# LOW MOOD IN RARE GENETIC SYNDROMES ASSOCIATED WITH INTELLECTUAL DISABILITY

By

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## Thesis Overview

This thesis contains four chapters. The first chapter is a literature review that discusses a systematic review and meta-analysis on the prevalence of depression in genetic syndromes associated with intellectual disability. The pooled prevalence estimates of depression are reported in four genetic syndromes where there were five or more studies that reported the depression prevalence. The pooled prevalence rates ranged from 9% in Williams syndrome to 13% in 22q11.2 deletion syndrome. The methodological quality of studies is reported and the need for further research reporting the prevalence of depression in genetic syndromes is highlighted.

The second chapter describes an empirical research project on correlates and predictors of low mood in three genetic syndromes associated with intellectual disability: Cornelia de Lange syndrome; fragile X syndrome; and Rubinstein-Taybi syndrome. The study found differences in the correlates and predictors of low mood in each syndrome group, suggesting there might be syndrome specific pathways to low mood. The clinical implications of understanding correlates of low mood in people with genetic syndromes are discussed.

The third and fourth chapters are two press releases and provide a summary of the literature review and the empirical research paper, respectively.

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### Chapter One: Literature review



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# Chapter One: Literature review

## The Prevalence of Depression in Genetic Syndromes Associated with Intellectual Disability: A Systematic Review and Meta-Analysis.

**Word count: 8191**

## Abstract

**Background:** Research has shown people with genetic syndromes associated with intellectual disability are at a heightened risk of mental health difficulties, and the rates of mental health difficulties vary across syndrome groups. However, there is limited research reporting depression prevalence in genetic syndromes. Understanding the prevalence of depression can inform clinical service provision.

**Aims:** The study aimed to explore the point prevalence rate of depression across genetic syndromes associated with intellectual disability whilst accounting for the methodological quality of studies.

**Method:** The study was reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. A scoping search and an appraisal of existing reviews identified 10 genetic syndromes to be included in the study. Three electronic databases were searched, and papers were screened for eligibility. A total of 40 papers were included and pooled prevalence estimates were calculated for syndromes with five or more studies reporting depression prevalence. Further analyses were completed to explore sources of heterogeneity.

**Results:** Four syndrome groups were included in the meta-analysis. The pooled prevalence estimates were found to be higher than the prevalence of depression in the general population. The pooled prevalence was 9% in Williams syndrome, 10% in Down syndrome, 10% in tuberous sclerosis complex, and 13% in 22q11.2 deletion syndrome.

**Conclusions:** Similar pooled prevalence rates of depression were found across syndrome groups. The differences in study methodology in the existing literature were highlighted.

Further research distinguishing the prevalence of depression in genetic syndromes is required to inform treatment strategies.

## Introduction

Depression is an umbrella term for common mental health difficulties (WHO, 2023) characterised by depressed mood and a loss of interest or pleasure in activities (American Psychiatric Association, 2013). Depression is often assessed using diagnostic criteria that provide standardised definitions for depressive disorders and can facilitate the development of evidence-based treatment guidelines. The Diagnostic Statistical Manual-5 (DSM-5) outlines depressive disorders that include major depressive disorder, persistent depressive disorder, and unspecified depressive disorder (APA, 2013). Major depressive disorder involves a persistent depressed mood or a reduction of interest and pleasure in activities that is present for at least two weeks and significantly impacts daily functioning (APA, 2013). Persistent depressive disorder is regarded as a lower severity of depression with long-term symptoms that are present for at least two years (APA, 2013). A diagnosis of unspecified depressive disorder is made if depressive symptoms do not meet the criteria for another diagnosis of depression. Persistent depressive disorder and unspecified depressive disorder were updated diagnoses in the DSM-5; persistent depressive disorder combined the terms dysthymic disorder and chronic major depressive disorder, and unspecified depressive disorder replaced the term depression not otherwise specified (APA, 2013). Having diagnostic classifications of depression has clinical importance.

Depression in people with intellectual disability (ID) can present differently to people in the general population (Sturmey, 1995), and depressive symptoms can vary dependent on the level of ID (Davis et al., 1997). Previous research has suggested that people with mild to moderate ID show symptoms of depression included in diagnostic criteria used in the general population (McBrien, 2003), suggesting that using diagnostic classifications including DSM-V are appropriate (Eaton et al., 2021). The main symptoms

reported in people with mild to moderate ID include sadness, loss of interest in activities, tiredness, loss of energy, agitation, self-criticism, changes related to sleep, and irritability (McGillivray & McCabe, 2007). Previous research has shown that people with severe ID experience depressive symptoms including depressed affect, anhedonia, low energy, sleep disturbance, irritability, and tearfulness (Eaton et al., 2021). Additionally, people with severe ID show behaviours that challenge including aggression, disruptive behaviour, and self-injurious behaviour (Davis et al., 1997; Eaton et al., 2021). Previous research has debated whether behaviours that challenge could be 'depressive equivalents' (Eaton et al., 2021; Marston et al., 1997), with caution raised due to research suggesting that behaviours that challenge and depression might co-occur independently in people with severe ID (Paclawskyj et al., 1997), or a third variable, such as pain, might explain the co-occurrence (Eaton et al., 2021).

Depression is classified as one of the largest contributors to years lived with a disability globally (Carapetis & Dadi, 2017), and depression negatively impacts a person's physical health and quality of life (Baglioni et al., 2011; Horovitz et al., 2014; Rand & Malley, 2017). People with ID might have a biological predisposition to experiencing depression (Collacott et al., 1992) and might also be exposed to negative psychosocial experiences (McGillivray & McCabe, 2007). Previous research has found the impact of psychosocial factors and social context on the development of depression in people with ID; risk factors of depression include a higher number of negative life events, lower levels and quality of social support, lower socioeconomic status, regular changes in residence, and stigma (Ali et al., 2015; McGillivray & McCabe, 2007; Tomić et al., 2011). In addition, people with ID are more at risk of being bullied compared to the general population (Christensen et al., 2012) and being bullied has been found to be associated

with depression in children with ID (Whitney et al., 2019). Furthermore, negative life experiences might have a larger impact in people with ID due to lower levels of social support, and difficulties with problem solving and coping skills (Ali et al., 2015; Jahoda et al., 2006; McGillivray & McCabe, 2007). Thus, the importance of understanding the risk of depression in people with ID is highlighted.

However, there are difficulties assessing depression in people with ID which can result in diagnostic overshadowing and underestimations of the prevalence rate (Davies & Oliver, 2014; Reiss et al., 1982). Difficulties assessing depression in people with ID can be due to communication difficulties, difficulties in self-reporting subjective experiences and internal states, difficulties with depression symptoms being recognised in people with ID, and symptoms being incorrectly attributed to a physical health difficulty (Adams & Oliver, 2011; Eaton et al., 2021; Hagopian & Jennett, 2008; Hermans et al., 2013; Levitas et al., 2001; NICE, 2016). The difficulties in measuring depression are heightened in people with severe to profound ID due to difficulties recognising and reporting psychological and internal mood states (Adams & Oliver, 2011; Eaton et al., 2021), and the assessment of depression can rely on observable symptoms including sleep disturbances and changes in appetite (Adams & Oliver, 2011). In addition, there are limited number of depression measures that are validated for people with ID and the absence of a consensus in the measures used to screen and diagnose mental health difficulties in people with ID (Perez-Achiaga et al., 2009). Thus, a diagnosis of depression often relies on carer reports which have been shown to have poor reliability for depression (Burt, 1999; Davies & Oliver, 2014). Considering how depression is measured is important to understand the risk of depression in people with ID.

The rate of depression in the general population is estimated to be 4.4% (WHO, 2017). The prevalence rate of depression has been found to be higher in people with ID with estimates between 2.2% and 15.8% (Buckley et al., 2020; Cooper, 1997; Cooper et al., 2007; Cooper et al., 2015; Deb et al. 2001; Hsieh et al., 2020; Hermans et al. 2013; Maïano et al., 2018; Smiley, 2005; Tsakanikos et al., 2006; White et al., 2005). These prevalence estimates increase up to 46.5% when depression symptomatology is also included (Scott & Havercamp, 2015). The differences in prevalence rates of depression might be explained by differences in study methodology, including different assessment methods, different diagnostic criteria, and differences in how depression is defined (Kessler, 2013; NICE, 2023; Vereenooghe & Langdon, 2013). Thus, the differences in study methodology should be considered when pooling prevalence estimates as determining accurate prevalence rates, and identifying people who are at high risk of experiencing depression is essential for care planning and to ensure people receive appropriate support to promote positive outcomes (Caron & Rutter, 1991; Hansen et al., 2018).

Despite the importance of distinguishing accurate prevalence rates, there are difficulties distinguishing the “true prevalence” rate of depression in people with ID due to the limitations in research (Scott & Havercamp, 2015). The methodological limitations in studies reporting the prevalence of mental health difficulties for people with ID include small sample sizes, biases in the sampling, focusing on historic information from case notes, using measures that are screening tools, and the absence of reporting whether the prevalence rate is a point or lifetime prevalence (Cooper et al., 2007). Thus, the limitations in the methodology of studies limit the accuracy of the prevalence rates reported and

highlight the need for more robust estimates of depression prevalence to inform clinical service provision.

People with genetic syndromes associated with ID have been found to be at higher risk of co-occurring physical and mental health conditions compared to the general population (Agar et al., 2021; Edwards et al., 2022; Glasson et al., 2020). Higher rates of sleep difficulties were found in genetic syndromes compared to the general population (Agar et al., 2021). Additionally, the pooled prevalence estimates of anxiety were found to be higher for people with genetic syndromes compared to the general population and people with ID of mixed aetiology, with pooled prevalence estimates ranging from 9% in people with Down syndrome to 73% in people with Rett syndrome (Edwards et al., 2022). A meta-analysis described mental health difficulties in children and adolescents with a genetic syndrome associated with ID (Glasson et al., 2020) and found the pooled prevalence of mental health difficulties was 74% in Prader-Willi syndrome, 67% in Williams syndrome, 61% in fragile X syndrome, 46% in 22q11.2 deletion syndrome, and 32% in Down syndrome. As the prevalence of physical and mental health conditions in people with genetic syndromes associated with ID is higher than prevalence estimates for people with ID of mixed aetiology and the general population, people with genetic syndromes might also be at a heightened risk of depression.

Risk of depression in genetic syndromes has been indicated in the literature. Previous reviews found the prevalence of depression ranged from 2% to 13% in Down syndrome (Walton & Kerr, 2015), and between 12% to 29% in 22q11.2 deletion syndrome (Bertrán et al., 2018). A systematic review found the prevalence rate of mood disorders in children and adolescents with 22q11.2 deletion syndrome ranged between 3% to 7% (Glasson et al., 2020; Schneider et al., 2014; Sobin et al., 2009; Young et al., 2011), and

found one study that reported a prevalence of mood disorders of 3% in children and adolescents with Williams syndrome (Dodd & Porter, 2009; Glasson et al., 2020). In addition, studies exploring depression in tuberous sclerosis complex have found a prevalence rate between 19 to 43% (de Vries & Bolton, 2002; Lewis et al., 2004; Muzykewicz et al., 2007; Pulsifer et al., 2007; Raznahan et al., 2006). The higher rates compared to the general population and the range of prevalence rates reported highlight the need for a synthesis of depression prevalence in genetic syndromes associated with ID that considers differences in study methodology.

The heightened risk of mental health difficulties in people with genetic syndromes associated with ID might be explained by gene-environment interactions which can inform causal models of mental health difficulties. Research has found evidence for gene-environment interactions in genetic syndromes associated with ID (Taylor & Oliver, 2008), and genetic syndromes have specific behavioural, physical, emotional, and cognitive phenotypes that interact with environmental factors and developmental factors (Waite et al., 2014). For example, hyper-arousal to auditory sensory stimuli is common in Williams syndrome, which can impact behaviours in loud environments (Royston et al., 2020; Waite et al., 2014). In addition, specific mental health difficulties are more common in different syndromes. High rates of affective psychosis are found in Prader-Willi syndrome (NICE, 2016), psychosis is prevalent in 22q11.2 deletion syndrome (Chawner et al., 2019), and anxiety disorders are highly prevalent in Williams syndrome (Royston et al., 2017). Sleep difficulties are common in Smith-Magenis syndrome (Agar et al., 2021), and sleep difficulties have been found to be a risk factor of low mood (Steiger & Pawlowski, 2019). Additionally, sensory differences are common in Williams syndrome and fragile X syndrome (Waite et al., 2014), and sensory differences are associated with depressive

symptoms (Rossow et al., 2022). Thus, gene-phenotype-environment interactions might account for differentially higher prevalence of mental health difficulties in people with specific syndromes associated with ID compared to the general population and compared to other syndromes also associated with ID.

In summary, depression is a key contributor to poor quality of life (Rand & Malley, 2017), and the prevalence of depression is higher in people with ID compared to the general population. As genetic syndromes are associated with co-occurring mental health difficulties, distinguishing the prevalence of depression across different genetic syndromes is essential to identify syndrome groups that have a heightened risk of depression to inform early intervention strategies (Oliver et al., 2013). However, to the author's knowledge, there is no previous meta-analysis synthesising the prevalence of depression across genetic syndromes in the literature. This absence of epidemiological data limits clinical provision of support and precludes the exploration of mechanisms that contribute to risk via gene x environment interactions.

Therefore, the current study aimed to explore the point prevalence of depression across genetic syndromes associated with ID. For the purpose of the current study, depression refers to depressive disorders (e.g. major depressive disorder, dysthymia, and depression not otherwise specified) and clinical levels of depression as measured by standardised measures. Point prevalence refers to people who have depression at a point in time (e.g. when the assessment was completed) whereas lifetime prevalence refers to people who have depression across their life (Hudson et al., 2019). The current study is the first meta-analysis exploring the point prevalence rate of depression in people with genetic syndromes across ages whilst accounting for the methodological quality of studies. The specific aims of the study were to:

1) Synthesise data from previous research and calculate the point prevalence estimates of depression in people with genetic syndromes associated with ID.
2) Account for the methodological quality of studies included in the review when calculating point prevalence estimates.
3) Describe the point prevalence estimates of depression across genetic syndromes with reference to prevalence estimates for the general population.

## Methods

The current systematic review and meta-analysis was reported following the PRISMA guidelines (Page et al., 2021). The systematic review followed a similar methodology to a previous review which explored the prevalence of anxiety in genetic syndromes associated with ID (Edwards et al., 2022). The present study was pre-registered on PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023394628).

### Identifying genetic syndromes

The current study aimed to explore whether there are different prevalence rates of depression across rare genetic syndromes associated with ID. Due to the high number of genetic syndromes associated with ID, it was beyond the scope of the current study to explore the risk for depression in all genetic syndromes. Genetic syndromes were identified for inclusion where it was anticipated that there would be studies that have reported the depression prevalence in the literature. Thus, an appraisal of existing reviews and a scoping search were completed to identify the syndromes.

### *Appraisal of pre-existing systematic reviews*

Eight of the genetic syndromes that were included in the present study were the same syndromes that were included in a previous systematic review exploring the prevalence rate of anxiety (Edwards et al., 2022) as depression and anxiety are commonly co-occurring mental health difficulties (Gorman, 1996; Hirschfeld, 2001; Lamers et al., 2011; Sartorius et al., 1996). Williams syndrome is associated with high anxiety and was also a syndrome included in the current review as Edwards et al. (2022) stated Williams syndrome was identified though the scoping search but excluded due to another meta-analysis being published around the same time that focused on Williams syndrome (Royston et al., 2017). Therefore, the nine genetic syndromes identified from a previous review to be included in the current study include: Down syndrome, fragile X syndrome, Rett syndrome, 22q11.2 deletion syndrome, tuberous sclerosis complex, 3q29 deletion syndrome, CHARGE syndrome, 7q11.23 duplication syndrome, and Williams syndrome.

### *Scoping search*

A scoping search was completed to identify any additional genetic syndromes to be included. The scoping search used search terms for syndrome, ID, and depression which were based on previous reviews (Edwards et al., 2022; Eaton et al., 2021), as shown in Appendix 3.1. The search terms relating to depression were derived from the search terms included in a previous review and the two most common behavioural indicators, depressed affect and anhedonia (Eaton et al., 2021).

The scoping search was completed on 1st March 2023 using the APA PsycInfo (1967 to February Week 3 2023), Ovid Medline (1946 to February 28 2023), and Embase (1974 to February 28 2023) databases. The scoping search was limited to the past five

years to provide a 'snapshot' of the literature given the current review did not aim to explore depression in all the genetic syndromes associated with ID. The scoping search resulted in 2458 papers. The title and abstract were screened for a focus on depression and a genetic syndrome associated with ID, and 142 papers were included for full text screening. A genetic syndrome was included in the current study if the scoping search identified one or more empirical study that reported the prevalence rate of depression. Exclusion criteria included: reviews, case studies, case series with less than 10 participants, genetic syndromes that were not associated with ID, and if the paper did not report the prevalence rate of depression.

The scoping search identified four of the same syndromes identified from a previous meta-analysis (Edwards et al., 2022; fragile X syndrome, Down syndrome, tuberous sclerosis complex, 22q11.2 deletion syndrome). One additional syndrome, Phelan-McDermid syndrome, was identified through the scoping search to be appropriate for the current study, resulting in a total of 10 genetic syndromes included in the study.

## Identifying primary studies

### *Search strategy*

A systematic search was completed on 12th September 2023 using Ovid Medline (1946 to September 11 2023), Embase (1974 to September 11 2023), and APA PsychInfo (1967 to September Week 1 2023) databases. The search terms for the genetic syndromes were generated following previous reviews (Edwards et al., 2022; Royston et al., 2017; Kolevzon et al., 2019). GeneReviews, an international peer-reviewed resource, and OMIM, a database of genetic disorders, were also explored to identify additional search terms and synonyms for the genetic syndromes. The search terms for depression were the same as the

scoping search and were derived from a previous review and common behavioural indicators of depression (Eaton et al., 2021). Each of the searches for the ten syndromes were combined with the 'OR' operator. The result from combining the genetic syndromes and the search for depression were combined with the 'AND' operator. The search fields were limited to abstract, keyword, and title, as shown in Table 1.1.

**Table 1.1**

*Search terms used for the current study*

| Search | Search terms (.ab.kw.ti) |
|---|---|
| Depression | (depress* or low mood or affective disorder or low affect or negative affect or flat affect or dysthym* or depressed affect or anhedonia).ab,kw,ti. |
| Fragile X syndrome | (Fragile X or Fragile-X or Fragile X syndrome or FXS or FRAXA syndrome or AFRAX or Martin-Bell* syndrome or Marker X syndrome or "fraX syndrome" or "fra(X) syndrome" or X-linked mental retardation or Macroorchidism or Escalante* syndrome or Escalante* or Fragile X Mental Retardation Syndrome or Mental Retardation X-Linked associated with marXq28).ab,kw,ti. |
| 22q11.2 deletion syndrome | (VCF or VCFS or Velocardiofacial syndrome or CTAF or Velo-cardio-facial syndrome or DiGeorge* syndrome or Conotruncal anomaly face syndrome or CATCH22 or "Autosomal dominant Opitz G/BBB syndrome" or Autosomal dominant Opitz G BBB syndrome or Cayler cardiofacial syndrome or "Deletion 22q11/2 syndrome" or "22q11/2 deletion syndrome" or "22q11/2DS" or 22q11 deletion syndrome or Sedlackova* syndrome or Shprintzen* syndrome or DGS or "chromosome 22q11.2 deletion syndrome").ab,kw,ti. |
| Down syndrome | (Down* syndrome or Trisomy 21 or Trisomy G or "47,XX,+21" or "47,XY,+2").ab,kw,ti. |
| Tuberous sclerosis complex | (Tuberous sclerosis or Tuberous sclerosis syndrome or Bourneville* disease or Bourneville* phakomatosis or Cerebral sclerosis or Cerebral sclerosis syndrome or Epiloia or Sclerosis tuberose or Tuberose sclerosis or Tuberose sclerosis syndrome or Tuberous sclerosis complex or TSC or TSS or TSC1 or tuberous sclerosis 1).ab,kw,ti. |
| 7q11.23 duplication syndrome | ("7q11.23*" or "7q11.23 duplication syndrome" or "7q11.23 microduplication syndrome" or "chromosome 7q11.23 duplication" or "chromosome 7q11.23 duplication syndrome" or "dup(7)(q11.23)" or Somerville-Van der Aa syndrome or "trisomy 7q11.23" or WBS duplication syndrome or Williams-Beuren region duplication syndrome).ab,kw,ti. |

| Search | Search terms (.ab.kw.ti) |
|---|---|
| CHARGE syndrome | (CHARGE or CHARGE syndrome or CHARGE association or Hall-Hittner* syndrome or Hall* Hittner* syndrome or Coloboma or charge association-coloboma or HHS).ab,kw,ti. |
| 3q29 syndrome | (3q29* or 3q29 mircodeletion syndrome or 3q subtelomere deletion syndrome or 3q29 deletion syndrome or 3q29 recurrent deletion or chromosome 3q29 deletion syndrome or microdeletion 3q29 syndrome or monosomy 3q29).ab,kw,ti. |
| Rett syndrome | (Rett* or Rett* syndrome or Rett* disorder or RTS or RTT or Cerebroatrophic hyperammonemia or "Autism-dementiaataxia-loss of purposeful hand use syndrome").ab,kw,ti. |
| Williams syndrome | (beuren syndrome* or elfin facies syndrome* or elfin facies with hypercalcemia* or hypercalcemia-supravalvar aortic stenosis* or infantile hypercalcemia* or supravalvar aortic stenosis syndrome* or WBS or williams beuren syndrome* or WMS or WS or williams syndrome* or "chromosome 7q11.23 deletion syndrome*" or contiguous gene syndrome* or williams contiguous gene syndrome* or Williams-Beuren Syndrome).ab,kw,ti. |
| Phelan McDermid syndrome | (Phelan-McDermid Syndrome or Phelan McDermid Syndrome or "22q13.3 deletion syndrome" or "chromosome 22q13.3 deletion syndrome" or deletion 22q13 syndrome or SHANK3 or Ring Chromosome 22 or PROSAP2 or PHMDS or telomeric 22q13 monosomy syndrome).ab,kw,ti. |

### *Inclusion criteria*

The screening process and inclusion criteria were based on a previous review (Edwards et al., 2022). The texts were screened following a two-stage process; stage one included screening the title and abstract, and stage two involved screening the full text of included papers with additional criteria applied, as shown in Table 1.2. Inclusion criteria at stage one included studies published in peer reviewed journals that focus on a genetic syndrome included in the current study and terms related to mental health being included in the title or abstract. Non-human studies, studies that focus on other genetic difficulties, and studies that focus on parent mental health were excluded. Reviews and case studies were included at stage one to allow further papers to be identified through citation

searching of the full texts. Studies were included at stage two if the point prevalence rate of depression was reported.

**Table 1.2**

*Inclusion and exclusion criteria*

| Stage one screening<br>Inclusion criteria | Exclusion criteria |
|---|---|
| Studies with participants with a genetic syndrome associated with ID that is included in the study.<br><br>The title or abstract of studies mentioning mental health.<br><br>Studies published in English.<br><br>Peer reviewed journals. | Conference abstracts/ papers, dissertation abstracts, editorials, book chapters, letters, notes, brief reports.<br><br>Studies that focus on other genetic difficulties relating to the syndrome e.g. fragile X syndrome pre-mutation or carriers.<br><br>Non-human studies.<br><br>Studies that focus on parental or sibling mental health.<br><br>Studies that focus on genetics e.g. proteins |
| **Stage two screening**<br>**Inclusion criteria** | **Exclusion criteria** |
| Studies that report the point prevalence rate of a diagnosis of depression (e.g. major depressive disorder, dysthymic disorder, depressive episodes, depression not otherwise specified[1]).<br><br>Studies that report depression as measured by a clinical cut-off score on a standardised measure. | Reviews.<br><br>Case Studies.<br><br>Case series with less than 10 people.<br><br>Studies with recruitment bias (e.g. participants recruited from a psychiatric clinic or due to having a mental health diagnosis).<br><br>Studies that provide combined prevalence rates (e.g. mood disorders or depression and anxiety as a single combined prevalence estimate).<br><br>Studies that only report the prevalence rate of bipolar disorder.<br><br>Studies that report a prevalence rate based on the number of people receiving medication. |

| | |
|---|---|
| | Studies that do not include distinct genetic syndrome groups.<br><br>Studies that solely report behavioural symptoms of depression (e.g. withdrawn, depressed mood) that are not measured by a clinical cut-off score. |

[1] Although dysthymia and depression not otherwise specified are not diagnostic classifications in the DSM-5, the previous literature has used these terms and dysthymia is one of the main classifications of depressive disorders (WHO, 2017). Thus, the current study included these diagnostic classifications.

