X	autis*
Fragile X Syndrome	autism*
Fragile-X	autistic*
FXS	ASD
FRAXA Syndrome	autism spectrum disorder*
AFRAX	PDD-NOS
Martin Bell* Syndrome	PDDNOS
Marker X Syndrome	PDD
fraX Syndrome	unspecified PDD
fra(X) Syndrome	pervasive developmental disorder*
X-linked mental retardation	pervasive developmental disorder not otherwise specified
Macroorchidism	Asperger*
Escalante* Syndrome	Asperger* syndrome
Escalante*	
FRAXE Syndrome	
Fragile X mental retardation	
Fragile X-F mental retardation	
Mar(X) Syndrome	
Mental retardation, X-linked	
FMR1	
FMRP	

Terms within each list were combined with OR operators; the two lists were combined with the AND operator

Abstract and full paper review

See Fig. 1 for PRISMA flowcharts summarising results of the search processes at the two timepoints. A total of 34 papers (28 up to July 2018 and 8 from July 2018 up to February 2020) were identified for inclusion.

Hand searching was also used to check references of the final papers, and a search was completed on Google to search the 'grey literature', which are materials and research produced by organisations outside of the traditional academic publishing channels. This may have included dissertations, non-published work, data provided by charities or other organisations. No additional papers were identified.

Risk-of-bias/quality assessment

A risk-of-bias/quality rating tool was utilised that specifically appraises studies of ASD in genetic syndromes ([6]; see Table 2 for risk-of-bias criteria and visual colour coding). The tool addresses variability in risk of bias in ASD assessment (from parental report or screening tools to assessment using multiple 'gold standard' diagnostic measures), as well as potential sources of bias based on the nature of the sample or confirmation of diagnosis [6]. A score of 0–3 (with higher scores indicating higher quality/lower risk of bias) is given based on the study risk of bias in three areas: sample identification, confirmation of genetic syndrome and ASD assessment. A total score for each study, which could range from 0 to 9, was calculated as the sum of these three scores. The first author rated all papers for quality/risk-of-bias. Independent blind ratings were also obtained from a second rater (fourth author) for the calculation of inter-rater reliability. Agreement was excellent for individual domains, with weighted kappa calculated to be 0.80 (95% CI 0.53–1.1) for sample identification, 0.77 (95% CI 0.62–0.92) for ASD assessment and 0.75 (95% CI 0.58–0.93) for assessment of syndrome. For the total score, a two-way random effects, consistency, average-measures intraclass correlation [23, 24] also indicated high levels of agreement between raters (ICC .93, 95% CI .85–.96).

An overall quality/risk-of-bias weighting between 0 and 1 was calculated by dividing the total score by the maximum possible total score of nine. This score was used in the weighting of individual studies in the quality effects weighted average prevalence estimate and was considered when discussing the further findings. Ratings from the first author are the ratings presented in the paper and used in meta-analyses. However, quality effects meta-analyses were repeated, replacing ratings from the first author with ratings from the second author; these analyses confirmed that results did not change appreciably.

Overall quality/risk-of-bias assessment scores ranged from 0.11 to 0.78 (with higher scores indicating higher quality/lower risk of bias). In accordance with findings from Dixon-Woods et al. [25] and Stroup et al. [26], articles were not omitted due to risk-of-bias/quality (though see below in relation to meta-analysis).

Data analysis

ASD prevalence

To determine the prevalence of ASD in females with FXS, the total number of females reported in the sample, and the number meeting cut-off for ASD were extracted from each paper. Where an assessment provided different cut-offs (e.g. Autistic Disorder rather than the broader spectrum cut-off), data regarding the most stringent cut-off level were used (following [6]). Similarly, where multiple assessments were used, data were extracted from the most robust assessment measure as determined by the risk-of-bias assessment tool used [6].

Meta-analytic weighted prevalence values were generated using a random effects model, selected to allow for between-study variation reflecting both sampling errors and other factors (such as variation in risk of bias in different methodologies) [27]. Since initial Q-Q plots indicated possible non-normality of distribution of prevalence estimates, the restricted maximum likelihood estimator was used to calculate between studies variance, due to its relative robustness to non-normal distributions of effects. A leave-one-out methodology, whereby each paper was omitted in turn and the weighted prevalence re-calculated, was used to identify studies of disproportionate influence (with the visual aid of Baujat charts). An additional quality effects model was also utilised, with adjusted weightings according to studies' overall risk-of-bias ratings.

The existence of possible publication bias was assessed using the visual aid of a funnel plot, in which the magnitude of the study's proportion estimate is plotted against the square root of the study's sampling variances. If there is an absence of publication bias, the effects from the studies with small sample sizes which show greater variability will scatter more widely at the bottom of the plot compared to studies with larger samples at the top which will lie closer to the overall meta-analytic effect, creating a symmetrical funnel shape. If there is an absence of studies in the area of the plot associated with small sample sizes and low prevalence (for this meta-analysis it will be the bottom left-hand corner) then it is likely there is some publication bias leading to an over-estimation of the true effect. Following Terrin et al. [28] demonstration of the unreliability of subjective judgments of funnel plot symmetry, Egger et al.'s [29] linear regression test of funnel plot asymmetry was also carried out. A trim and fill method was then used to model and

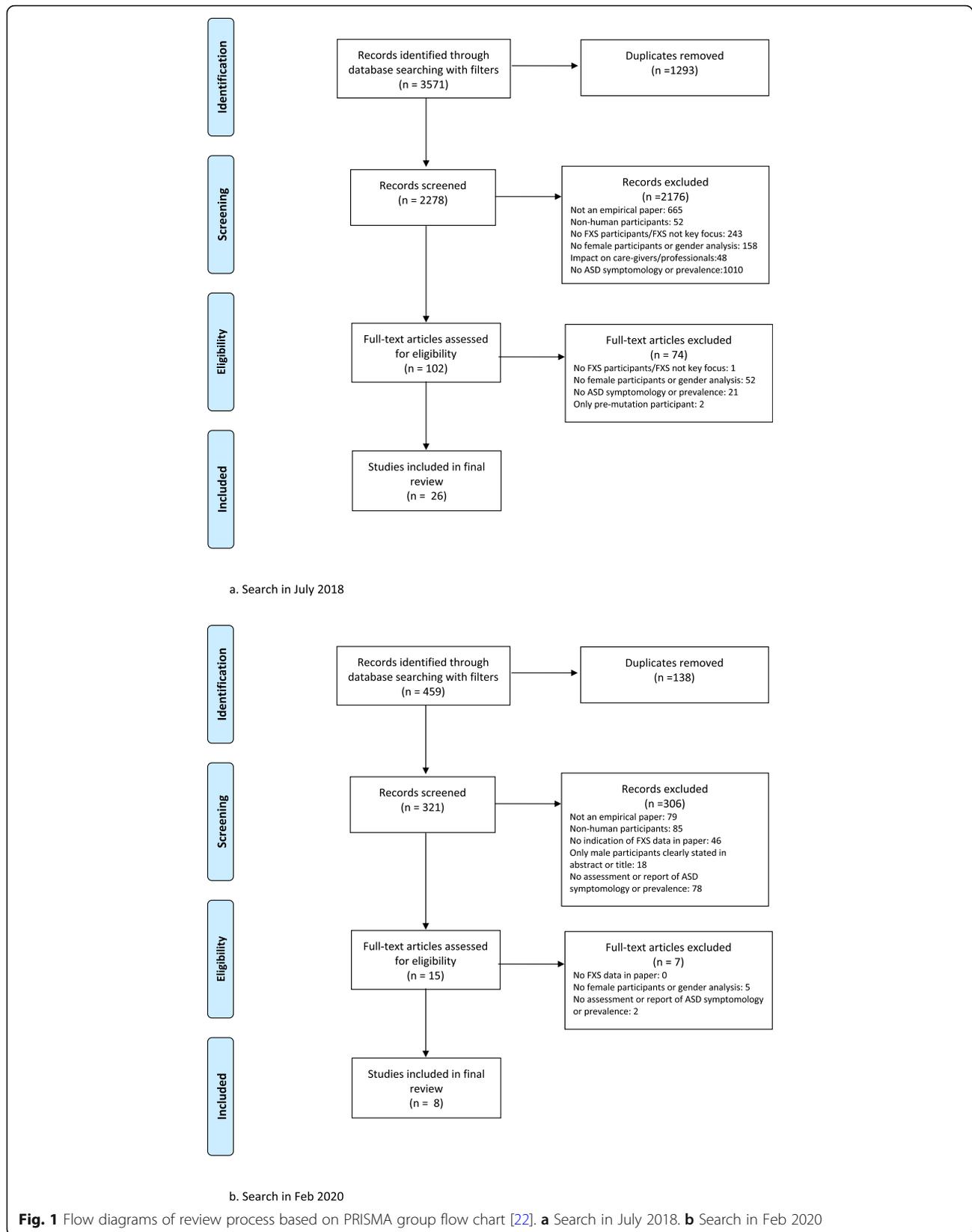


Fig. 1 Flow diagrams of review process based on PRISMA group flow chart [22]. **a** Search in July 2018. **b** Search in Feb 2020

