Prevalence of autism spectrum disorder phenomenology in genetic disorders: a systematic review and meta-analysis

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Summary

Background Autism spectrum disorder (ASD) phenomenology is reported to be more common in individuals with some genetic syndromes than in the general population; however, no meta-analysis has provided prevalence data within and between syndromes. In this systematic review and meta-analysis, we aimed to synthesise data from a wide range of papers to provide accurate estimates about ASD phenomenology in genetic and metabolic syndromes.

Methods We identified syndromes reported as most likely to be associated with ASD. We searched Ovid PsycINFO, Ovid MEDLINE, Ovid Embase, and PubMed Central for English-language papers published from database creation up to early 2014 with use of syndrome-specific keywords and a set of ASD keywords. We screened and extracted papers that had ASD prevalence data for ten or more people within a genetic syndrome. With use of a prespecified set of reliable criteria, we applied quality weighting to papers and estimated a quality-effects prevalence of ASD phenomenology for each syndrome. We then calculated relative risks to compare ASD between all syndromes and also calculated odds ratios to compare prevalence with the general population taking the current estimate of one in 68 people.

Results We identified 168 papers reporting the prevalence of ASD phenomenology and found widely varying methods and quality of data. Quality-weighted effect prevalence estimates of ASD phenomenology were established for Rett's syndrome (female individuals only 61%), Cohen's syndrome (54%), Cornelia de Lange syndrome (43%), tuberous sclerosis complex (36%), Angelman's syndrome (34%), CHARGE syndrome (30%), fragile X syndrome (male individuals only 30%; mixed sex 22%), neurofibromatosis type 1 (18%), Down's syndrome (16%), Noonan's syndrome (15%), Williams' syndrome (12%), and 22q11.2 deletion syndrome (11%). Relative risks and the odds ratio compared with the general population were highest for Rett's syndrome and Cohen's syndrome. In all syndromes, odds ratios showed ASD phenomenology to be significantly more likely than in the general population.

Interpretation ASD phenomenology varied between syndromes, but was consistently more likely than in the general population. Further research is needed in these populations, including how ASD in genetic and metabolic syndromes differs from idiopathic autism and what that can tell us about the mechanisms underlying ASD.

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Introduction

Autism spectrum disorder (ASD) is a broad term for a group of behaviourally defined neurodevelopmental disorders that historically includes autistic disorder, childhood autism, pervasive developmental disorder—not otherwise specified (PDD-NOS), and Asperger's syndrome.[1,2] ASD is defined by the presence of abnormalities or impairments in social interaction and communication, with accompanying restricted or repetitive behaviours, activities, or interests. Estimates for the prevalence of ASD in the general population range from one in 100 people[3,4] to one in 68.[5] However, despite the high prevalence and robust research documenting heritability,[6] a genetic aetiological cause has yet to be identified. This absence might be partly because of the methodological challenges caused by the behavioural heterogeneity within the spectrum.[7]

ASD phenomenology seems more prevalent in individuals with specific genetic and metabolic syndromes than in those without these sydromes.[8,9] Study of the prevalence and phenomenology of ASD within and across these syndromes could disentangle the genetic and biological pathways that underlie idiopathic ASD.[7,10,11] Recent findings show that particular rare de-novo or transmitted copy number variations substantially increase risk of ASD.[12] Through studying the downstream disruption caused by these variations, researchers are identifying candidate ASD-associated genes. From these biological markers, it might be possible to identify specific cognitive deficits that underpin characteristic idiopathic ASD behaviours.

Evidence is emerging that individuals with certain genetic and metabolic syndromes might have an atypical profile of ASD phenomenology, which would support a distinction between syndromic variants of ASD and idiopathic ASD.[13–15] A pragmatic strategy to evaluate the presence of syndromic variants of ASD would be to conduct detailed analysis of ASD phenomenology in syndromes in which prevalence estimates for ASD are consistently high. However, despite many systematic reviews[16–19] no meta-analytic studies have documented the consistency of prevalence data within syndromes,

calculated variation of prevalence estimates between syndromes, or compared prevalence estimates to those for the general population.

Several methodological challenges complicate synthesis of prevalence data for ASD phenomenology across syndromes. First, the diagnosis of ASD in clinical practice requires rigorous multicomponent assessment, with information collected from many sources and across contexts.[19] This depth and breadth of diagnostic assessment is rarely replicated in research, and any prevalence statistics are thus more accurately described as estimates of the presence of ASD phenomenology, rather than estimates of the presence of diagnostically defined ASD. Additionally, many studies rely solely on screening measures, which take less time and resources. However, screening measures often have low specificity and sensitivity[14,20] and thus the prevalence data have wide confidence intervals. Diagnostic measures have greater sensitivity and specificity, however, prevalence data might be biased because accuracy is lowest for marginal or unusual cases, such as those with intellectual disability.[20]