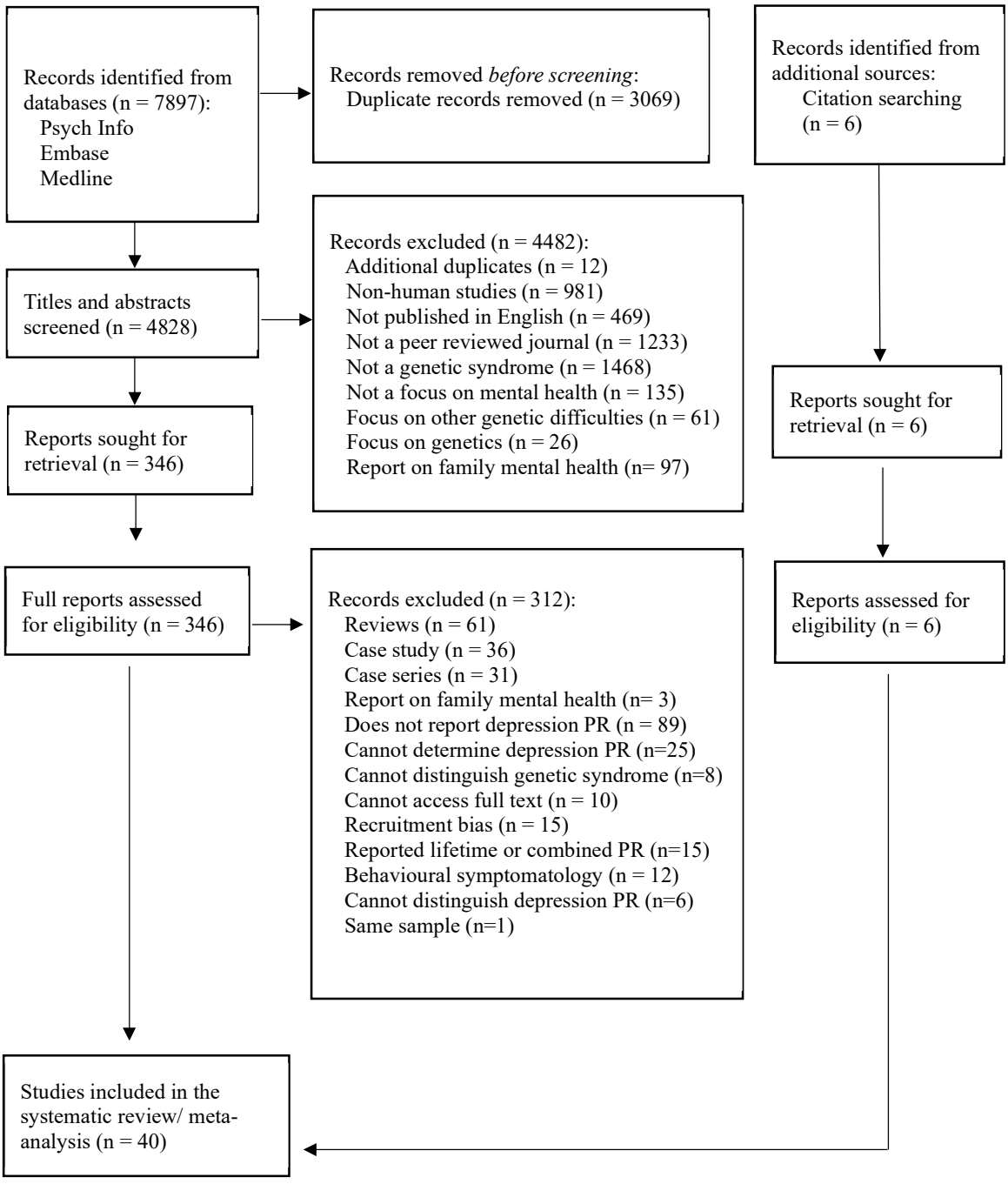
### *Study selection*

The search identified a total of 7897 papers, as shown in Figure 1.1. After 3069 duplicates were removed, there was a total of 4828 papers to be included in stage one screening. The titles and abstracts of the articles were screened using the inclusion and exclusion criteria by three raters. A training phase was completed for 10 papers where the titles and abstracts were screened, discrepancies were discussed, and a consensus was gained. Three researchers screened the 4828 papers; the author screened 1828 (38%), researcher two screened 1500 (31%), and researcher three screened 1500 papers (31%). The screening was checked by a fourth researcher who screened 1207 (25%) of all 4828 papers to compare their decisions regarding the papers to the researchers who completed the initial screening to ensure integrity between the ratings. Excellent agreement was found (Kappa = 0.81). When there were discrepancies regarding whether papers should be included at stage one, the papers were discussed and a consensus was reached, and appropriate studies were included for stage two. Common reasons for exclusion at stage one included: studies not including participants with a genetic syndrome (n = 1468), papers not being published in a peer reviewed journal e.g. conference abstracts (n = 1233), and non-human studies (n = 981).

The full text of 346 papers were screened by the author (100%) with the additional stage two inclusion and exclusion criteria applied. A second rater screened 87 papers (25%) of papers to establish inter-rater reliability, with excellent agreement achieved (Kappa = 0.82). Any discrepancies about the inclusion at stage two were discussed and a consensus was reached. Common reasons for exclusion at stage two included: studies not reporting the prevalence rate of depression (n = 89), reviews (n = 61), and case studies (n = 36). Attempts were made to access the papers where the full text was not available and the authors of one paper were contacted where it was unclear if the prevalence rate of depression could be extracted. There was a total of 34 papers that met the inclusion criteria for the systematic review and an additional six papers were identified through citation searching of the reference lists. Overall, 40 papers were included for the current study.

**Figure 1.1**

*PRISMA flowchart showing the systematic search strategy and identification of studies*




*Note.* Adapted from *The PRISMA 2020 statement: An Updated Guideline for Reporting Systematic Reviews,* by Page et al. (2021).

**Data extraction**

The data for the 40 included papers were extracted by the author. The data that were extracted from each paper included the total number of participants in the study, the number of participants with depression, demographics of the participants (including age and sex), the country where the paper was published, how the participants were recruited, how depression was measured, how the genetic syndrome was confirmed, and how depression was defined in the study (e.g. psychiatric diagnosis or a cut-off score from a measure of depression). The reliability of the data extraction was derived from 25% of the included 40 papers (n = 10). Two researchers acted as second raters and completed the data extraction for five papers each. Any discrepancies in the data extracted was discussed and a consensus was reached.

The event rates were reported as the number of people with depression divided by the entire sample size of each study. Where prevalence rates were reported separately for different subgroups in the same study (e.g. samples from different counties), these rates were combined to provide a single prevalence rate for the full sample. Where papers reported multiple rates (e.g. psychiatric diagnosis and clinical cut-off scores), the prevalence rate for the more conservative/ severe classification was reported, typically the psychiatric diagnosis. Where papers reported multiple prevalence rates of depression based on different classifications, the DSM classification was extracted as it was the most consistent classification of depression across studies. Multiple outcomes from a single study were not included as the inclusion of multiple outcomes from the same study violates the assumptions of the meta-analytic tests and would result in a biased reduction of the confidence intervals for the weighted mean prevalence.

**Quality assessment**

Each study was evaluated using a quality rating tool that was developed to explore prevalence data across genetic syndromes associated with ID (Richards et al., 2015). This assessment tool was used for the current meta-analysis as the tool focuses on key methodological issues that are relevant for studies involving genetic syndromes (Edwards et al., 2022). The quality rating criteria has been adapted from previous systematic reviews and meta-analyses (Agar et al., 2021; Edwards et al., 2022; Royston et al., 2017). The three areas included in the quality assessment are sample identification, confirmation of the diagnosis of the genetic syndrome, and the assessment method of depression.

The author rated all the papers using the quality assessment tool. Each study was rated on a 4-point Likert scale from poor (0) to excellent (3) for the three methodological areas, providing a maximum score of nine. Studies were rated zero if they did not report or specify on the three areas on interest. Studies were rated three if the sample identification involved a random sample, if genetic testing confirmed the genetic syndrome, and if a consensus across multiple assessments was used to measure depression. The total scores were divided by the maximum score of nine to calculate the quality weighting for each study, resulting in a total score between zero and one. A traffic light colour coding system was used for the quality ratings, as shown in Appendix 3.2.

The reliability of the quality assessment was based on 25% of the 40 included papers (n = 10). Two researchers acted as second raters and completed the quality rating for five papers each. Good agreement between the quality ratings was found for the total score for the papers (Weighted Kappa = 0.68) across rater one (the author) and second

raters. Any discrepancies in the quality assessment ratings were discussed and a consensus was reached.

**Data analysis**

Data analysis was completed using the "Metafor" package on R Studio, version 6.9, and was conducted using the guidelines for methodology and analysis provided by the Centre for Applied Psychology, University of Birmingham. A random-effects model was used to generate pooled prevalence estimates as the random-effects model accounts for study variation (Hedges & Vevea, 1998). The random effects model was calculated with the generic inverse variance method. The quality effects model was also used to account for the methodological quality of the studies.

Genetic syndromes were included in the meta-analysis where there were a minimum of five papers that reported the point prevalence of depression, consistent with a previous meta-analysis (Thomas et al., 2022). Thus, there was a total number of 36 papers included in the meta-analysis; the included syndromes were Down syndrome (n = 14), 22q11.2 deletion syndrome (n = 9), tuberous sclerosis complex (n = 8), and Williams syndrome (n = 5). Due to the small number of studies reporting on depression prevalence (n < 10), the results described for 22q11.2 deletion syndrome, tuberous sclerosis complex, and Williams syndrome should be interpreted with caution. An additional four studies were included in the qualitative analysis with point prevalence estimates reported for Phelan-McDermid syndrome (n = 2) and fragile X syndrome (n = 2). There were no studies that met the inclusion criteria for Rett syndrome, 3q29 deletion syndrome, CHARGE syndrome, and 7q11.23 duplication syndrome.

Heterogeneity refers to between study variation that results from sources other than the true variation in depression prevalence, such as differences in methodologies. Higgins $I^2$ was used as a measure of heterogeneity (Higgins et al., 2003), and an $I^2$ value larger than 75% indicated problematic heterogeneity. Where problematic heterogeneity occurred, further analyses were completed to explore factors that might have contributed to the differences in depression prevalence estimates.

The analyses were conducted separately for each genetic syndrome as genetic syndromes have specific phenotypes (Waite et al., 2014) and previous research exploring the prevalence of mental health difficulties in genetic syndromes found differences in prevalence rates for different genetic syndromes (Edwards et al., 2022; Glasson et al., 2020). In addition, a high level of heterogeneity ($I^2 = 95\%$, $t^2 = .011$, $p < .01$) was found for all papers included in the meta-analysis before the "leave-one-out" analysis and after the "leave-one-out" analysis ($I^2 = 93\%$, $t^2 = .005$, $p < .01$), suggesting high variation between studies (Higgins et al., 2003), as shown in Appendix 4.1-4.2.

***Further analyses for problematic heterogeneity***

For syndrome groups with high levels of heterogeneity, a "leave-one-out" analysis was completed to identify the impact of studies with a disproportionate influence on depression prevalence rates. The random effects model was calculated separately for Down syndrome and tuberous sclerosis complex. Two studies reporting the prevalence rates for Down syndrome were reviewed and found to have recruitment bias. As recruitment bias was an exclusion criterion for the current study, each influential study was removed sequentially. The random effects model was recalculated with the remaining 12 studies. One influential study reporting the prevalence rates for tuberous sclerosis complex was

reviewed for methodological bias. As the study met the inclusion criteria for the current study and no recruitment bias was identified, it was not deemed appropriate to exclude the study from further analysis due to methodological quality and the study was included in the meta-analysis. Thus, 34 studies were included in the meta-analysis following the "leave-one-out" analysis.

Subgroup analyses and meta regression analyses were also completed to explore sources of variation of prevalence estimates across studies. Previous research has recommended subgroup analyses should be completed only when there are 10 studies or more (Edwards et al., 2022; Richardson et al., 2019). Thus, subgroup analyses on the quality assessment ratings were only completed for Down syndrome (and not for the other three syndrome groups that comprised less than 10 studies) to identify the impact of study level variation on the estimated prevalence rates.

Exploration of publication bias and small study bias were also completed. Publication bias results from studies with statistically significant results being published more frequently than papers that generate non-significant results (Begg & Berlin, 1988; Lin & Chu, 2018). Small study bias is where papers with small sample sizes show a larger variability in the measurement of the prevalence rate. Publication bias can be identified by reviewing a funnel plot for asymmetry (Egger et al., 1997; Lin & Chu, 2018). A trim and fill procedure (Duval & Tweedie, 2000) can be used to create the effect of publication bias.

***Selection of the meta-analytic model***

The distribution of effects in the included studies are shown in Figure 1.2-1.5. The restricted maximum-likelihood estimator was used to calculate the variance between studies ($tau^2$). There was evidence of non-linearity in the distribution of prevalence rates

when the fixed-effects model was used for Down syndrome and tuberous sclerosis complex, as shown in Appendix 4.3. When using the fixed-effects model, some evidence of non-linearity for 22q11.2 deletion syndrome was found, and there was no evidence of non-linearity in the distribution of prevalence rates for Williams syndrome.

As shown in Figure 1.2-1.3, there was no evidence of non-linearity in the distribution of prevalence rates of depression within the primary studies for 22q11.2 deletion syndrome and Williams syndrome when using the random effects model restricted maximum-likelihood estimator. Although there was some evidence of non-linearity in the distribution of prevalence rates of depression for Down syndrome, 95% of the prevalence rates fell within the 95% confidence intervals (CI) for the expected rates, see Figure 1.4. There was some evidence of non-linearity in the distribution of prevalence rates of depression for tuberous sclerosis complex, see Figure 1.5. As the restricted maximum-likelihood estimator is robust to deviations from a normal distribution (Banks et al., 1985), using the random effects model calculated with the restricted maximum-likelihood estimator was indicated to be an appropriate method to calculate the variation of the true effect for all four genetic syndromes.

**Figure 1.2**

*QQ plot of the distribution of prevalence rate of depression within the primary studies for 22q11.2 deletion syndrome*

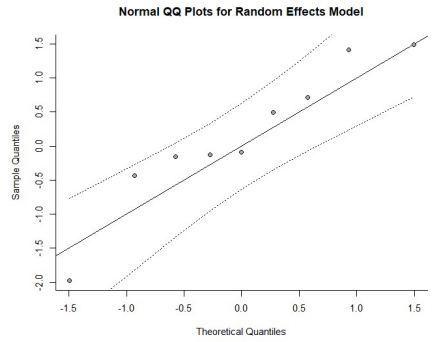



**Figure 1.3**

*QQ plot of the distribution of prevalence rate of depression within the primary studies for Williams syndrome*

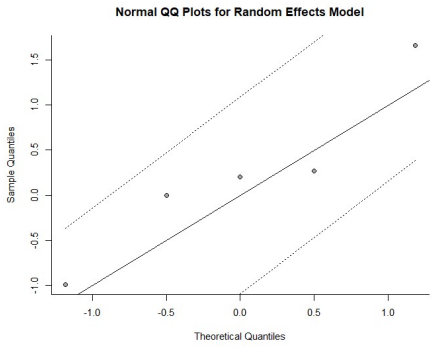


**Figure 1.4**

*QQ plot of the distribution of prevalence rate of depression within the primary studies for Down syndrome*

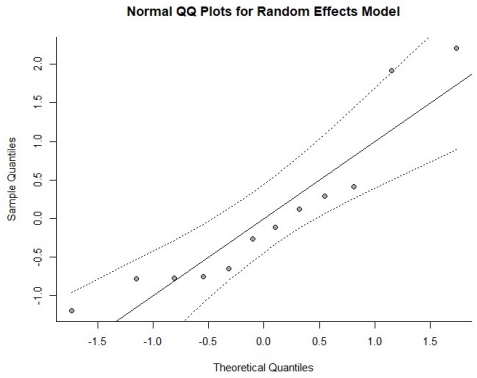
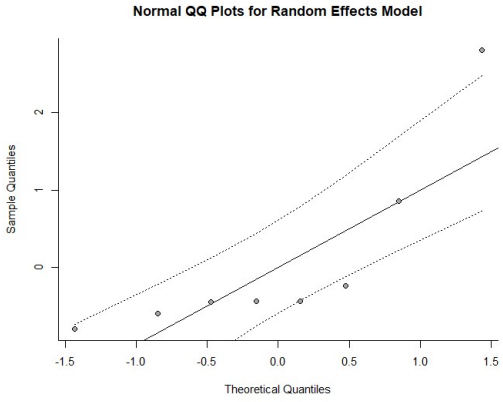



**Figure 1.5**

*QQ plot of the distribution of prevalence rate of depression within the primary studies for tuberous sclerosis complex*



## Results

Qualitative analysis is presented first for fragile X syndrome and Phelan Mc-Dermid syndrome due to the limited number of studies, followed by the results of the meta-analysis for the syndromes where there were five or more studies reporting the point prevalence of depression.

### Qualitative analysis

There were two studies that reported the point prevalence of depression in fragile X syndrome which found a point prevalence rate of 9% and 26% (Haessler et al., 2016; Lachiewicz, 1992, respectively). Haessler et al. (2016) reported the prevalence of depression in a sample of 75 participants as assessed by physicians. The higher prevalence (26%) was found in the study which used T scores greater than 70 on the Child Behaviour Checklist (CBCL) as the measure of depression (Lachiewicz, 1992). As the CBCL is a screening measure with a clinical cut-off (T score > 70), the study received a quality rating of one for the depression diagnosis. Both studies obtained a total quality rating of 0.67, as shown in Table 1.3.

The point prevalence rate of depression in Phelan-McDermid syndrome was reported in two papers, with rates of 3% (Shaw et al., 2011) and 7% (Levy et al., 2022). One study reported the prevalence in children with Phelan-McDermid syndrome with 22q13 deletion and participants with ring chromosomes or translocations were excluded (Shaw et al., 2011), and one study reported the prevalence in people with class one and class two deletions (Levy et al., 2022). These two rates were combined in the current study to generate a prevalence for the full sample; however, higher rates were found for class 1

deletions (13%) compared to class 2 deletions (2%). Both studies obtained a quality rating of 0.67.

**Table 1.3**

*Study characteristics for papers reporting the point prevalence rate in studies included in the review.*

| Authors | Syndrome | Quality rating | | | Sample Size | Age (mean, SD, range) | Sex (% Male) | Syndrome Confirmation (SC) | Depression Diagnosis (DD) | Outcome data | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SI | SC | DD | | | | | | Quality score | Depression prevalence |
| Haessler et al., 2016 | Fragile X syndrome | | | | 75 | 16.7 14.5, 2-82 | 84 | Genetic testing. | Established by physicians. | 0.67 | 9% |
| Lachiewicz, 1992 | Fragile X syndrome | | | | 38 | NR, NR, 4-11 | 0 | Cytogenetically diagnosed. | CBCL | 0.67 | 26% |
| Levy et al., 2022 | Phelan-McDermid syndrome | | | | 130 | 12, 9.1, 5-45[1] | 51.8 | Genetic reports reviewed. | Psychiatric evaluation. | 0.67 | 7% |
| Shaw et al., 2011 | Phelan-McDermid syndrome | | | | 35 | NR, NR, 2.3-41[2] | 40 | FISH analysis | Previous diagnosis[3]. | 0.67 | 3% |

[1] Demographics including age and sex were based on full sample of 170 participants, depression was reported in participants aged five and older.
[2] Median age was 7.7.
[3] The prevalence rate was reported based on previous diagnosis which is reflected in the quality score. However, the study also reported mean scores for measures of depression including the Children's Interview for Psychiatric Symptoms (ChIPS), the Parent Form of the ChIPS (P-ChIPS), interviews based on DSM-IV criteria, and Reiss Scales for Children's Dual Diagnosis.

**Meta-analysis**

A total of 36 studies reporting on a total of 16766 participants across the genetic syndromes were initially included in the meta-analysis. The “leave-one-out” analysis resulted in two papers being excluded from the meta-analysis, as described in the data analysis and influential studies sections. Thus, a total of 34 studies reporting on a total of 16301 participants across the four genetic syndromes (22q11.2 deletion syndrome, Down syndrome, tuberous sclerosis complex, Williams syndrome) were included in the meta-analysis. The study characteristics for the 34 papers are shown in Table 1.4-1.7.

**Table 1.4**

*Study characteristics and outcome data for studies reporting the point prevalence of depression in 22q11.2 deletion syndrome*

| Authors | Quality rating | | | Sample Size | Age (mean, SD, range) | Sex (% Male) | Syndrome Confirmation (SC) | Depression Diagnosis (DD) | Outcome data | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SI | SC | DD | | | | | | Quality score | Depression Prevalence |
| Antshel et al., 2010 | | | | 80 | 11.9, 2.2, NR[1] | NR | DNA testing. | K-SADS-PL. | 0.67 | 18% |
| Baker et al., 2005 | | | | 25 | 16.4, 2, 13-25 | 60% | NR. | CAPA. | 0.44 | 28% |
| Green et al., 2009 | | | | 172 | 15.9, 9.1, 5-54 | 52.3% | FISH, DNA. | K-SADS or SCID. Reviewed by two psychiatrists. | 0.89 | 16% |
| Leader et al., 2023 | | | | 101 | 25.2, 7.9, 18-60 | 47.5% | Professional diagnosed. | Parent report of diagnosis. | 0.33 | 4% |
| Ousley et al., 2013 | | | | 31 | 19.3, 4.1, 14-29 | 45.2% | FISH. | SCID-I. | 0.78 | 26% |
| Tang et al., 2014 | | | | 112 | 18.1, 8.1, 8-24+ | 53% | Confirmed deletion. | K-SADS, SCID, consensus review. | 0.89 | 13% |
| Schneider et al., 2014 | | | | 1292 | 18.8, 10.7, 6-68[2] | 47% | Genetically confirmed. | SCID, K-SADS, CAPA, or SCAN. | 0.78 | 11% |
| Jolin et al., 2009 | | | | 24 | 9.7, 3.3, 4-17 | 37.5% | FISH. | ChIPS and P-ChIPS. | 0.67 | 13% |
| Papolos et al., 1996 | | | | 25 | 15.64, NR, 5-34[3] | 52% | NR. | SCID or DICA-R, consensus review. | 0.44 | 12% |

[1] NR = not reported.
[2] Demographics (age and sex) reported for the full sample of 1402 participants, depression was assessed in 1292 participants.
[3] Median age was 15.

