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Prevalence of anxiety symptomatology and diagnosis in syndromic intellectual disability: A systematic review and meta-analysis

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ABSTRACT

Individuals with syndromic intellectual disability are at increased risk of experiencing anxiety. Comparing prevalence estimates of anxiety will allow the identification of at-risk groups and inform causal pathways of anxiety. No known study has explored estimates of anxiety symptomatology and diagnosis, including specific anxiety profiles, across groups whilst accounting for methodological quality of studies. This systematic review and meta-analysis aimed to fill this gap. Prior to review completion, methodology and analysis plans were registered and documented in a protocol (CRD42019123561). Data from 83 papers, involving a pooled sample of 13,708 across eight syndromes were synthesised using a random effects model. Anxiety prevalence ranged from 9 % (95 % CI: 4–14) in Down syndrome to 73% in Rett syndrome (95 % CI: 70–77). Anxiety prevalence across syndromic intellectual disability was higher than for intellectual disability of mixed aetiology and general population estimates. Substantial variability between syndromes identified groups at higher risk than others. The identification of high-risk groups is crucial for early intervention, allowing us to refine models of risk and identify divergent profiles.

1. Introduction

Annual health checks for people with intellectual disability (ID) are a welcome initiative that begins to address inequalities in health care provision experienced by this group (Robertson et al., 2014; Slowie and Martin, 2014). One challenge to delivering effective health care for this population is the diagnosis of physical and mental health problems when self-report is compromised and the clinical presentation atypical (Doherty et al., 2020; Kripke, 2018; Whittle et al., 2018). These problems can be partially mitigated when there is a known and elevated risk of specific physical and mental health problems associated with an identified cause of ID. Awareness of this association enables clinicians and carers to be vigilant for future and unidentified existing problems. The substantial literature on the association between syndromic ID and the associated physical and mental health problems enables the identification of risk for these problems in syndromes and so can inform

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prevention, early intervention, and clinical management.

With regard to mental health problems and conditions that affect mental health, a number of difficulties are more prevalent in specific syndromes. Examples include psychosis in 22q11.2 deletion syndrome (Chawner et al., 2019; Weisman et al., 2017), and Prader-Willi syndrome caused by uniparental disomy (Boer et al., 2002; Soni et al., 2007), dementia caused by Alzheimer's disease in Down syndrome (Hithersay et al., 2017; Rubenstein et al., 2020) and autism in Cohen's syndrome (Richards et al., 2015), and Tuberous Sclerosis Complex (Vignoli et al., 2015). Importantly, there are often critical differences in the clinical course and presentation of mental health problems and conditions that affect mental health between those with a specific syndrome and: (1) people of typical development, (2) people with non-syndromic ID or ID of mixed aetiology and (3) people with a different syndrome. First, the age of onset and developmental trajectory can differ. For example, anxiety is evident in children with fragile X syndrome as young as 18 months old (Roberts et al., 2019a,b), dementia has a significantly earlier onset in people with Down syndrome (Holland et al., 1998; Lautarescu et al., 2017), and an atypical developmental trajectory of autism is evident in Cornelia de Lange syndrome (Cochran et al., 2019). Second, the broader domains that define diagnostic criteria can drive diagnosis differentially. For example, for attention deficit and hyperactivity disorder (ADHD) in fragile X syndrome the domain of overactivity is comparatively more prominent than impulsivity whilst the opposite is true for Smith-Magenis syndrome (Oliver et al., 2011), and in Cornelia de Lange syndrome two domains of depression; pervasive low mood, and loss of interest and pleasure, are dissociated (Groves et al., 2019). Third, even when the criteria for a specific diagnosis such as autism spectrum disorder are fulfilled, the profile of characteristics within domains can differ significantly. For example, the presentation of atypical social behaviour and the presence of restricted behaviour and interests differ between Cornelia de Lange and fragile X syndromes, and those syndromes and non-syndromic autism (Moss et al., 2013). Finally, for a mental health problem such as anxiety, different types of anxiety diagnosis might be more prevalent with different co-morbidities across anxiety diagnosis evident (Crawford et al., 2017). In combination, these differences in clinical course, presentation and trajectory indicate the importance for clinicians' awareness of the association between syndromic ID and the risk and presentation of mental health problems.

One strategy for collating syndrome sensitive information about common mental health problems is to identify and review robust research on prevalence, course, and presentation of these problems in different syndromes. Anxiety is one of the most common mental health problems in the general population with lifetime prevalence estimated at 33.7 %, rising to 52.3 % when studies include subthreshold diagnosis or symptomatology (Bandelow and Michaelis, 2015; Bryant et al., 2008). Anxiety is often disabling, persistent and associated with poor long-term outcomes, and a negative impact on quality-of-life, physical health, work, and social functioning (Asselmann et al., 2018; Copeland et al., 2015, 2014; Olatunji et al., 2007; Ormel et al., 2009; Senaratne et al., 2010). A number of studies indicate that individuals with ID are at substantially higher risk of anxiety than the general population, with an estimated prevalence rate of 22% in comparison to 4–5 % in the general population (Bratek et al., 2017; Einfeld et al., 2011; Green et al., 2015; James et al., 2018; Mazza et al., 2020; Munir, 2016; Reardon et al., 2015). A review of the association between anxiety and syndromic ID is likely to yield important information for risk, clinical presentation and aid diagnosis and management.

In the general population genetic risk and gene disorder-phenotype-environment interactions are implicated in the aetiology of anxiety and increased risk of an anxiety diagnosis (Meier and Deckert, 2019). Within the ID population, anxiety is associated with several syndromes. For example, individuals with Williams Syndrome are at heightened risk of experiencing anxiety (48 %) when compared to the general population and individuals with ID of heterogeneous aetiology (4 % and 5 % respectively (James et al., 2018; Maïano et al., 2018; Mazza et al., 2020; Royston et al., 2017)). There is also evidence of an association between anxiety and other syndromes, such as fragile X, 22q11.2 deletion, 7q11.23 duplication and CHARGE syndromes (Cordeiro et al., 2011; Hartshorne et al., 2017; Stephenson et al., 2015; Velleman and Mervis, 2011). Additionally, the identification of specific types of anxiety diagnosis across syndromes is of interest and raises the question of differing underlying causes of anxiety across groups. For example, in fragile X and 22q11.2 deletion syndromes, the most prevalent anxiety diagnoses are social anxiety and specific phobias (Bertrán et al., 2018; Gabis et al., 2011; Jolin et al., 2012). Noise related phobias are common in Williams syndrome, whereas separation distress is often reported in individuals with 7q11.23 duplication syndrome (Abbas et al., 2016; Mervis et al., 2012; Royston et al., 2017). High rates of obsessive-compulsive disorder (OCD) have been reported in CHARGE and Prader-Willi syndromes (Blake et al., 2005; Dykens and Shah, 2003; La Spata, 2019), although there is debate about whether the presentation of OCD is similar to that seen in the general population. These different levels of specific anxiety diagnoses allude to a shared general risk but potentially different causal pathways to type of anxiety disorder.