The association between ASD phenomenology and greater severity of intellectual disability[21] is hypothesised to contribute to the behavioural phenotypes associated with genetic syndromes, such that associated degree of disability, rather than the presence of the syndrome itself, more fully accounts for the presence of ASD in these groups.[22] Although this pattern of association is often evident in individual syndrome groups, sometimes the association between ASD and intellectual disability is less robust. For example, in Cri du Chat syndrome, intellectual disability is usually severe and prevalence of ASD is relatively low compared with syndromes with similar levels of intellectual disability, even after controlling for intellectual functioning.[23] Conversely, individuals with fragile X syndrome seem at increased risk of ASD phenomenology despite a wide range of intellectual functioning in the group—although within this group, ASD phenomenology is negatively associated with IQ.[14] Individuals with Cornelia de Lange syndrome show higher amounts of ASD phenomenology than do individuals with intellectual disability of heterogeneous aetiology with comparable adaptive functioning.[24] Available models of this association are based on individual empirical studies that are limited by small samples and cohort effects. The delineation of robust rates of ASD phenomenology for each syndrome through meta-analytic methods would advance attempts to evaluate comprehensively the association between ASD phenomenology and intellectual disability in syndromes.

In this systematic review and meta-analysis, we aimed to describe and evaluate the scientific literature for ASD phenomenology in genetic and metabolic syndromes and to generate pooled estimates for prevalence of ASD phenomenology within each syndrome, weighted by the quantity and quality of the available evidence; to make preliminary comparisons of the pooled prevalence estimates across syndromes; and to compare pooled prevalence estimates in the syndromes with estimates of ASD in the general population.

Methods
Search strategy and selection criteria
With use of a 2009 review, we generated a list of 21 syndromes most likely to be associated with ASD.[15] The review highlighted genetic syndromes in which at least one empirical study had been done and previous systematic reviews had described the syndrome to be associated with ASD. We did literature searches in Ovid PsycINFO, Ovid MEDLINE, Ovid Embase, and PubMed Central for English-language papers published from database creation up to early 2014 (appendix). Searches were done by combining autism search terms with all variations of the syndrome search terms (listed in appendix). The autism search terms included "autis*", "autism*", "autistic*", "ASD", "autism spectrum disorder*", "PDD-NOS", "PDDNOS", "unspecified "PDD", "pervasive developmental disorder*", "pervasive developmental disorder not otherwise specified", "Asperger*", and "Asperger* syndrome". Additionally, we hand-searched the reference list of Moss and Howlin[15] to identify papers.

We then assessed papers from the search in three stages. LG screened papers by review of abstracts and titles. Papers were included if they were empirical papers; published or available in English; included a participant sample of ten people or more; and indicated in the abstract that the paper reported on the prevalence of ASD within a genetic syndrome group. For any papers where suitability was unclear CR reviewed the paper for consensus.

CR read the full texts of screened papers to assess eligibility of the data. The same inclusion and exclusion criteria were used at screening and eligibility. However, the following additional inclusion criteria were specified at the eligibility stage: the paper reports the number of participants who met a clinical cutoff for ASD, participants were recruited without any specific bias, and the study reports on a unique sample (or a potentially overlapping sample, but the proportion of overlap cannot be readily determined). When samples were identical, the paper with the highest quality weighting was included in the analysis to ensure the most robust pooled prevalence estimates.

The quality of the remaining papers was then assessed according to the quality criteria listed later. Papers were included if they had a minimum quality weighting of 0·33 by a combination of scores from at least two criteria. If, at any stage, the number of papers remaining in a syndrome group was lower than two, the group was removed from the analysis (appendix).

Quality review and data extraction
We generated a numerical quality weighting for each study through a quality review and used these data to weight the influence of individual studies in the quality-effects pooled

prevalence estimate for each syndrome. Because this was the first statistical meta-analysis of ASD phenomenology in syndromes and research was scarce for some syndromes, a pragmatic decision was taken to delineate broad quality criteria that allowed for the maximum inclusion of studies, while weighting prevalence estimates from the most robust studies more heavily.

The quality criteria were generated through review of standardised quality criteria for intervention studies[25] and prevalence studies.[26] To control for key threats to validity, we devised idiosyncratic quality criteria for the selection of the samples with syndromes, the confirmation of syndrome, and the assessment of ASD. For each of these criteria, we did literature reviews and consulted active research experts in autism and rare syndromes for advice about areas of methodological concern.

To provide a simple visual matrix, when quality ratings are provided for each syndrome, the criteria were coded as red for a score of zero, yellow for a score of one, amber for a score of two, and green for a score of three (appendix). The quality weighting was calculated by dividing the total quality score by the maximum possible total of nine. All studies that met the inclusion criteria were read by CR and rated for quality with these criteria.

From each paper selected, we extracted the number and percentage of the sample individuals who met clinical cutoff for ASD phenomenology. The clinical cutoff varied for each measure of ASD assessment used. When an assessment provided multiple cutoffs (eg, PDD-NOS vs autistic disorder), the most conservative cutoff for the most severe level of ASD phenomenology was entered into the meta-analysis.