**Table 1.5**

*Study characteristics and outcome data for studies reporting the point prevalence of depression in Down syndrome*

| Authors | Quality rating SI | SC | DD | Sample Size | Age (mean, SD, range) | Sex (% Male) | Syndrome Confirmation (SC) | Depression Diagnosis (DD) | Outcome data Quality score | Depression prevalence |
|---|---|---|---|---|---|---|---|---|---|---|
| Ailey et al., 2006 | | | | 100 | NR, NR, 30-57 | 49% | NR. | PIMRA-AD. | 0.44 | 4% |
| Carfi et al., 2019 | | | | 430 | NR, NR, 18-75 | 59.5% | NR. | DRS. | 0.33 | 29% |
| Coppus et al., 2006 | | | | 506 | 51.9, 6.2, NR | 60.1% | Characteristics, cytogenetic. | Chart review. | 0.44 | 4% |
| Dekker et al., 2018 | | | | 281 | NR, NR, 31-74 | 49.8% | Chromosomal analysis for part of the cohort. | Interview, BPSD-DS scale. | 0.56 | 13% |
| Dekker et al., 2021 | | | | 524 | NR, NR, 30-74 | 53.1% | Reports on testing, percentage unknown. | BPSD-DS-II. | 0.56 | 4% |
| Esbensen, 2016 | | | | 75 | 51.1, 6, 37-65 | 65.3% | NR. | PAS-ADD. | 0.22 | 8% |
| Heller et al., 2004 | | | | 53 | 39.7, NR, 30-54 | 45.3% | NR. | CDI. | 0.33 | 30% |
| Mallardo et al., 2014 | | | | 49 | 26.8, NR, 20-31 | 57.1% | NR. | PAS-ADD. | 0.22 | 14% |
| Mantry et al., 2008 | | | | 186 | 41.1, 11.8, 16-74 | 48.9% | Cytogenetic testing for part of the cohort. | PAS-ADD, PPS-LD. | 0.67 | 1% |
| Prasher, 1995 | | | | 201 | 42.2, 12.5, 16-76 | 50.8% | Cytogenetics for 171 participants. | Interviewed based on DCR-10 criteria | 0.56 | 5% |
| Rivelli et al., 2022 | | | | 6078 | 27.9, 20.4, 0-89[1] | 52% | NR. | Chart review. | 0.22 | 9% |
| Burt et al., 1992 | | | | 61 | 33.5, 10.3, 20-60 | 49.2% | Genetic screening. | DSI. | 0.67 | 11% |

[1] Paper referenced another study which reported the demographics.

**Table 1.6**

*Study characteristics and outcome data for studies reporting the point prevalence of depression in tuberous sclerosis complex*

| Authors | Quality rating | | | Sample Size | Age (mean, SD, range) | Sex (% Male) | Syndrome Confirmation (SC) | Depression Diagnosis (DD) | Outcome data | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SI | SC | DD | | | | | | Quality score | Depression prevalence |
| de Vries et al., 2020 | | | | 894 | NR, NR, NR[1] | 48.3% | Genetic testing for part of the cohort. | TAND checklist. | 0.44 | 5% |
| de Vries et al., 2018 | | | | 1371 | NR, NR, 1-71[2] | 47.9% | Molecular testing for part of the cohort. | Diagnostically defined. | 0.56 | 6% |
| Gupta et al., 2020 | | | | 954 | 16[3], NR, 9-62 | 51.4% | Genetically or clinically confirmed. | Diagnostic tools. | 0.56 | 6% |
| Kothare et al., 2014 | | | | 916 | 3.3, 7.5, NR | 49% | Reported gene mutation status. | Chart review. | 0.33 | 3% |
| Pulsifer et al., 2007 | | | | 42 | 34.9, 12.3, NR | 33.3% | Genetic testing. | SCL-90-R. | 0.56 | 43% |
| Ruiz-Falcó Rojas et al., 2022 | | | | 179 | 27.1[4], NR, 0-65 | 40.8% | NR. | TOSCA. | 0.22 | 8% |
| Lewis et al., 2004 | | | | 36 | 27, 14, 6-70[5] | 48% | Gene mutation analysis. | HADS. | 0.67 | 19% |
| Kingswood et al., 2017 | | | | 1301 | NR, NR, 0-71[6] | 48.2% | Molecular testing in part of the cohort. | TOSCA. | 0.44 | 6% |

[1] Child and adult sample. Participants of any age.
[2] Demographics including age and sex for full sample of 2216 participants. Data for depression available for 1371 people. Median age was 13.
[3] Demographics including age mean and sex for full sample of 1657 participants. Depression measured in 954 participants with the age range of 9-62.
[4] Median age was 27.
[5] Demographics including age and sex for full sample of 98 participants.
[6] Demographics including age and sex for full sample of 2093 participants. Median age range for full sample was 13.

**Table 1.7**

*Study characteristics and outcome data for studies reporting the point prevalence of depression in Williams syndrome*

| Authors | Quality rating | | | Sample Size | Age (mean, SD, range) | Sex (% Male) | Syndrome Confirmation (SC) | Depression Diagnosis (DD) | Outcome data | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SI | SC | DD | | | | | | Quality score | Depression prevalence |
| Dodd & Porter, 2009 | | | | 50 | 18.53, NR, 6-59 | 48% | FISH. | K-SADS-PL | 0.78 | 6% |
| Stinton et al., 2010 | | | | 92 | 32, NR, 19-55 | 45.7% | FISH. | PAS-ADD | 0.67 | 9% |
| Stinton et al., 2012 | | | | 19 | 32, NR, 20-42 | 52.6% | Genetic testing. | PAS-ADD | 0.67 | 11% |
| Cherniske et al., 2004 | | | | 20 | 38.8, NR, 30-51 | 50% | FISH, clinically confirmed for 3 people. | ADIS, SADS | 0.67 | 10% |
| Kennedy et al., 2006 | | | | 21 | 16, NR, 7-28 | 33.3% | FISH. | ADIS | 0.67 | 24% |

### *Forest plots*

The forest plots showing the prevalence of depression in each genetic syndrome are included in Figures 1.6-1.9. The point prevalence rate of depression as calculated by the random-effects model was found to be 13% in 22q11.2 deletion syndrome, 10% in Down syndrome, 10% in tuberous sclerosis complex, and 9% in Williams syndrome. The forest plot showing the prevalence of depression in Down syndrome before the "leave-one-out" analysis is shown in Appendix 4.4. The prevalence rates of depression in genetic syndromes are compared to a rate of 4.4% in the general population (WHO, 2017).

**Figure 1.6**

*Forest plot showing the point prevalence rate (PR) of depression in 22q11.2 deletion syndrome*

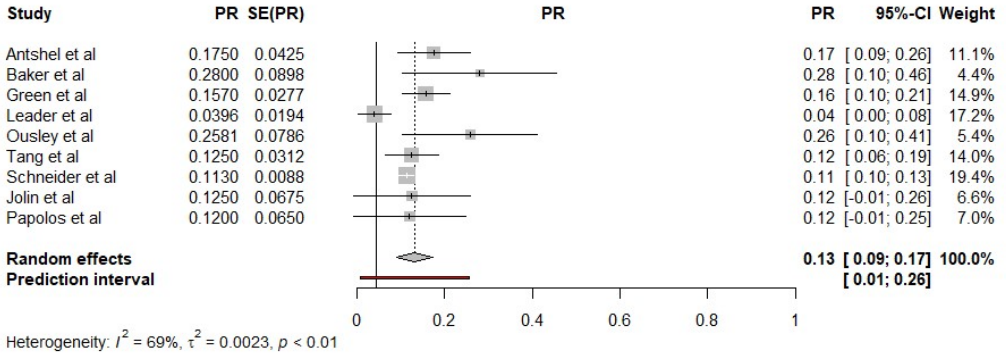


**Figure 1.7**

*Forest plot showing the point prevalence rate (PR) of depression in Down syndrome*

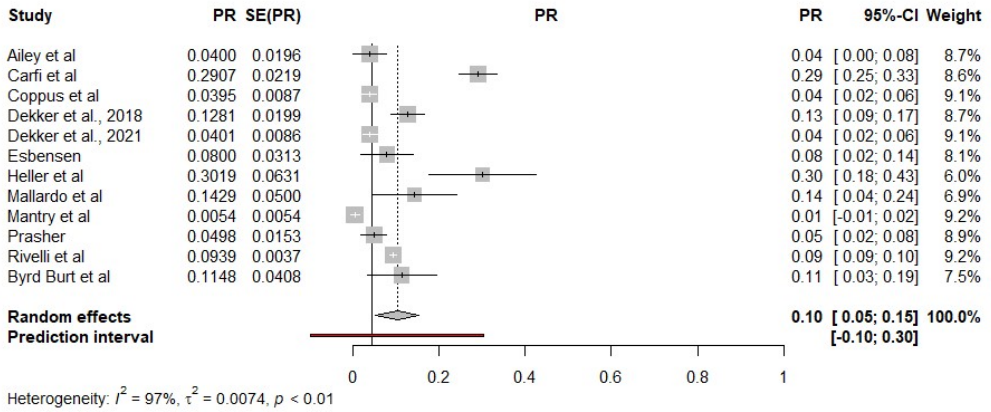



**Figure 1.8**

*Forest plot showing the point prevalence rate (PR) of depression in tuberous sclerosis complex*

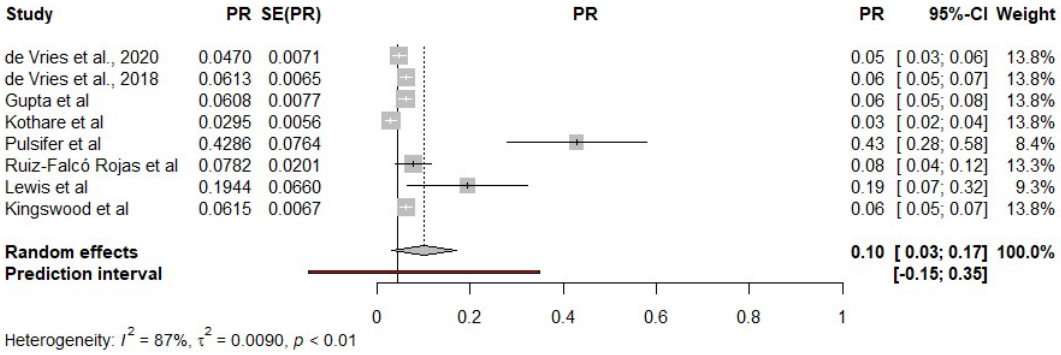
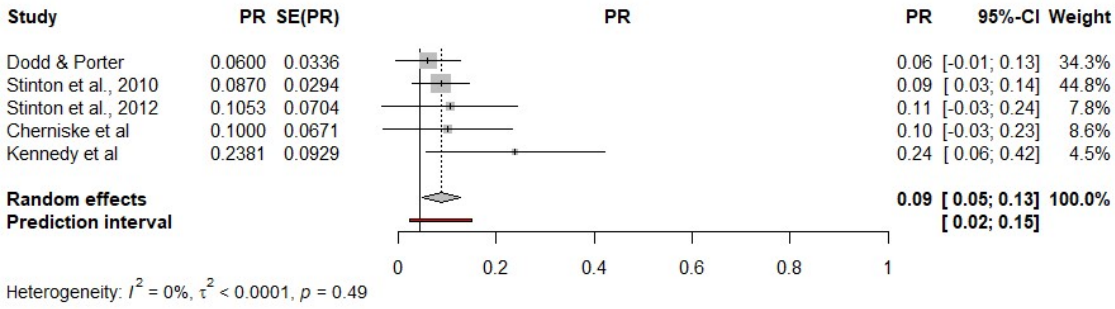


**Figure 1.9**

*Forest plot showing the point prevalence rate (PR) of depression Williams syndrome*




***The impact of methodological variation***

The quality effects model was calculated for each genetic syndrome using the total quality rating score, as shown in Table 1.8. No studies obtained the highest quality score for sample identification across the four genetic syndromes. 13 (38%) studies included in the meta-analysis obtained the highest quality rating score for the confirmation of the genetic syndrome, and 3 (9%) of the studies obtained the highest quality score for the assessment of depression.

**Table 1.8**

*Pooled prevalence estimates for depression across genetic syndromes and the quality ratings for the included studies*

| | | | | Individual scores | | | Prevalence of depression | | |
|---|---|---|---|---|---|---|---|---|---|
| | Studies | Participants (n) | Mean quality rating (SD) | Score of 3 for sample | Score of 3 for syndrome | Score of 3 for depression | Random-effects pooled prevalence (CI) | Quality-effects pooled prevalence (CI) | $I^2$ |
| 22q11.2 deletion syndrome | 9 | 1862 | 0.63 (0.19) | 0 | 6 (67%) | 3 (33%) | 13% (9-17) | 14% (10-18) | 69% |
| Down syndrome[1] | 12 | 8544 | 0.44 (0.17) | 0 | 1 (8%) | 0 | 10% (5-16) | 9% (4-15) | 97% |
| Tuberous sclerosis complex | 8 | 5693 | 0.47 (0.15) | 0 | 2 (25%) | 0 | 10% (3-17) | 11% (4-18) | 87% |
| Williams syndrome | 5 | 202 | 0.69 (0.05) | 0 | 4 (80%) | 0 | 9% (5-13) | 9% (5-12) | 0% |

[1] Based on 12 studies following the exclusion of two studies in the "leave-one-out analysis"

An acceptable level of heterogeneity was observed in the studies for 22q11.2 deletion syndrome and Williams syndrome. Although this appears to suggest an acceptable level of variation in the studies, strong conclusions cannot be made due to the small number of studies. An unacceptable level of heterogeneity was observed in studies reporting the depression prevalence rate for tuberous sclerosis complex (Higgin's $I^2$ = 87%, $tau^2$ = .009, $p < .01$), and for Down syndrome (Higgin's $I^2$ = 97%, $tau^2$ = .007, $p < .01$). As this suggests an unacceptable level of variation in the studies (Higgens et al., 2003), further analyses were completed to identify sources of variation.

***The impact of influential primary studies***

A "leave-one-out" analysis was completed and two studies (Patti et al., 2005; Tsiouris et al., 2014) reporting the prevalence in Down syndrome were found to be markedly influential and discrepant from the rest of the studies. Thus, each study was removed sequentially, as described in the data-analysis section. The corrected random effects model found a prevalence rate of 10% (95% CI 5%-16%) in Down syndrome, as reported above. The corrected point prevalence estimate is approximately a 5% decrease from the uncorrected model which reported a prevalence rate of 15% (95% CI 8%- 22%). The changes in the weighted average effect size and the changes in heterogeneity are included in Table 1.9. The Baujat plots (Baujat et al., 2002) showing the influential and discrepant studies for Down syndrome and tuberous sclerosis complex are shown in Appendix 4.5.

**Table 1.9**

*"Leave-one-out" analysis showing the impact of influential studies on the prevalence rate*

| Study | Uncorrected prevalence | Corrected Prevalence | Difference | 95% CI | Corrected $I^2$ | $I^2$ difference |
|---|---|---|---|---|---|---|
| Tsiouris et al., 2014 | 15.0% | 13% | 2% | 6-19 | 96.9% | 0.9% |
| Patti et al., 2005 | 15.0% | 10% | 5% | 5-16 | 96.7% | 1.1% |

***Subgroup analyses***

The subgroup analysis was only completed for Down syndrome due to the other syndrome groups having less than 10 studies. There were no significant differences for sample identification or syndrome confirmation. A significant difference was found between the ratings for the assessment of depression ($\chi^2 = 10.4$, $p = .006$), as shown in Table 1.10. Studies that were rated "adequate" generated a significantly higher prevalence rate compared to papers rated "good" (14% and 2%, respectively; $\chi^2 = 9.59$, $p = .002$). There was no significant difference between papers rated "poor" and papers rated "adequate", and no significant difference was found between for studies rated "poor" and studies rated "good".

**Table 1.10**

*Subgroup analysis showing the impact of quality rating on the prevalence rate of depression*

| | Prevalence | | | | $\chi^2$ | *p* |
|---|---|---|---|---|---|---|
| | Poor (k) | Adequate (k) | Good (k) | Excellent (k) | | |
| Sample identification | N/A (0) | 10% (2) | 10% (10) | N/A (0) | .01 | .92 |
| Syndrome confirmation | 15% (6) | N/A (0) | 5% (5) | 12% (1) | 5.62 | .06 |

| | Prevalence | | | | $\chi^2$ | *p* |
|---|---|---|---|---|---|---|
| | Poor (k) | Adequate (k) | Good (k) | Excellent (k) | | |
| Depression diagnosis | 7% (2) | 14% (8) | 2% (2) | N/A (0) | 10.4 | .006* |

*Note.* * = significant result

A subgroup analysis was also conducted for the classification of depression which was based upon a psychiatric diagnosis or a score above a clinical cut-off on a measure of depression. Studies that used a clinical cut-off score reported a significantly higher prevalence rate compared to studies that reported psychiatric diagnosis of depression, at rates of 23% and 6%, respectively ($\chi^2 = 7.59$, $p = .006$), see Table 1.11.

**Table 1.11**

*Subgroup analysis showing the impact of the classification on depression prevalence*

| | Prevalence | | $\chi^2$ | *p* |
|---|---|---|---|---|
| | Psychiatric diagnosis (k) | Clinical cut-off score (k) | | |
| Depression classification | 6% (9) | 23% (3) | 7.59 | .006* |

*Note.* * = significant results

***Meta regression analyses***

No statistically significant differences were found for mean age, sex (percentage male), or year of publication on the depression prevalence in Down syndrome.

***The impact of publication and small study biases***

The funnel plots of the point prevalence rates of depression for the four syndrome groups included in the meta-analysis are presented in Figure 1.10-1.13. The inverted "funnel" represents the 95% Confidence Interval (CI) of the expected distribution of the prevalence rates. The results suggest that studies with small sample sizes are associated

with greater than expected prevalence rates of depression across the genetic syndromes. It is difficult to estimate the presence of publication bias due to the limited number of studies for 22q11.2 deletion syndrome, tuberous sclerosis complex, and Williams syndrome. Egger's regression test was not able to be completed for these three syndromes as the test requires a minimum of 10 studies to ensure there is sufficient power to distinguish between chance and real asymmetry. Thus, further analyses were only completed for studies reporting the prevalence rate in Down syndrome.

There was some suggestion of publication bias in the distribution of the prevalence of depression in people with Down syndrome, as shown in Figure 1.10. However, Egger's regression test of funnel plot asymmetry was not statistically significant ($\beta = 1.75$, $t = .71$ $p = .49$). Therefore, the estimation and correction of publication bias using the trim and fill procedure (Duval & Tweedie, 2000) was not completed.

**Figure 1.10**

*Funnel plot of the prevalence of depression in Down syndrome*

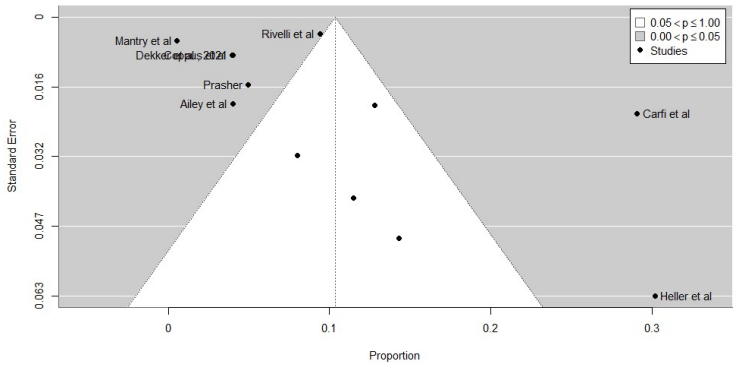


**Figure 1.11**

*Funnel plot of the prevalence of depression in 22q11.2 deletion syndrome*

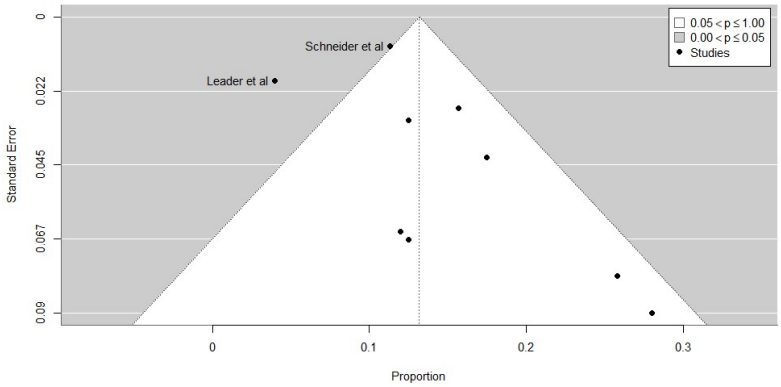



**Figure 1.12**

*Funnel plot of the prevalence of depression in tuberous sclerosis complex*

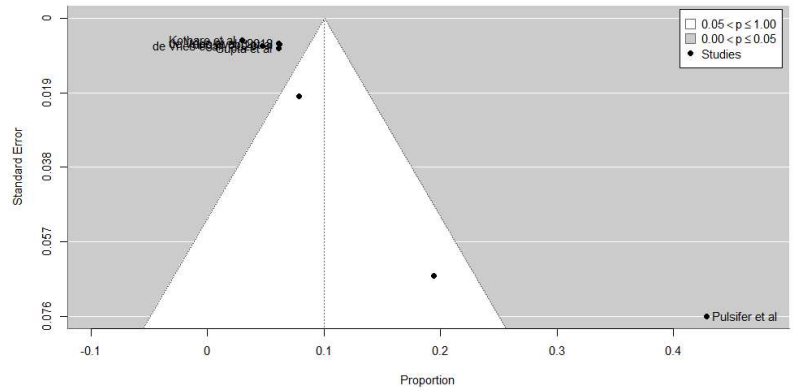
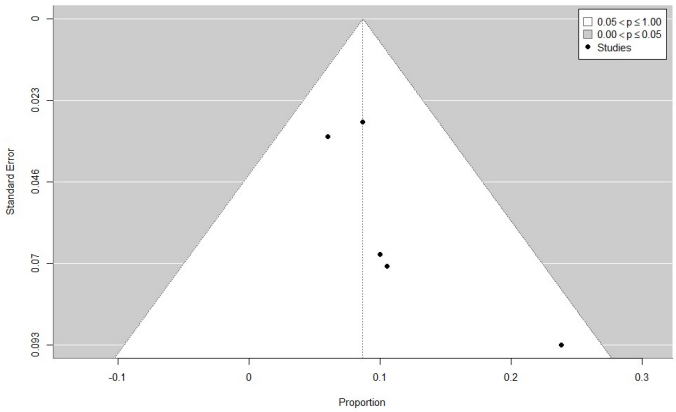


**Figure 1.13**

*Funnel plot of the prevalence of depression in Williams syndrome*




## Discussion

The current study is the first meta-analysis to explore the point prevalence of depression across genetic syndromes associated with ID whilst accounting for the methodological quality of studies. The pooled prevalence estimates of depression were found to be similar across the syndromes which contradicts the initial prediction that differences in depression prevalence rates would be found across genetic syndromes. The study found pooled prevalence rates of 9% in Williams syndrome, 10% in Down syndrome, 10% in tuberous sclerosis complex, and 13% in 22q11.2 deletion syndrome. Two studies reported the point prevalence of depression in fragile X syndrome, with rates of 9% and 26% (Haessler et al., 2016; Lachiewicz et al., 1992, respectively), and two studies reported the point prevalence in Phelan-McDermid syndrome, with a prevalence of 3% and 7% (Shaw et al., 2011; Levy et al., 2022, respectively). Four syndromes were not included in the results due to the absence of studies. Importantly, the pooled prevalence rates of depression were higher than the estimated prevalence of depression in the general

population (4.4%; WHO, 2017), and similar to prevalence estimates in people with ID with estimates ranging between 2.2% and 15.8% (Deb et al., 2001; Cooper et al., 2015, respectively). The higher prevalence rates compared to the general population highlights the need for clinical provision of support and for future research to further understand the risk of depression across genetic syndromes.

The findings are partly consistent with previous reviews reporting on individual syndromes. The pooled prevalence of depression in Down syndrome was in the higher range of previous reviews that reported prevalence estimates ranging between 2% and 13% (Walton & Kerr, 2015) and 0 to 11% (Walker et al., 2011). The depression prevalence in 22q11.2 deletion syndrome was found to be in the lower range of a previous review which reported prevalence estimates between 12% to 29% (Bertrán et al., 2018). To the author's knowledge, there has not been a previous systematic review reporting depression prevalence in tuberous sclerosis complex or Williams syndrome. However, previous studies exploring depression in tuberous sclerosis complex have found a higher prevalence rate than the current study, with prevalence estimates between 19% and 43% (de Vries & Bolton, 2002; Lewis et al., 2004; Muzykewicz et al., 2007; Pulsifer et al., 2007; Raznahan et al., 2006). Differences in study methodology might account for the differences in prevalence estimates compared to the current study. A previous review found one study that reported a prevalence of mood disorders in children and adolescents with Williams syndrome at a lower rate than the current study (Dodd & Porter, 2009; Glasson et al., 2020). However, the current study included studies reporting the prevalence in children and adults, which might account for the higher prevalence as depression increases with age in Williams syndrome (Gosch & Pankau, 1997). In addition, the previous review reported on the umbrella term "mood disorders" which limits the ability to compare results. Overall,

the consistency between the current results and previous systematic reviews increases confidence in the study findings for Down syndrome and 22q11.2 deletion syndrome. The differences in prevalence rates for tuberous sclerosis syndrome and Williams syndrome might be accounted for by differences in study methodology. As the current study used stringent inclusion criteria, the pooled estimates in the current study are likely to be more robust estimates of the point prevalence rate of clinical levels of depression.