The presence of anxiety in a large proportion of individuals with a specific syndrome, where predictive characteristics often have relative stability, affords the opportunity to determine causal pathways to anxiety (Oliver et al., 2020). The noise related phobias frequently reported in Williams syndrome (e.g., sounds such as sirens) for example, are associated with hyperacusis, indicating likely classical conditioning of fear responses (Gothelf et al., 2006; Royston et al., 2017). Conversely, current health difficulties have been found to be predictive of broader psychopathology in Williams syndrome. These psychological, biological mechanisms, and possible interactions, indicate the value of examining syndrome associated genetic factors and gene disorder-phenotype-environment interactions. Such an approach also has the potential to inform causal models of anxiety more generally and has implications for the general population by identifying candidate genetic risk markers for anxiety vulnerability. In Williams syndrome lower social anxiety has been associated with the deletion of gene, GTF2I (Dykens, 2003; Klein et al., 1990; Procyshyn et al., 2017; Royston et al., 2017). This has broader relevance because in the general population, variations in GTF2I are associated with social anxiety (Jabbi et al., 2015; Procyshyn et al., 2017; Swartz et al., 2017).

It is clear therefore that anxiety is common and disabling in people with ID and that syndromic ID appears to be associated with the clinical course and presentation of anxiety. Collating and evaluating information on risk and profiles of anxiety across syndromes is likely to inform clinical practice and identify useful group contrasts for future research. To date, one meta-analysis has investigated mental health across syndromes, reporting anxiety prevalence of 38 % in 22q11.2 deletion and 42% in fragile X syndromes (Glasson et al., 2020). The remaining analyses focused on general psychiatric symptoms, without a focus on anxiety. To date, no study has investigated the prevalence of anxiety symptomatology and diagnosis, including specific anxiety profiles, across syndromes in children and adults, while accounting for methodological quality.

There are significant challenges when assessing mental health within the ID population that can impinge on the quality of research. Individuals with ID may have significant communication difficulties, hindering self-report (Hagopian and Jennett, 2008). Other factors that complicate the assessment of mental health difficulties are diagnostic overshadowing, a lack of validated measures developed specifically for individuals across varying levels of ID and the heavy reliance on proxy report, which may lead to misattribution of behaviours (Emerson et al., 2013; Flynn et al., 2017; Hagopian and Jennett, 2008). These challenges mean the quality of the literature should be examined, to weight and then synthesise the findings.

Therefore, the aim of this study is to systematically review the prevalence of anxiety symptomatology and diagnosis, and types of anxiety across syndromes associated with ID. Due to identified

challenges of mental health assessment in individuals with ID, studies were included that explored anxiety symptomatology, taking an over inclusive approach to the literature. A scoping search was used to select syndromes included in the review by combining search terms for ID, syndrome, and anxiety in a database search.

The specific study aims were to:

1. Synthesise data from the existing literature and calculate pooled prevalence estimates of anxiety symptomatology and diagnosis across syndromes, while accounting for the methodological quality of included studies.
2. Complete subgroup and meta-regression analyses to explore methodological factors and their potential influence on anxiety prevalence.
3. Compare pooled prevalence estimates across syndromes with previously reported prevalence estimates from the general population and individuals with ID of mixed aetiology.

2. Methods

The current study is a systematic review and meta-analysis, completed according to PRISMA guidelines (Moher et al., 2009). Methodology and analysis details were documented in a PROSPERO protocol prior to completion of this review (CRD42019123561).

2.1. Scoping search

A scoping search was conducted to identify syndromes to be included in this review. The search was completed using search terms for ID, syndrome and anxiety to provide a 'snapshot' of available literature (See Supplementary material). The search terms were generated based on previous reviews (Dagnan et al., 2018; Kaur et al., 2017; Royston et al., 2017). A syndrome was included in the review if there was at least one empirical study identified reporting anxiety prevalence during the scoping search. The current review did not endeavour to explore all possible syndromes associated with ID and anxiety, and therefore the scoping search was used to systematically narrow the review focus and ensure a manageable synthesis of the literature was completed relating to a selection of specific syndromes.

The scoping search was completed on Web of Science (all years, all databases) on 5th December 2018 resulting in 1632 papers. The full text of papers was screened to identify studies where prevalence of anxiety had been reported in a sample of individuals with a syndrome associated with ID. GeneReviews; an expert-written, peer-reviewed, international resource, was also consulted to identify any syndrome that may not have been identified in the scoping search. 31 syndromes were identified during the scoping search (see Supplementary material). Although identified in the scoping search with empirical studies reporting anxiety prevalence, Williams syndrome was not included due to the completion of a recent systematic review and meta-analysis at the time that the current review was conceptualised (Royston et al., 2017). GeneReviews identified Tuberous Sclerosis Complex (TSC) as a condition associated with ID and anxiety, no further syndromes were identified. Therefore, eight syndromes were deemed appropriate for inclusion in the current review; fragile X (FXS), Tuberous Sclerosis Complex (TSC), 22q11.2 deletion, Down (DS), Rett (RS), CHARGE, 7q11.23 duplication and 3q29 deletion syndromes.

2.2. Search strategy and selection criteria

Individual searches were completed with search terms for each syndrome and anxiety search terms used in the scoping search (see Supplementary material). Searches were completed on Web of Science, Ovid PsycINFO, Ovid Embase and CINAHL Plus with no restriction on year of publication, up to mid 2019. All syndromes involve gene disorders that were not discovered until recently (1959–2005). Syndrome search terms were selected based on a previous meta-analysis (Richards et al., 2015). For syndromes identified in the scoping search not included in the previous review, search terms were selected from Genetics Home Reference, an expert-reviewed online resource and GeneReviews was also consulted to identify additional synonyms.

Returned papers were assessed for inclusion by GE and RR. A training phase of screening was completed with the first 50 abstracts screened and discrepancies discussed. A further 100 abstracts were screened, where consensus was obtained (Polanin et al., 2019). Following this, the study selection process was completed with GE screening 82 % (24,914) and RR screening 38 % (11,594) of total papers. For stage one screening, papers were screened by review of titles and abstracts using predefined criteria (see Table 1). In line with similar reviews, inter-rater reliability was established on 20 % (6091) of total papers, with substantial agreement achieved between GE and RR (Kappa = 0.91) (Flynn et al., 2017; Tough et al., 2017). Where there were discrepancies regarding inclusion at stage one, an over inclusive approach was adopted, and studies included to ensure relevant studies were not missed.

The full texts of articles included at stage one were screened to assess inclusion at stage two where additional criteria were deployed (see Table 1). In line with previous reviews, studies were included if they reported a prevalence of anxiety symptomatology (e.g., cut off on the Child Behaviour Checklist; Achenbach and Rescorla, 2001) or anxiety diagnosis (e.g., DSM/ICD criteria) (Buckles et al., 2013; Buckley et al., 2020; Green et al., 2015). At stage two, substantial inter-rater reliability was established between GE and RR (Kappa = 0.73). To resolve discrepancies of inclusion at stage two, a third reviewer (JW) was consulted, and a consensus reached.

Following screening, GE and EP completed backward searching of reference lists of included studies, identifying an additional 20 papers (see Fig. 1).