Statistical analysis
We used MetaXL version 2.0 (EpiGear, QLD, Australia) to generate pooled prevalence estimates. Because studies in this review are all of variable methodological quality, we used a random-effects model to calculate prevalence. Additionally, we constructed a quality-effects model based on methodological quality ratings. Here, the weightings were derived directly from the quality index score (as reported above) as well as the study's sample size. To avoid confidence intervals for the pooled prevalence estimates falling outside of the 0·1 boundaries, we applied the double-arcsine back transformation to both the random-effects and quality-effects models.

To make comparisons across syndromes, we plotted the random-effects and quality-effects pooled prevalence estimates for each group against one another. Due to the large number of between-group tests, more conservative (99%) confidence intervals were selected. We calculated relative risk statistics using 99% CIs to assess the relative likelihood of ASD phenomenology in each syndrome using the quality-effects prevalence.

Finally, to compare ASD phenomenology in each syndrome with an estimated prevalence in the general population, we generated odds ratios (OR) with 95% CI,

comparing the quality-effects pooled prevalence for each syndrome with the most recent total population prevalence estimate for ASD diagnosis (one in 68).[5] Although this total population prevalence estimate of ASD diagnosis is significantly higher than that from previous estimates, we felt it to be the most appropriate comparison for meta-analysis, because any identified increased likelihood of ASD phenomenology in the syndrome groups could not be attributed to overly conservative estimates for the general population prevalence.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
We identified 32 230 papers and selected 168 papers, across 16 syndromes, as suitable for qualitative review (figure 1, table 1). Across syndromes, only nine (5·4%) papers met criteria for the highest quality rating for sample identification, whereas 89 (53·0%) obtained the highest quality rating for syndrome confirmation, and 43 (25·6%) for ASD assessment. Only one (0·6%) paper met the highest quality rating for all three quality criteria. Nine (5·4%) papers were excluded from the pooled
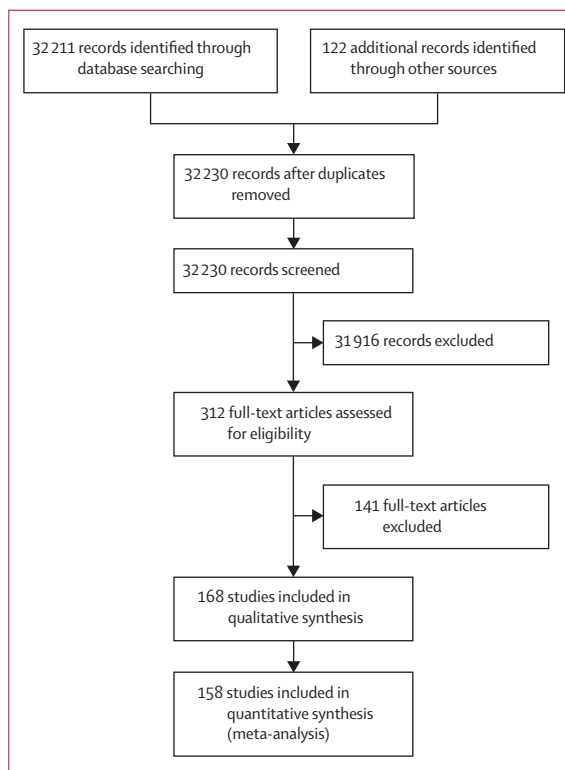

Figure 1: Study selection
*For more detailed explanation about exclusions see appendix.