Table 2 Quality/risk of bias criteria for sample identification, confirmation of syndrome and ASD assessment

	Quality Rating			
	0 Poor (red in supplemental material)	1 Adequate (yellow in supplemental material)	2 Good (amber in supplemental material)	3 Excellent (green in supplemental material)
Sample Identification	Not specified/reported	Single restricted or non-random sample e.g., a specialist clinic or previous research study ^a	Multiple restricted or non-random samples e.g., multi-region specialist clinics	Random or total population sample
Confirmation of syndrome	Not confirmed/reported Clinical diagnosis only suspected	Single regional sample e.g., a regional parent support groups Clinical diagnosis by 'generalist' e.g., General Practitioner or Paediatrician	National non-random sampling e.g., national parent support groups Clinical diagnosis by 'expert' e.g., Clinical Geneticist or Specialist Paediatrician	Molecular/Cytogenetic/Metabolic confirmation of diagnosis
ASD assessment	Not specified/reported Clinician judgement only	Screening instrument e.g., SCQ, M-CHAT Clinician judgement against specified diagnostic criteria e.g., DSM-IV or ICD-10	Diagnostic instrument e.g., ADI-R, DISCO, ADOS, 3Di	Consensus from multiple assessments, including at least one diagnostic instrument

^aWhere individuals were recruited as part of a larger ongoing study, if the recruitment strategy of this study is described, this is coded. If not described, it is coded as 1 by default, indicating the sample has come from one source (i.e. the larger ongoing study)

correct for asymmetry due to potential publication bias [30, 31], producing adjusted weighted average prevalence estimates. The trim and fill procedure builds on the assumption that publication bias would lead to an asymmetrical funnel plot. It iteratively removes the most extreme small studies from the side of the funnel plot associated with positive effects, re-computing the effect size at each iteration until the funnel plot is symmetric about the (corrected) effect size. Whilst this trimming yields the adjusted effect size, it also reduces the variance of the effects, resulting in a biased and narrow confidence interval. Therefore, the original studies are returned into the analysis, and the procedure imputes a mirror image for each on the side of the funnel plot associated with small effect sizes. The L_0 estimator was used in the current analysis, as outlined by Duval [32] and as is the default in the metafor (V2.4) procedure within R [33].

Nature of ASD: relationship of ASD with IQ and FMRP levels

Due to limitations in available statistical information, formal statistical analysis was not carried out for the review of the nature of ASD-related behaviours nor any associations with IQ or FMRP levels; therefore, synthesis is narrative in these areas.

Results

There were 34 papers with findings pertaining to females with FXS (see Table 3 for a summary).

Prevalence of ASD in females with FXS

Twenty-eight papers reported prevalence data for ASD in females with FXS. Reported prevalence ranged from 0

to 66%. Weighted average prevalence of ASD among female participants with FXS was 17% (95% CI 12 to 22%; $z = 6.8$, $p < .0001$) for the random effects model, and the analysis indicated moderate heterogeneity (Higgins' $I^2 = 72\%$; $\tau^2 = .01$; $Q(26) = 92.0$, $p < .0001$) (Fig. 2a). A leave-one-out analysis indicated that two papers—Symons et al. [62] and, to a lesser extent, Baker et al. [35]—may have exerted disproportionate influence in the analysis (see Baujat plot in Fig. 2c). Omitting Symons et al. [62] led to the greatest change in the meta-analytic estimate (15.8%). Symons et al. [62] also received ratings indicative of high risk of bias (i.e. low ratings on the quality assessment tool), especially with respect to confirmation of ASD. This was not the case for Baker et al. [35], whose risk-of-bias ratings indicated a high-quality study. A further analysis was therefore conducted without the inclusion of Symons et al. [62]. The revised weighted average prevalence estimate was 14% (95% CI 13 to 18%, $z = 7.6$, $p < .0001$), with reduced heterogeneity ($I^2 = 63\%$; $\tau^2 = .005$; $Q(25) = 67.8$, $p < .0001$) (see Fig. 2b).

For the quality effects model, weighted average prevalence was 22% (95% CI 16 to 29%; $z = 6.9$, $p < .001$; $I^2 = 82.4\%$; $\tau^2 = .01$; $Q(26) = 92.0$, $p < .0001$) using all papers, and 22% (95% CI 16 to 27%; $z = 7.7$, $p < .0001$; $I^2 = 67.2\%$; $\tau^2 = .005$; $Q(25) = 67.8$, $p < .0001$) after omission of the Symons et al. [62] paper.

Forest plots for random and quality effects models, with and without the Symons et al. [62] paper, are shown in Figs. 2 and 3. A Baujat plot is also shown (Fig. 2c), illustrating the disproportionate influence of this specific paper.

A funnel plot (Fig. 4) indicated possible publication bias, a conclusion backed by Egger et al.'s [29] linear

Table 3 Main findings and papers from the review [10, 12, 18, 19, 34–64]

Authors and country of study	Sample of FXS females	Age (Years), Ethnicity and IQ	Confirmed Fragile X Syndrome (FXS)	Comparison groups	Autistic Spectrum Disorder (ASD) Measures	Prevalence of ASD and findings related to ASD behaviours for females or associations with other areas (e.g., Intellectual Disability)	Quality/risk of bias Assessment Score, weight*		
							Sample	Syndrome	ASD
Bailey et al. (2008) USA	259	Both sexes age; 11% 0-4 years, 34% 5-11, 24% 12-18, 10% 19-22, 10% 23-30, and 11% 30+ Both sexes ethnicity 92% Caucasian, 4% Hispanic or Latino, 2% African American or Black, 1% Asian and <1% other IQ not reported	Parent report	Males with full mutation and pre-mutation and a matched control group	Parent report of ASD diagnosis	16 (6.2%) ASD in FXS No differences in autism prevalence to matched non-FXS females. No ASD behaviours explored.		2 (0.22)	
Baker et al. (2019) Australia	36	Female M age 10.9 (SD9.23), range 1.71-34.13 Ethnicity 66.7% Australian/European, 18.5% Mestizo, 14% other. IQ (Mullen Scales or appropriate Wechsler tests) 47.2% met criteria for intellectual disability (ID). FSIQ M 67.8 (SD 17.8)	Genetic	Males with FXS	Autism Diagnostic Observation Schedule 2 (ADOS 2)	21 (58%) of females met criteria for ASD A significant higher proportion of male FXS had an ID compared to females. Significantly higher proportion of males met criteria for ASD than females, but after controlling for ID there was no significant difference. Males had more significant difficulties with eye contact, showing, initiation of joint attention, rapport, sensory, response to name, amount of social overtures (examiner), amount of social overtures (caregiver), amount of reciprocal communication, functional play, and imaginative/creative play.		7 (0.78)	
Barstein et al. (2018) USA	37	M age 8.7 years (SD 4.1) FXS-ASD and 9.2 (SD 3.3) FXS-non FXS Leiter – Non-verbal mental age FXS-ASD M 5.1 (SD 0.8), range 4.0-6.1, FXS-non ASD M 7.0 (SD 2.3), range 3.9-12.8	Not reported	Males FXS and ASD, males FXS and no ASD, males with idiopathic ASD, Downs Syndrome, and TD	Autism Diagnostic Observation Schedule (ADOS)	12 (32%) females with FM met ASD criteria. No female ASD behaviour findings No non-verbal mental age/ASD analysis		3 (0.33)	
Clifford et al. (2007) Australia	31	No info for females only. M age both sexes FXS 23.15 years 100% Caucasian No female IQ data	Genetic	FXS boys with ASD	Autism Diagnostic Interview-Revised (ADI-R) ADOS-G (Generic)	3 (9.7%) of FXS females met ASD category on both tests – nearly half the rate seen in males. An additional 2 met criteria on at least 1 test (16% in total). 13% when considering broader spectrum on both tests, 23% broader criteria on one test. ASD behaviours not broken down by sex. IQ/ASD analysis for females not considered.		7 (0.78)	
Cordeiro et al. (2011) USA	39	M age females 12.35 years (SD 6.17) Both sexes ethnicity: Caucasian (78.4%) and not Hispanic or Latino (64.9%) IQ tested by WASI, WPPSI III, WAIS-III, WISC-III or WISC-IV. M IQ for females 77.20; 33.3% in ID range	Genetic	Boys with FXS	ADOS-G, ADI-R, DSM-IV criteria and clinical team consensus	11 (28%) met criteria for ASD No female specific ASD behaviours or associations explored. No ASD/ID analysis completed		6 (0.67)	
Denmark, Feldman & Holden (2003) Canada	3	M age both sexes 11.8 years (SD 2.6) No ethnicity reported No Female IQ data	Genetic	Children with autism but no FXS	Childhood Autism Rating Scale (CARS)	0 (0%) met the criteria for ASD. No female specific behaviour findings. No female specific mental retardation links with ASD.		7 (0.78)	
Flenthrope & Brady (2010) USA	4	M age both sexes 27 months (SD 7.14) Ethnicity both sexes 88% white, 8% African American, 4% Hispanic IQ not measured	Not reported	Boys with FXS	CARS	2 (50%) of girls met cut off for ASD No ASD behaviours explored.		4 (0.44)	