The differences in study methodologies were highlighted in the current study. High levels of heterogeneity were found for studies reporting depression prevalence in Down syndrome and tuberous sclerosis complex, and moderate heterogeneity was found for 22q11.2 deletion syndrome, which suggests variations in methodology. Further sub-group analyses were completed to explore the sources of variation. The sub-group analysis found the depression prevalence in Down syndrome was significantly higher for clinical levels on standardised measures compared to psychiatric diagnoses. Although the sub-group analysis could not be completed for three syndromes, similar observations were found. For example, in tuberous sclerosis complex, studies using clinically significant scores found higher prevalence rates of 43% and 19% (Pulsifer et al., 2007; Lewis et al., 2004, respectively), compared to studies reporting a psychiatric diagnosis where the prevalence ranged between 3% and 8% (Kothare et al., 2014; Ruiz-Falcó Rojas et al., 2022, respectively). Thus, differences in depression measures can result in differences in prevalence rates and relying on the more conservative rate (e.g. psychiatric diagnosis) might result in an underestimation of depression prevalence.

One interpretation of the lower prevalence rates found for psychiatric diagnosis compared to screening measures is that diagnostic criteria based on the general population are not sensitive to identify depression in people with ID, and alternative classifications

should be used (Smiley & Cooper, 2003) as diagnostic classifications can result in underestimations of the prevalence of depression (Hermans et al., 2013). Additionally, there might be lower rates of diagnosed depression in people with ID due to diagnostic overshadowing (Davies & Oliver, 2014; Reiss et al., 1982). However, an alternative explanation to the differences in prevalence rates might be the limitations of using screening measures to determine prevalence estimates as screening measures are designed to identify whether further psychiatric assessment is required rather than representing the number of people with a diagnosable condition (Lachiewicz, 1992; Scott & Havercamp, 2015). Although the limitations of screening measures were reflected in the lower quality rating, the use of these measures might account for the inflated prevalence for clinically significant scores. This is indicated by the subgroup analysis which found studies rated "adequate" (e.g. screening measures) reported significantly higher prevalence estimates for Down syndrome compared to studies rated "good" (e.g. diagnostic interviews). In summary, the findings highlight the importance of considering the measures used to assess depression and the accuracy of prevalence rates might be constrained by the absence of a consensus of measures that are sensitive to identify depression in syndromic ID.

The absence of a consensus of measures to assess depression was shown in the current study. The most common measures across the four syndromes were each used in five (15%) of studies. The measures included the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997), Psychiatric Assessment Schedule for Adults with Developmental Disabilities (PAS-ADD; Moss et al., 1993), and Structured Clinical Interview for axis I DSM-IV (SCID 1; First et al., 1997). The variations in the measures used might account for the moderate to high levels of heterogeneity found in the current study and reduces the confidence that similar prevalence rates were being

compared. Further research into the assessment of depression in people with syndromic ID is required as using measures that are sensitive to diagnose depression in syndromes associated with ID is essential to accurately identify people at risk of depression to inform intervention strategies.

An additional consideration in the assessment of depression is the choice of diagnostic classification as different classifications generate different prevalence estimates (Slade & Andrews, 2001). A previous study found the prevalence of mental health difficulties in adults with ID ranged from 15.7% as a DSM-IV-TR diagnosis, 16.6% as an ICD-10-DCR diagnosis, 35.2% as a Diagnostic Criteria for Psychiatric Disorders for Use in Adults with learning Disabilities (DC-LD; Royal College of Psychiatrists, 2001) diagnosis, and 40.9% as a clinical diagnosis (Cooper et al., 2007), which indicates the DC-LD might be a more sensitive classification to diagnose mental health difficulties in people with ID compared to the DSM-IV and ICD-10 criteria. In addition, research has suggested that diagnostic criteria used to identify depression in the general population (e.g. DSM) is appropriate for people with mild ID, and the DC-LD should be used for people with moderate, severe, and profound ID (Smiley & Cooper, 2003). The current study favoured diagnostic instruments and many of the included studies reported a DSM diagnosis; however, the current findings and previous research indicate diagnostic classifications might result in an underestimation of depression prevalence (Hermans et al., 2013). Although it was beyond the scope of the current study to include behavioural symptomatology not measured by a clinical cut-off score, including depressive symptomatology might overcome the issues with diagnostic classifications resulting in an underestimation of the prevalence rate. Including symptoms of depression might have particular importance for syndromes associated with severe ID where there are challenges

in the assessment of depression and the self-report of emotions (Cianfaglione et al., 2015). Thus, future research could expand on the current findings by including depression symptomatology in pooled prevalence estimates.

The current study highlighted the limited research reporting depression prevalence in genetic syndromes associated with ID. A particular absence of research was found for fragile X syndrome, Phelan McDermid syndrome, Rett syndrome, 3q29 deletion syndrome, CHARGE syndrome, and 7q11.23 duplication syndrome. The limited number of studies for Williams syndrome, tuberous sclerosis complex, and 22q11.2 deletion syndrome ($n < 10$) limits the confidence in the conclusions due to impacting the accuracy of the true prevalence rate and increasing the effect of heterogeneity (Edwards et al., 2022). Thus, future research is essential to provide prevalence estimates to identify syndromes at risk of depression and inform treatment strategies (Oliver et al., 2013). It is important to acknowledge that the publication of future prevalence estimates will likely change the prevalence estimates in the current study.

Due to the limited research, an over-inclusive approach was taken for the inclusion of studies where it was unclear if the study reported a point or lifetime prevalence. Numerous studies reporting depression prevalence in tuberous sclerosis complex used the TAND-checklist, which is primarily a lifetime measure of neuropsychiatric disorders associated with tuberous sclerosis complex. As the TAND-checklist is recommended to be completed yearly to enhance the assessment and identification of neuropsychiatric difficulties (de Vries et al., 2015) and the included studies appeared to use the TAND-checklist at numerous time points, the rates were suggestive of point prevalence. However, the results for tuberous sclerosis complex should be interpreted with caution due to the ambiguity around the type of prevalence reported in the included studies. The ambiguity in

the type of prevalence included in the studies highlights the limitations of previous research not reporting whether the prevalence rate is a point or lifetime prevalence (Cooper et al., 2007). Thus, it is recommended for future research to report the type of prevalence measured to ensure similar prevalence rates are being compared, and to determine incidence and remittance rates.

A limitation of the current study is reporting a combined prevalence for children and adults (Cooper et al., 2007). Previous research has shown that depression varies across the lifespan for genetic syndromes associated with ID (Dykens, 2000; Fiksinski et al., 2021; Gosch & Pankau, 1997; Green et al., 2009; Schneider et al., 2014). Although the sub-group analysis found no significant difference for age as a moderator variable for Down syndrome, this finding cannot be generalised to syndrome groups where it was not possible to run the sub-group analysis. Thus, future research should attempt to report the prevalence for children and adults separately to distinguish prevalence rates across different ages to inform developmental trajectories.

A further limitation to the current meta-analysis is that some of the included studies appeared to use similar samples to other studies. The overlap of participants in multiple studies has been found in previous research (Edwards et al., 2022; Richards et al., 2015), and the samples were included in the current meta-analysis as the samples were not identical. However, the inclusion of similar samples in multiple studies can reduce the representativeness of the results (Edwards et al., 2022), and therefore highlights the need for future research to report when similar samples have been used across studies.

In conclusion, the current study found higher prevalence rates of depression in genetic syndromes associated with ID compared to the general population. The study

highlights the methodological differences across included studies and adds to existing considerations around how depression is assessed in people with ID. The study highlights the need for future research to further distinguish the risk of depression across genetic syndromes to inform service provision and intervention strategies.

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# Chapter Two: Empirical Research Paper

## Correlates of Low Mood in Cornelia de Lange Syndrome, Fragile X Syndrome, and Rubinstein-Taybi Syndrome

**Word count: 8474**

## Abstract

**Background:** People with genetic syndromes associated with intellectual disability are at risk of experiencing mental health difficulties. However, the factors that contribute to the development of depression in genetic syndromes are not well understood.

**Aims:** The study aimed to explore how age, adaptive ability, health difficulties, sleep difficulties, autism characteristics, and sensory processing differences contribute to low mood in Cornelia de Lange syndrome (CdLS), fragile X syndrome (FXS), and Rubinstein-Taybi syndrome (RTS).

**Method:** The study was part of a larger longitudinal study. Caregivers completed questionnaires, including two measures of low mood: the Mood, Interest and Pleasure Questionnaire (MIPQ), and the Anxiety, Depression and Mood Scale (ADAMS). Correlational analyses were completed to identify correlates of low mood scores. Regression analyses were completed to identify predictors of low mood within each syndrome groups.

**Results:** The results found group differences in gender, level of adaptive ability, number of current health difficulties, and sleep difficulties. No group differences in low mood scores were found. The regression analyses found age, sensory processing differences, and sleep difficulties predicted low mood scores in people with CdLS. In FXS, age, autism characteristics, and sleep difficulties predicted low mood. Age, sensory processing differences, and current health difficulties predicted low mood in RTS.

**Conclusion:** The findings indicate the possibility of syndrome specific pathways to low mood. Further research is required to further understand contributing factors to the development of low mood in rare genetic syndromes.

## Introduction

There is a heightened risk of people with intellectual disability (ID) experiencing mental health difficulties (Matson & Shoemaker, 2011), including depression (Tsiouris et al., 2004). Depression is characterised by low mood and a lack of interest and pleasure (American Psychiatric Association, 2013), and negatively impacts quality of life (Hansson, 2002; Rand & Malley, 2017). Previous research has found depression prevalence estimates ranging between 2.2% and 15.8% in people with ID (Cooper et al., 2015; Deb et al., 2001; Hsieh et al., 2020), compared to a rate of 4.4% in the general population (WHO, 2017). However, the depression prevalence estimates reported are likely an underestimation of the "true prevalence" in people with ID due to limitations in research and difficulties assessing depression in people with ID which can lead to diagnostic overshadowing (Davies & Oliver, 2014; Hsieh et al., 2020; Perez-Achiaga et al., 2009; Reiss et al., 1982; Scott & Havercamp, 2015). Due to the increased risk of people with ID experiencing depression and the difficulties in the assessment of depression in this population, understanding factors associated with the development of depression is important in informing assessment and treatment strategies (Hsieh et al., 2020).

The increased risk of mental health difficulties in people with ID has also been shown in people with a genetic syndrome associated with ID (Edwards et al., 2022; Glasson et al., 2020). This heightened prevalence might be partly explained by a genetic susceptibility to mental health difficulties (Royston et al., 2018) and gene-phenotype-environment interactions. For example, people with fragile X syndrome (FXS) show sensory processing differences including a hypersensitivity to sensory stimuli, which might contribute to behavioural responses including anxiety, avoidance of loud environments, and little eye contact (Rais et al., 2018). Hyperarousal can result in social avoidance in

FXS (Hall et al., 2009), and social avoidance can contribute to low mood (Dudley & Kuyken, 2013; Moorey, 2010). Thus, understanding the unique mechanisms in given syndromes can inform the formulation and intervention approaches taken to reduce low mood and depression in genetic syndromes.

Previous research has demonstated individual and environmental factors associated with low mood in the general population; however, research exploring pathways to low mood in genetic syndromes associated with ID is limited. Risk factors to depression in the general population include gender, family history of depression, life stresses, co-occurring mental health difficulties, little social support, and sleep difficulties (Baglioni et al., 2011; Cyranowski et al., 2000; Hölzel et al., 2011; Jackson et al., 2014; Kuehner, 2017; Monroe et al., 2013; Steiger & Pawlowski, 2019; WHO, 2023). Although the factors that contribute to depression in people with ID are less known (Hsieh et al., 2020), people with genetic syndromes have a heightened risk of experiencing some factors associated with depression, including sleep difficulties (Agar et al., 2021). Thus, further research to understand contributing factors of low mood across genetic syndromes is required to inform causal models of depression and ensure access to early interventions (Royston et al., 2020).

Previous research has demonstrated the importance of comparisons across syndromes to identify mental health difficulties and risk factors in specific syndromes (Royston et al., 2018). These comparisons can indicate whether certain behaviours and risk factors are similar across genetic syndromes associated with ID or if risk factors are associated with a specific syndrome (Hodapp, 1997; Royston et al., 2018), and can inform causation models (Arron et al., 2011). As research has suggested there might be differences in the profile of low mood across different genetic syndromes (Groves et al., 2019), the

need to explore predictors of low mood in different syndrome groups is highlighted. Thus, the current study will explore correlates and predictors of low mood in three genetic syndromes that might be at risk of low mood: Cornelia de Lange syndrome (CdLS); FXS; and Rubinstein-Taybi syndrome (RTS).

**CdLS**

CdLS is a genetic syndrome associated with mild to profound ID, with severe or profound ID being more prevalent (Berney et al., 1999; Oliver et al., 2008). CdLS is caused primarily by mutations on the NIPBL gene at chromosome 5 (5p13.1), and by mutations on the SMC3 gene located at chromosome 10, the SMC1A gene, HDAC8 gene, and RAD21 (Deardorff et al., 2007, 2012; Gillis et al., 2004; Huisman et al., 2013; Krantz et al., 2004; Musio et al., 2006; Oliver et al., 2013; Tonkin et al., 2004). The prevalence of CdLS is approximately 1.6/ 100,000 to 2.2/ 100,000 (Barisic et al., 2008). CdLS is characterised by physical characteristics including short stature, distinctive facial features, and limb differences (Berney et al., 1999; Kline et al., 2007; Nelson et al., 2017).

**FXS**

FXS is the most common form of inherited ID and has been estimated to occur in approximately one in 4000 to 5000 males and one in 4000 to 8000 females (Coffee et al., 2009; Crawford et al., 2001; Turner et al., 1996; Verkerk et al., 1991). FXS is caused by mutations in the fragile X mental retardation 1 (FMR1) gene, located at Xq27.3, which results in cytosine-guanine-guanine (CGG) repeats and a reduction of the FMR1 protein (FMRP) (Crawford et al., 2018; Krueger & Bear, 2011; Penagarikano et al., 2007; Saldarriaga et al., 2014; Verkerk et al., 1991). There are differences in the physical, cognitive, and behavioural phenotype of FXS dependent on sex (Crawford et al., 2001),

with males being affected more severely compared to females (Garber et al., 2008) due to FXS being linked with the X chromosome (Coffee et al., 2009). FXS is linked to autism (Crawford et al., 2001; Krueger & Bear, 2011), and common behaviors in FXS include repetitive behaviour, self-injurious behaviour, and aggressive behaviour (Arron et al., 2011; Crawford et al., 2018; Richards et al., 2012).

**RTS**

RTS is a genetic syndrome associated with ID which occurs in approximately 1 in 100,000 to 1 in 125,000 births (Hennekam et al., 1990; Hennekam, 2006). RTS is caused by the CREBBP gene, located at chromosome 16p13.3, and the EP300 gene which encode the CREB-binding protein and E1A-binding protein (p300), respectively (Awan et al., 2021; Cohen et al., 2020; Hennekam, 2006; Lacombe et al., 2024; Waite et al., 2014). The genetic cause is not known in approximately 30% of cases (Bartsch et al., 2005; Negri et al., 2019). RTS is characterised by distinctive facial features, big toes, and broad thumbs (Hennekam, 2006; Rubinstein & Taybi, 1963). RTS is associated with mental health difficulties, autism characteristics, and repetitive behaviour, including body stereotypy and asking repeated questions (Awan et al., 2021; Waite et al., 2014).

**Risk of low mood in CdLS, FXS, and RTS**

There is a heightened risk of mental health difficulties in CdLS, FXS, and RTS. A systematic review and meta-analysis distinguishing the prevalence of mental health symptoms found a pooled prevalence rate of 61% in FXS, and found one study that reported a prevalence estimate of 53% in CdLS (Glasson et al., 2020). Additionally, a review found mental health difficulties ranged from 31% to 61% in RTS (Awan et al., 2021). The risk of low mood has also been demonstrated in these syndrome groups. High

levels of negative affect were found in adults with CdLS (Oliver et al., 2011), and there is a heightened risk of depression in FXS (Tomić et al., 2011), and of mood disorders in RTS (Awan et al., 2021). Due to the high prevalence of mental health difficulties, further research exploring the pathways to low mood in these groups is essential to inform clinical provision of support.

The risk of low mood in these genetic syndromes has been found to be influenced by individual factors, including age. For example, mood changes with age are common in CdLS (Basile et al., 2007; Berney et al., 1999; Nelson et al., 2014; Oliver et al., 2011), and one study found low mood is more prevalent in people with CdLS older than 15 years (Nelson et al., 2014). Additionally, lower levels of interest and pleasure were found with age in CdLS (Groves et al., 2019). Mood changes with age are also part of the behavioural phenotype in RTS, with depression becoming apparent in adolescence (Yagihashi et al., 2012). The relationship between mood and age in FXS is less established in the literature, and previous studies have found no significant associations between mood and age in FXS (Nelson et al., 2014; Royston et al., 2020). Distinguishing the contribution of age on low mood in specific syndromes will increase the understanding of developmental trajectories and inform intervention strategies.

Another individual factor that might contribute to low mood is level of adaptive ability. Research reporting on the relationship between level of ability and low mood has found mixed results. In a study exploring the lifespan trajectory of low affect, low mood was found to be associated with lower levels of ability in FXS and not in CdLS (Groves et al., 2019). However, a study reporting on predictors of mental health difficulties found adaptive ability did not significantly contribute to low mood in FXS (Royston et al., 2020).

Further research is required to further understand the influence of adaptive ability on the development of low mood.

In addition to the heightened risk of mental health difficulties in genetic syndromes, these syndrome groups are also at risk of experiencing factors associated with low mood, including sleep difficulties. There is a well-established asociation between sleep difficulties and low mood in the general population (Baglioni et al., 2011; Jackson et al., 2014; Steiger & Pawlowski, 2019), and people with genetic syndromes associated with ID are at heightened risk of experiencing sleep difficulties (Agar et al., 2021). A meta-analysis found a pooled prevalence rate of general sleep difficulties of 37% in FXS and 32% in CdLS (Agar et al., 2021). Additionally, sleep difficulties have been found in 62% of people with RTS (Douzgou et al., 2022). Due to the heightened risk of sleep difficulties in these syndromes and the association between low mood and sleep, the risk of low mood might be further heightened in these syndromes, and distinguishing the contribution of sleep difficulties on low mood is important to inform treatment strategies.

An additional risk factor of low mood in people with ID is health difficulties (Hsieh et al., 2020). Health difficulties are prominent in CdLS (Hall et al., 2008), and there is some evidence that people with CdLS with a health difficulty are more likely to experience low mood compared to people with CdLS without health difficulties (Berg et al., 2007). Health difficulties are also common in RTS, with one study reporting gastrointestinal problems in 73% of people with RTS (Douzgou et al., 2022), and one study reporting the most common medical problems were visual difficulties and keloids, which affected 79% and 57% people, respectively (Stevens et al., 2011). As there are high rates of physical health difficulties in CdLS and RTS, and health difficulties are associated

with low mood, further research distinguishing the impact of health difficulties on low mood in genetic syndromes is required.

Furthermore, autism characteristics are more prevalent in genetic syndromes compared to the general population (Richards et al., 2015). There is a high prevalence of autism related characteristics in CdLS (Nelson et al., 2014; Oliver et al., 2008), FXS (Moss & Howlin, 2009; Moss et al., 2012; Oliver et al., 2011; Richards et al., 2015; Waite et al., 2014), and in RTS (Ajmone et al., 2018; Awan et al., 2021; Crawford et al., 2017). As low mood was found to be associated with autism characteristics in CdLS and FXS (Groves et al., 2019), further research exploring the contribution of autism characteristics on the development of low mood in genetic syndromes is essential.

One characteristic of autism is sensory processing differences (Tomchek & Dunn, 2007), and sensory processing differences are evident in CdLS and FXS (Heald et al., 2020). There are differences in the type of sensory processing differences with hypo-responsivity common in CdLS and hyper-responsivity apparent in FXS (Heald et al., 2020). Importantly, sensory processing differences are associated with low mood; one study found higher levels of symptoms of depression were associated with higher levels of hyper-reactivity (Rossow et al., 2023), and another study found depression was associated with hypo-reactivity and with sensory seeking in children with a neurodevelopmental condition (Rossow et al., 2021). Thus, the high prevalence of autism characteristics and of sensory processing differences might further heighten the risk of low mood in genetic syndromes, and further research is required to further understand the contributing factors to the development of low mood in rare genetic syndromes.

**The current study: summary and aims**

In summary, research has shown a heightened prevalence of mental health difficulties and factors associated with low mood in genetic syndromes, including sleep difficulties and physical health difficulties (Agar et al., 2021; Douzgou et al., 2022; Edwards et al., 2020; Glasson et al., 2020; Hall et al., 2008). Thus, further research exploring the factors associated with low mood in genetic syndromes is warranted. Research has demonstrated the benefits of exploring predictors of mental health difficulties across syndrome groups to inform assessment and intervention strategies (Royston et al., 2018). Therefore, the current study aims to expand on the existing literature to explore the contributions of predictor variables on low mood. The specific aims of the study were:

- To explore group differences in low mood, age, adaptive ability, health difficulties, sleep difficulties, sensory processing difficulties, and autism characteristics.
    - Due to the limited research in this area, there were no specific hypotheses for the group differences in the three syndrome groups.
- To examine how age, adaptive ability, health difficulties, sleep difficulties, sensory processing differences, and autism characteristics contribute to low mood within three genetic syndromes (CdLS, FXS, and RTS).
    - Based on previous literature and as genetic syndromes have specific phenotypes, it was hypothesised that there will be differences in the predictors of low mood in each syndrome group.
    - Based on previous research, it was hypothesised that there would be a significant correlation between age and low mood in CdLS and RTS. No hypotheses were made for the relationship between low mood and age in FXS.

    - Due to mixed results in previous literature, no hypotheses were made for the associations between low mood and adaptive ability.
    - Based on pre-existing literature, it was hypothesised that sleep difficulties, health difficulties, autism characteristics, and sensory processing differences would significantly predict low mood.
- To explore whether similar predictors of low mood are found across two measures of low mood. Two measures were used as there is no gold standard tool for the assessment of depression in people with ID (McBrien, 2003; Eaton et al., 2021).
    - It was hypothesised that the two measures of low mood would be significantly correlated.
    - There were no specific hypothesis around the variables that will predict low mood in each measure of low mood.

## Methods

### Recruitment

The current study was part of a larger longitudinal study which aimed to assess the Behavioural and Emotional Outcomes in people with Neurodevelopmental Disorders (BEOND). The BEOND project was pre-registered on OSF registries (osf.io/n89x7) and obtained ethical approval by the Wales Research Ethics Committee (REC) 1 Cardiff (reference: 22/WA/0086). The ethics approval for the current study fell under the existing ethics approval for the BEOND project, see Appendix 1 for the approval letter.

The participants for the current study were recruited from an existing cross-syndrome participant database held by the Cerebra Network for Neurodevelopmental Disorders which included people who had participated in previous research studies by the

Cerebra Network and had consented to be contacted about future research projects. All participants on the database were invited to take part in the study. Participants were also recruited from social media and syndrome support groups.

**Participants**

Participants were eligible to participate in the current study if they were caregivers of a person with CdLS, FXS, or RTS. There were a total of 182 caregivers who participated in the study, reporting on 48 people with CdLS, 70 people with FXS, and 64 people with RTS. Participants were excluded if the data was missing from the two questionnaires assessing mood, as mood was the primary outcome variable (n = 28), and if they were under age four (n = 9) as one of the measures is validated for people aged four and over. Four caregivers reported on females with FXS; as FXS is an X linked syndrome and males are affected more severely (Garber et al., 2008), these four participants were also excluded.