	Studies	Patients (n)	Mean quality weighting	Individual scores			Quality weighting score			Prevalence of ASD	
				Obtained score of 3 for sample	Obtained score of 3 for syndrome confirmation	Obtained score of 3 for ASD assessment	Poor	Adequate	Good	Random-effects pooled prevalence	Quality-effects pooled prevalence
Fragile X syndrome	56	4089	0·63 (0·16)	1 (1·8%)	50 (89·3%)	15 (26·8%)	10 (17·9%)	31 (55·4%)	15 (26·8%)	26·0% (20·0–31·0)	22·0% (15·0–30·0)
Fragile X syndrome (boys and men only)*	28	1370	0·61 (0·17)	0	23 (82·1%)	7 (25·0%)	6 (21·4%)	16 (57·1%)	6 (21·4%)	28·0% (21·0–36·0)	30·0% (22·0–38·0)
Tuberous sclerosis complex	25	1434	0·55 (0·15)	2 (8·0%)	5 (20·0%)	8 (32·0%)	11 (44·0%)	10 (40·0%)	4 (16·0%)	37·0% (33·0–40·0)	36·0% (33·0–40·0)
22q11.2 deletion syndrome	14	830	0·69 (0·15)	0	14 (100%)	6 (42·9%)	1 (7·1%)	6 (42·9%)	7 (50·0%)	12·0% (6·0–19·0)	11·0% (5·0–19·0)
Cornelia de Lange syndrome	12	598	0·55 (0·13)	0	1 (8·3%)	2 (16·7%)	6 (50·0%)	4 (33·3%)	2 (16·7%)	43·0% (33·0–54·0)	43·0% (32·0–53·0)
Down's syndrome	10	1084	0·54 (0·20)	3 (30·0%)	4 (40·0%)	1 (10·0%)	6 (60·0)	2 (20·0%)	2 (20·0%)	16·0% (9·0–23·0)	16·0% (8·0–24·0)
Angelman's syndrome	7	245	0·68 (0·18)	0	5 (71·4%)	3 (42·9%)	2 (28·6%)	1 (14·3%)	4 (57·1%)	35·0% (24·0–38·0)	34·0% (24·0–37·0)
Neurofibromatosis type 1	6	412	0·57 (0·18)	2 (33·3%)	0	1 (16·7%)	3 (50·0%)	2 (33·3%)	1 (16·7%)	16·0% (8·0–26·0)	18·0% (9·0–29·0)
Williams' syndrome	5	119	0·65 (0·20)	0	5 (100·0%)	1 (20·0%)	1 (20·0%)	1 (20·0%)	3 (60·0%)	14·0% (8·0–21·0)	12·0% (6·0–20·0)
Rett's syndrome (girls and women only)†	5	194	0·51 (0·10)	0	2 (40·0%)	0	3 (60·0%)	1 (20·0%)	1 (20·0%)	61·0% (47·0–75·0)	61·0% (46·0–74·0)
CHARGE syndrome	4	232	0·64 (0·21)	1 (25·0%)	0	2 (50·0%)	1 (25·0%)	1 (25·0%)	2 (50·0%)	29·0% (14·0–48·0)	30·0% (13·0–48·0)
Möbius' syndrome*	4	94	0·59 (0·11)	0	0	2 (50·0%)	1 (25·0%)	3 (75·0%)	0	9·0% (0·0–25·0)	7·0% (0·0–22·0)
Phenylketonuria syndrome*	3	267	0·59 (0·17)	0	2 (66·7%)	1 (33·3%)	1 (33·3%)	1 (33·3%)	1 (33·3%)	10·0% (1·0–27·0)	9·0% (0·0–23·0)
Cohen's syndrome	2	96	0·67 (0)	0	0	2 (100·0%)	0	2 (100%)	0	54·0% (44·0–64·0)	54·0% (44·0–64·0)
Noonan's syndrome	2	86	0·62 (0·08)	0	1 (50·0%)	0	0	2 (100%)	0	16·0% (7·0–27·0)	15·0% (7·0–26·0)
Joubert's syndrome*	2	54	0·56 (0·16)	0	0	0	1 (50·0%)	1 (50·0%)	0	9·0% (0·0–50·0)	9·0% (0·0–49·0)
Hypomelanosis of Ito syndrome*	1	25	0·33	0	0	0	1 (100%)	0	0	..	..

Data are n (%), mean (SD), or prevalence (95% CI). Syndromes listed in order of size of evidence base. Quality weighting categories are poor (0·33–0·55), adequate (0·56–0·77), and good (0·78–1·0; appendix). ASD=autism spectrum disorder. *Excluded from subsequent between-groups analysis. †Rett's syndrome predominantly affects female individuals; papers identified in the meta-analysis included only girls and women.

Table 1: **Study characteristics and weighting scores, and pooled prevalence for ASD for all 16 genetic and metabolic syndromes**

prevalence estimates because they did not meet the required quality inclusion criteria. To establish the reliability of our quality criteria, 52 (32%) of all studies were independently rated by a second researcher. The correlation coefficient for total quality weighting was good ($r(52)=0·78$, $p<0·001$).

In total, 54 (32·1%) papers reported on the profile of ASD phenomenology within a syndrome, in addition to reporting the prevalence. Most papers (n=91; 54·1%) reported the proportion of the sample that had an intellectual disability. Further data for participant characteristics, the ASD measures used, and forest plots of the random-effects and quality-effects prevalence estimates are in the appendix.

ASD phenomenology ranged in prevalence across the 12 syndromes that met inclusion criteria for comparison, from a quality-weighted effect prevalence of 61% (95% CI 46·0–74·0) in individuals with Rett's syndrome to 11% (5·0–19·0) in those with 22q11.2 deletion syndrome (table 1; figure 2). Prevalence estimates were also generated for Möbius' syndrome, phenylketonuria, and

Joubert's syndrome (table 1), but these data were not deemed to be robust due to the wide confidence intervals including zero. Data for fragile X syndrome in male individuals were excluded to prevent overlap.

Table 2 presents the relative risk for ASD prevalence between the 12 syndromes that were robust enough for comparison. ASD phenomenology was significantly more likely in Rett's and Cohen's syndromes than in all other syndromes (table 2). Relative risks were moderate for tuberous sclerosis complex, Cornelia de Lange syndrome, CHARGE syndrome, and Angelman's syndrome compared with others. ASD phenomenology was significantly less likely in Noonan's, 22q11.2 deletion, Williams', and Down's syndromes than in most other syndromes.

For the final aim of the meta-analysis, we generated odds ratios to compare each syndrome with the most recent estimates for ASD diagnoses in the general population (figure 3). ASD phenomenology was significantly more likely in all syndromes than in the general population. Odds ratios ranged from 8·3

(95% CI 1·04–65·73) for 22q11.2 deletion syndrome to 104·8 (95% CI 13.97–786.08) for Rett's syndrome. ASD phenomenology was significantly more likely for boys and men with fragile X syndrome, compared with the general population (OR 28·7, 95% CI 3·8–216·5).