Table 3 Main findings and papers from the review [10, 12, 18, 19, 34–64] (Continued)

Hall <i>et al.</i> (2010) USA	33	M age both sexes 13.24 years (SD 3.27) No ethnicity reported IQ (WISC-III and WAIS-III) M 76.77 (SD 22.76), range 40-116 FMRP M 53.02 (SD 18.59), range 14.5-90	Genetic	Reference percentages and autism samples in the measures and boys with FXS and autism.	ADOS Social Communication Questionnaire (SCQ)	3 (4.3%) in ASD category on two measures 9 (18.8%) in autism category in SCQ only. 7(21.2%) in autism category for ADOS only. No female ASD behaviour findings Lower IQ levels associated with significantly higher autistic behaviours. Some behaviours similar to the autism sample (attachment to objects, inappropriate questions, gestures and inappropriate facial expressions), but most occurred at lower rates than the reference samples. Significantly lower scores on four of the five communication domain items both to FXS boys and reference group. Lower scores on nine of the 10 reciprocal social interaction domain items. 'Less impaired' than idiopathic Autism. No effect of FMRP levels on autism-associated behaviours when controlling for age, IQ and medication use.	 7 (0.78)
Hall, Lightbody & Reiss (2008) USA	29	M age 13.06 years (SD 3.93) No breakdown of ethnicity WISC III and WAIS-III FSIQ M 70.76 (SD 20.91) M FMRP 52.02% (SD 16.97), range 15%-84.5%	Genetic	Boys with FXS	ADOS-G	6 (20.7%) met criteria for ASD. 7 girls met criteria for wider spectrum category (45% in either the AD or broader spectrum category). Boys were more likely to score in the Autistic categories than girls. Those girls with lower IQs were more likely to show autistic behaviours. No ASD behaviours for girls examined No association with FMRP and ASD for females.	 7 (0.78)
Hartley <i>et al.</i> (2011) USA	89	M age 30.27 (7.76) 87% Caucasian IQ not reported	Parent reported	Boys with FXS	Parent reported pre-diagnosis	8 (9%) pre-diagnosed via carers report of ASD. No ASD behaviours examined. Autism was not a predictor for independence in life for women.	 2 (0.22)
Hatton <i>et al.</i> (2006) USA	32	M age 50.7 months (SD 36.9) European American 90.6% FMRP females M 40.5 No IQ reported	Not reported	FXS boys with ASD and non-ASD	CARS	2 (6.3%) met cut off for ASD Girls had significantly lower CARS scores than boys. Autistic behaviour increases slowly but significantly over time for both sexes. FMRP predicted mean scores on CARS – low levels were associated with higher means of autistic behaviour. No IQ/ASD analysis.	 3 (0.33)
Hatton <i>et al.</i> (2009) USA	15	M age 30.1 months Ethnicity 100% white FMRP (sub-sample of 11) M 41.5, range 9-67.5 IQ not reported	Genetic	None	CARS	1 (6.67%) scored above the cut-off for ASD Autistic behaviour associated with poorer developmental outcomes. FMRP not associated with developmental outcome. No FMRP/ASD analysis.	 6 (0.67)
Hessl <i>et al.</i> (2001) USA and Canada	40	M age 10.42 years (3.10) Mixed sex ethnicity 91.7% white, 2.5% Hispanic, 2.5% Black, 1.7% Asian, 0.8% Pacific Islander, and 0.8% multi-ethnic. WISC-III FSIQ M 75.48 (SD 22.30) FMRP M 51.03 (SD 18.57)	Genetic	Unaffected siblings and boys with FXS	Autism Behaviour Checklist (ABC)	No cut off data given. Girls with FXS had mild levels of autistic behaviours. IQ was a significant predictor accounting for approx. 33% of the variability. FMRP was not a significant predictor of autistic behaviour.	 6 (0.67)
Hustyi <i>et al.</i> (2015) USA	35	No sex breakdown. M age mixed sex 20.57 years (SD 3.09) No ethnicity details given No Female IQ data	Genetic	FM males and matched controls on age, sex, IQ and autistic behaviours	ADOS	4 (11.4%) met criteria for ASD. Extra 2 for wider autism spectrum (17% were ASD or wider spectrum). Females had significantly lower scores than FXS males. Those with FXS with greater levels of autistic behaviours were more dependent on the support of others than those with fewer autistic behaviours, even when controlling for IQ.	 7 (0.78)

Table 3 Main findings and papers from the review [10, 12, 18, 19, 34–64] (Continued)