Thus, a total of 141 participants were included in the current study (mean age = 22.8, SD = 12.9). Caregivers reported on a total of 96 male participants (68.1%) and 45 participants were female (31.9%). There were 140 caregivers who reported that the gender of the person they care for is the same gender they were assigned at birth, and this information was missing for one person. There were 37 people with CdLS (mean age = 19.1, SD = 12.4), 60 people with FXS (mean age = 25, SD = 12.4), and 44 people with RTS (mean age = 22.8, SD = 13.4), as shown in Table 2.1. The majority of participants (n = 139, 98.6%) had also been diagnosed with ID.

The diagnosis of a genetic syndrome was confirmed by a professional. There were 100 participants who were diagnosed by a clinical geneticist (70.9%), 27 participants were

diagnosed by a paediatrician (19.1%), 3 participants were diagnosed by their GP (2.1%), and 11 participants were diagnosed by other professionals or sources (7.8%).

**Table 2.1**

*Demographics of participants included in the current study*

| | CdLS (n = 37) | FXS (n=60) | RTS (n=44) | All participants (n = 141) |
|---|---|---|---|---|
| Mean age (SD) | 19.1 (12.4) | 25.0 (12.4)[1] | 22.8 (13.4) | 22.8 (12.9) |
| Gender | | | | |
| Female (%) | 19 (51.4%) | 0 (0%) | 26 (59.1%) | 45 (31.9%) |
| Male (%) | 18 (48.6%) | 60 (100%) | 18 (40.9%) | 96 (68.1%) |
| ID | | | | |
| Mild | 7 (18.9%) | 0 (0%) | 2 (4.5%) | 9 (6.4%) |
| Moderate | 13 (35.1%) | 23 (38.3%) | 15 (34.1%) | 51 (36.2%) |
| Severe | 12 (32.4%) | 27 (45%) | 20 (45.5%) | 59 (41.8%) |
| Profound | 3 (8.1%) | 2 (3.3%) | 4 (9.1%) | 9 (6.4%) |
| Unknown | 1 (2.7%) | 6 (10%) | 2 (4.5%) | 9 (6.4%) |
| Other | 1 (2.7%) | 0 (0%) | 1 (2.3) | 2 (1.4%) |
| No ID | 0 (0%) | 2 (3.3%) | 0 (0%) | 2 (1.4%) |
| Autism diagnosis | | | | |
| Yes | 9 (24.3%) | 28 (46.7%) | 12 (27.3%) | 49 (34.8%) |
| No | 28 (75.7%) | 32 (53.3%) | 32 (72.7%) | 92 (65.2%) |

[1] Demographics for age were based of 59 participants due to missing data for one person.

## Procedure

The study used a cross sectional design. All participants completed a series of screening questions to ensure that they were eligible for the study. Caregivers were emailed a link to the online survey that included information sheets, consent forms, and the questionnaires, see Appendix 2. Caregivers could request paper copies of the study.

## Measures

### *Background information questionnaire*

The background questionnaire gathered demographic information for each participant including the participant's gender, date of birth, ethnicity, diagnosis, mobility, and verbal ability. The background questionnaire also gathered information about the caregiver including the caregivers' age, gender, and education.

### *Mood Interest and Pleasure Questionnaire – Short Form (MIPQ-S; Ross & Oliver, 2003; Ross et al., 2008)*

The MIPQ-S is an informant questionnaire consisting of 12 items rated on a five-point Likert Scale. The rating ranges from 0 ("all the time / everyday") to 4 ("never / less than once each week"). The MIPQ was developed for people with severe and profound ID and can be used as a proxy measure of low mood (Oliver et al., 2021). The items are based on the two main symptoms of depression in the DSM-IV to provide a mood subscale and an interest and pleasure subscale with scores based on the previous two weeks. The MIPQ-S also provides a total score that combines the two subscales. The maximum scores are 24, 24, and 48 for the mood subscale, interest and pleasure subscales, and total score, respectively. Low scores indicate low mood and low levels of interest and pleasure. The

MIPQ-S was found to have good test-retest reliability, inter-rater reliability, and internal consistency (Oliver et al., 2021; Ross & Oliver, 2003).

### *Anxiety Depression and Mood Scale (ADAMS; Esbensen et al., 2003)*

The ADAMS is a measure of anxiety and depression that was developed for people with ID. The ADAMS consists of 28 items rated on a four-point Likert scale by an informant. The Likert scale ranges from a minimum score of 0 ("not a problem") to a maximum score of 3 ("severe problem"). The ADAMS provides five subscales: depressed mood, general anxiety, manic/ hyperactive behaviour, social avoidance, and compulsive behaviour. Only scores on the depressed mood subscale were included in the current study. Higher scores on the ADAMS suggest higher severity of depression symptoms. Good test-retest reliability (0.81) and internal consistency (0.80) has been found for the ADAMS (Esbensen et al., 2003; Shelley et al., 2023).

### *Wessex Questionnaire (Wessex; Kushlick et al., 1973)*

The Wessex is a proxy measure for adaptive ability and consists of questions about continence, mobility, self-help, speech, literacy, vision, and hearing. The items are rated on a three-point Likert scale. The overall self-help score was used in the current study as a proxy measure of adaptive ability. The self-help score combined the responses on the items about the participant's ability to wash, dress, and feed themselves. The overall self-help score ranged from 3 to 9, with higher scores representing a higher level of ability. The inter-rater reliability has been found to range from .54 to .72 (Oliver et al., 2021; Palmer & Jenkins, 1982).

***Heath Questionnaire (HQ; Hall et al., 2008)***

The HQ measures the presence and severity of physical health difficulties for the previous month and across the lifetime. Health difficulties are rated on a four-point Likert scale from 0 ("never") to 3 ("severe"). The current number of health difficulties present in the previous month was included in the current study. Good item-level reliability has been found for current health difficulties (Hall et al., 2008), and the intra-class correlation coefficient for the number of current health problems was found to be .73 (Oliver et al., 2021).

***Sensory Experiences Questionnaire (SEQ; Baranek et al., 2006)***

The SEQ is an informant questionnaire that measures behavioural responses to sensory situations. Items are rated on a five-point Likert scale ranging from 1 ("almost never") to 5 ("almost always"). High scores imply a higher intensity and frequency of sensory features. The SEQ provides a total score and the four subscales including hyper-social, hyper-nonsocial, hypo-social, and hypo-non-social (Baranek et al., 2009). The total score was used in the current study. Excellent internal consistency and test-retest reliability has been reported for the SEQ (Little et al., 2011; Royston et al., 2018).

***Social Communication Questionnaire - Current Version (SCQ-C; Rutter et al., 2003; Berument et al., 1999).***

The SCQ is a screening measure of autism that is validated for people aged four and older (Berument et al., 1999; Marvin et al., 2017). The SCQ consists of 40 items that are rated 0 ("no") or 1 ("yes"). The SCQ provides three subscales: reciprocal social interaction; communication; and restricted, repetitive, and stereotyped patterns of behaviour. The SCQ also provides a total score, and higher scores indicate a larger number

of autism characteristics (Edwards, 2022; Shelley et al., 2023). Good internal consistency has been found (Marvin et al., 2017).

### *Child Sleep Habits Questionnaire (CSHQ; Owens et al., 2000)*

The CSHQ is a clinically useful screening measure of sleep difficulties in children with neurodevelopmental conditions and typically developing children (Goodlin-Jones et al., 2008). The 33 items are rated on a three-point Likert scale that ranges from 1 ("rarely / 0 to 1 time per week") to 3 ("usually / 5 to 7 times per week"). The CSHQ provides eight subscales for specific sleep difficulties (e.g., sleep onset delay, night wakings, sleep-disordered breathing), and a total score. Higher scores indicate a higher number of sleep difficulties. Good internal consistency has been reported for community and clinical child samples (.68 and .78, respectively; Owens et al., 2000).

## Data analysis

The data were analysed on IBM SPSS Statistics 29.0.1.0. The dependent variables were the two measures of low mood (MIPQ-S total score and ADAMS depressed mood subscale). The independent variables included age, adaptive ability, current health difficulties, autism characteristics, sleep difficulties, and sensory processing differences. These factors were identified from previous research that has shown an association between the variables and low mood, and research has shown a heightened prevalence of these factors in genetic syndromes. The total scores were used for the predictor variables rather than subscales to minimise the number of variables in the regression analyses to ensure statistical power.

Tests of normality were completed using Shapiro-Wilk tests as Shapiro-Wilk has more power than other methods for small sample sizes (Mishra et al., 2019). Histograms

were also visually inspected to further assess for distributions from normality. The choice of parametric or non-parametric tests were based on the majority of the data. Kruskal-Wallis and Mann-Whitney tests were completed to assess whether there were group differences in scores for the dependent variables and independent variables. Chi-square tests were used to assess whether there were group differences in gender. Mann Whitney tests were used to assess gender differences in scores of low mood for CdLS and RTS; these tests were not completed for people with FXS as all the participants were males.

As most of the data were not normally distributed, Spearman's rho correlations were completed to investigate significant correlations between the outcome variables and predictor variables in each syndrome group. An alpha level of $p < .05$ was used for the analyses. The analyses did not adjust for multiple comparisons due to the exploratory nature of the study, similar to a previous study (Edwards, 2022). Although not adjusting for multiple comparisons increases the risk of Type 1 errors, it was deemed important to identify potential correlates and predictors of low mood which could be assessed further in future studies (Royston et al., 2018; see discussion for further commentary).

The correlation analyses aimed to identify predictor variables to be included in the multiple linear regression analyses; all six variables were not entered into the regression analyses as 10 people per predictor variable is recommended (Maxwell, 2000) to ensure statistical power. As there is strong theoretical evidence showing an association between age and mood in genetic syndromes, particularly for CdLS and RTS where mood changes with age are included as part of the behavioural phenotype (Basile et al., 2007; Berney et al., 1999; Nelson et al., 2014; Yagihashi et al., 2012), age was entered into all the regression analyses. As there is a less established association between mood and the remaining variables for each syndrome, the remaining predictors were selected based on

the correlations; variables that were significantly correlated with scores on the MIPQ-S or ADAMS were entered into the regression analyses for the specific syndrome. Multiple linear regression analyses were completed to identify variables that predict low mood, and to explore how these variables vary across the three syndromes.

### *Assumptions of regression analyses*

The multiple linear regression analyses were tested to ensure the assumptions were met. Assumptions of linearity between each dependent variable and independent variable were confirmed by visual inspection of scatter plots. As regression analyses assume the residuals are normally distributed (Williams et al., 2019), histograms and normal P-P plots were visually checked. The assumption of homoscedasticity was visually checked (Osborne & Waters, 2019) by inspection of the scatter plots with the standardised residual plotted against the standardised predicted value. The assumption was met for three of the regression models, which included MIPQ-S scores as the dependent variable. However, the plots of the residuals for the regression models involving the ADAMS subscale showed heteroscedasticity which can result in Type 1 errors (Osborne & Waters, 2019). Thus, square root case transformation for the ADAMS subscale was used to adjust for the heteroscedasticity and to improve normality (Osborne & Waters, 2019). Cook's Distance was used as a test for outliers (Williams et al., 2019), with scores larger than 1 indicating influential values (Stevens, 1984). As the values for the six regression analyses were less than 1, it was concluded that there were no influential values of concern in the dataset. Further assumptions of regression analyses are that there is an independence of errors and there is no correlation between predictor variables (Chatterjee & Hadi, 2012; Williams et al., 2019). Thus, the Durbin-Watson test for autocorrelation, and multicollinearity tests were completed. A concerning level of autocorrelation is indicated from a Durbin-Watson

value under one and over three (Field, 2009), with scores of two suggesting no autocorrelation. Thus, the Durbin-Watson tests suggested acceptable levels of autocorrelation, as shown in Table 2.2. The variance inflation factor (VIF) and tolerance were used as tests of multicollinearity, with acceptable levels of correlation between predictor variables found (Braun & Oswald, 2011).

**Table 2.2**

*Autocorrelation and multicollinearity tests for assumptions of regression analyses*

| | | **Autocorrelation** | **Multicollinearity** | |
|---|---|---|---|---|
| | | Durbin-Watson | VIF | Tolerance |
| **CdLS** | | | | |
| | MIPQ-S total score | 1.92 | 1.25-2.62 | 0.38-0.80 |
| | ADAMS mood sqrt | 1.52 | 1.32-2.60 | 0.39-0.76 |
| **FXS** | | | | |
| | MIPQ-S total score | 1.52 | 1.12-2.00 | 0.50-0.90 |
| | ADAMS mood sqrt | 1.34 | 1.12-2.00 | 0.50-0.89 |
| **RTS** | | | | |
| | MIPQ-S total score | 1.67 | 1.10-1.32 | 0.76-0.91 |
| | ADAMS mood sqrt | 2.20 | 1.08-1.23 | 0.81-0.92 |

## Results

### Group differences

Group differences in age, gender, adaptive ability, number of current health difficulties, sensory processing differences, sleep difficulties, autism characteristics, and low mood scores were explored, as shown in Table 2.3. There were no significant differences between syndrome groups for age, sensory processing differences, autism characteristics, or scores on the MIPQ-S and ADAMS, as shown in Appendix 5.1. There was a significant gender difference between the syndrome groups ($\chi^2$ (2) = 49.5, $p < .001$). The post hoc Chi-squared tests showed there were more males with FXS compared to the

number of males with CdLS ($\chi^2 = 38.3$, $p < .001$), and the number males with RTS ($\chi^2 = 47.3$, $p < .001$). There was a significant difference in level of adaptive ability as measured by self-help scores on the Wessex ($H$ (2) = 10.7, $p = .005$). The post hoc Mann Whitney U tests found significantly higher levels of adaptive ability in people with FXS compared to CdLS ($U = 659.5$, $p = .004$) and RTS ($U = 935$, $p = .015$). A Kruskal-Wallis test found the number of current health difficulties was significantly different between the three syndrome groups ($H$ (2) = 31.2, $p < .001$). Mann Whitney U tests showed people with CdLS and people with RTS had significantly more health difficulties than people with FXS ($U = 344.5$, $p < .001$; $U = 681$, $p < .001$, respectively). A significant group difference for sleep difficulties was found ($H$ (2) = 6.0, $p = .049$) with people with RTS scoring significantly higher for sleep difficulties compared to people with FXS ($U = 893$, $p = .028$). There were no significant gender differences in low mood scores in CdLS or RTS, as shown in Appendix 5.2.

**Table 2.3**

*Group differences across CdLS, FXS, and RTS with Chi-squared and Mann-Whitney U tests*

| Domain | | CdLS | FXS | RTS | Group comparisons | | |
|---|---|---|---|---|---|---|---|
| | | | | | Comparison | $\chi^2$ / U | p value |
| Gender | (% male) | 48.6 | 100 | 40.9 | FXS > CdLS | 38.3 | < .001*** |
| | | | | | FXS > RTS | 47.3 | < .001 *** |
| | | | | | CdLS ≈ RTS | 0.49 | .485 |
| Age | Mean (SD) | 19.1 (12.4) | 25.0 (12.4) | 22.8 (13.4) | CdLS ≈ FXS ≈ RTS[1] | - | - |
| | Median (IQR) | 16 (22) | 25 (21) | 22.5 (15.3) | | | |
| | Range | 4-58 | 4-55 | 4-48 | | | |
| Adaptive ability[2] | Mean (SD) | 5.9 (2.2) | 7.2 (1.6) | 6.4 (1.9) | FXS > CdLS | 659.5 | .004** |
| | | | | | FXS > RTS | 935 | .015* |
| | Median (IQR) | 6 (5) | 7 (2) | 7 (3) | CdLS ≈ RTS | 634.5 | .315 |
| | Range | 3-9 | 3-9 | 3-9 | | | |
| Current health difficulties | Mean (SD) | 3.3 (2.7) | 1.3 (1.8) | 2.6 (2) | FXS < CdLS | 344.5 | < .001*** |
| | | | | | FXS < RTS | 681 | < .001*** |
| | Median (IQR) | 3 (2) | 1 (2) | 2 (3) | CdLS ≈ RTS | 635 | .177 |
| | Range | 1-12 | 0-11 | 0-7 | | | |

| Domain | | CdLS | FXS | RTS | Group comparisons | | |
|---|---|---|---|---|---|---|---|
| | | | | | Comparison | $\chi^2$ / U | p value |
| Sensory processing differences | Mean (SD) | 57.5 (14.8) | 64.8 (13.4) | 63 (16.6) | CdLS ≈ FXS ≈ RTS | - | - |
| | Median (IQR) | 58 (25.5) | 66 (21.5) | 60 (22.5) | | | |
| | Range | 32-83 | 34-94 | 34-101 | | | |
| Sleep difficulties | Mean (SD) | 46.4 (8.7) | 43.2 (8.4) | 46.3 (8.3) | FXS < RTS | 893 | .028* |
| | | | | | CdLS ≈ FXS | 702 | .059 |
| | Median (IQR) | 44 (14.5) | 41 (10) | 45 (11) | CdLS ≈ RTS | 704 | .954 |
| | Range | 33-68 | 33-67 | 33-72 | | | |
| Autism characteristics | Mean (SD) | 17.6 (7.6) | 19.2 (7.2) | 18.3 (6) | CdLS ≈ FXS ≈ RTS | - | - |
| | Median (IQR) | 20 (12) | 19.5 (13) | 18 (9) | | | |
| | Range | 2-30 | 7-33 | 7-31 | | | |
| MIPQ-S total score | Mean (SD) | 35.7 (7.5) | 37.4 (6.2) | 36.4 (6) | CdLS ≈ FXS ≈ RTS | - | - |
| | Median (IQR) | 38 (12.5) | 38 (10) | 38 (8.8) | | | |
| | Range | 16-46 | 20-48 | 22-48 | | | |
| ADAMS mood subscale score | Mean (SD) | 3.5 (4.5) | 2.8 (3.4) | 2.6 (3) | CdLS ≈ FXS ≈ RTS | - | - |
| | Median (IQR) | 2 (5.3) | 2 (4.3) | 1.5 (4) | | | |

| Domain | CdLS | FXS | RTS | Group comparisons | | |
|---|---|---|---|---|---|---|
| | | | | Comparison | $\chi^2$ / U | p value |
| Range | 0-16 | 0-14 | 0-13 | | | |

*Note.* *** significant at $p < .001$, ** significant at $p < .001$, * significant at $p < .001$

[1]As the Kruskal-Wallis test was not significant, further group comparisons were not completed.

[2]As measured by the self-help score on the Wessex.

**Correlations**

All variables were entered into the correlation analyses for each syndrome group, as shown in Table 2.4. The full correlation analyses are included in Appendix 5.3-5.5[1]. The correlation analyses for CdLS found MIPQ-S total scores were significantly negatively correlated with the total SEQ score ($r_s(31) = -.59$, $p < .001$) total CSHQ score ($r_s(31) = -.50$, $p = .003$) and total SCQ score ($r_s(33) = -.54$, $p < .001$). These results indicate that lower levels of mood were associated with higher sensory processing differences, poorer sleep, and a higher number of autism characteristics, respectively. The ADAMS mood subscale score was significantly positively correlated with the total CSHQ score ($r_s(28) = .51$, $p = .004$) which suggests a higher severity of depressive symptoms were correlated with poorer sleep. The correlation analyses for FXS found lower total scores on the MIPQ-S were significantly correlated with more sensory processing differences ($r_s(51) = -.34$, $p = .012$), poorer sleep ($r_s(54) = -.49$, $p < .001$) and more autism characteristics ($r_s(52) = -.41$, $p = .002$). The ADAMS depressed mood subscale was significantly positively correlated with SEQ scores ($r_s(48) = .42$, $p = .002$) and CSHQ scores ($r_s(47) = .41$, $p = .003$), indicating greater severity of depression symptoms were associated with more sensory processing differences and poorer sleep, in FXS. The correlation analyses for RTS found no significant associations between variables and scores on the MIPQ-S. A significant positive relationship was found for the ADAMS mood subscale and current number of health difficulties in RTS ($r_s(38) = .51$, $p < .001$) and for SEQ total scores ($r_s(38) = .39$, $p = .013$), suggesting more severe depressive symptoms were associated with a higher number of health difficulties and more sensory processing differences, respectively.

[1] N varies due to missing data.

**Table 2.4**

*Correlations between each variable across each syndrome including the correlation coefficient and significance level.*

| | MIPQ-S total score | ADAMS mood subscale |
|---|---|---|
| **CdLS** | | |
| MIPQ-S total | - | -.56*** |
| ADAMS mood subscale | -.56*** | - |
| Age (in months) | -.05 | .29 |
| Adaptive ability (Wessex) | .25 | .30 |
| Health difficulties (HQ) | -.13 | -.00 |
| Autism related characteristics (SCQ-C) | -.54*** | .22 |
| Sensory processing differences (SEQ) | -.59*** | .25 |
| Sleep difficulties (CSHQ) | -.50** | .51** |
| **FXS** | | |
| MIPQ-S total | - | -.54*** |
| ADAMS mood subscale | -.54*** | - |
| Age (in months) | -.01 | -.07 |
| Adaptive ability (Wessex) | .19 | -.07 |
| Health difficulties (HQ) | -.12 | .25 |
| Autism related characteristics (SCQ-C) | -.41** | .26 |
| Sensory processing differences (SEQ) | -.34* | .42** |
| Sleep difficulties (CSHQ) | -.49*** | .41** |
| **RTS** | | |
| MIPQ-S total | - | -.44* |
| ADAMS mood subscale | -.44** | - |
| Age (in months) | -.20 | .08 |
| Adaptive ability (Wessex) | -.10 | -.01 |
| Health difficulties (HQ) | -.26 | .51*** |
| Autism related characteristics (SCQ-C) | -.27 | .09 |
| Sensory processing differences (SEQ) | -.25 | .39* |
| Sleep difficulties (CSHQ) | -.18 | .01 |

*Note.* *** significant at $p < .001$, ** significant at $p < .01$, * significant at $p < .05$.

**Multiple regression models**

Six multiple regression models were produced to identify predictors of low mood in each of the two outcome variables of low mood (MIPQ-S total score and ADAMS mood subscale) within the three syndrome groups. The predictor variables were identified based of correlation analyses and theoretical evidence; predictors were selected if the variables were significantly correlated at alpha level $p < .05$ on the correlation analyses, and age was included for all regression analyses based on theoretical evidence. Thus, the predictor variables for CdLS and FXS were age, sleep difficulties, sensory processing differences, and autism characteristics. The predictor variables for RTS were age, sensory processing differences, and number of current health difficulties.

The overall regression models of all predictors were significant for both outcome variables in all syndrome groups, as shown in Table 2.5. In CdLS, the regression model was significant for the MIPQ-S total score ($F(4,28) = 6.27$, $p < .001$, $R^2 = .47$) and the ADAMS subscale score ($F(4,25) = 3.67$, $p = .017$, $R^2 = .37$). The model accounted for 47% and 37% of the variance for the MIPQ-S and ADAMS, respectively. The regression model for the MIPQ-S total score was significant for FXS ($F(4,44) = 8.51$, $p < .001$, $R^2 = .44$) and for the ADAMS mood subscale score ($F(4,43) = 4.64$, $p = .003$, $R^2 = .30$). In RTS, the regression model for MIPQ-S was significant and explained 27% of the variance ($F(3,40) = 4.93$, $p = .005$, $R^2 = .27$) The regression model for the mood subscale on the ADAMS was also significant ($F(3,36) = 7.07$, $p < .001$, $R^2 = .37$).