Discussion

In this meta-analysis, we present pooled data and cross-syndrome comparisons for the prevalence of ASD phenomenology in rare genetic and metabolic syndromes. To our knowledge, this was the first meta-analysis of the prevalence of ASD phenomenology across many genetic syndromes and thus extended findings from previous systematic reviews.[14–17] Our wide search criteria and screening of both abstracts and titles during the initial search stages allowed the identification and inclusion of a greater number of studies than in previous systematic reviews. The creation of a unique quality rating scheme to evaluate and weight the prevalence data further strengthened the findings.

ASD phenomenology was highly prevalent in Cohen's and Rett's syndromes. Despite cross-syndrome differences, the odds of the presence of ASD phenomenology were increased by between eight and 105 times in all syndromes compared with the odds of ASD diagnosis in the general population. The pooled prevalence estimates ranged from 61% in individuals with Rett's syndrome to 11% in individuals with 22q11.2 deletion syndrome. Overall, the generated prevalence figures were similar to previous prevalence range estimates cited in systematic reviews.[14–17] However, there were several differences. First, the prevalence figure of 22% we show for fragile X syndrome was at the very low end of the range indicated by Moss and Howlin (21–50%)[15] and Zafeiriou and colleagues (22–33%).[16] The more conservative prevalence estimate from this meta-analysis was probably due to the inclusion of data from both male and female individuals with fragile X syndrome. Our prevalence estimate for only boys and men of 30% was consistent with that from previous reviews.[15,16] However, to maintain parity with other syndromes, we used the generated prevalence estimate including data from mixed sex samples to do cross-syndrome comparisons. Secondly, the generated prevalence estimates for Cornelia de Lange, Angelman's, Down's, and 22q11.2 deletion syndromes were slightly more conservative than some of the ranges reported in previous systematic reviews (Cornelia de Lange syndrome 50–67%,[14] 46–67%;[16] Angelman's syndrome 50–81%,[14] 50–61%;[16] 22q11.2 deletion syndrome 20–31%,[17] 14–50%[16]). In all cases, the prevalence estimates in the systematic reviews were based upon far fewer studies than the prevalence estimate for this meta-analysis.[15,16] Additionally, this review aimed to improve the quality of prevalence estimates for each of the syndromes by including quality review and weighting the most robust estimates more heavily. Thus, while the reported prevalence data might be more conservative than previous reports in some cases, it is probably also more robust.
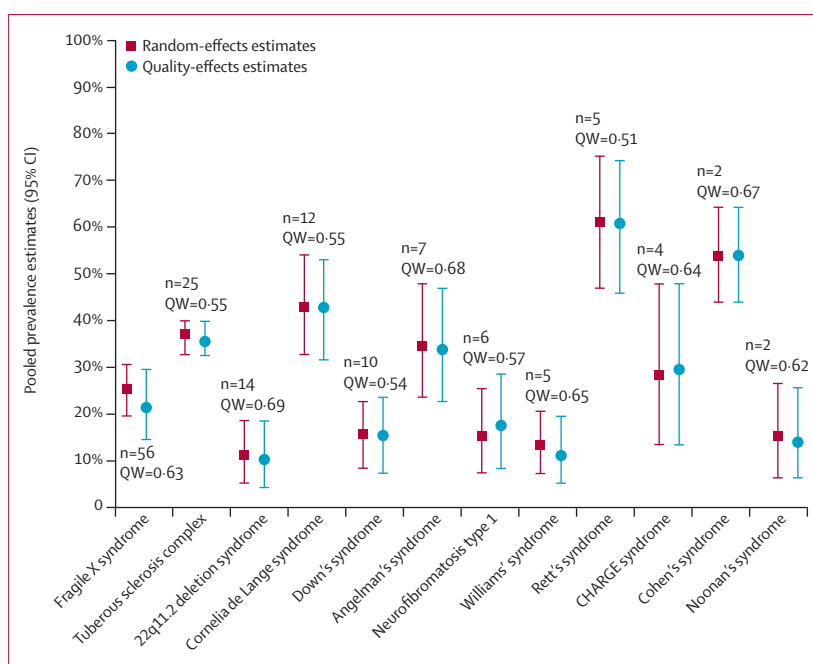

Figure 2: Pooled prevalence estimates of ASD phenomenology
ASD=autism spectrum disorder. n=number of papers used. QW=mean quality weighting for syndrome.