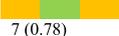
Kaufmann <i>et al.</i> (2017) USA	132	Both sexes 88.7% identified as 'white' No age breakdown for group No IQ data reported	Not reported	Boys with FXS with and without ASD	Clinician assessed	23 (18%) met criteria for ASD. ASD significantly more likely in males No female ASD behaviour findings.	 3 (0.33)
Kidd <i>et al.</i> (2019) USA	97	Both sexes age – ASD group 13.0 (SD 7.3), 4.0–46.7, Non ASD group 13.8 (SD 8.6), 4.0–51.7 No ethnicity data No IQ data	Genetic	FXS males	SCQ	22 females (23%) met cut off for ASD ASD behaviours not broken down by gender Male sex associated with ASD status	 6 (0.66)
Klusek, Martin & Losh (2014) USA	35	M age 9.38 years (SD 3.91) Ethnicity; white 71.4%, African American 8.6%, Other 11.4% Leiter M 84.63 (SD 21.25), range 38–124, mental age M 6.77 (SD 2.60), range 3.92–6.77	Not reported	FXS boys	ADI-R and ADOS	5 (14.3%) met criteria for ASD on both assessments. ADI-R only 22.9% ASD ADOS only 25.7% ASD. 8 met the criteria for at least one measure (23%). 22.9% of females diagnosed clinically. High agreement between ADI-R and ADOS but poor agreement between these measures and clinical diagnoses. 50% with clinical diagnoses not meeting criteria for instruments and approx. 20% identified by the instruments not having clinical diagnoses. FSIQ and mental age were not significant predictors of ASD diagnosis.	 5 (0.56)
Lee <i>et al.</i> (2016) USA	34	M age girls 8.96 years (SD 3.39), with ASD 9.11 years (SD 3.14), no ASD 8.50 years (SD 3.37) No ethnicity reported Leiter – Non-verbal mental age M girls time one 6.18 (SD 1.72) M girls ASD time one 5.39 (SD 0.99)	Not reported	Males FXS and males idiopathic ASD	ADOS ADI-R	10 (29.4%) met criteria for ASD at point one and 13 (38.2%) at time point two. Increased impairments in prosodic features of speech, facial expressions and social overtures (from ADOS). Overall ASD behaviours worsen with age for whole group. Sex no impact on this. Reduced rates of ASD classification relative to boys over time. No ASD/non-verbal mental age analysis for girls.	 5 (0.56)
Loesch <i>et al.</i> (2007) USA and Australia	Australia n 31 USA and Australia 14 3	Australian both sexes aged 5–70, American both sexes aged 4–50 Australian ethnicity all white and of European descent American ethnicity 84% white and non-Hispanic, 10.4% Hispanic, 5.6% mixed ethnicity, African American or American Indian FMRP M 59.9 (SD 21.0) FSIQ (WPPSI-R, WPPSI-III, WISC-III, WAIS-III) M 72.0 (SD 17.5)	Genetic	FXS males and a control group with no FXS	ADOS-G	Females are less significantly affected than males The two domain scores of the ADOS-G and their sum strongly related to the level of FMRP deficit. Significant correlations between lower IQ scores and higher scores in the major domains.	 7 (0.78)
Martin <i>et al.</i> (2017) USA	39	M age no ASD – 10.7 years (SD 3.0), M Age ASD 9.8 years (SD 3.8) Ethnicity not reported Non-verbal mental age (Leiter-Revised) M no ASD – 7.1 (SD 2.50), range 4.3–13.3, M ASD – 5.2 (SD 0.8), range 4–6.3	Genetic	FXS boys with and without ASD, boys idiopathic ASD, downs syndrome and TD	ADOS	12 (30.7%) met criteria for ASD. No mental age/ASD analysis	 7 (0.78)
Martin <i>et al.</i> (2018) USA	42	Female age FXS-ASD – 9.3 (SD 3.8), 4.9–15.9 FXS-O – 9.5 (SD 3.7), 4.2–14.9 No ethnicity given No IQ data	By expert but no full details	FXS boys, TD girls and boys, girls and boys Downs Syndrome	ADOS	No prevalence data as groups were specifically chosen to be a mix of ASD and non ASD from previous study. Girls with FXS and ASD used significantly more non-contingent language compared with all other female groups.	 6 (0.66)

Table 3 Main findings and papers from the review [10, 12, 18, 19, 34–64] (Continued)

Martin <i>et al.</i> (2019) USA	36	Female age FXS-ASD 9.1 (SD 4.0), 4.9-15.9, FXS-O 9.2 (SD 3.7), 4.2-14.9 No ethnicity No IQ data	By expert but no full details	FXS boys, TD girls and boys, girls and boys Downs Syndrome Idiopathic ASD	ADOS	No prevalence data as groups were specifically chosen to be a mix of ASD and non ASD from previous study. Noncontingent language and perseveration were characteristic of the pragmatic profiles of boys and girls with FXS-ASD	 6 (0.66)
Mazzocco <i>et al.</i> (1997) USA	30	M age 10.7 years (SD 3.2) No ethnicity confirmed FSIQ M 87.4 (SD 14.1), range 66 to 116 – WISC-R	Genetic	Peer comparisons matched on age and FSIQ	Neuropsychiatric Developmental Interview (NDI) for DSM III-R criteria	1 (3.33%) met criteria for of ASD. FXS girls had significantly more autistic behaviour than controls. No correlation between IQ and ASD. Behaviours similar to those described in research for boys (although frequency was lower).	 6 (0.67)
McDuffie <i>et al.</i> (2010) USA	15	M Age FXS only 12.35 years (SD 1.57) FXS + ASD 11.04 years (SD 0.59) Ethnicity not reported No female IQ reported	Genetic	Boys with FXS only and FXS + ASD	ADI-R	2 (13%) met criteria for ASD. No female ASD behaviour findings due to low female numbers. No female IQ/ASD explored.	 7 (0.78)
McKechanie <i>et al.</i> (2019) UK	4	M for both sexes ASD group 18 (6.2), non-ASD 27 (11.7) No ethnicity No IQ data	Not reported	Male FXS	ADOS 2	2 (50%) females FXS met criteria for ASD No ASD behaviour gender differences reported	 4 (0.44)
Muller <i>et al.</i> (2019) USA	11	Age both genders between 8yrs 11 months to 10 years 1 month (M 9 years 6 months) Ethnicity both genders 91% Caucasian, 2% African American, 1% Latino Leiter females mental age 5 years 3 months (SD 1.2, range 3.03-7.11)	General diagnosis but no detail	Boys FXS	Parent report	2 females (18%) reported as having diagnosis of ASD No ASD findings by gender	 3 (0.33)
Reilly, Senior & Murtagh (2015) UK and Republic of Ireland	21	M age both sexes 11.58 years (SD 3.60) Part of a larger study with other genetic groups – larger group ethnicity 80% white British or white Irish. FXS group not specifically reported IQ not reported	Not reported	Males with FXS and both sexes with Prader-Willi Syndrome, Williams Syndrome and Velo-cardio-facial Syndrome.	Parent report of professional diagnosis	3 (14%) had professional diagnosis of ASD. Lower number diagnosed than males with FXS (44%). Compared with other syndromes FXS children (both sexes) more likely to be diagnosed with ASD. Relationship still holds when adjusting for sex. No female ASD behaviour findings.	 2 (0.22)
Russon-Ponsaran <i>et al.</i> (2014) USA	11	M age 11.23 years (SD 2.92) Ethnicity; 10 white, 1 African American WASI FSIQ range 52-97 M 76.81	Genetic	TD girls	SCQ ADOS	5 (45%) met criteria for ASD. No female ASD behaviour findings. No IQ/ASD analysis.	 7 (0.78)

Table 3 Main findings and papers from the review [10, 12, 18, 19, 34–64] (Continued)

Shaffer et al. (2020) USA	11	Both gender M age 19.96 (SD 8.47) No ethnicity No IQ data	Expert diagnosis but no detail given	Male FXS and TD	SCQ	No numbers for ASD cut offs given FXS males had more impairment on SCQ score than female FXS	 4 (0.44)
Smith et al. (2012) USA	29	M age FXS + ASD 18.47 years (SD 5.37) Ethnicity for all FXS + ASD, 97% white No female IQ reported	Genetic	ASD only group and FXS only group (mixed sexes)	Maternal report, medical and educational records and SCQ	3 (10.3%) met criteria for ASD. FXS +ASD group showed similar levels of overall autism to ASD group. Repetitive-restricted behaviours significantly higher in FXS +ASD than ASD alone. Not significant when co-varied for sex indicating similar findings for both sexes. No female only intellectual disability/ASD analysis.	 6 (0.67)
Smith et al. (2016) USA	26	M age both sexes 20.6 years (SD 1.2) No ethnicity given No female IQ reported	Genetic	Boys with FXS	SCQ	Being female associated with fewer autistic behaviours than being male. No significant changes over time to autistic behaviours. “Maternal warmth” is associated with lower levels of autism behaviours. No analysis for ID and ASD.	 6 (0.67)
Symons & Byiers 2010 USA	51	M age both sexes 15.9 years (SD 10.9) Both sexes ethnicity; 90% Caucasian, 6% Hispanic, 1% African American, remaining 3% Asian, American Indian, Alaska Native or reported mixed races/ethnicity IQ not reported	None	Males with FXS and females with and without Self-Injurious Behaviours (SIBs)	Parent report of diagnosis	34 (67%) parent reported ASD diagnosis. Males more likely than females to have an autism diagnosis. Females with SIBs were more likely to have a diagnosis of Autism than those without.	 2 (0.22)
Wheeler et al. (2015) USA	119	M age 14.6 years Ethnicity; 85.7% Caucasian, 2.5% African America, 5% Hispanic and 6.7% other IQ not reported	Parent report	Boys with FXS	Previous ASD diagnosis by parent report Survey designed by researcher for ASD traits based on existing measures and mapping onto DSM-IV and DSM-5 criteria	Based on observable behaviours endorsed by caregivers 29 (24.7%) of females met DSM-IV criteria and 13 (11.3%) for DSM-5. Of the females who met DSM-IV criteria only 37.5% also met DSM-5 criteria. 18 (15%) pre-diagnosed parent reported ASD. Most common behaviours were avoidance of eye contact (55%), excessive questioning or pre-occupation with particular topics (45%) and echoing questions or statements made by others (40%).	 2(0.22)
Wheeler et al. (2019) USA	72	M age 20.6 (SD 6.9) Ethnicity 65 white, 2 Asian, 2 Non-Hispanic Black, 1 Latino, 1 multiple, 1 missing IQ – 70.1 (SD 17.7) - Stanford Binet Intelligence Scales 5th edition.	Expert diagnosis but no detail given	FXS makes	SCQ and ADOS 2	5 females (7%) met cut off for both SCQ and ADOS 2. No gender breakdown for ASD findings.	 5 (0.55)