**Table 2.5**

*ANOVA models and $R^2$ values for the multiple regression models across each dependent variable and syndrome group*

| | | F | *Df*[1] | $R^2$ | *p* |
|---|---|---|---|---|---|
| **CdLS** | | | | | |
| | MIPQ-S total score | 6.27 | 4, 28 | 0.47 | < .001*** |
| | ADAMS mood sqrt[2] | 3.67 | 4, 25 | 0.37 | .017* |
| **FXS** | | | | | |
| | MIPQ-S total score | 8.51 | 4, 44 | 0.44 | < .001*** |
| | ADAMS mood sqrt | 4.64 | 4, 43 | 0.30 | .003*** |
| **RTS** | | | | | |
| | MIPQ-S total score | 4.93 | 3, 40 | 0.27 | .005** |
| | ADAMS mood sqrt | 7.07 | 3, 36 | 0.37 | < .001*** |

*Note.* *** significant at $p < .001$, ** significant at $p < .01$, * significant at $p < .05$.
[1] N varies due to missing data.
[2] Sqrt = square root

The contribution of each predictor variable on each outcome variable is shown in Figures 2.1-2.3. The full regression analyses are included in Appendix 5.6. In CdLS, older ages and higher number of sensory processing differences significantly predicted low mood as measured by lower total scores on the MIPQ-S (b = -.02, β = -.36, $p$ = .026; b = -.24, β = -.47, $p$ = .044, respectively). Higher sleep difficulties on the CSHQ significantly predicted higher severity of depressive symptoms as measured by higher scores on the ADAMS mood subscale (b = .08, β = .55, $p$ = .009) in CdLS. In FXS, more sleep difficulties significantly predicted lower scores on the MIPQ-S (b = -.36, β = -.48, $p$ < .001) and higher scores on the ADAMS depressed mood subscale (b = .05, β = .37, $p$ = .017). A higher number of autism characteristics predicted lower scores on the MIPQ-S (b = -.28, β = -.32, $p$ = .036), in FXS. Older ages significantly predicted lower scores on the MIPQ-S in FXS (b = -.01, β = -.33, $p$ = .009), and lower scores on the MIPQ-S in RTS (b = -.01, β = -.38, $p$ = .015). In RTS, higher number of sensory processing differences significantly predicted lower scores on the MIPQ-S (b = -.15, β = -.43, $p$ = .009) and

higher scores on the ADAMS mood subscale (b = .02, β = .33, *p* = .031). Higher numbers of current health difficulties also predicted higher scores on the ADAMS mood subscale for RTS (b = .22, β = .43, *p* = .003), indicating more health difficulties was associated with a higher severity of symptoms of depression.

**Figure 2.1**

*Predictors of low mood in CdLS from the regression analyses*

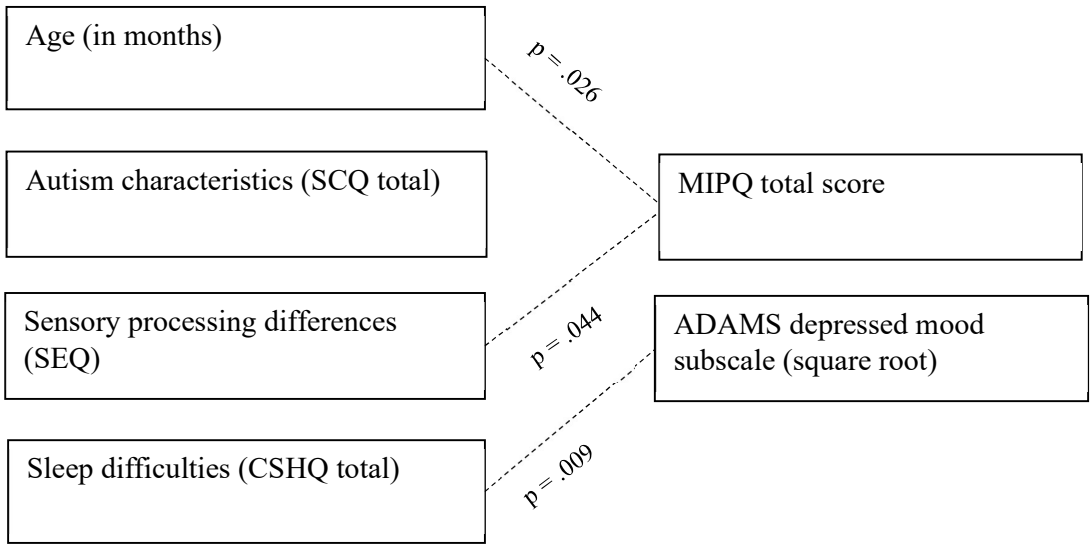



**Figure 2.2**

*Predictors of low mood in FXS from the regression analyses*

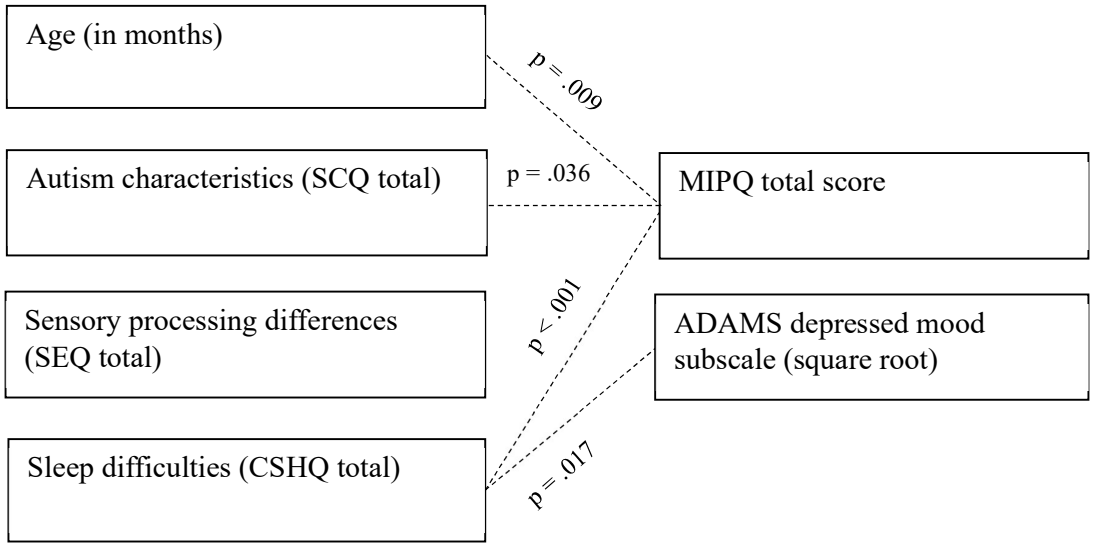
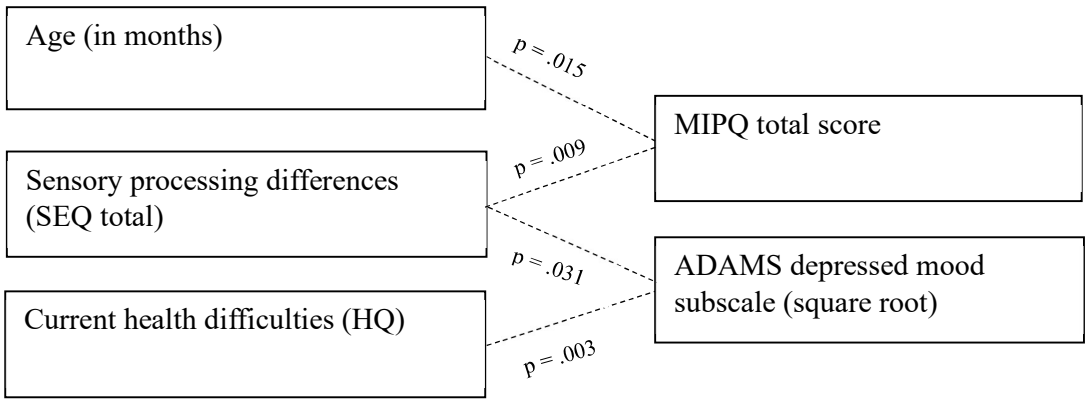


**Figure 2.3**

*Predictors of low mood in RTS from the regression analyses*




**Associations between the two measures of low mood**

To explore whether the two measures of low mood were significantly associated, Spearman Rho correlations were conducted, as shown in Table 2.4 and Appendix 5.3-5.5. In CdLS, total scores on the MIPQ-S were significantly negatively correlated with scores on the depressed mood subscale on the ADAMS ($r_s(28) = -.56$, $p = .001$), suggesting lower levels of mood were associated with a higher severity of symptoms of depression, as measured by the MIPQ-S and ADAMS, respectively. Significant negative associations were also found between the two scores for FXS ($r_s(48) = -.54$, $p < .001$) and RTS ($r_s(38) = -.44$, $p = .004$).

## Discussion

The current study explored correlates and predictors of low mood in people with CdLS, FXS, and RTS, and found differences in the predictors of low mood in each genetic syndrome. Age was the only variable found to predict MIPQ-S scores across all three syndromes. Higher sensory processing differences were found to predict low mood in

CdLS and RTS, and sleep difficulties predicted low mood in CdLS and FXS. A higher number of autism characteristics were found to predict low mood in FXS, and a higher number of current health difficulties predicted low mood in people with RTS. No group differences in low mood scores for each syndrome group were found. The current study identified syndrome specific predictors of low mood that should be assessed in future research to further establish the associations between these variables and low mood in rare genetic syndromes associated with ID.

The study used two measures of low mood, the total score on the MIPQ-S and the depressed mood subscale on the ADAMS. The two measures of low mood were used as there are difficulties in the assessment of low mood in people with ID (Adams & Oliver, 2011; Davies & Oliver, 2014; Hermans et al., 2013; Levitas et al., 2001) and there are a limited number of validated measures to measure low mood in people with ID (Perez-Achiaga et al., 2009). The two scores were found to significantly correlate across the three syndrome groups which indicated lower levels of mood as measured by the MIPQ-S was associated with a higher severity of depression symptoms. However, differences in the predictors of low mood were found depending on the measure used. The ADAMS was developed for people with mild to profound ID (Esbensen et al., 2003; Shelley et al., 2023) and the MIPQ is a reliable and valid measure for people with severe and profound ID (Ross & Oliver, 2003; Flynn et al., 2017). Thus, the MIPQ might be less sensitive in detecting low mood in people with mild or moderate ID, which might partly account for some of the differences in predictors found.

The factors that predicted low mood were largely consistent with previous research. Older ages predicted lower levels of low mood across syndrome groups, consistent with previous research that has shown mood changes with age are common in CdLS and RTS

(Basile et al., 2007; Berney et al., 1999; Nelson et al., 2014; Oliver et al., 2011; Yagihashi et al., 2012). However, the finding that older ages predicted low mood in FXS differed to previous research that found age was not significantly associated with mood in FXS (Nelson et al., 2014; Royston et al., 2020). As the current study included people with FXS aged between 4 and 55 and previous research involved people older than 12 years old (Royston et al., 2020), the large age range in the current study might partly account for the reported findings. The current study found no significant association between level of adaptive ability and low mood across the three syndromes. This finding adds to the inconsistencies in the literature whereby some studies have found an association between low mood and lower levels of adaptive ability in FXS (Groves et al., 2019), whereas other studies report levels of adaptive functioning did not predict depressed mood and anxiety scores in this group (Royston et al., 2020). Due to the inconsistencies in studies, further research exploring individual factors, including age and level of ability, is required to inform models of low mood.

The findings were consistent with previous research that has reported associations between autism characteristics and low mood. Higher number of autism characteristics were significantly correlated with lower MIPQ-S scores in FXS and CdLS, and predicted lower MIPQ-S total scores in FXS. This finding is consistent with previous research that found a higher number of autism characteristics were associated with lower mood and lower levels of interest and pleasure in CdLS and FXS (Groves et al., 2019). The findings add to existing considerations in the interpretation of results showing an association between autism characteristics and levels of interest and pleasure due to an overlap of behaviours, in particular the similarities in social withdrawal (Groves et al., 2019; Ross & Oliver, 2003). This consideration is important for the current study given that significant

associations were found between the SCQ score and the MIPQ-S total score but not the SCQ and the ADAMS depressed mood scale, as the MIPQ-S score includes items related to interest and pleasure. Thus, further research is required to further understand the relationship between autism characteristics and low mood in genetic syndromes.

The current study found that the number of health difficulties significantly predicted low mood in RTS. This finding is consistent with previous research which has demonstrated relationships between health difficulties and pain on low mood in people with ID (Findlay et al., 2014; Hsieh et al., 2020). There were group differences in the number of current health difficulties across syndrome groups, where people with RTS and CdLS had significantly more health difficulties compared to people with FXS. The increased number of health difficulties in RTS and CdLS is consistent with previous research showing a high prevalence of health difficulties in RTS and CdLS (Berg et al., 2007; Douzgou et al., 2022; Hall et al., 2008; Stevens et al., 2011). As health difficulties significantly predicted low mood in people with RTS, and there is a high prevalence of health difficulties in RTS, the results highlight the importance of routine assessment of low mood in people with RTS.

There are statistical limitations to the current study. One limitation is that the study did not adjust for multiple comparisons (e.g. the use of a Bonferroni correction or a more stringent significant level; Royston et al., 2018). The current study used an alpha level of $p < .05$ due to the exploratory, clinical nature of the study and it was considered important to be inclusive of potential predictors of low mood to inform future research exploring low mood in rare genetic syndromes. However, an alpha level of .05 increases the risk of Type 1 errors. Although there were no differences in the predictors that would have been included in the regression analyses if a more conservative significance level was used (e.g.

$p$ = .01) for the analyses for CdLS and FXS, there were differences for RTS. Sensory processing differences scores were significantly correlated with low mood scores ($p$ = .013); thus, these scores were included in the regression analyses for RTS. However, the inclusion of sensory processing differences might have influenced the findings and differences in the results might have been found if a more stringent alpha level was used. A further consideration for the results is the level of autocorrelation in one of the regression analyses. The Durbin-Watson value was 1.34 for the regression for ADAMS scores in FXS, and previous studies have reported an acceptable range of 1.5 to 2.5 (Rambod et al., 2023) rather than values less than one (Field, 2009). Thus, there might have been a positive autocorrelation. Additionally, although the sample sizes in the current study are good for these rare genetic syndromes, the regression analyses for CdLS were likely underpowered due to the small sample size as 10 people per predictor is recommended (Maxwell, 2000). Thus, further research (e.g. research that includes direct assessments, longitudinal studies, and larger sample sizes to ensure statistical power) is required to further understand predictors of low mood in rare genetic syndromes and confirm the findings of the current study.

Due to the small sample sizes, the total scores of measures rather than subscales were included to reduce the number of predictors in the regression analyses to ensure statistical power. However, the use of a total score might have resulted in less specificity in the factors contributing to low mood. For example, the current study used the total score of sensory processing differences, but previous research has demonstrated differences in the profile of sensory processing differences across syndrome groups, with hyper-responsivity common in FXS and hypo-responsivity common in CdLS (Heald et al., 2020). Thus, using subscale scores might have allowed for a further understanding of the profile of sensory

processing differences that contribute to low mood across genetic syndromes. The current study also used the total of autism characteristics which hinders the understanding of specific behaviours that might be associated with low mood. Previous research found higher levels of difficulties with social interaction were significantly associated with lower mood in FXS, greater levels of repetitive behaviour were found to be associated with lower mood in CdLS, and difficulties with social interaction were associated with lower levels of interest and pleasure in FXS and in CdLS (Groves et al., 2019). These findings suggest that there are differences in specific behaviours that contribute to low mood in each syndrome group, and further highlight the importance of using subscale scores that represent specific behaviours to understand syndrome specific factors associated with low mood. Exploring specific and clearly defined behaviours has clinical importance in informing pathways and differences across syndrome groups (e.g. Oliver, 2017; Shelley et al., 2023).

The current study identified correlates and predictors of low mood in rare genetic syndromes. However, the findings do not explain how the variables are associated with low mood and causation relationships cannot be established (Edwards, 2022). Although the regression analyses found sleep difficulties predict low mood in CdLS and FXS, sleep difficulties both increase the risk of developing depression and are a symptom of low mood (Steiger & Pawlowki, 2019). Thus, future research is required to further understand the associations between predictors and low mood to inform causal pathways and treatment strategies.

The study findings can inform possible pathways to low mood in people with genetic syndromes associated with ID. For example, the finding that sensory processing differences predicted depressive scores in people with CdLS and RTS might be explained by social withdrawal and the behavioural model of depression (Bitsika et al., 2021).

Sensory differences are associated with reduced social activities (Hochhauser & Engel-Yeger, 2010), and can result in withdrawal or avoidance of environmental situations in response to distressing sensory stimuli, such as loud noises (Bitsika et al., 2021). Subsequently, withdrawing from situations results in a reduction of positive reinforcement from the environment which can result in the onset and maintenance of depression symptoms (Carvalho & Hopko, 2011; Martell et al., 2001). Thus, future research could expand the findings from the current study and explore the impact of social withdrawal and social isolation on depression in people with genetic syndromes associated with ID.

The possible pathway between sensory differences, social withdrawal, and low mood has clinical implications in informing interventions. One approach might be to reduce the impact of sensory sensitivities by adapting the environment to reduce social withdrawal; for example, through noise control strategies (Kanakri et al., 2017). These strategies could be paired with behaviour activation interventions which aim to increase behaviours that lead to positive reinforcement and result in a reduction in depression symptoms (Lejuez et al., 2011). Importantly, behavioural activation might be more accessible for people with severe and profound ID compared to cognitive based interventions which are more dependent on a person verbally communicating their thoughts and emotions (Gillooly et al., 2024). Thus, behaviour activation interventions and strategies to reduce the impact of sensory sensitivities might alleviate depressive symptoms in people with genetic syndromes associated with ID.

Furthermore, sleep difficulties were found to predict low mood scores in people with CdLS. Although the mechanisms underlying the pathways and association between sleep difficulties and low mood is unknown (Baglioni et al., 2011; O'Leary et al., 2017), research has suggested sleep difficulties can contribute to the development of low mood

due to the impact on brain development (Palagini et al., 2018). An alternate explanation suggests that sleep difficulties negatively impact emotion regulation which can result in symptoms of depression (O'Leary et al., 2017). Emotion regulation has also been implicated as a factor explaining the link between depression and pain (Linton & Bergbom, 2011), and people with health difficulties might experience higher levels of pain. In addition, executive functioning is involved in self-regulation (Feller et al., 2020; Solberg Nes et al., 2009), and people with chronic pain were found to have executive functioning difficulties, in particular emotional control and working memory (Baker et al., 2016). Thus, future research could explore emotion regulation and executive functioning on low mood in people with genetic syndromes.

In addition, the current study found that older ages predicted low mood scores in CdLS, FXS, and RTS. Changes over time in people with CdLS include a decline in cognitive ability and executive functioning skills, and an increase in autism characteristics and levels of anxiety (Groves et al., 2019; Kline et al., 2007; Reid et al., 2017). Future research could explore the relationship between these factors and low mood to further understand the association between age and low mood.

A limitation of the current study is the focus on how individual factors might contribute to the development of low mood and not exploring the impact of social context and psychosocial factors. Previous research has demonstrated risk factors to depression in people with ID include parental depression, life events, stigma, reduced social support, and lower socioeconomic status (Kiddle & Dagnan, 2011; McGillivray & McCabe, 2007; Tomić et al., 2011), and research has recommended the use of psychosocial interventions for people with ID including interventions with the person and with their immediate and wider social context (Dagnan, 2007a; Dagnan, 2007b). People with ID are more likely to

experience more frequent life events (Hatton & Emerson, 2004), and experience negative psychosocial experiences that can have a larger impact due to difficulties with problem solving, coping skills, and reduced social support (Jahoda et al., 2006; McGillivray & McCabe, 2007). In addition, these risk factors might be important in explaining the association between age and low mood. For example, previous research found a positive correlation between age and self-reported stigma where older adults reported a higher number of stigmatising experiences (Ali et al., 2016). Thus, these findings highlight the importance of considering psychosocial factors and social support when exploring depression in people with genetic syndromes associated with ID. Future research could focus on the number of life events experienced, socioeconomic status, social isolation, stigma, and levels of social support to further understand the risk of depression in people with genetic syndromes associated with ID.

Despite these limitations, the current study has multiple strengths. One strength of the current study is the use of measures that are appropriate for people with ID and rare genetic syndromes. The measures have been used in previous rare genetic syndrome research (Edwards et al., 2022; Groves et al., 2019; Royston et al., 2020; Shelley et al., 2023) and have been validated for people with ID. In addition, the findings from the current study have clinical and research implications in identifying potential targets for future interventions and in informing areas for future research to address, respectively.

In summary, the current study identified correlates and predictors of low mood in CdLS, FXS, and RTS, namely older ages, sleep difficulties, health problems, autism characteristics, and sensory processing differences. The study has clinical importance in supporting the identification of people at risk of low mood in rare genetic syndromes and informing assessment and treatment strategies. The current study has limitations inherent

in rare genetic syndrome research but is an important first step in identifying correlates of low mood that may be important to pursue in further research with these syndrome groups. Future research is important to further understand correlates to the development of low mood in rare genetic syndromes.

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**Chapter Three:**

**Press Release: Literature Review**

**Word count: 497**

**Rates of Depression in People with Genetic Syndromes Associated with Intellectual Disability are Higher Than Rates in the General Population.**

Higher rates of depression in people with genetic syndromes associated with intellectual disability compared to the general population have been found, highlighting the need for support.

A new study completed at the University of Birmingham reviewed previous research that has reported the rates of depression in people with genetic syndromes. The rates of depression were found to be 9% in Williams syndrome, 10% in Down syndrome, 10% in tuberous sclerosis complex, and 13% in 22q11.2 deletion syndrome. These rates can be compared to a lower percentage of 4.4% of people who experience depression in the general population (WHO, 2017).

The lead author commented: "Professionals should be aware of the increased risk of depression in people with genetic syndromes to ensure support is provided – ensuring people receive support as early as possible is important due to the negative impacts associated with depression."

The study discussed 40 studies that reported the rates of depression at a point in time. The study planned to report the depression rates in 10 genetic syndromes; however, four genetic syndromes were not included in the results due to an absence of suitable studies, highlighting the limited research in this area. Only two studies reported rates of depression in fragile X syndrome, with rates of 9% and 26% (Haessler et al., 2016; Lachiewicz et al., 1992). Two studies reported the rates in Phelan-McDermid syndrome, and the studies reported depression rates of 3% and 7% (Shaw et al., 2011; Levy et al., 2022, respectively).

The author added “The small numbers of studies highlight the need for more research in this area to fully understand the risk of depression in people with genetic syndromes.”

Differences between the included studies were explored. Lower rates of depression were found for a diagnosis of depression compared to questionnaires of depression. This finding adds to existing considerations in how depression in assessed in people with intellectual disability, and how diagnostic criteria used for the general population might not be suitable to identify the presence of depression in people with intellectual disability (Hermans et al., 2013; Smiley & Cooper, 2003).

The study provides an initial insight into the likelihood of depression in genetic syndromes and adds to the existing literature that has shown a higher risk of mental health difficulties (Edwards et al., 2022; Glasson et al., 2020) in people with genetic syndromes associated with intellectual disability. Interestingly, the study found the prevalence rates of depression were similar for the syndrome groups, unlike previous studies that has found differences in the rate of mental health difficulties in different genetic syndromes (Edwards et al., 2022; Glasson et al., 2020).

Future studies are required to further understand the risk of depression across genetic syndromes which can support people who are experiencing depression in these syndrome groups to receive support.

For media enquiries, please contact Phoebe Armitage, School of Psychology, University of Birmingham, email: pea362@student.bham.ac.uk

## References


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# Chapter Four

## Press Release: Empirical Research Paper

**Word count: 491**

**Age, Poor Sleep, Health Difficulties, and Autism Characteristics can Predict Low Mood in People with Genetic Syndromes Associated with Intellectual Disability.**

A new research study identified factors that are linked to low mood in three genetic syndromes associated with intellectual disability.

The study, completed at the University of Birmingham, found differences in the factors that predict low mood in Cornelia de Lange syndrome, fragile X syndrome, and Rubinstein-Taybi syndrome.

The results showed older ages, sensory processing differences, and poor sleep were linked to low mood in Cornelia de Lange syndrome; older ages, autism characteristics, and poor sleep were linked to low mood in fragile X syndrome; and older ages, sensory processing differences, and health difficulties were important factors linked to low mood in Rubinstein-Taybi syndrome.