Our meta-analysis allowed comparisons of ASD prevalence between syndromes and with the general population. Findings show syndromes can be clustered into groups of prevalence; those in which ASD phenomenology was comparatively highly likely (Rett's and Cohen's syndromes), moderately likely (tuberous sclerosis complex, Cornelia de Lange, CHARGE, and Angelman's syndromes), less likely (fragile X syndrome and neurofibromatosis type 1), and least likely (22q11.2 deletion, Noonan's, Williams', and Down's syndromes). The results show that even within a group of syndromes known to have increased ASD phenomenology, much variation exists. These data can be used to guide research into underlying pathways of idiopathic ASD. Focus on mechanisms in syndromes in which ASD is highly likely might allow exploration of the cognitive and genetic explanations for idiopathic ASD. Some researchers have begun to reject unified explanations of ASD pheno-menology and instead suggest fractionation of the social communicative and repetitive impairments present in idiopathic ASD.[27] However, research in idiopathic ASD is made difficult by the constraint of behavioural diagnosis—ie, individuals are included in studies because of an ASD diagnosis that necessitates impairments in social communicative and repetitive domains, and then these same individuals are assessed to investigate the unitary coherence of these impair-ments. Investigation of the overlap and differences of social communication and repetitive impairments in these high-risk syndromes would progress unitary or fractionated models of ASD, while also removing the inclusion bias in studies of individuals with idiopathic

	Fragile X syndrome	Tuberous sclerosis complex	22q11.2 deletion	Cornelia de Lange syndrome	Down's syndrome	Angelman's syndrome	Neuro-fibromatosis type 1	William's syndrome	Rett's syndrome	CHARGE	Cohen's syndrome	Noonan's syndrome
Fragile X syndrome (moderate to severe)	..	1·64 (0·90–2·97)	0·50 (0·21–1·21)	1·95 (1·11–3·45)	0·73 (0·34–1·56)	1·55 (0·84–2·83)	0·82 (0·39–1·71)	0·55 (0·23–1·28)	2·77 (1·64–4·70)	1·36 (0·73–2·55)	2·45 (1·43–4·22)	0·68 (0·31–1·49)
Tuberous sclerosis complex (normal to profound)	0·61 (0·34–1·11)	..	0·31 (0·14–0·69)	1·19 (0·76–1·88)	0·44 (0·22–0·88)	0·94 (0·57–1·55)	0·50 (0·26–0·96)	0·33 (0·15–0·73)	1·69 (1·13–2·53)	0·83 (0·49–1·41)	1·50 (0·99–2·28)	0·42 (0·21–0·84)
22q11.2 deletion (normal to severe)	2·00 (0·83–4·82)	3·27 (1·46–7·36)	..	3·91 (1·77–8·63)	1·45 (0·57–3·73)	3·09 (1·37–7·00)	1·64 (0·65–4·10)	1·09 (0·40–3·00)	5·55 (2·59–11·89)	2·73 (1·19–6·27)	4·91 (2·27–10·62)	1·36 (0·52–3·55)
Cornelia de Lange syndrome (mild to profound)	0·51 (0·29–0·90)	0·84 (0·53–1·32)	0·26 (0·12–0·56)	..	0·37 (0·19–0·72)	0·79 (0·50–1·26)	0·42 (0·22–0·78)	0·28 (0·13–0·60)	1·42 (0·99–2·04)	0·70 (0·43–1·14)	1·26 (0·86–1·84)	0·35 (0·18–0·69)
Down's syndrome (moderate to severe)	1·38 (0·64–2·96)	2·25 (1·14–4·46)	0·69 (0·27–1·76)	2·69 (1·39–5·21)	..	2·13 (1·06–4·24)	1·13 (0·50–2·52)	0·75 (0·30–1·87)	3·81 (2·04–7·13)	1·88 (0·92–3·82)	3·38 (1·78–6·38)	0·94 (0·40–2·20)
Angelman's syndrome (severe to profound)	0·65 (0·35–1·18)	1·06 (0·64–1·74)	0·32 (0·14–0·73)	1·26 (0·79–2·02)	0·47 (0·24–0·94)	..	0·53 (0·27–1·02)	0·35 (0·16–0·77)	1·79 (1·19–2·72)	0·88 (0·52–1·50)	1·59 (1·03–2·44)	0·44 (0·22–0·90)
Neurofibromatosis type 1 (mild)	1·22 (0·59–2·55)	2·00 (1·04–3·83)	0·61 (0·24–1·53)	2·39 (1·28–4·47)	0·89 (0·40–1·99)	1·89 (0·98–3·65)	..	0·67 (0·27–1·62)	3·39 (1·88–6·10)	1·67 (0·85–3·28)	3·00 (1·65–5·47)	0·83 (0·37–1·90)
Williams' syndrome (mild)	1·83 (0·78–4·29)	3·00 (1·38–6·54)	0·92 (0·33–2·53)	3·58 (1·68–7·66)	1·33 (0·53–3·33)	2·83 (1·29–6·22)	1·50 (0·62–3·65)	..	5·08 (2·45–10·53)	2·50 (1·12–5·58)	4·50 (2·15–9·41)	1·25 (0·49–3·17)
Rett's syndrome (severe to profound)	0·36 (0·21–0·61)	0·59 (0·40–0·88)	0·18 (0·08–0·39)	0·70 (0·49–1·01)	0·26 (0·14–0·49)	0·56 (0·37–0·84)	0·30 (0·16–0·53)	0·20 (0·09–0·41)	..	0·49 (0·32–0·77)	0·89 (0·65–1·21)	0·25 (0·13–0·47)
CHARGE (normal to severe)	0·73 (0·39–1·37)	1·20 (0·71–2·02)	0·37 (0·16–0·84)	1·43 (0·88–2·35)	0·53 (0·26–1·09)	1·13 (0·66–1·93)	0·60 (0·30–1·18)	0·40 (0·18–0·89)	2·03 (1·30–3·17)	..	1·80 (1·14–2·85)	0·50 (0·24–1·04)
Cohen's syndrome (mild to severe)	0·41 (0·24–0·70)	0·67 (0·44–1·01)	0·20 (0·09–0·44)	0·80 (0·54–1·17)	0·30 (0·16–0·56)	0·63 (0·41–0·97)	0·33 (0·18–0·61)	0·22 (0·11–0·46)	1·13 (0·82–1·55)	0·56 (0·35–0·88)	..	0·28 (0·14–0·54)
Noonan's syndrome (normal–moderate)	1·47 (0·67–3·21)	2·40 (1·19–4·85)	0·73 (0·28–1·91)	2·87 (1·45–5·67)	1·07 (0·45–2·50)	2·27 (1·11–4·62)	1·20 (0·53–2·74)	0·80 (0·32–2·03)	4·07 (2·13–7·77)	2·00 (0·96–4·15)	3·60 (1·86–6·96)	..