2.3. Data extraction and quality assessment

All studies were then evaluated against quality rating criteria adapted from a previous meta-analysis (Royston et al., 2017; See Supplementary material). The quality rating tool was developed by Richards

Table 1
Inclusion and exclusion criteria for stage 1 and stage 2 screening of papers.

Stage one screening	
Inclusion criteria	**Exclusion criteria**
Studies including individuals with a given syndrome	Non-human studies
Studies that mention psychopathology/ mental health/socio-emotional factors in abstract	Conference abstracts/papers, book chapters, patents, letters, editorial material, notes, brief reports
Studies published in English	Studies focusing on other genetic problems related to syndrome e.g., being a carrier of the syndrome/ premutation in Fragile X syndrome
Studies published in peer reviewed journals	Studies focusing only on parental mental health
Stage two screening	
Inclusion criteria	**Exclusion criteria**
Studies reporting anxiety prevalence rates (e.g., any anxiety disorder, specific phobia, social anxiety disorder, panic disorder with/without agoraphobia, separation anxiety disorder, generalised anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, selective mutism)	Reviews
	Case studies or series
	Studies with specific recruitment/ eligibility bias (e.g., psychiatric clinic)
	Studies with identified identical samples[a]

[a] No studies had identified identical samples

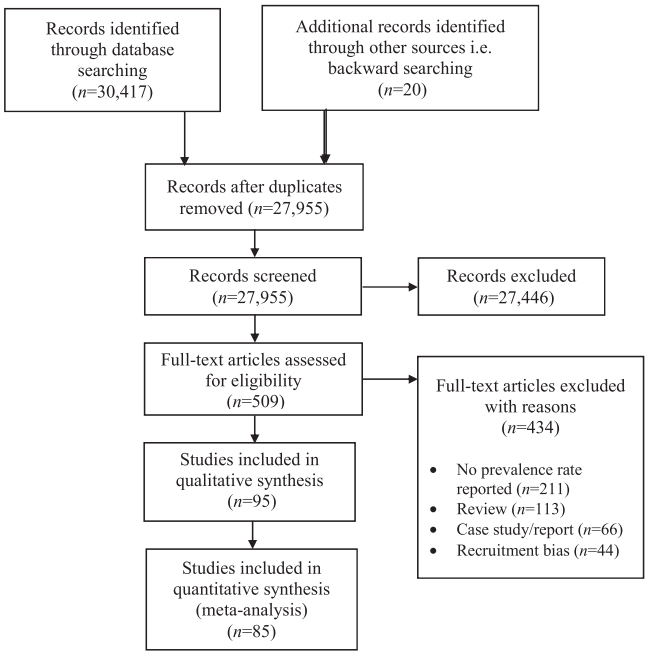

Fig. 1. PRISMA diagram detailing study selection. See Supplementary material for further information.

et al. (2015) specifically for exploring prevalence data across syndromes associated with ID. Literature reviews and consultation from active research experts informed the development of the idiosyncratic quality criteria to highlight key areas of methodological concern; these evaluated sample identification, confirmation of syndrome diagnosis and method of anxiety assessment. Richards et al. (2015) criteria were deemed the most appropriate to assess quality of included studies due to the focus on methodological issues and key threats to validity that are specific to the genetic syndrome field. GE received training from the primary author (CR) who developed the rating tool (Richards et al., 2015) to ensure the quality criteria were used as developed and intended.

There was no minimum quality rating needed for inclusion in the current meta-analysis to prevent large samples with valuable data being excluded and to ensure that the analysis was a comprehensive review of available literature for each syndrome. To account for this, analyses were conducted to identify any potential influence of methodological quality on the overall effect and therefore, those of poorer quality rated studies. Furthermore, 59 % (49) of studies obtained a 'good' rating for sample identification, suggesting the data were obtained from representative samples.

Each study was given a rating on a scale from poor to excellent (0−3) for the three areas of methodological concern: sample identification, confirmation of syndrome diagnosis and method of anxiety assessment. Scores of 0 were given to studies that did not specify, report or relied solely on parent report for the areas of interest in the quality criteria, while scores of 3 were given to studies that utilised random samples, completed genetic confirmation of syndrome diagnosis and obtained consensus from multiple assessments of anxiety. The quality weighting was calculated by dividing the total quality ratings for each study by the maximum score of nine. A traffic light colour coding system was used to visually present quality ratings (See Supplementary material). GE quality rated all studies while EP quality rated 26 % (22) of studies, establishing substantial inter-rater reliability (Kappa= 0.74). The reported number and percentage of participants experiencing anxiety were extracted from each paper by GE and checked independently.

2.4. Data analysis

Data analysis was conducted utilising the meta-analysis strategy of the Centre for Applied Psychology, University of Birmingham. Analysis was calculated using the 'Metafor' package for R, version 3.6.2. For each study, variables were extracted (e.g., age, sex, anxiety measure) with the reported anxiety prevalence, including specific anxiety profiles, to generate pooled prevalence estimates (See Supplementary material).

Decisions about inclusion of studies that reported an event rate of 0 were made on a case-by-case basis due to variation of study quality across syndromes. The study was either removed from further analysis due to the likelihood of the failure to detect an effect (i.e., in small samples) or a continuity correction of 0.5 was added to the event rate to avoid division by zero errors (Cheng et al., 2016; Higgins et al., 2019). The continuity correction was applied only if the study sample size was considered to be sufficient to make a valid estimation of anxiety prevalence. Two papers reported an event rate of 0 with sample sizes of 14 and 371; the former was removed while the latter was retained with a continuity correction applied (Collacott et al., 1992; Way and Rojahn, 2012).

Pooled prevalence estimates were generated using a random-effects model, as opposed to the fixed-effects model, as the former considers variation between studies and does not assume a common effect size (Hedges and Vevea, 1998; Tufanaru et al., 2015). The quality-effects model was implemented to account for quality ratings for each study (Barendregt et al., 2013; Detsky et al., 1992; Doi and Thalib, 2008). The random and quality-effects estimates were plotted to allow comparison across syndromes (see Fig. 2).

To identify influential studies impacting the overall meta-analytic effect, a Baujat chart was used (See Supplementary material) (Baujat et al., 2002). A Baujat chart is a graphical method used to identify studies that are heterogeneous, a 'leave-one-out' procedure is used to portray the change in the overall effect when each study is removed, one at a time, against the contribution of each study to the overall heterogeneity. This procedure allows us to explore how each individual study affects the overall prevalence estimate (Viechtbauer and Cheung, 2010). If omitting a study results in an effect outside the 95% CI for the meta-analytic synthesis with all studies included, then that study is deemed to have a disproportionate influence on the overall effect and is removed from subsequent analysis (Steenfeldt-Kristensen et al., 2020). Higgins I^2 was used as a measure of heterogeneity to explore inconsistency between study findings (Higgins et al., 2003).

To explore the impact of study level characteristics on anxiety prevalence, planned a priori subgroup analyses were conducted exploring quality ratings and outcome type (i.e., behavioural/psychiatric report of anxiety). Outcome type was chosen as a potential moderator as prevalence may differ when exploring behavioural vs. psychiatric report of mental health symptomatology in individuals with ID (Buckley et al., 2020). Reliance on psychiatric assessment and/or diagnosis may lead to the underestimation of anxiety due to the identified challenges when assessing individuals with ID, behavioural reports may ensure that anxiety is not missed due to individuals not meeting psychiatric criteria (Bertelli et al., 2015). Meta-regression analyses explored the impact of year of publication and sample size.