TD typically developing, M mean, SD standard deviation

*Colour code—red = poor, yellow = adequate, orange = good, green = excellent

regression test of funnel plot asymmetry (bias 2.3, $t(25) = 5.3$, $p < .0001$). Using the trim and fill procedure [30, 31], eight studies were introduced, leading to an imputed estimate of the prevalence of 12% (95% CI 5–19%).

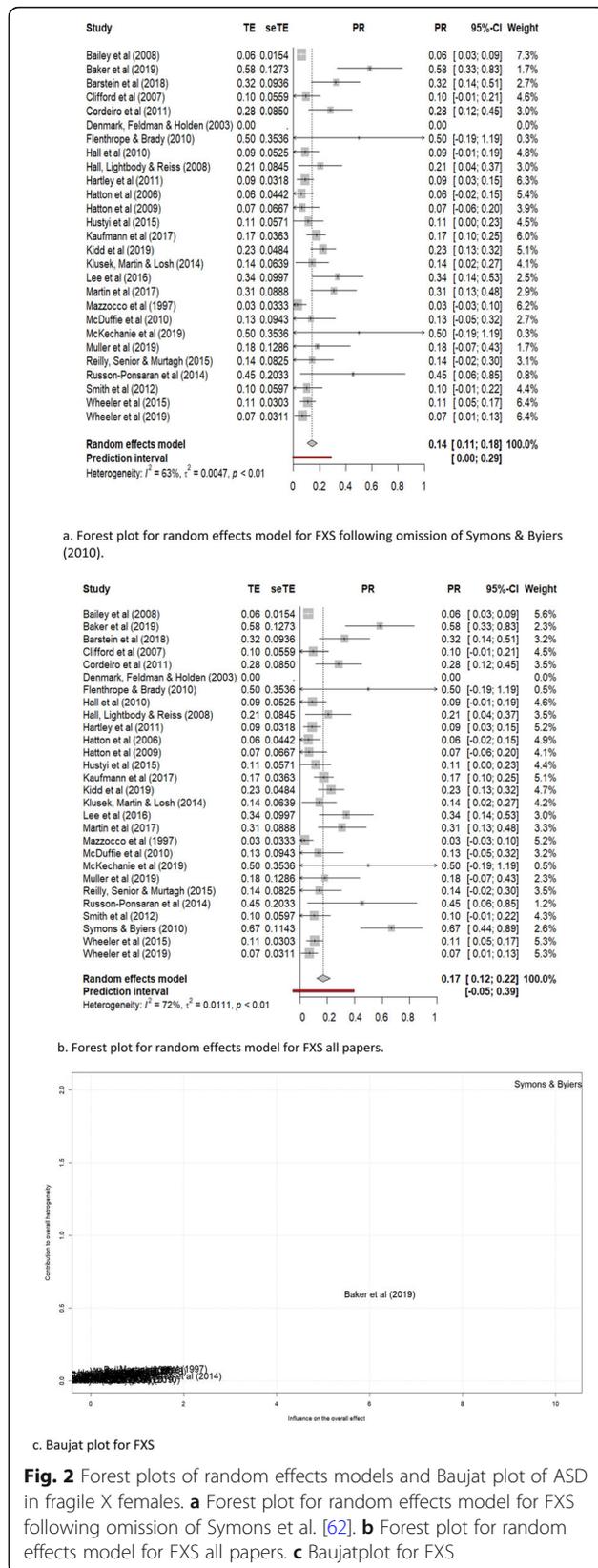
Profile of behavioural characteristics associated with ASD

A number of papers reported on the frequency and topography of specific behaviours associated with ASD (see Table 4 for main findings from the papers exploring ASD-associated behaviours).

Studies generally reported that females with FXS showed fewer behaviours associated with ASD than the reported contrast groups, including males with FXS (e.g.

[19, 35, 40, 43–45, 47, 56, 61, 62]). Interestingly, Baker et al. [35] found, in a paper rated high for quality, that whilst a greater proportion of males than females met criteria for ASD, this effect disappeared when controlling for the level of ID. Results also suggest that females with FXS were more likely to have ‘mild’ autistic behaviours, showing more characteristics than their unaffected siblings, unaffected typically developing peers and peers with other neurogenetic disorders but fewer characteristics than males with FXS [52, 56].

Females with FXS who met criteria for ASD were found to show similar rates and types of ASD symptomatology to individuals with idiopathic autism [40, 60]



and to those described for males with FXS [52]. These appear to be robust findings from papers with relatively high ratings for quality (low risk of bias).

Associations between IQ/cognitive ability and ASD characteristics

The majority of papers (17; 61%) did not report the cognitive ability of female participants, and correlations between IQ and ASD characteristics were also not reported. Eleven papers reported IQ levels or non-verbal mental age, but only six considered these in relation to ASD characteristics or diagnosis (see Table 5 for results and papers for IQ).

Several studies scoring high on quality ratings reported a statistically significant negative association between IQ and autistic features in females with FXS, such that lower IQ scores were associated with significantly more autistic behaviours [18, 40, 41, 48]. In contrast, two studies reported that IQ and mental age were not significant predictors of ASD diagnosis or ASD characteristics in females with FXS [46, 52].

Associations between FMRP levels and ASD characteristics

Six papers reported and analysed FMRP levels in relation to ASD characteristics or diagnosis (see Table 6). This is reported in all papers as the percentage of lymphocytes expressing FMRP.

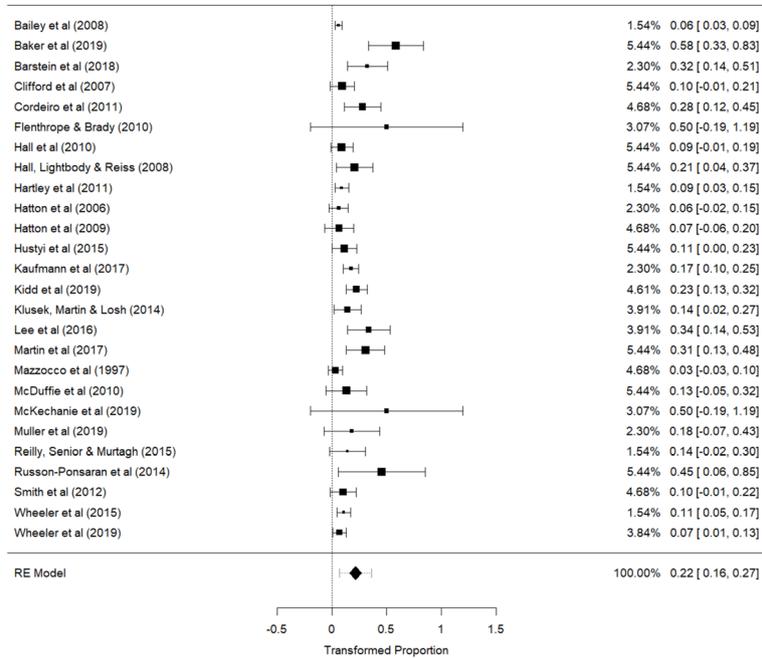
Mean FMRP scores ranged from 40.5 to 59.9%. Two papers suggested links between FMRP and autistic features [19, 48], whilst three papers reported no significant relationship [18, 40, 41].