The associated degree of intellectual disability for each syndrome is shown in parentheses in the first column. ASD=autism spectrum disorder.

Table 2: Relative risks (99% CI) for the prevalence of ASD phenomenology in each included syndrome compared with other syndromes
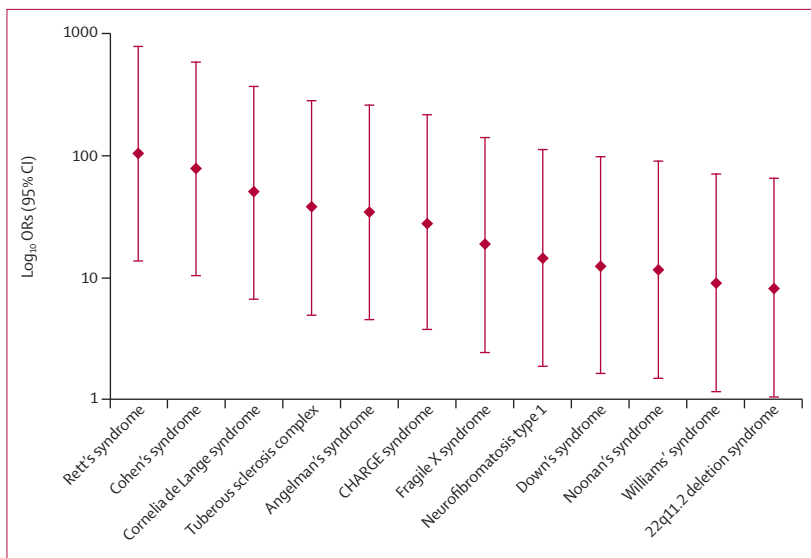

Figure 3: Likelihood of ASD phenomenology in each syndrome compared with the general population
OR=odds ratios. ASD=autism spectrum disorder.

The results of this analysis have important implications for clinical and educational services for individuals with genetic syndromes, in all of which our results show a greater risk of ASD-type behaviours than in the general population. Irrespective of empirical or conceptual questions about whether these behaviours are commensurate with idiopathic ASD, the presence of ASD-like difficulties in communication, social interaction, and restrictive and repetitive behaviours in those with these syndromes should lead to the same tailored support for affected individuals that has been proposed for those with idiopathic ASD. Assessments should also include an exploration of the effect of any identified ASD impairments on the individual's quality of life, and that of their families and carers. In some cases, specific educational placements might be of benefit. Also, ASD-specific clinical interventions to support communication and social skills development could be useful. Most importantly, these results show the importance of reducing diagnostic overshadowing, in which all social and communicative difficulties in a syndrome are attributed solely to the genetic syndrome, and highlights the need to assess and identify concurrent ASD impairments.[15]

The meta-analysis has also provided opportunity to evaluate and compare research methodologies used to

ASD. Examples of this include delineation of the profile of ASD in Cornelia de Lange syndrome,[28] fragile X syndrome,[14,28] and Down's syndrome.[29]

assess the prevalence of ASD phenomenology within and between syndromes. A key issue that arose was a propensity for research groups to publish data that appeared to have been collected in a similar but not identical sample in multiple papers. Although legitimate reasons might exist for doing so, specifically for publishing data about different aspects of the same syndrome, it is imperative for authors to fully describe their sample, and whether the whole sample or a proportion of the sample have been reported previously. This is a key area for improvement in future research.

We identified much variability in the reporting of the professional who interpreted the ASD assessments. When ASD assessments require clinical interpretation (eg, Childhood Autism Rating Scale [CARS]) or substantial pre-assessment training (eg, Autism Diagnostic Interview-Revised [ADI-R] or Autism Diagnostic Observation Schedule [ADOS]), studies should report the role, qualification, or level of training of the examiner clearly. For the purposes of this review, we needed to include as many studies as possible. However, future reviews should seek to use more stringent inclusion criteria, requiring adequate description of the delivery and interpretation of ASD assessment tools. Use of these inclusion criteria would have reduced the number of papers in the present meta-analysis.