3. Results

30,417 papers were identified through database searching and 85 papers, across eight syndromes, were included in the meta-analysis (See Fig. 1; see Supplementary material). From use of the Baujat chart, two studies were re-reviewed and subsequently excluded due to identified bias, resulting in a final 83 papers, totalling 13,708 participants (See Supplementary material). Characteristics for each included study are presented in the Supplementary material.

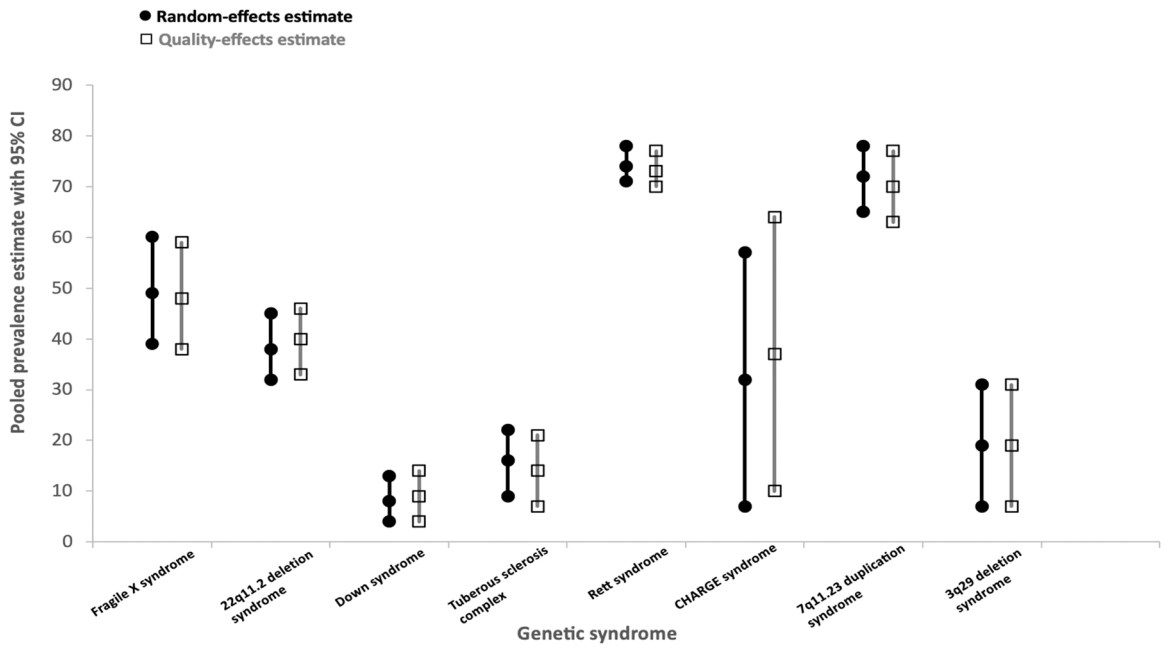

Fig. 2. Pooled prevalence estimates for anxiety across syndromes.

Table 2
Quality ratings for each syndrome and pooled prevalence estimates for anxiety.

	Studies[a]	Patients (n)	Mean quality weighting	Individual scores			Quality weighting score[b]			Prevalence of anxiety	
				Obtained score of 3 for sample	Obtained score of 3 for syndrome confirmation	Obtained score of 3 for anxiety assessment	Poor	Adequate	Good	Random-effects pooled prevalence	Quality-effects pooled prevalence
Fragile X syndrome	19	3882	0.53 (0·12)	0	4 (21%)	0	9 (47%)	8 (42%)	2 (11%)	49% (39–60)	48% (38–59)
Fragile X syndrome (boys and men only)	7	1214	0.53 (0·11)	0	0	0	2 (29%)	5 (71%)	0	43% (23–62)	42% (22–62)
22q11.2 deletion syndrome	34	2272	0.63 (0·13)	0	10 (29%)	8 (24%)	7 (21%)	18 (53%)	9 (26%)	38% (32–45)	40% (33–46)
Down syndrome	11	2152	0.41 (0·17)	0	0	1 (9%)	8 (73%)	2 (18%)	1 (9%)	8% (4–13)	9% (4–14)
Tuberous sclerosis complex	8	6494[c]	0.37 (0·12)[d]	0	0	1 (13%)	10 (91%)	1 (9%)	0	16% (9–22)[e]	14% (7–21)
Rett syndrome	6	676	0.40 (0·06)	0	0	0	6 (100%)	0	0	74% (71–78)	73% (70–77)
CHARGE syndrome	2	140	0.17 (0·08)	0	0	0	2 (100%)	0	0	32% (7–57)	37% (10–64)
7q11.23 duplication syndrome	2	178[f]	0.44 (0·12)[g]	0	1 (50%)	0	2 (67%)	1 (33%)	0	72% (65–78)[h]	70% (63–77)
3q29 deletion syndrome	1	42	0.33	0	0	0	1 (100%)	0	0	19% (7–31)	19% (7–31)

[a] Based on 83 studies across syndromes due to the exclusion of 2 studies that were identified as highly discrepant and heterogeneous.
[b] Categories based on quality weighting score of poor (0.33–0.55), adequate (0.56–0.77) and good (0.78–1.0).
[c] Number of participants based on 8 studies with 3 studies reporting both a behavioural and psychiatric prevalence of anxiety. Therefore, the total number of participants is inflated due to overlap of participants within the 3 studies reporting multiple anxiety prevalence rates.
[d] Mean quality weighting and categories of quality weighting scores also based on 11 reported rates.
[e] Prevalence of anxiety based on 11 reported rates. Behavioural prevalence of anxiety based on 4 reports of 2525 participants; psychiatric prevalence of anxiety based on 7 reports of 3969 participants. Behavioural prevalence was significantly higher than psychiatric prevalence (25% and 10% respectively; $p = 0.0289$).
[f] Number of participants based on 2 studies with 1 study reporting both a behavioural and psychiatric prevalence of anxiety. Therefore, the total number of participants is inflated due to overlap of participants in 1 study reporting multiple anxiety prevalence rates.
[g] Mean quality weighting and categories of quality weighting scores based on 3 reported prevalence rates.
[h] Prevalence of anxiety based on 3 reported rates. Behavioural prevalence of anxiety based on 1 report of 53 participants; psychiatric prevalence of anxiety based on 2 reports of 125 participants. Behavioural prevalence was not significantly different than psychiatric prevalence (72% and 71% respectively; $p = 0.9715$).

3.1. Prevalence of anxiety

The prevalence of anxiety ranged from 9 % (95 % CI 4–14) in individuals with DS to 73 % (95% CI 70–77) in individuals with RS (See Table 2; Fig. 2). See Figs. 3–6 for a subset of forest plots documenting the prevalence of anxiety across FXS, 22q11.2 deletion, TSC and CHARGE syndromes respectively. The remaining forest plots are shown in the Supplementary material.