Additional variables potentially related to ASD

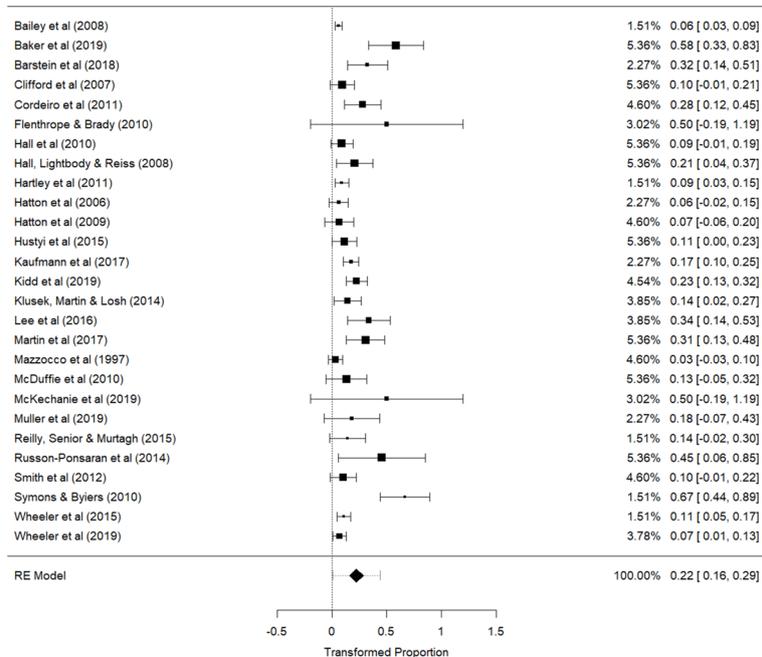
ASD in females with FXS was associated with greater levels of dependency and poorer developmental outcomes [10, 42, 43]. Anxiety and the presence of self-injurious behaviour was strongly correlated with ASD characteristics [52].

Conclusions

This review examines and meta-analyses the prevalence of ASD among females with FXS. It also addresses the severity and nature of ASD characteristics in these groups, and evidence related to factors potentially associated with ASD, including IQ and FMRP levels. Data were reviewed from 34 studies. The quality/risk-of-bias of these studies was assessed using a published quality/risk-of-bias appraisal tool and considered as part of prevalence meta-analysis and in narrative interpretation of further findings.



a. Forest plot for quality effects model for FXS omitting Symons & Byiers (2010).



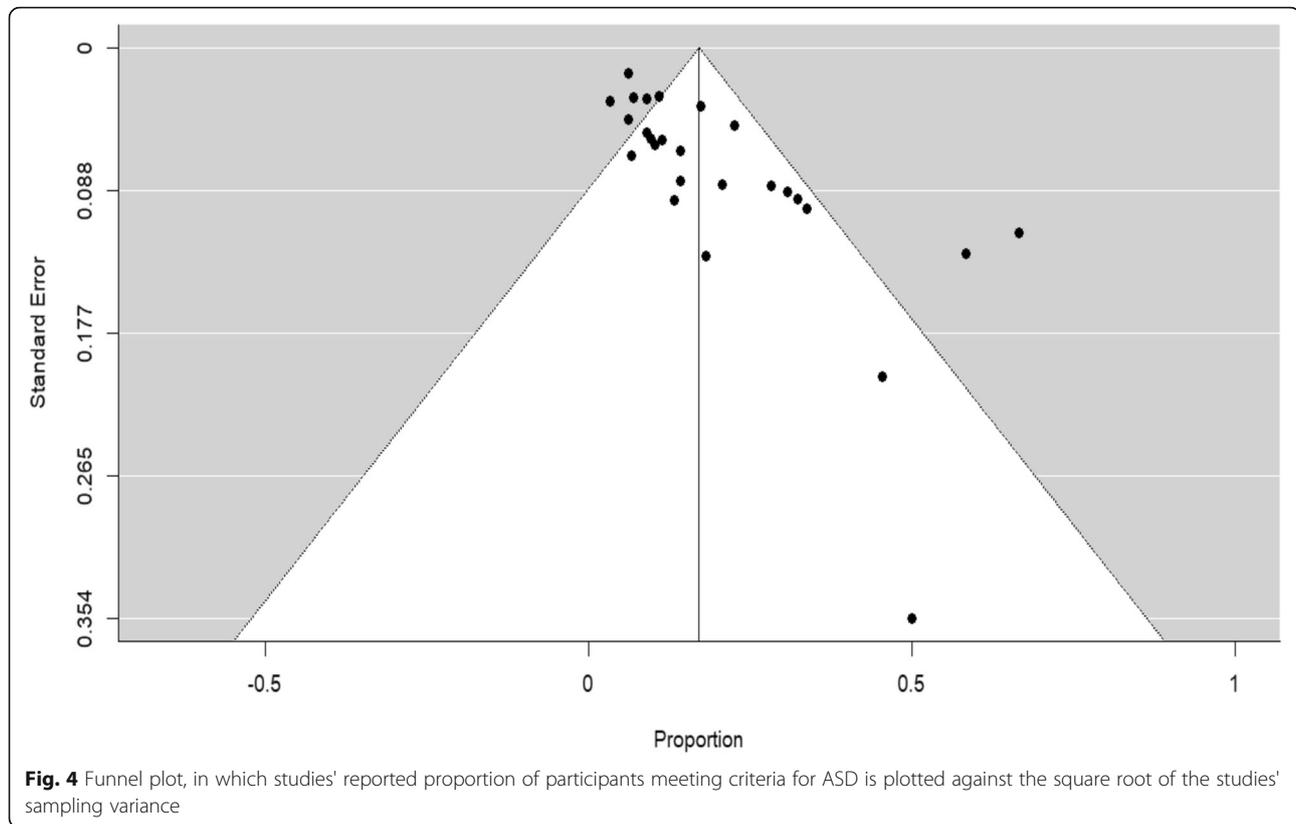
b. Forest plot for quality effects model FXS all papers

Fig. 3 Forest plots of quality effects model of ASD in fragile X females. **a** Forest plot for quality effects model for FXS omitting Symons et al. [62]. **b** Forest plot for quality effects model FXS all papers

ASD in females with FXS

Published prevalence values were highly heterogenous, impeding confident interpretation of a single weighted average prevalence value based on all available papers (17%, 95% CI 12–22%). Following exclusion of a single

disproportionately influential paper rated as having a high risk of bias [62], data were less heterogenous and a slightly lower weighted average prevalence (14%; 95% CI 13–18%) was estimated. When studies were additionally weighted by their quality/risk of bias, the estimate of



prevalence was higher, at 22% (and was also relatively unchanged by omission/inclusion of the Symons and Byiers paper, reflecting in part its lower weight in the analysis due to its rating indicative of high risk of bias), although 95% confidence intervals (16 to 29%) overlap with those for the random effects model. Asymmetry of distribution of effects as observed in funnel plots may potentially reflect lack of reporting of ASD prevalence in smaller studies in which ASD prevalence was relatively low. If this is the case, then weighted average prevalence values in the uncorrected meta-analyses may represent over-estimates; models correcting for this possible bias produced slightly lower estimates (12%, 95% CI 5–19%). Overall, existing data do not allow a precise statement of a single meta-analytic prevalence value; however, an estimate taking into account studies' risk of bias (the importance of which is highlighted by, e.g. [65]) suggests that over a fifth of females with FXS may meet criteria for ASD. Whether this represents an overestimate due to possible reporting bias should remain a focus of future research, in which care should be taken to publish ASD prevalence whether or not this is high within any particular study. It should be noted that the lower 95% confidence interval of every meta-analytic estimate of ASD prevalence for females with FXS was higher than reports in the general population (approximately 1 in 189 girls [3], or .53%), indicating that females with FXS are at increased risk for ASD. Lower

95% CIs also all exceeded the 1–3% estimate for females with FXS stated in a previous review [4]. These findings suggest that the FXS mutation increases ASD risk for females, perhaps to a greater degree than previously assumed, despite the potentially protective effect of the additional, unaffected X chromosome (whose influence may be demonstrated by the consistently lower levels of autistic behaviours found for girls than boys with FXS).