The quality of description of intellectual disability within our included studies was also variable. Only half of the studies (54%) reported the proportion of their participants with an intellectual disability, and there was great variability in the assessment used (ranging from an individual question delivered to parents or carers to psychometrically robust cognitive assessment). Between-groups visual inspection showed that groups with higher levels of intellectual functioning (Williams' syndrome and neurofibromatosis type 1) had substantial lower risk of ASD phenomenology compared with groups with expected low intellectual functioning. Conversely, Rett's syndrome had the highest risk of ASD phenomenology; individuals with Rett's syndrome typically have an intellectual disability in the severe to profound range. These broad associations are in line with models that suggest that impaired intellectual functioning in syndromes accounts for the presence of ASD phenomenology, whether that be through a reduction in the ability to compensate for inherited autistic traits or through other mechanisms.[21] However, in several groups in whom intellectual functioning is reported to be variable, heightened risk of ASD phenomenology was also evidenced (Cornelia de Lange syndrome, Cohen's syndrome). Thus, the role of intellectual functioning in the presence and prevalence of ASD in syndromes should be further elucidated. Investigators should appropriately assess intellectual disability using robust direct cognitive measures, and analyse how far intellectual disability can account for ASD phenomenology. Also needed is statistical meta-analytic review for the contribution of intellectual disability to the prevalence of ASD phenomenology in syndromes. The

combination of robust empirical studies and comprehensive meta-analytic review would substantially progress understanding for the relative contributions of mechanisms underlying genetic syndromes, intellectual functioning, and ASD phenomenology.

The results from this meta-analysis can serve to highlight areas for future research. First, six syndromes (Goldenhar's, Sotos', Ehlers-Danlos, Lujan-Fryns, Leber's congenital amaurosis, and hypomelanosis of Ito) were excluded from the meta-analysis on the basis of a paucity of research about the prevalence of ASD phenomenology in these groups (appendix). Additionally, generated pooled prevalence estimates for phenylketonuria and Joubert's and Möbius' syndromes were not sufficiently robust to allow for further interpretation or cross-syndrome comparison. Thus, given the putative associations between each of these syndromes and ASD phenomenology, robust research for each of these groups is needed to detail the prevalence and profile of ASD phenomenology. Second, given the wide range of ASD assessments and reported differences in the sensitivity and specificity of instruments,[20] researchers should evaluate the reliability and validity of ASD assessments in marginal populations such as individuals with syndromes and intellectual disability, and to examine the differing prevalence data that these assessments generate. Johansson and colleagues[30] present a useful way to do this type of research and contrast the use of the ADI-R, CARS, and Autism Behavior Checklist to identify ASD phenomenology in Möbius', CHARGE, and Goldenhar's syndromes. This method could be usefully applied across other groups to reach a consensus on the most appropriate ASD assessments for use in syndromes, in both research and clinical practice.

A final and key area for future research is to detail more robustly the profile of ASD phenomenology in each syndrome. Emerging evidence suggests that the profile of ASD impairments within syndromes might be qualitatively different in phenomenology to that of idiopathic ASD. This might be evidenced through uneven profiles of impairments, in which individuals with certain syndromes evidence difficulties in some areas of ASD phenomenology, but not others.[14,15] Thus the generated prevalence data in this meta-analysis might not reflect the prevalence of diagnosable ASD in which impairment is necessary in both social communicative domains and repetitive and restricted behaviours.

This meta-analysis has highlighted those syndromes in which the data for the profile of ASD are accumulating (eg, fragile X, Cornelia de Lange, Down's, and Angelman's syndromes) and by exclusion, those syndromes in which this is still under-researched. Work should seek to synthesise findings across studies on the profile of ASD in these well researched syndromes. Additionally, further empirical research is needed in the remaining syndromes to delineate the profile of ASD in these groups. A review of syndromes that have been identified to be associated with ASD phenomenology more recently should also be

done. Genetic or metabolic confirmation of syndromes, where appropriate, would allow more precise links between causal mechanism and ASD profile. Gold-standard assessments of the profile of ASD phenomenology should include comparison with other syndrome groups to assess degree of intellectual disability and comparisons to idiopathic ASD to evaluate the similarities and differences in the profile of behaviour. The generation of these data could improve delineation of the psychological constructs associated with ASD in each of these syndromes, specifically the cognitive and social profiles and their developmental trajectories, although these will be mediated by the intellectual disability associated with each syndrome. As detailed assessment of the behavioural phenomenon in each syndrome develops, differences in ASD phenomenology might emerge, which might align with or disagree with the postulated cognitive underpinnings of idiopathic ASD (eg, theory of mind deficits, weak central coherence, deficits in executive functioning).

In summary, this meta-analysis has generated robust estimates for the prevalence of ASD phenomenology for 12 genetic and metabolic syndromes. Despite between-syndrome variations in these prevalence data, ASD phenomenology was significantly more likely in all of the syndromes than in the general population.

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