No studies obtained the highest quality rating for sample identification. 15 (17.6 %) studies obtained the highest quality rating for syndrome confirmation whilst ten (11.8 %) obtained the highest quality rating for anxiety assessment. The 'leave-one-out' procedure indicated that across syndromes, no one study had a disproportionate effect on the pooled prevalence estimates of anxiety and so all studies were retained. A marked level of heterogeneity (Higgin's $I^2 = >75$ %) between reported prevalence rates was identified in five syndromes, suggesting that these analyses were biased by uncontrolled or confounding factors.

3.1.1. Subgroup analyses

Consistent with previous literature, subgroup analyses were conducted on three syndromes where there were ten studies or more (Richardson et al., 2019). Firstly, subgroup analyses were conducted on the quality ratings of studies (See Supplementary material). For 22q11.2 deletion syndrome, papers rated as 'poor' for anxiety assessment reported significantly lower anxiety prevalence than papers rated as 'good' (13 % vs. 42 % respectively; $p < 0.0001$). For DS, papers rated as 'poor' on sample identification reported significantly higher anxiety prevalence than papers rated as 'good' (16 % vs. 7 % respectively; $p = 0.0532$). Additionally, papers rated as 'poor' for anxiety assessment also reported significantly higher anxiety prevalence than papers rated as 'good' for DS (9 % vs. 3 % respectively; $p = 0.0235$; See Supplementary material).

Secondly, subgroup analyses were conducted based on outcome type. For 22q11.2 deletion syndrome, behavioural reports of anxiety were significantly lower than psychiatric reports (5 % vs. 42 % respectively; $p < 0.0001$). For DS, behavioural reports of anxiety were significantly higher than psychiatric reports of anxiety (25 % vs. 7 % respectively; $p = 0.0011$; See Supplementary material).

3.1.2. Meta-regression analyses

Meta-regression analyses found no significant differences in the estimated prevalence of anxiety, except for DS where, as the number of participants increased, the estimated prevalence of anxiety decreased ($p = 0.0004$).

3.2. Specific anxiety symptomatology/diagnosis prevalence

Across syndromes, there were 42 studies that also reported specific anxiety profiles. There were eight additional studies that did not report 'any anxiety' prevalence but did report specific anxiety profiles, totalling 50 studies across the eight included syndromes (See Supplementary material). Pooled prevalence estimates ranged from 1 % to 52 % (See Supplementary material). High rates of specific phobia were evident for individuals with fragile X, 22q11.2 deletion and 7q11.23 duplication syndromes (52 %, 28 %, 50 % respectively). Social anxiety was common in fragile X and 7q11.23 duplication syndromes (28 % and 51 % respectively). Additionally, for FXS, physical injury fears and PTSD were noted (37 % and 32 % respectively). High rates of OCD were found in CHARGE syndrome (35 %) and separation anxiety in 7q11.23 duplication syndrome (16 %). Selective mutism was reported in 7q11.23 duplication and Down syndrome (29 % and 6 % respectively) whilst panic attacks were common in 3q29 deletion syndrome (29 %). A high level of heterogeneity (Higgin's $I^2 = >75$ %) was identified in four syndromes suggesting that these analyses were biased by uncontrolled or confounding factors.

3.2.1. Subgroup analyses for specific anxiety symptomatology/diagnosis

Only 22q11.2 deletion syndrome had a sufficient number of studies to conduct subgroup analyses (Richardson et al., 2019). Analyses were conducted for specific phobia (SP), social anxiety (SA), generalised anxiety (GAD), separation anxiety (SAD) and OCD. For SP, papers rated as 'good' for sample identification had significantly higher anxiety prevalence than those rated as 'poor' (34 % vs. 18 % respectively; $p = 0.0045$). Papers rated as 'good' for syndrome confirmation had significantly higher anxiety prevalence than papers rated as 'poor' (31 % vs. 5 % respectively; $p < 0.0001$). For GAD, papers rated as 'good' for syndrome confirmation had significantly lower anxiety prevalence than papers rated as 'poor' (12 % vs. 32 % respectively; $p = 0.0372$). For SAD, papers rated as 'good' for sample identification had significantly higher anxiety prevalence than papers rated as 'poor' (8 % vs. 4 % respectively; $p = 0.0187$). All papers reported a psychiatric prevalence of anxiety, so analyses concerning outcome type were not conducted.

3.2.2. Meta-regression analyses for specific anxiety symptomatology/diagnosis

There were no significant differences for meta-regression analyses concerning year of publication and sample size on the prevalence of specific anxiety profiles in 22q11.2 deletion syndrome (See Supplementary material).

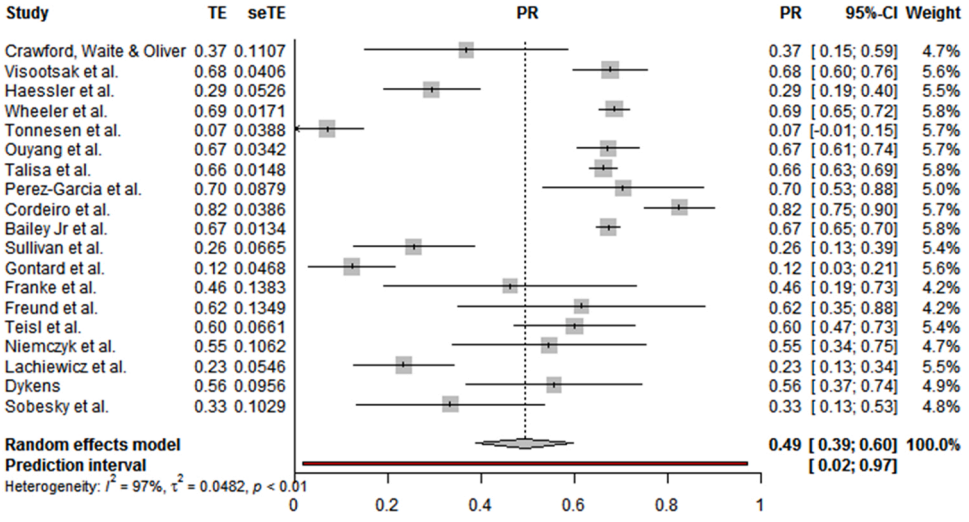

Fig. 3. Forest plot for anxiety in Fragile X syndrome using a random-effects model.