It is important to note that the instruments utilised for ASD diagnosis varied across studies, ranging from the parental report of diagnosis and broad screening measures to the 'gold standard' use of multiple comprehensive diagnostic instruments. It is well established that agreement between instruments can be variable. The studies outlined in this review indicate that this is also evident. For instance, Klusek et al. [46] reported significant differences in prevalence rates derived from the ADI-R and the ADOS, with 14.3% meeting the criteria on both the ADI-R and ADOS, 22.9% on the ADI-R but not the ADOS, and 25.7% for the ADOS but not the ADI-R.

ASD characteristics were reported in 21 papers, and included both social communication difficulties (e.g. difficulties both with non-verbal communication and language form, [47, 52, 63]) and repetitive/restrictive behaviours [52, 60, 63]. Differences in ASD characteristics relative to males with FXS [35, 36, 49, 58] were consistent with lower levels of atypicality (which in turn

Table 4 ASD behaviour findings [18, 19, 34, 35, 40, 41, 43–45, 47, 48, 50–52, 56, 59–63]

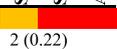
Authors and country of study	Sample of FXS females	Findings in relation to comparison groups	Findings in relation to DSM V criteria		Quality/risk of bias Assessment Score, weight
			Social communication and interaction	Restricted, repetitive patterns of behaviours, interests or activities	
Bailey et al. (2008)	259	No differences between females and matched group	Not reported	Not reported	 2 (0.22)
Baker et al (2019)	36	Significantly higher proportion of FXS males met criteria for ASD than FXS females, but after controlling for ID there was no significant difference. Males had more significant difficulties with eye contact, showing, initiation of joint attention, rapport, sensory, response to name, amount of social overtures (examiner), amount of social overtures (caregiver), amount of reciprocal communication, functional play, and imaginative/creative play.	Not reported	Not reported	 7 (0.78)
Hall et al. (2010)	33	Girls showed a few behaviours similar to reference sample of idiopathic autism but majority of items occurred at significantly lower rates. Significantly lower scores in communication domain items than FXS boys and reference group.	Not reported	Not reported	 7 (0.78)
Hall, Lightbody & Reiss (2008)	29	Boys more likely to score in the Autistic categories than girls. Males show higher scores in the communication scale, reciprocal social interaction scale and total score.	Not reported	Not reported	 7 (0.78)
Hatton et al. (2006)	32	Girls had significantly lower CARS scores than boys.	Not reported	Not reported	 3 (0.33)
Hessl et al. (2001)	40	Girls with FXS had mild levels of autistic behaviours, which were of greater number than unaffected siblings but fewer autistic behaviours than boys with FXS.	Not reported	Not reported	 6 (0.67)
Hustyi et al. (2015)	35	Females had significantly lower scores on ADOS than FXS males.	Not reported	Not reported	 7 (0.78)
Kaufmann et al. (2017)	132	ASD significantly more likely in males.	Not reported	Not reported	 3 (0.33)
Kidd et al. (2019)	97	Male sex associated with ASD status	Not reported	Not reported	 6 (0.66)
Lee et al. (2016)	34	Not reported.	Increased impairments in prosodic features of speech, facial expressions and social overtures (from ADOS) for FXS girls	Not reported	 5 (0.56)
Loesch et al. (2007)	45	Females are less significantly affected for ASD than males	Not reported	Not reported	 7 (0.78)

Table 4 ASD behaviour findings [18, 19, 34, 35, 40, 41, 43–45, 47, 48, 50–52, 56, 59–63] (Continued)

Martin et al. (2018)	42	Not reported	Girls with FXS-ASD used significantly more non-contingent language compared with all other female groups	Not reported	6 (0.66)	
Martin et al. (2019)	36	Not reported	Noncontingent language and perseveration were characteristic of the pragmatic profiles of boys and girls with FXS-ASD	Not reported	6 (0.66)	
Mazzocco et al. (1997)	30	FXS girls had significantly more autistic behaviour than TD controls Behaviours similar to those described in research for boys (frequency was lower).	Abnormalities in social and imaginative play, nonverbal communication, and language form. Less reported for girls awareness of others, lack of seeking comfort, and impaired imitation skills.	Abnormalities in stereotypic/restricted behaviours described.	6 (0.67)	
Reilly, Senior & Murtagh (2015)	21	Lower number diagnosed than males with FXS (44%). Compared with other syndromes, children with FXS more likely to be diagnosed with ASD.	Not reported	Not reported	2 (0.22)	
Shaffer et al. (2020)	11	FXS males had more impairment on SCQ score than female FXS	Not reported	Not reported	4 (0.44)	
Smith et al. (2012)	29	FXS +ASD group showed similar levels of overall autism to idiopathic ASD group.	Not reported	Repetitive-restricted behaviours were significantly higher in FXS +ASD than ASD alone.	6 (0.67)	
Smith et al. (2016)	26	Being female associated with fewer autistic behaviours than being male.	Not reported	Not reported	6 (0.67)	
Symons & Byiers 2010	51	Males more likely than females to have an autism diagnosis.	Not reported	Not reported	2 (0.22)	
Wheeler et al. (2015)	119	Not reported	Common - avoidance of eye contact (55%), excessive questioning and echoing questions or statements made by others (40%).	Common - a pre-occupation with particular topics (45%).	2 (0.22)	

TD typically developing

*Colour code—red = poor, yellow = adequate, orange = good, green = excellent

may relate to higher adaptive functioning) in girls. No papers reported greater levels of difficulty for girls than boys in any specific area. However, it remains possible that there are specific ASD-related clinical concerns for this group. Anxiety and the presence of self-injurious behaviour were both strongly correlated with ASD in this population [52]. These associations are also seen for people with idiopathic ASD and males with FXS [38, 66].

The findings were mixed when considering the associations between ASD and IQ and FMRP, with some studies indicating strong associations between ASD severity and IQ and FMRP levels and others reporting no correlations. Given that the nature of IQ assessment and sample sizes were similar across these studies, it is not clear why the resultant findings regarding IQ were inconsistent. Due to the focus on ASD in this paper, we reviewed potential relationships of FMRP and IQ with ASD

symptomatology. However, it should be noted that IQ and FRMP are also associated with each other [20, 21], and levels of FMRP may be considered to underlie both ASD and low IQ [67] in FXS in general. Understanding of the possible interrelationships between the three variables for females with FXS is still relatively rudimentary, and it remains possible that knowledge of the ways in which FMRP, ASD and IQ interrelate in males with FXS does not entirely generalise to females. For example, if relationships between IQ and ASD are non-linear (as may be the case for idiopathic ASD, [68, 69]), then the different ability levels seen in girls and boys with FXS may mean that the relationship between IQ and ASD is also different for these two groups. Future research may continue to assess the strengths of linear associations (as has been generally undertaken) between FMRP, IQ and ASD in larger groups, and also may consider potentially non-linear aspects of these relationships.