The lead author, from the University of Birmingham, stated “knowing older ages, poor sleep, health difficulties, autism characteristics, and sensory processing differences are linked to low mood in people with genetic syndromes can inform assessment and treatment strategies to ensure people receive support as early as possible.”

The study reports on 60 people with fragile X syndrome, 44 people with Rubinstein-Taybi syndrome, and 37 people with Cornelia de Lange syndrome. Parents and caregivers completed questionnaires about the person they care for with a genetic syndrome. Importantly, the study used questionnaires that are suitable for people with an intellectual disability.

The study also found there were no differences in the scores of low mood across the three syndrome groups. There were differences in the number of current health problems and

sleeping difficulties experiences; people with Cornelia de Lange syndrome and Rubinstein-Taybi syndrome experienced more health difficulties than people with fragile X syndrome, and poorer sleep was found in people with Rubinstein-Taybi syndrome than people with fragile X syndrome.

The author added "one important finding is the higher number of health problems in people with Rubinstein-Taybi syndrome as health difficulties were found to be linked to low mood in this population. These findings highlight the importance of assessing the presence of health difficulties and low mood in people with Rubinstein-Taybi syndrome to ensure access to support".

Previous research has shown people with genetic syndromes associated with intellectual disability are at risk of mental health difficulties (Edwards et al., 2020; Glasson et al., 2020). However, the factors that contribute to depression in people with an intellectual disability are less known than for the general population (Hsieh et al., 2020). Thus, the current study is an important step in identifying factors linked to low mood in genetic syndromes associated with intellectual disability.

The study provides an insight into factors that contribute to low mood in genetic syndromes associated with intellectual disability. The findings can inform areas for future research to explore and can inform assessment and treatment strategies. Future research is needed to further understand how these factors contribute to low mood across genetic syndromes.

For media enquiries, please contact Phoebe Armitage, School of Psychology, University of Birmingham, email: pea362@student.bham.ac.uk

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Edwards, G., Jones, C., Pearson, E., Royston, R., Oliver, C., Tarver, J., ... & Waite, J. (2022). Prevalence of anxiety symptomatology and diagnosis in syndromic intellectual disability: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, *138*, 1-13. https://doi.org/10.1016/j.neubiorev.2022.104719

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## Appendices

## Appendix 1: Ethics approval letter for empirical research study

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Caroline Richards
[redacted]

[redacted]

09 May 2022

Dear Dr Richards

**HRA and Health and Care Research Wales (HCRW) Approval Letter**

| | |
|---|---|
| **Study title:** | **Behavioural and Emotional Outcomes in Individuals with Neurodevelopmental Disorders** |
| **IRAS project ID:** | **299757** |
| **Protocol number:** | **RG_21-140** |
| **REC reference:** | **22/WA/0086** |
| **Sponsor** | **University of Birmingham** |

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

**How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?**
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

**How should I work with participating non-NHS organisations?**
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

**What are my notification responsibilities during the study?**

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

**Who should I contact for further information?**
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **299757**. Please quote this on all correspondence.

Yours sincerely,

[redacted]
Approvals Specialist

Email [redacted]

*Copy to:* [redacted]

## Appendix 2: Measures used in the empirical research study

### Appendix 2.1: The Background Questionnaire

**The Background Questionnaire**



**SECTION 1**

**The following questions are about your child/the person you care for:**

1. Which of the following best describes their gender?
   - ☐ Male
   - ☐ Female
   - ☐ Prefer to self-describe as: _____
     *(e.g. non-binary, gender fluid, agender)*
   - ☐ Prefer not to say

   Does their current gender identity match the gender they were assigned at birth?
   - ☐ Yes
   - ☐ No - assigned male at birth
   - ☐ No - assigned female at birth

2. Date of Birth: ____/____/_____ Age in years: _____
   Due date: ____/____/_____ ☐ *Tick if due date is not known*

3. Does your child/the person you care for use at least 30 different signs/words in their vocabulary?
   - ☐ Yes
   - ☐ No

4. Is your child/the person you care for able to walk unaided?
   - ☐ Yes
   - ☐ No

5. Which of the following best describes your child/the person you care for's ethnic group?
   - ☐ White
   - ☐ Mixed or multiple ethnic groups
   - ☐ Asian or Asian British
   - ☐ Black, African, Caribbean, or Black British
   - ☐ Not listed: _____

6. Has your child/the person you care for been diagnosed with a genetic syndrome?
   - ☐ Yes – **Please indicate which syndrome below and answer questions 7-9**
   - ☐ No – **Please move on to question 10**

- ☐ 1p36
- ☐ 8p23
- ☐ 9q34
- ☐ 15q
- ☐ 19p13
- ☐ Angelman Syndrome
- ☐ CHARGE Syndrome
- ☐ Coffin-Siris Syndrome
- ☐ Cornelia de Lange Syndrome
- ☐ Cri du Chat Syndrome
- ☐ Down Syndrome
- ☐ Dravet Syndrome
- ☐ DYRK1A Syndrome
- ☐ Fragile X Syndrome
- ☐ Jansen de Vries Syndrome
- ☐ KBG Syndrome
- ☐ Kleefstra Syndrome
- ☐ Lowe Syndrome
- ☐ Pallister-Killian Syndrome
- ☐ Phelan McDermid Syndrome
- ☐ Pitt-Hopkins Syndrome
- ☐ Potocki-Lupski Syndrome
- ☐ Prader Willi Syndrome
- ☐ Rubinstein-Taybi Syndrome
- ☐ SATB2-associated Syndrome
- ☐ Smith-Magenis Syndrome
- ☐ Soto Syndrome
- ☐ Tuberous Sclerosis Complex
- ☐ Wiedemann-Steiner Syndrome
- ☐ Williams Syndrome
- ☐ Wolf-Hirschhorn Syndrome

☐ Not listed: _____

7. What is the genetic mechanism causing your child/the person you care for's syndrome?
   - ☐ Uni-Parental Disomy
   - ☐ Deletion
   - ☐ Sequence repetition
   - ☐ Not listed: _____
   - ☐ Translocation
   - ☐ Unknown

8. At what age was your child/the person you care for diagnosed?
   _____

9. Who diagnosed your child/the person you care for?
   - ☐ Pediatrician
   - ☐ GP
   - ☐ Clinical Geneticist
   - ☐ Other: _____

10. Has your child/the person you care for been diagnosed with an intellectual disability, learning disability or global developmental delay?
    - ☐ Yes – **Please indicate the level of disability below**
    - ☐ No – **Please move on to question 11**

    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Profound
    - ☐ Unknown
    - ☐ Other: _____

11. Has your child/the person you care for been diagnosed with autism?
    - ☐ Yes – **Please indicate their diagnosis below**
    - ☐ No – **Please move on to question 12**

    - ☐ Autism
    - ☐ Asperger Syndrome
    - ☐ Autistic Features
    - ☐ Autistic Continuum
    - ☐ Atypical Autism
    - ☐ Autism Spectrum Disorder
    - ☐ High Functioning Autism
    - ☐ Autistic (like) Traits
    - ☐ Pervasive Developmental Disorder
    - ☐ Autistic Spectrum

12. Has your child/the person you care for been diagnosed with ADHD?
    - ☐ Yes
    - ☐ No

13. Which of the following best describes your child/the person you care for's living arrangement?
    - ☐ Lives with caregivers at least 50% of the time
      **Please complete section 2 and then move on to next questionnaire**
    - ☐ Lives away from caregivers at least 50% of the time *(either independently or in a supported setting)*
      **Please complete section 3 and then move on to next questionnaire**

**SECTION 2**

**The following questions are about you and your household:**

1. How would you describe your gender?

   ☐ Male
   ☐ Female
   ☐ Prefer to self-describe as: _____
   *(e.g. non-binary, gender fluid, agender)*
   ☐ Prefer not to say

2. What was your age in years on your last birthday? _____ years

3. Which of the following best describes your ethnic group?

   ☐ White
   ☐ Mixed or multiple ethnic groups
   ☐ Asian or Asian British
   ☐ Black, African, Caribbean, or Black British
   ☐ Not listed: _____

4. Please select the option which best describes your highest level of formal education.

   ☐ No formal education
   ☐ Secondary school, GCSEs or equivalent
   ☐ College, sixth form, A levels or equivalent
   ☐ University, undergraduate degree or equivalent
   ☐ University, postgraduate degree or equivalent
   ☐ Not listed: _____

5. Who else, aside from yourself and your child/the person you care for, lives with you?

| **Relationship to the person you care for** | **Age** | **Gender** |
|---|---|---|
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |

6. Does the person you care for stay overnight away from home? *(Tick all that apply)*

☐ No

☐ Shared custody arrangement — How often? _____

☐ Overnight visits with another relative — How often? _____

☐ Respite Care — How often? _____

☐ Residential School — How often? _____

☐ Not listed:_____ — How often? _____

*Recent data from research with families of children with special needs has shown that a family's financial resources are important in understanding family member's views and experiences. With this in mind, we would be very grateful if you could answer the additional question below. We are not interested in exactly what your family income is, but we would like to be able to look at whether those with high versus lower levels of financial resources have different experiences.*

*7.* How does your total household income compare to the national average? (£29,000 in the UK) Please include a rough estimate of total salaries and other income (including benefits) before tax and national insurance/pensions.
(*If you are responding from outside the UK, please respond according to your national median income.)*

☐ Below the national average
☐ Roughly the same as the national average
☐ Above the national average
☐ Would prefer not to answer

**<u>Please check your answers and move on to the next questionnaire</u>**

**<u>SECTION 3</u>**

**The following questions are about the placement that your child/the person you care for resides in:**

1. What kind of placement does your child/the person you care for reside in?

   _____
   *(e.g. residential school, secure facility, supported living)*

2. Which of the following best categorises the service providing the placement?
   ☐ Learning disability service
   ☐ Autism service

☐ Mental health service
☐ Unsure/don't know
☐ N/A
☐ Other:_____

3. Excluding staff members, approximately how many other people does your child/the person you care for share their lodgings/living space with?

   _____

4. On an average day shift, how many support staff are on shift?

   _____

5. Does your child/the person you care for have an allocated key worker?
   ☐ Yes
   ☐ No

6. How long has your child/the person you care for lived here?
   ☐ Less than a year
   ☐ 1-3 years
   ☐ 3-5 years
   ☐ More than 5 years

7. Does your child/the person you care for have regular visits with their family?
   ☐ Overnight stays at family home
   ☐ Day trips with family *(Either to family home or elsewhere)*
   ☐ Family members visit at placement
   ☐ No/limited contact with family

**Please check your answers and move on to the next questionnaire**

**Appendix 2.2: The Mood, Interest, and Pleasure Questionnaire – Short Form**

**The MIPQ**



**Instructions for completing the MIPQ:**

This questionnaire contains 12 questions – you should complete all 12 questions. Each question will ask for your opinion about particular behaviours, which you have observed in the **last two weeks**. For every question you should tick the most appropriate response.

**1. In the last two weeks, did the person seem…**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| sad all of the time | sad most of the time | sad about half of the time | sad some of the time | never sad |

*Please comment if anything has happened in the last two weeks which you feel might explain sadness if it has been observed (e.g. a bereavement):*

**2. In the last two weeks, how often did you hear positive vocalizations* when the person was engaged in activities*?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| all of the time | most of the time | about half of the time | some of the time | never |

*Positive vocalizations**:** e.g. laughing, giggling, "excited sounds" etc.
*Engaged in activities**:** e.g. when someone is actively involved in any activity such as a mealtime, a social interaction, a self-care task or social outing etc.

**3. In the last two weeks, do you think the facial expression of the person looked "flat" *…**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| all of the time | most of the time | about half of the time | some of the time | never |

*Flat expression: expression seems lifeless; lacks emotional expression; seems unresponsive.

**4. In the last two weeks, would you say the person…**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| cried every day | cried nearly every day | cried 3-4 times each week | cried once or twice each week | cried less than once each week |

**5. In the last two weeks, how interested did the person appear to be in his/her surroundings?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| interested all of the time | interested most of the time | interested about half of the time | interested some of the time | never interested |

**6. In the last two weeks, did the person seem to have been enjoying life…**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| all of the time | most of the time | about half of the time | some of the time | never |

*Please comment if there are any reasons why this person might not have been enjoying him/herself e.g. illness, being in pain, experiencing a loss etc:*

**7. In the last two weeks, would you say the person smiled…**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| at least once every day | at least once nearly every day | 3-4 times each week | once or twice each week | less than once each week |

**8. In the last two weeks, how disinterested did the person appear to be in his/her surroundings?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| disinterested all of the time | disinterested most of the time | disinterested about half of the time | disinterested some of the time | never disinterested |

**9. In the last two weeks, when the person was engaged in activities*, to what extent did his/her facial expressions* suggest that s/he was interested in the activity?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| interested all of the time | interested most of the time | interested about half of the time | interested some of the time | never interested |

*Engaged in activities**:** e.g. when someone is actively involved in any activity such as a mealtime, a social interaction, a self-care task or social outing etc.
*Facial expressions: interest might be indicated by the degree to which the person's gaze is being directed at the person/things involved in an activity.

**10. In the last two weeks, would you say the person…**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| laughed every day | laughed nearly every day | laughed 3-4 times each week | laughed once or twice each week | laughed less than once each week |

**11. In the last two weeks, how often did you see gestures which appeared to demonstrate enjoyment* when the person was engaged in activities*?**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| all of the time | most of the time | about half of the time | some of the time | never |

*Gestures which appear to demonstrate enjoyment: e.g., clapping, waving hands in excitement etc.
*Engaged in activities: i.e., when someone is actively involved in any activity such as a mealtime, social interaction, self-care task or social outing etc.

**12. In the last two weeks, did the person's vocalizations* sound distressed…**

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| all of the time | most of the time | about half of the time | some of the time | never |

*Vocalizations: any words, noises or utterances.

*Please feel free to make any additional comments about the behaviour of the person over the last two weeks (continue overleaf if necessary):*

**Please check your answers and move on to the next questionnaire**

**Appendix 2.3: The Anxiety, Depression and Mood Scale**

**The ADAMS**

*Taken from: Ebensen et al., 2003*

**Instructions**

The ADAMS contains a list of behaviours that can be found among individuals with intellectual disability. Please describe the individual's behaviour over the last 6 months.

0 Behaviour has not occurred, or is not a problem
1 Behaviour occurs occasionally, or is a mild problem
2 Behaviour occurs quite often, or is a moderate problem
3 Behaviour occurs a lot, or is a severe problem

| | | Not a problem | Mild problem | Moderate problem | Severe problem |
|---|---|---|---|---|---|
| 1. | Nervous……. | 0 | 1 | 2 | 3 |
| 2. | Problems initiating communication…… | 0 | 1 | 2 | 3 |
| 3. | Does not relax or settle down…… | 0 | 1 | 2 | 3 |
| 4. | Has periods of over-activity…… | 0 | 1 | 2 | 3 |
| 5. | Sleeps more than normal…… | 0 | 1 | 2 | 3 |
| 6. | Withdraws from other people……. | 0 | 1 | 2 | 3 |
| 7. | Tense…… | 0 | 1 | 2 | 3 |
| 8. | Engages in ritualistic behaviours……... | 0 | 1 | 2 | 3 |
| 9. | Depressed mood…….. | 0 | 1 | 2 | 3 |
| 10. | Sad……. | 0 | 1 | 2 | 3 |
| 11. | Worried…… | 0 | 1 | 2 | 3 |
| 12. | Has developed difficulty staying on task or completing work……... | 0 | 1 | 2 | 3 |
| 13. | Shy……. | 0 | 1 | 2 | 3 |
| 14. | Easily fatigued (not due to being overweight)…..…… | 0 | 1 | 2 | 3 |

| | | | | | |
|---|---|---|---|---|---|
| 15. | Anxious…… ……. | 0 | 1 | 2 | 3 |
| 16. | Repeatedly checks items…… | 0 | 1 | 2 | 3 |
| 17. | Easily Distracted…….. | 0 | 1 | 2 | 3 |
| 18. | Lacks energy…… | 0 | 1 | 2 | 3 |
| 19. | Avoids others, spends much of time alone…….. | 0 | 1 | 2 | 3 |
| 20. | Easily upset if ritualistic behaviours are interrupted... | 0 | 1 | 2 | 3 |
| 21. | Lacks emotional facial expressions…….. | 0 | 1 | 2 | 3 |
| 22. | Has shown difficulty in starting routine tasks…….. | 0 | 1 | 2 | 3 |
| 23. | Listless…… …... | 0 | 1 | 2 | 3 |
| 24. | Experiences panic attacks…….. | 0 | 1 | 2 | 3 |
| 25. | Avoids eye contact…….. | 0 | 1 | 2 | 3 |
| 26. | Trembles when frightening situations are not present…… …... | 0 | 1 | 2 | 3 |
| 27. | Avoids peers……. | 0 | 1 | 2 | 3 |
| 28. | Tearful.…… ….. | 0 | 1 | 2 | 3 |

**Appendix 2.4: The Wessex Questionnaire**

**The Wessex Questionnaire**

*© Albert Kushlick, Psychological Medicine*

Please provide the following information for your child/the person you care for. It is important that you respond to every item. Please tick the most appropriate response.

| | | | |
|---|---|---|---|
| A) Wetting (nights) | ☐ 1. Frequently | ☐ 2. Occasionally | ☐ 3. Never |
| B) Soiling (nights) | ☐ 1. Frequently | ☐ 2. Occasionally | ☐ 3. Never |
| C) Wetting (days) | ☐ 1. Frequently | ☐ 2. Occasionally | ☐ 3. Never |
| D) Soiling (days) | ☐ 1. Frequently | ☐ 2. Occasionally | ☐ 3. Never |
| E) Walk with help* | ☐ 1. Not at all | ☐ 2. Not upstairs | ☐ 3. Upstairs & elsewhere |
| | ***note**: if this person walks by himself/herself upstairs and elsewhere, please also tick '3. Upstairs and elsewhere' for 'Walk with help'* | | |
| F) Walk by himself | ☐ 1. Not at all | ☐ 2. Not upstairs | ☐ 3. Upstairs & elsewhere |
| G) Feed himself | ☐ 1. Not at all | ☐ 2. With help | ☐ 3. Without help |
| H) Wash himself | ☐ 1. Not at all | ☐ 2. With help | ☐ 3. Without help |
| I) Dress himself | ☐ 1. Not at all | ☐ 2. With help | ☐ 3. Without help |
| J) Vision | ☐ 1. Blind or almost | ☐ 2. Poor | ☐ 3. Normal |
| K) Hearing | ☐ 1. Deaf or almost | ☐ 2. Poor | ☐ 3. Normal |

| | | | | |
|---|---|---|---|---|
| L) Speech | ☐ 1. Never a word | ☐ 2. Odd words only | ☐ 3. Sentences & normal | ☐ 4. Can talk but doesn't |

If this person talks in sentences, is his/her speech:

☐ 1. Difficult to understand even by acquaintances, impossible for strangers?
☐ 2. Easily understood for acquaintances, difficult for strangers?
☐ 3. Clear enough to be understood by anyone?

| | | | |
|---|---|---|---|
| M) Reads | ☐ 1. Nothing | ☐ 2. A Little | ☐ 3. Newspapers and/or books |
| N) Writes | ☐ 1. Nothing | ☐ 2. A Little | ☐ 3. Own correspondence |
| O) Counts | ☐ 1. Nothing | ☐ 2. A Little | ☐ 3. Understands money values |

## Appendix 2.5: The Health Questionnaire

### The Health Questionnaire



**PART A: Instructions**

- Have these problems **EVER** affected your child or the person you care for?
- Please rate as **0** if the problem has never affected the person you care for, **1** if it has been a mild problem, **2** if the problem has been moderately serious, or **3** if the problem has been severe.
- If the person you care for has had these problems, please state whether any treatment has been implemented by circling **yes** or **no.**

| | Never | Mild | Moderate | Severe |
|---|---|---|---|---|
| 1a. Eye problems (e.g. glaucoma / blocked tear duct/s) | **0** | **1** | **2** | **3** |
| 1b. Corrective surgery /medication / treatment | | **Yes / No** | | |
| 2a. Ear problems (e.g. infection, glue ear) | **0** | **1** | **2** | **3** |
| 2b. Corrective surgery / medication / treatment (e.g. grommets) | | **Yes / No** | | |
| 3a. Dental problems (e.g. toothache/gum problems/mouth ulcers/delayed eruption of teeth) | **0** | **1** | **2** | **3** |
| 3b. Dental surgery / treatment (e.g. teeth removal) | | **Yes / No** | | |
| 4a. Cleft Palate | **0** | **1** | **2** | **3** |
| 4b. Repaired | | **Yes / No** | | |
| 5a. Gastrointestinal Difficulties (e.g. reflux / stomach problems) | **0** | **1** | **2** | **3** |
| 5b. Corrective surgery / medication / treatment (e.g. Nissen fundoplication) | | **Yes / No** | | |
| 6a. Bowel Problems (e.g. obstruction) | **0** | **1** | **2** | **3** |
| 6b. Corrective surgery / treatment | | **Yes / No** | | |
| 7a. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur) | **0** | **1** | **2** | **3** |
| 7b. Corrective surgery / medication / treatment | | **Yes / No** | | |
| 8a. Problems with Genitalia (e.g. prostate/ testicular problems i.e. undescended testes) | **0** | **1** | **2** | **3** |
| 8b. Corrective surgery / treatment | | **Yes / No** | | |
| 9a. Hernia (e.g. inguinal or hiatal) | **0** | **1** | **2** | **3** |
| 9b. Repair / treatment | | **Yes / No** | | |
| 10a. Limb Abnormalities (e.g. malformed arm) | **0** | **1** | **2** | **3** |
| 11a. Epilepsy / Seizures / Neurological Referrals | **0** | **1** | **2** | **3** |
| 11b. Medication | | **Yes / No** | | |
| 12a. Lung or Respiratory Problems (asthma/bronchitis) | **0** | **1** | **2** | **3** |
| 12b. Corrective surgery / medication / treatment | | **Yes / No** | | |
| 13a. Liver or Kidney Problems | **0** | **1** | **2** | **3** |
| 13b. Corrective surgery / medication / treatment | | **Yes / No** | | |
| 14a. Diabetes or Thyroid Function Problems | **0** | **1** | **2** | **3** |
| 14b. Corrective surgery / medication / treatment | | **Yes / No** | | |
| 15a. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin) | **0** | **1** | **2** | **3** |
| 15b. Medication / treatment | | **Yes / No** | | |
| 16a. Other *(please specify problem, severity from 0-3):* _____ | **0** | **1** | **2** | **3** |
| 16b. Corrective surgery / medication / treatment | | **Yes / No** | | |

**PART B: Instructions**

- Have these medical problems affected the person you care for in the **PAST MONTH**?

| Please rate as **0** if your child has not been affected by this problem in the past month, **1** if they have been mildly affected, **2** if the problem has moderately affected your child and **3** if your child has been severely affected by the problem. | Never | Mild | Moderate | Severe |
|---|---|---|---|---|
| 1. Eye problems (e.g., glaucoma / blocked tear duct/s) | **0** | **1** | **2** | **3** |
| 2. Ear problems (e.g., infection, glue ear) | **0** | **1** | **2** | **3** |
| 3. Dental problems (e.g. toothache/gum problems/mouth ulcers/delayed eruption of teeth) | **0** | **1** | **2** | **3** |
| 4. Cleft Palate | **0** | **1** | **2** | **3** |
| 5. Gastrointestinal Difficulties (e.g. reflux / stomach problems) | **0** | **1** | **2** | **3** |
| 6. Bowel Problems (e.g. obstruction) | **0** | **1** | **2** | **3** |
| 7. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur) | **0** | **1** | **2** | **3** |
| 8. Problems with Genitalia (e.g. prostate/ testicular problems i.e. undescended testes) | **0** | **1** | **2** | **3** |
| 9. Hernia (e.g. inguinal or hiatal) | **0** | **1** | **2** | **3** |
| 10. Limb Abnormalities (e.g. malformed arm) | **0** | **1** | **2** | **3** |
| 11. Epilepsy / Seizures / Neurological Referrals | **0** | **1** | **2** | **3** |
| 12. Lung or Respiratory Problems (asthma/bronchitis) | **0** | **1** | **2** | **3** |
| 13. Liver or Kidney Problems | **0** | **1** | **2** | **3** |
| 14. Diabetes or Thyroid Function Problems | **0** | **1** | **2** | **3** |
| 15. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin) | **0** | **1** | **2** | **3** |
| 16. Other *(please specify problem, severity from 0-3):* _____ | **0** | **1** | **2** | **3** |

**Appendix 2.6: Sensory Experiences Questionnaire**

## The SEQ

*Version 2.1 © 1999 Grace T. Baranek, Ph.D., OTR/L*

**Directions:** The following are some brief questions about how your child/the person you care for uses his/her senses (for example hearing, vision, touch etc.) to experience the world. No two people are alike. This questionnaire asks about behaviours that make your child/the person you care for unique. Consider their usual responses to these situations or activities. The questions ask **how often they respond or behave in a certain way.** Check the box that fits best (almost never, once in a while, sometimes, frequently, almost always). Answer all questions completely.