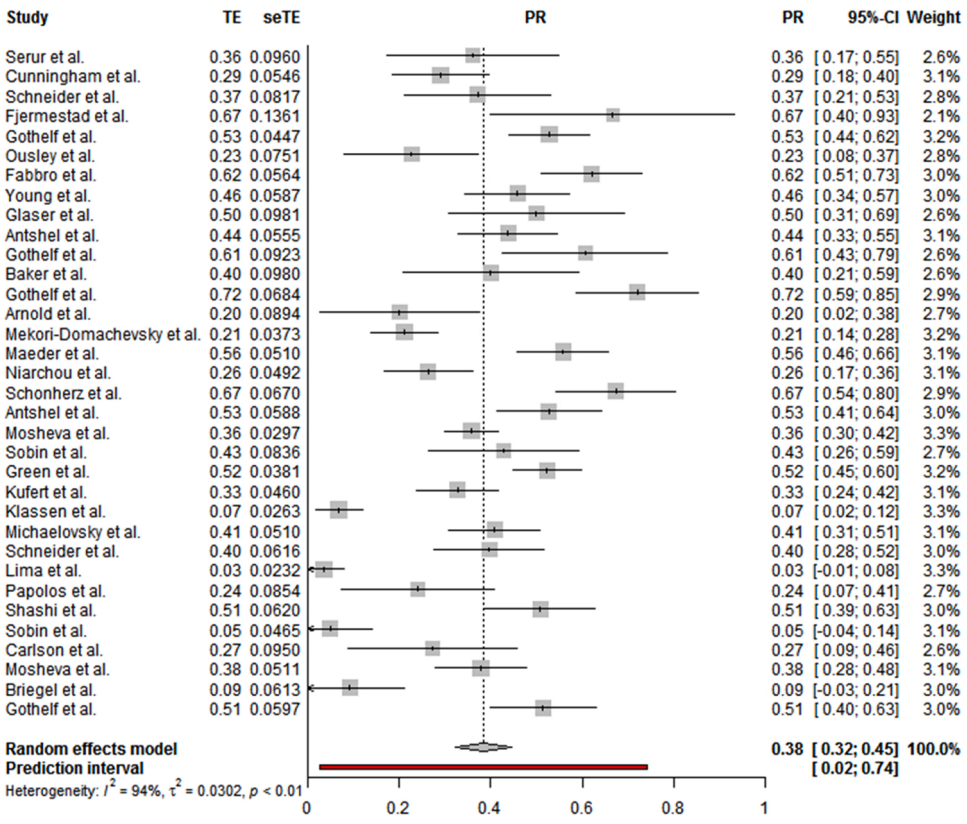

Fig. 4. Forest plot for anxiety in 22q11.2 deletion syndrome using a random-effects model.

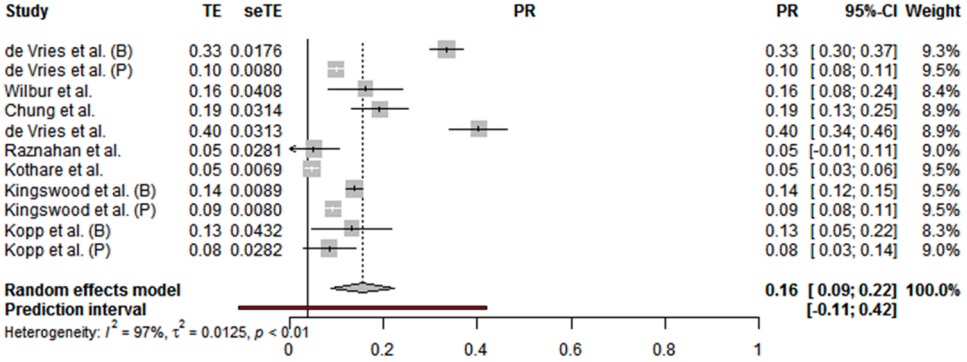

Fig. 5. Forest plot for anxiety in Tuberous Sclerosis Complex using a random-effects model (final analysis with removal of Smalley).

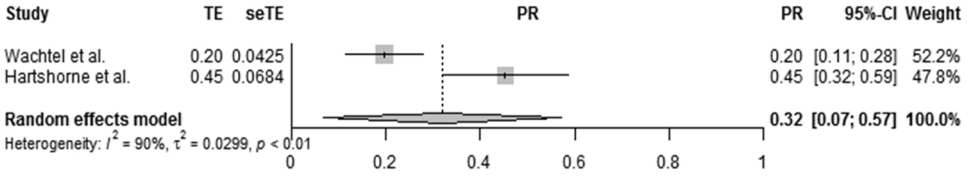

Fig. 6. Forest plot for anxiety in CHARGE syndrome using a random-effects model.

3.3. Comparison to general and ID population prevalence estimates

Finally, prevalence estimates for syndromes were compared to general and ID of mixed aetiology population estimates (See Table 3). These comparison estimates report psychiatric prevalence of anxiety while the current review includes studies that report the prevalence of anxiety symptomatology; therefore, it is important to apply caution when comparing prevalence rates across studies. Despite this, 80% (66) of studies in the current review reported a psychiatric prevalence of anxiety. Additionally, where subgroup analyses were completed comparing outcome type, the estimates for psychiatric prevalence of anxiety alone were still higher across syndromes than that reported for the general and ID of mixed aetiology populations.

In terms of specific anxiety profiles, meta-analytic studies, population-based studies, or the most recent study with the largest sample size known to the authors were used for comparison to the

Table 3
Prevalence rate estimates of anxiety for the general population and intellectual disability of mixed aetiology populations.

	General population estimate for children/adolescents	General population estimate for adults	Intellectual disability estimate based on children and adolescents[a]	Intellectual disability estimate based on adults
Anxiety	3.2%[b]	3.86%[c]	5.4%	5.5%[d]
Specific phobia	0.8%[e]	7.4%[f]	11.5%	13.3%[g]
Social anxiety disorder	0.8%	4%[h]	2.7%	0.3%
Generalised anxiety disorder	1.5%	3.7%[i]	2.2%	1.7%
Separation anxiety disorder	0.7%	4.8%[j]	5%	N/A[k]
Obsessive-compulsive disorder	0.4%	2.3%[l]	2.4%	4%[m]
Post-traumatic stress disorder	0.6%	3.9%[n]	1.1%	0.3%
Agoraphobia	0.5%	1.5%[o]	0.6%	0.7%
Panic disorder	1.1%	1.7%	0.3%	0.2%
Panic disorder with agoraphobia	0.8%[p]	0.3%	0.4%	0.2%
Panic disorder without agoraphobia	0.8%	1.2%	0.2%	0%
Selective mutism	0.18%[q]	N/A[r]	N/A[s]	N/A[t]

[a] Any anxiety disorder and specific anxiety disorder prevalence rates based on reports from Maïano et al. (2018)
[b] Any anxiety disorder prevalence rate based on Erskine et al. (2017)
[c] Any anxiety disorder prevalence rate based on James et al. (2018) (GBD 2017), based on all ages
[d] Any anxiety disorder prevalence rate based on Mazza et al. (2020). Specific anxiety disorder prevalence rates based on reports from Reid, Smiley and Cooper (2011) except reported prevalence rates for OCD and specific phobia
[e] Remaining specific anxiety disorders based on Sadler et al. (2018) except for Panic disorder with and without agoraphobia
[f] Specific phobia prevalence rate from Wardenaar et al. (2017)
[g] Specific phobia prevalence rate from Hove and Havik (2008)
[h] Social anxiety disorder prevalence rate from Stein et al. (2017)
[i] Generalised anxiety disorder prevalence rate from Ruscio et al. (2017)
[j] Separation anxiety disorder prevalence rate from Silove et al. (2015)
[k] The removal of the age-of-onset criterion (before 18 years of age) for separation anxiety disorder in DSM-5, allows the diagnosis of separation anxiety experienced across the lifespan. Perhaps due to this recent change, there were no identified studies that explored the prevalence of separation anxiety disorder in adults with intellectual disability
[l] OCD prevalence rate from Ruscio, Stein, Chiu and Kessler (2010)
[m] OCD prevalence rate from Schützwohl et al. (2016)
[n] PTSD prevalence rate from Koenen et al. (2017)
[o] Agoraphobia and panic disorder prevalence rates for general population estimate for adults from Roest et al. (2019)
[p] Prevalence rate for panic disorder with and without agoraphobia based on Reed and Witthcen (1998)
[q] Reported prevalence rate from Sharkey and McNicholas (2012)
[r] No identified study reporting prevalence of selective mutism in a general population sample of adults as it is usually diagnosed during childhood (DSM-5; American Psychiatric Association, 2013).
[s] No identified study reporting prevalence of selective mutism in children with intellectual disability
[t] No identified study reporting prevalence of selective mutism in adults with intellectual disability as it is usually diagnosed during childhood (DSM-5; American Psychiatric Association, 2013).