Table 5 Results and papers for IQ and ASD [18, 35, 36, 38, 40, 41, 46–49, 52, 58, 64]

Authors	Sample of FXS females	IQ Measure	Statistics for females with FXS	IQ and ASD findings	Quality/risk of bias
					Assessment Score, weight
					<div style="display: flex; justify-content: space-around; font-size: 8px;"> Sample Syndrome ASD </div>
Baker <i>et al.</i> (2019)	36	Mullen Scales or appropriate Wechsler tests	FSIQ M all females 67.8 (SD 17.8) Not broken down by ASD or non-ASD	Significantly higher proportion of males met criteria for ASD than females, but after controlling for ID there was no significant difference.	7 (0.78)
Barstein <i>et al.</i> (2018)	37	Leiter International Performance Scale-Revised (Leiter-R) – non-verbal mental age	FXS-ASD (n=12) M 5.1 (SD 0.8), range 4.0-6.1, FXS-Non ASD (n=25) M 7.0 (SD 2.3), range 3.9-12.8	No non-verbal mental age/ASD analysis.	3 (0.33)
Cordeiro <i>et al.</i> (2011)	39	WASI, WPPSI III, WAIS-III, WISC-III or WISC-IV – FSIQ	M all females 77.20 (SD 20.65), range 30-117; 33.3% in ID range Not broken down by ASD on non-ASD	No ASD/FSIQ analysis completed.	6 (0.67)
Hall <i>et al.</i> (2010)	33	WISC-III and WAIS-III – FSIQ	M all females 76.77 (SD 22.76), range 40-116 Not broken down by ASD on non-ASD	Lower IQ levels associated with significantly higher autistic behaviours.	7 (0.78)
Hall, Lightbody & Reiss (2008)	29	WISC III and WAIS-III - FSIQ	M all females 70.76 (SD 20.91) Not broken down by ASD on non-ASD	Girls with lower IQs more likely to show autistic behaviours.	7 (0.78)
Hessl <i>et al.</i> (2001)	40	WISC-III - FSIQ	M all females 75.48 (SD 22.30) Not broken down by ASD on non-ASD	IQ a significant predictor of autistic behaviour accounting for approx. 33% of the variability.	6 (0.67)
Klusek, Martin & Losh (2014)	35	Leiter- Revised - IQ and non-verbal mental age	IQ all females M 84.63 (SD 21.25), range 38-124, Mental age all females M 6.77 (SD 2.60), range 3.92-6.77 Not broken down by ASD on non-ASD	IQ and mental age not significant predictors of ASD diagnosis.	5 (0.56)
Lee <i>et al.</i> (2016)	34	Leiter – Revised - non-verbal mental age	All females time one M 6.18 (SD 1.72) FXS-ASD M time one 5.39 (SD 0.99) FXS – non-ASD M time one 6.51 (SD 1.87) All females time two M 7.31 (SD 3.04) FXS-ASD M time two 6.06 (SD 1.18) FXS – non-ASD M time two 8.12 (SD 3.60)	No ASD/non-verbal mental age analysis for girls.	5 (0.56)
Loesch <i>et al.</i> (2007)	Australian 31 American 14	WPPSI-R, WPPSI-III, WISC-III, WAIS-III - FSIQ	All females M 72.0 (SD 17.5) Not broken down by ASD on non-ASD	Significant correlations between lower IQ scores and higher scores i ADOS-G for FM	7 (0.78)
Martin <i>et al.</i> (2017)	39	Leiter-Revised - non-verbal mental age	FXS – Non- ASD M 7.1 (SD 2.50), range 4.3-13.3 FXS – ASD M 5.2 (SD 0.8), range 4-6.3	No mental age/ASD analysis.	7 (0.78)
Mazzocco <i>et al.</i> (1997)	30	WISC-R – FSIQ	M all females 87.4 (SD 14.1), range 66 to 116 Not broken down by ASD on non-ASD	No correlation between IQ and autistic behaviours.	6 (0.67)
Russon-Ponsaran <i>et al.</i> (2014)	11	WASI - FSIQ	M all females 76.82 (SD 12.8), range 52-97 Not broken down by ASD on non-ASD	No FSIQ/ASD analysis.	7 (0.78)
Wheeler <i>et al.</i> (2019)	72	Stanford Binet Intelligence Scales 5 th edition	Female FXS group IQ – 70.1 (SD 17.7) Not broken down by ASD or non-ASD	No IQ/ASD analysis	5 (0.55)

TD typically developing, M mean, SD standard deviation

*Colour code—red = poor, yellow = adequate, orange = good, green = excellent

Strengths and limitations

The findings should be considered in light of several methodological constraints. Given the range of ASD

diagnostic assessments used across studies, and the reported variability in sensitivity and specificity of these measurement tools, the prevalence data reported in this

Table 6 Results for FMRP and ASD [10, 18, 19, 40, 41, 48]

Authors	Sample of FXS females	FMRP Measure	Statistics for females with FXS	FMRP and ASD findings	Quality Assessment Score, weight		
					Sample	Syndrome	ASD
Hall et al. (2010)	33 f	% of lymphocytes expressing FMRP	FMRP all females M 53.02 (SD 18.59), range 14.5-90 Not broken down by ASD on non-ASD	No effect of FMRP levels on autistic behaviours.	7 (0.78)		
Hall, Lightbody & Reiss (2008)	29	% of lymphocytes expressing FMRP	M all females FMRP 52.02 (SD 16.97), range 15-84.5 Not broken down by ASD on non-ASD	No association between FMRP and ASD for females.	7 (0.78)		
Hatton et al. (2006)	32	% of lymphocytes expressing FMRP	M all females 40.5 (SD 20.1) Not broken down by ASD on non-ASD	FMRP predicted mean CARS – low levels associated with higher autistic behaviour.	3 (0.33)		
Hatton et al. (2009)	15	% of lymphocytes expressing FMRP	Sub-sample of 11 females M 41.5, range 9-67.5 Not broken down by ASD on non-ASD	FMRP not associated with developmental outcome. No FMRP/ASD analysis.	6 (0.67)		
Hessl et al. (2001)	40	% of lymphocytes expressing FMRP	M all females 51.03 (SD 18.57) Not broken down by ASD on non-ASD	FMRP not a significant predictor of ASD-behaviour.	6 (0.67)		
Loesch et al. (2007)	Australian 31 American 4	% of lymphocytes expressing FMRP	M 59.9 (SD 21) Not broken down by ASD on non-ASD	Significant correlations between FMRP and the COM domain and the total score of ADOS-G.	7 (0.78)		

*Colour code—red = poor, yellow = adequate, orange = good, green = excellent

review should be considered as estimates only. Whilst the weighting of individual studies in the generation of quality weighted meta-analytic prevalence estimates is based partly on the risk of bias of the ASD measures, this cannot completely account for the wide and complex variability in ASD measurement in the reviewed papers. Further limitations relate to the use of the most stringent level of ASD assessment in each paper in the meta-analysis (a decision following Richards et al. [6], which allows for consistency with previous reviews, and replicability). Greater consistency within the literature in the stringency of reported ASD diagnosis may be important in the future.

Recruitment bias (e.g. for papers recruiting via specialist medical centres, participants may be more likely to be those with difficulties of clinical relevance) may also confound interpretation of prevalence estimates. Given the relatively small population of females with FXS, it is also possible that the same participants are included in more than one study, introducing further biases.

A large proportion of studies did not include appropriate contrast groups, as a large proportion only had males with FXS and the discrepancies between males and females with FXS are well-documented. Also, most contrast groups reported do not appear to be matched on IQ or age, which would also be important factors when

considered appropriateness of controls. Future studies which are matched for gender, age and IQ would be most appropriate in order to not limit the findings.

The results reported are found for females across a wide variety of ages, with a few papers looking at ages across the lifespan but most having a focus on either children or adults. Research has shown differences in behaviours caused by FXS across the lifespan [70, 71], but none of the papers reviewed explored the impact of age ranges as potentially confounding factors, either in the analysis or discussion.

Strengths of this review include the systematic search strategy and use of a tool for risk-of-bias appraisal specifically developed for research into ASD in genetic syndromes, and with good levels of inter-rater reliability. Greater research focus on females with FXS is important in order to improve understanding and awareness of the challenges faced by affected individuals and their families.

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Authors' contributions

MM completed the systematic search and took the lead role in the write-up (including conducting an initial prevalence data analysis and interpreting the results and findings). AW contributed to the writing of the review and conducted and interpreted the meta-analysis. CJ directed and advised on the meta-analysis and its interpretation, and provided R scripts. SR completed

the role of second reviewer for quality and search purposes. JM conceptualised the review, reviewed and refined analysis and interpretation of data and reviewed and edited manuscript drafts. AW and JM both held supervisory roles for student projects. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors. No informed consent was required as this article is a review and no individual participants have identifying information.

Consent for publication

Not applicable

Competing interests

The authors declare that there are no competing interests.

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