estimates for specific anxiety diagnoses across syndromes. FXS, 22q11.2 deletion and 7q11.23 duplication syndromes had particularly high prevalence estimates compared to the general and ID of mixed aetiology populations (See Table 3 and Supplementary material).

4. Discussion

This is the first systematic review and meta-analytic study to document the prevalence of anxiety and types of anxiety diagnosis across syndromes associated with ID, whilst accounting for methodological quality of included studies. The prevalence of anxiety was notably high in Rett (73 %), 7q11.23 duplication (70 %) fragile X (48 %), 22q11.2 deletion (40 %), CHARGE (37 %), 3q29 deletion (19 %) syndromes and Tuberous Sclerosis Complex (14 %), with the lowest prevalence in Down Syndrome (9 %). It is striking that all syndrome prevalence estimates were higher than reports from general and ID of mixed aetiology populations (4 % and 5 % respectively; James et al., 2018; Maïano et al., 2018; Mazza et al., 2020). These estimates indicate the importance of clinicians knowing the cause of ID to inform risk of a specific, common, and treatable mental health problem.

There is concordance between the results of this review and meta-analysis and the results of reviews of single syndromes. Gold et al. (2018) reported that anxiety is notably common in RS, although there are very few research studies confirming anxiety prevalence. The high prevalence reported in 7q11.23 duplication syndrome is consistent with a previous review for that syndrome (Velleman and Mervis, 2011) and the prevalence estimates of 40 % for 22q11.2 deletion syndrome and 48% for FXS are each consistent with previous meta-analyses for these syndromes (Glasson et al., 2020). Published estimates of prevalence rates for CHARGE syndrome are consistent with the 37 % estimate from the current study but the comparatively large confidence intervals indicate the need for further research (Kennert et al., 2020; Souriau et al., 2005). Since the completion of the current study, two larger studies of 3q29 deletion syndrome have reported a higher anxiety prevalence rate of 28 % compared to 19 % in the current study based on a single estimate (Pollak et al., 2019, 2020). Anxiety is a known problem experienced by individuals with TSC, with variability depending on whether prevalence of anxiety symptomatology or diagnosis is considered (de Vries et al., 2018). Research investigating the prevalence of anxiety in DS is limited. However, individuals seem to be at lower risk of mental health problems and disorders (with the exception of dementia) than other ID groups, but at higher risk than the general population. This pattern was evident in the current review (Dykens, 2007; Glasson et al., 2020; Vicari et al., 2013). The concordance between the results of this

study and published reviews supports the validity of the review methodology and meta-analytic strategy.

Similarly, for profiles of specific anxiety diagnoses, our findings are consistent with previous literature. For FXS, specific phobia and social anxiety were common (Cordeiro et al., 2011; Crawford et al., 2017; Ezell et al., 2019; Gabis et al., 2011; Groves et al., 2018). For 22q11.2 deletion syndrome, specific phobia had the highest prevalence rate and OCD was common in CHARGE syndrome (Bertrán et al., 2018; Blake et al., 2005; Jolin et al., 2012; La Spata, 2019). Individuals with 7q11.23 duplication syndrome experience social anxiety, separation anxiety, specific phobia and selective mutism (Abbas et al., 2016; Mervis et al., 2012). Panic attacks may be experienced in 3q29 deletion syndrome and selective mutism in Down syndrome (Pollak et al., 2019, 2020). It is striking to note the lack of research focusing on the presentation of trauma and PTSD in genetic syndrome populations. There is evidence of increased prevalence in ID populations more generally which may be explained by the risk of abuse and negative life experiences that ID populations are exposed to (Daveney et al., 2019; Dion et al., 2018). However, there is still a need for further research focusing on assessment and intervention within ID populations more generally (Daveney et al., 2019; McNally et al., 2021). Changes to the conceptualisation of PTSD from DSM-IV to DSM-5 may have impacted the studies identified in the current study, however, research has noted the exploration of this topic as a gap in the literature. It is crucial for future studies to explore the presentation of trauma and PTSD in genetic syndrome populations (Fjermestad et al., 2015). Furthermore, the specific anxiety profile findings should be interpreted with caution due to the majority of analyses (81 %) including five studies or less, with studies less likely to explore specific anxiety profiles than anxiety more generally. This could preclude the identification of syndrome specific anxiety profiles and therefore may hinder effective intervention development.

However, the studies that did report specific anxiety profiles clearly indicate the presence of specific and divergent profiles of anxiety diagnosis that allude to syndrome associated causal pathways or gene disorder-phenotype-environment interactions that are syndrome related. This highlights the importance of exploring environmental, cognitive, emotional, and psychophysiological correlates of anxiety diagnoses that might indicate likely drivers of the development and maintenance of anxiety within syndromes. Previous studies of anxiety in Williams syndrome demonstrate this strategy, whereby high rates of generalised anxiety and specific phobia including noise stimuli, blood and injury are found (Gothelf et al., 2006; Royston et al., 2017). These specific diagnoses have been linked to phenotypic features of Williams syndrome such as hyperacusis and regular medical intervention due to complex physical health difficulties (Morris et al., 2020; Royston et al., 2017). For clinicians, there are implications for delivering preventative and responsive interventions that might target specific anxiety diagnoses differentially across syndromes. For example, the treatment of phobias differs from that for generalised anxiety; the former focuses on gradual exposure techniques whilst the latter on cognitive-behavioural strategies (Maskey et al., 2014; McConachie et al., 2014).

The subgroup analyses of individual syndromes revealed that for 22q11.2 deletion syndrome, anxiety symptomatology prevalence was significantly lower than psychiatric prevalence while the opposite was true for DS. One interpretation of this is that relying only on report of anxiety symptomatology for 22q11.2 deletion syndrome may underestimate anxiety prevalence. As 22q11.2 deletion syndrome is mostly associated with moderate to mild ID, the use of psychiatric assessment developed for the general population that relies on DSM/ICD criteira may be more appropriate for this group, as evidenced by the majority of included papers assessing anxiety using such criteria (94 %) (De Smedt et al., 2007). For DS, report of anxiety symptomatology was higher compared to psychiatric anxiety prevalence, as might be expected from missed diagnoses due to an individual not meeting diagnostic criteria but still experiencing anxiety. However, across all DS papers, as sample size increased the prevalence of anxiety decreased, suggesting that when more representative samples are considered, estimates of anxiety prevalence are lower and hence more valid.

In terms of specific anxiety profiles, for specific phobia in 22q11.2 deletion syndrome, better quality rated papers for sample identification and syndrome confirmation reported significantly higher rates of anxiety prevalence than lower quality rated papers. This was also the case in terms of sample identification for separation anxiety. These findings indicate that studies that are more representative and have implemented more robust methods to obtain syndrome confirmation appear to show higher prevalence of anxiety, increasing confidence in the findings. For generalised anxiety, lower quality rated papers in terms of syndrome confirmation showed significantly higher reports of anxiety prevalence compared to higher quality rated papers. In combination, these relationships between differences in estimates and quality indicate the need for more robust methods in research.

Meta-regression analyses indicated that year of publication and sample size did not have significant impact on anxiety prevalence across syndromes with the only exception being sample size in DS. It is important to note that in some cases there were a small number of papers included in the subgroup analyses and so future research would need to confirm these findings.

The current review utilised a broad search strategy and inclusive search criteria with the number of papers evaluated ranging from 70 in 7q11.23 duplication syndrome to 8882 in CHARGE syndrome, with 83 studies included in the final analysis. The scale of the selection process enabled a comprehensive synthesis and evaluation of the quality of the literature. The results can inform both clinical practice and potential future research strategies. It is important to note that the current review did not endeavour to include all syndromes associated with ID and there were papers that reported anxiety prevalence that were not identified in the scoping search that subsequently came to light during the individual syndrome searches, for example, Crawford et al. (2017) reported anxiety prevalence in Fragile X, as well as Cornelia de Lange and Rubinstein-Taybi syndromes. The decision not to conduct a scoping review according to defined guidelines e.g., PRISMA Extension for Scoping Reviews (PRISMA-ScR; Tricco et al., 2018) could be considered a limitation of the study (Peters et al., 2015). However, the systematic application of scoping criteria used was deemed appropriate within the timeframe of the study completion to limit the search as it was not possible to review all possible syndromes associated with ID. The study highlights variation across syndromes and the value of considering syndromic mechanisms that may drive anxiety presentation across groups. Future research should focus on characterising difference in presentation and profile of anxiety, and to explore the role of genetic factors and gene-disorder-phenotype-environment interactions within and across syndromes. This work will continue to inform clinicians as to the risk and type of anxiety diagnoses that might warrant proactive assessment and intervention.

A particular lack of research was highlighted in Rett, 7q11.23 duplication, CHARGE, 3q29 deletion and Down syndromes and TSC. Having a limited number of studies compromises accuracy of prevalence as this enhances the effect of heterogeneity of methods, decreasing confidence in conclusions and limiting ability to generalise findings. Striving to delineate the phenotypic characteristics of syndromes and identifying those groups most at risk of anxiety should be a high priority.

As noted in previous research, it was apparent in the current review that research groups publish multiple papers that appear to include similar but not identical samples (Richards et al., 2015). Consequently, it is not possible to avoid reporting on overlapping samples, potentially reducing the representativeness of findings. Whilst data may be collected that address a number of manifestations within a particular syndrome, authors should strive to explicitly report overlap of participants across studies to increase transparency.

The current review documented and evaluated the methods used to assess anxiety across syndromes. Diagnostic criteria developed for the general population may not be appropriate for individuals with ID,

particularly those with moderate-profound ID (Flynn et al., 2017). The use of criteria, such as the DSM or ICD, may underestimate anxiety in ID due to the reliance on items requiring verbal response and/or the description of emotions, and atypical presentations of anxiety such as self-injurious behaviour (Bailey and Andrews, 2003). Consequently, an individual may not meet diagnostic threshold and therefore be 'counted' within a prevalence rate but be experiencing anxiety that is impacting their quality of life. In the current review, 66% (55) of studies used DSM/ICD criteria, and therefore rates may underestimate anxiety prevalence.

While the quality rating applied favoured the use of a diagnostic instrument over proxy report, the latter may be important for exploring symptomatology not bound by diagnostic criteria, highlighting the importance of including studies reporting the prevalence of anxiety symptomatology (Bertelli et al., 2015). There was variation in methods of assessments across syndromes; In RS, studies relied exclusively on proxy reports of anxiety symptomatology, for 22q11.2 deletion syndrome, most studies used diagnostic interviews with the person, therefore comparing prevalence rates between syndromes is difficult. It is also crucial to note discrepancies in reports of anxiety when relying on self vs. proxy report, where studies have indicated that diagnoses of anxiety were more frequently derived from self-report rather than proxy report. Therefore, clinicians should be aware of this potential discrepancy and the impact of assessment method on anxiety prevalence (Stinton et al., 2010, 2012). If an individual is unable to self-report, relying solely on proxy report of anxiety may lead to individuals not receiving the support they require.

Currently, there are no consensus guidelines for assessing anxiety in individuals with ID (Flynn et al., 2017), stressing the need for the consideration of issues such as method of assessment (observation, diagnostic interview, rating scales), who completes the assessment (self, proxy), assessment outcome (symptoms/behaviours vs. diagnosis) and exploration of frequency, severity and impact of anxiety to determine clinical significance. Clinicians need to be aware of these factors when assessing mental health in ID and use multi-method assessment to elucidate the clinical presentation. Researchers should strive to develop tools created and validated specifically for different groups to improve the validity of diagnosis and prevalence estimates.

The current study extends the existing evidence base highlighting the importance of identifying mental health difficulties in people with ID, as recognised as a key policy priority (National Institute for Health and Care Excellence NICE, 2016). The findings indicate that individuals with syndromic ID are at increased risk of experiencing anxiety, in comparison to individuals in general and ID of mixed aetiology populations. Therefore, clinicians and professionals who support individuals with syndromes should promote early identification, assessment, and intervention. Studies investigating anxiety prevalence are sparse for the majority of the included syndromes and future studies should aim to extend the current study findings, enabling future reviews to include a larger number of studies, increasing the generalisability of the findings to the wider syndrome populations. Additionally, the unmet need in mental health care for individuals with ID more generally has been highlighted, stressing the need for future research and further service provision to support these vulnerable groups (Venville et al., 2015; Whittle et al., 2018).

Declarations

Patient and Public Involvement statement

As this is a review study, we did not have contact with human participants and therefore patient and public involvement was not applicable.

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Patient consent for publication

As this is a review study, we did not have contact with human participants and therefore informed consent was not applicable.

CRediT authorship contribution statement

GE, CO and JW conceived the study. GE, JT, CO and JW designed the study. GE and RR selected the papers for inclusion in the study. GE, EP and LS extracted data from included studies. GE and EP quality rated included studies. GE and CJ completed the statistical analyses. GE and JT reviewed inclusion of studies that were identified as heterogeneous and highly influential. GE wrote the drafts of the manuscript, CJ, JT, HC, CO and JW provided feedback on revisions of the draft manuscript.

Competing interests

None.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104719.

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