**Experiences with Sound:**

| | | | | |
|---|---|---|---|---|
| Does your child react sensitively or startle easily to unexpected or loud sounds? (For example, covers ears when hearing a vacuum, baby cry, door close etc.) | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |
| Does your child enjoy listening to music? | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |
| Does your child ignore you when you call his/her name? | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |
| Does your child seem to ignore or tune-out loud noises? (For example, no reaction when alarms go off, vacuum turns on or objects fall to the floor). | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |
| Does your child notice sounds in the environments (such as planes, trains, faucets, dripping, lights buzzing etc.) before other people do? | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |
| Does your child show distress (startles, covers ears etc.) during loud conversations or singing? | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |

**Experiences with Sight:**

| | | | | |
|---|---|---|---|---|
| Does your child enjoy looking at picture books? | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |
| Is your child disturbed by too much light inside or brightness outside? | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |
| Does your child stare at lights or objects that spin or move? | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |
| Is your child slow to notice new objects or toys in the room, or slow to look at objects that are placed or held near him/her? | | | | |
| *Almost Never* ☐ | *Once in a While* ☐ | *Sometimes* ☐ | *Frequently* ☐ | *Almost Always* ☐ |

Does your child avoid looking at your face during social games/play?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child seem to ignore *(doesn't notice)* when someone new or differ enters the room

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child enjoy watching children's videos or TV programs?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

**Experiences with Touch:**

Does your child dislike cuddling or being held?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child show distress during grooming (For example, cries or fusses during face washing, hair combing, fingernail cutting or teeth brushing)?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child avoid touching certain textures (such as fuzzy or squishy toys) or playing with messy materials (such as sand, lotion)?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child react negatively or pull away when toucher by a person? (For example, pulls away when head is patted).

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child have trouble adjusting to the water temperature during bath time or does she/he dislike being in water?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child seem slow to react to pain (For example, he/she isn't bothered by bumps, scrapes, cuts or falls)?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child dislike being tickled?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child ignore (doesn't notice) when you tap him/her on the shoulder for attention?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

**Experiences with Taste or Smell:**

Does your child refuse to try new foods or avoid certain tastes, smells or textures *(consistencies)* of food?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child smell objects or toys during play or other activities?

*Almost Never* ☐ *Once in a While* ☐ *Sometimes* ☐ *Frequently* ☐ *Almost Always* ☐

Does your child seem interested in the way people smell *(For example, smells hair, breath)*?

| *Almost Never* | *Once in a While* | *Sometimes* | *Frequently* | *Almost Always* |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Does your child put objects, toys or other non-food items in his/her mouth to lick, suck or explore?

| *Almost Never* | *Once in a While* | *Sometimes* | *Frequently* | *Almost Always* |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**Experiences with Movement:**

Does your child enjoy riding in a car?

| *Almost Never* | *Once in a While* | *Sometimes* | *Frequently* | *Almost Always* |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Does your child like to jump up/down, rock back/forth or spin in circles?

| *Almost Never* | *Once in a While* | *Sometimes* | *Frequently* | *Almost Always* |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Does your child seek out physical rough-housing play *(For example, craves being tossed in the air or spun around)*?

| *Almost Never* | *Once in a While* | *Sometimes* | *Frequently* | *Almost Always* |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Does your child seem uneasy or become dizzy when moving on a swing or rocking chair?

| *Almost Never* | *Once in a While* | *Sometimes* | *Frequently* | *Almost Always* |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

Does your child flap his/her arms or hands repeatedly, particularly when excited?

| *Almost Never* | *Once in a While* | *Sometimes* | *Frequently* | *Almost Always* |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

List any other comments you would like to make about your child's preferred experiences or avoidances/sensitivities to sound, sight, touch, smell, taste or movement.

_____

_____

_____

_____

_____

_____

**<u>Please check your answers and move on to the next questionnaire</u>**

**Appendix 2.7: Social Communication Questionnaire - Current Version**

SCQ is omitted due to copyright.

**Appendix 2.8: Child Sleep Habits Questionnaire**

*The following questionnaire was designed to assess sleep in children. As such we acknowledge that some of the wording and the questions asked might not feel like they apply to teen or adult participants. However it is important that information is collected on these questions across the entire lifespan so we would ask that you still complete the following questions even if some of them might not feel like the best fit.*
*If a question really does not apply to the person you care for (e.g. sleeping in parent/sibling's bed for an adult who lives away from the family home), select 'Rarely' for the frequency, and 'N/A' for whether it is a problem.*

## The CSHQ

*Taken from: Owens, Spirito & McGuinn (2000)*

The following statements are about your child's sleep habits and possible difficulties with sleep. Think about the past week in your child's life when answering the questions. If last week was unusual for a specific reason (such as your child had an ear infection and did not sleep well or the TV set was broken), choose the most recent typical week. Answer USUALLY if something occurs 5 or more times in a week; answer SOMETIMES if it occurs 2-4 times in a week; answer RARELY if something occurs never or 1 time during a week. Also, please indicate whether or not the sleep habit is a problem by circling "Yes," "No," or "Not applicable (N/A)"

**Bedtime**

Write in child's bedtime: _____

| | 3 Usually (5-7) | 2 Sometimes (2-4) | 1 Rarely (0-1) | Problem? | | |
|---|---|---|---|---|---|---|
| 1. Child goes to bed at the same time at night | ☐ | ☐ | ☐ | Yes | No | N/A |
| 2. Child falls asleep within 20 minutes after going to bed | ☐ | ☐ | ☐ | Yes | No | N/A |
| 3. Child falls asleep alone in own bed | ☐ | ☐ | ☐ | Yes | No | N/A |
| 4. Child falls asleep in parents or sibling's bed | ☐ | ☐ | ☐ | Yes | No | N/A |
| 5. Child needs parent in the room to fall asleep | ☐ | ☐ | ☐ | Yes | No | N/A |
| 6. Child struggles at bedtime (cries, refuses to stay in bed, etc.) | ☐ | ☐ | ☐ | Yes | No | N/A |
| 7. Child is afraid of sleeping in the dark | ☐ | ☐ | ☐ | Yes | No | N/A |
| 8. Child is afraid of sleeping alone | ☐ | ☐ | ☐ | Yes | No | N/A |

**Sleep Behaviour**

Child's usual amount of sleep each day: _____ hours and _____ minutes
(combining night-time sleep and naps)

| | 3 Usually (5-7) | 2 Sometimes (2-4) | 1 Rarely (0-1) | Problem? | | |
|---|---|---|---|---|---|---|
| 9. Child sleeps too little | ☐ | ☐ | ☐ | Yes | No | N/A |
| 10. Child sleep the right amount | ☐ | ☐ | ☐ | Yes | No | N/A |
| 11. Child sleeps about the same amount each day | ☐ | ☐ | ☐ | Yes | No | N/A |

| | | | | | | |
|---|---|---|---|---|---|---|
| 12. Child wets the bed at night | ☐ | ☐ | ☐ | Yes | No | N/A |
| 13. Child talks during sleep | ☐ | ☐ | ☐ | Yes | No | N/A |
| 14. Child is restless and moves a lot during sleep | ☐ | ☐ | ☐ | Yes | No | N/A |
| 15. Child sleepwalks during the night | ☐ | ☐ | ☐ | Yes | No | N/A |
| 16. Child moves to someone else's bed during the night (parent, brother, sister, etc.) | ☐ | ☐ | ☐ | Yes | No | N/A |

| | **3 Usually (5-7)** | **2 Sometimes (2-4)** | **1 Rarely (0-1)** | **Problem?** | | |
|---|---|---|---|---|---|---|
| 17. Child grinds teeth during sleep (your dentist may have told you this) | ☐ | ☐ | ☐ | Yes | No | N/A |
| 18. Child snores loudly | ☐ | ☐ | ☐ | Yes | No | N/A |
| 19. Child seems to stop breathing during sleep | ☐ | ☐ | ☐ | Yes | No | N/A |
| 20. Child snorts and/or gasps during sleep | ☐ | ☐ | ☐ | Yes | No | N/A |
| 21. Child has trouble sleep away from home (visiting relatives, vacation) | ☐ | ☐ | ☐ | Yes | No | N/A |
| 22. Child awakens during night screaming, sweating and inconsolable | ☐ | ☐ | ☐ | Yes | No | N/A |
| 23. Child awakens alarmed by a frightening dream | ☐ | ☐ | ☐ | Yes | No | N/A |

**Waking During the Night**

| | **3 Usually (5-7)** | **2 Sometimes (2-4)** | **1 Rarely (0-1)** | **Problem?** | | |
|---|---|---|---|---|---|---|
| 24. Child awakes once during the night | ☐ | ☐ | ☐ | Yes | No | N/A |
| 25. Child awakes more than once during the night | ☐ | ☐ | ☐ | Yes | No | N/A |

Write the number of minutes a night waking usually lasts: _____

**Morning Waking/Daytime Sleepiness**

Write in the time-of-day child usually wakes in the morning: _____

| | **3 Usually (5-7)** | **2 Sometimes (2-4)** | **1 Rarely (0-1)** | **Problem?** | | |
|---|---|---|---|---|---|---|
| 26. Child wake up by him/herself | ☐ | ☐ | ☐ | Yes | No | N/A |
| 27. Child wakes up in negative mood | ☐ | ☐ | ☐ | Yes | No | N/A |
| 28. Adults or siblings wake up child | ☐ | ☐ | ☐ | Yes | No | N/A |

| | | | | | | |
|---|---|---|---|---|---|---|
| 29. Child has difficulty getting out of bed in the morning | ☐ | ☐ | ☐ | Yes | No | N/A |
| 30. Child takes a long time to become alert in the morning | ☐ | ☐ | ☐ | Yes | No | N/A |
| 31. Child seems tired | ☐ | ☐ | ☐ | Yes | No | N/A |

Child has appeared very sleep or fallen asleep during the following (check all that apply):

| | **1 Not sleepy** | **2 Very Sleepy** | **3 Falls Asleep** |
|---|---|---|---|
| 32. Watching TV | ☐ | ☐ | ☐ |
| 33. Riding in car | ☐ | ☐ | ☐ |

**Please check your answers and move on to the next questionnaire**

## Appendix 3: Supplementary tables for the meta-analysis

### Appendix 3.1: Search terms for the scoping search

| No. | Search | Search terms | Results |
|---|---|---|---|
| 1 | Intellectual disability | (mental deficiency or mental retardation or intellectual disabilit* or intellectual difficult* or intellectual impairment or developmental delay or learning disabil*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx, tc, id, tm] | 345,067 |
| 2 | Depression | (depress* or low mood or affective disorder or low affect or negative affect or flat affect or dysthym* or depressed affect or anhedonia).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx, tc, id, tm] | 2,070,778 |
| 3 | Syndrome | (syndrom* or gene* or geno*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx, tc, id, tm] | 21,656,008 |
| 4 | | 1 and 2 and 3 | 7,657 |
| 5 | | limit 4 to the last 5 years | 2,458 |

**Appendix 3.2: Quality rating framework (adapted from Agar et al., 2021; Edwards et al., 2022; Royston et al., 2017).**

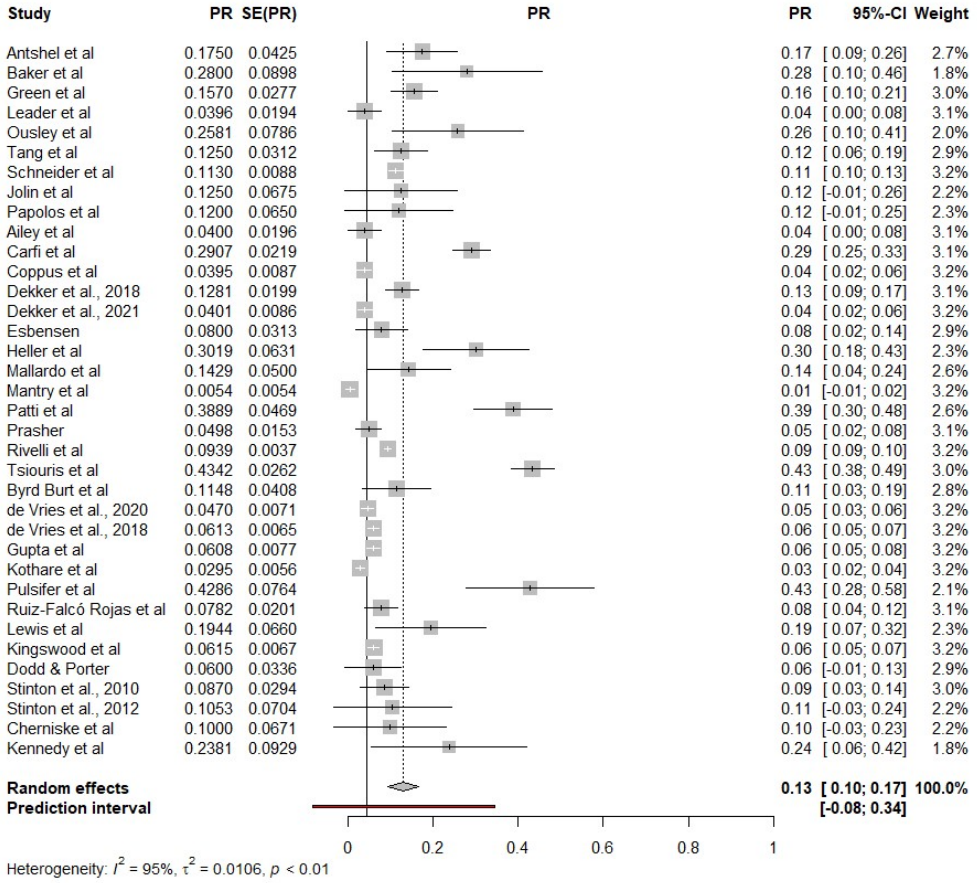
| | 0 – Poor | 1 – Adequate | 2 – Good | 3 – Excellent |
|---|---|---|---|---|
| **Sample Identification**[1] | Not specified/reported | Single restricted or non-random sample (e.g., specialist clinic or previous research study)<br><br>Single regional sample e.g., a regional parent support groups | Multiple restricted or non-random samples (multi-region specialist clinics)<br><br>National non-random sampling e.g., national parent support groups | Random or total population sample |
| **Confirmation of syndrome**[2] | Not confirmed/reported<br><br>Clinical diagnosis only suspected | Clinical diagnosis by 'generalist' e.g., General Practitioner or Paediatrician<br><br>Parent confirmation of genetic diagnosis (e.g. through a questionnaire) | Clinical diagnosis by 'expert' e.g., Clinical Geneticist or Specialist Paediatrician | Genetic confirmation of diagnosis/ fluorescence in situ hybridization (FISH) tested |
| **Depression diagnosis** | Not specified/reported<br><br>Clinician judgement only<br><br>Parent report only<br><br>Report of chart review only | Informant report/ self-report instrument e.g., DBC-A<br><br>Screening instrument e.g., PAS-ADD, CDI, HADS, DRS<br><br>Clinician judgement against specified diagnostic criteria e.g., DSM-IV or ICD-10 | Diagnostic instrument/ interviews e.g., K-SADS, ADIS, SCID, CAPA, SCAN, DICA, ChIPS. PPS-LD, PIMRA | Consensus from multiple assessments, including at least one diagnostic instrument |

*Note.* Developmental Behavioural Checklist-Adults (DBC-A), Psychiatric Assessment Schedule for Adults with Developmental Disabilities (PAS-ADD), Children's Depression Inventory (CDI), Hospital Anxiety and Depression Scale (HADS), Depression Rating Scale (DRS), Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), Anxiety Disorders Interview Schedule (ADIS), Structured Clinical Interview for axis I DSM-IV (SCID), Child and Adolescent Psychiatric Assessment (CAPA), Schedules for Clinical Assessment in Neuropsychiatry (SCAN), Diagnostic Interview for Children and Adolescents (DICA), Children's Interview for Psychiatric Syndromes (ChIPS), Present Psychiatric State for Adults with Learning Disabilities (PPS-LD), Psychopathology Instrument for Mentally Retarded Adults (PIMRA).

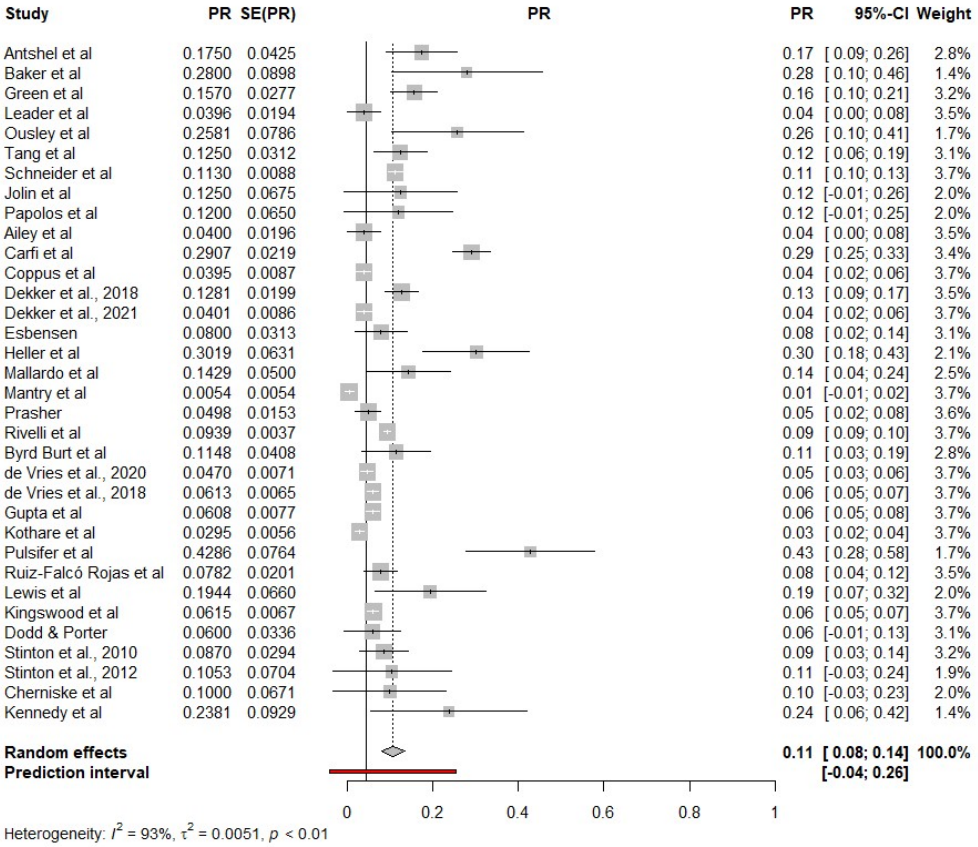
[1]For papers that stated people were recruited as part of a larger ongoing study, if the study reported how people were recruited, the sample identification was coded. If no further information was included, the paper was rated a 1.
[2]Studies were scored based on whether the syndrome was confirmed for all participants by the described method e.g. if genetic confirmation was not tested or reported for 100% of the sample, the paper received a rating of 2.

## Appendix 4: Supplementary figures for the meta-analysis

### Appendix 4.1: Forest plot all syndromes before "leave-one-out" analysis

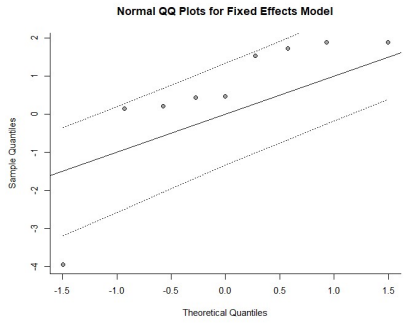


## Appendix 4.2: Forest plot all syndromes after "leave-one-out" analysis

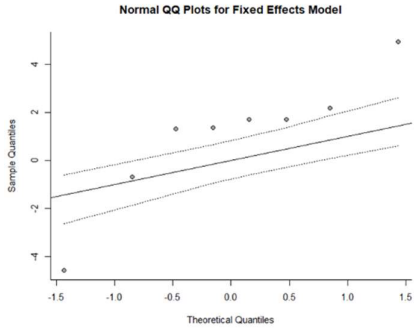


**Appendix 4.3: Fixed effects model**

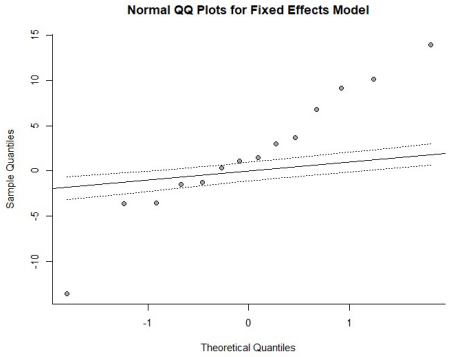
22q11.2 deletion syndrome



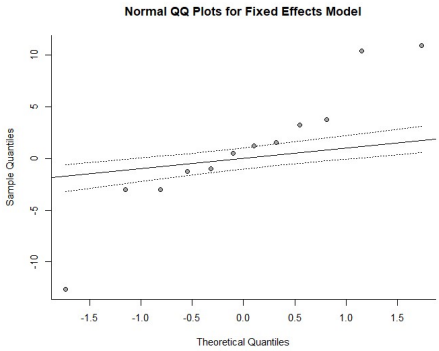

tuberous sclerosis complex



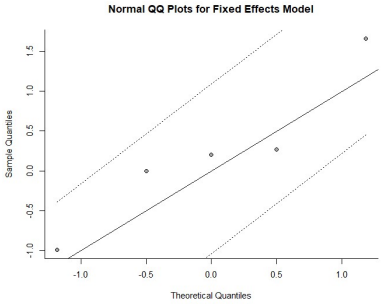

Down syndrome (before “leave-one-out”)



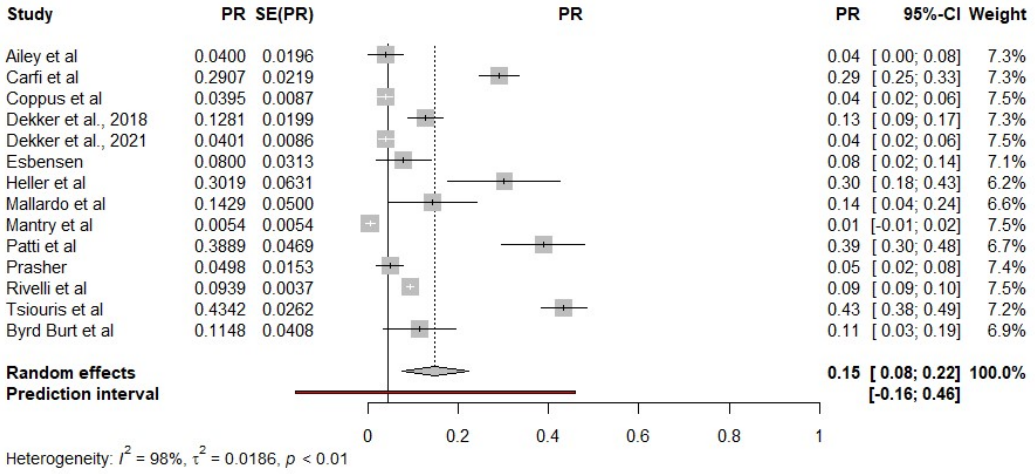

Down Syndrome (after “leave-one-out”)




Williams syndrome

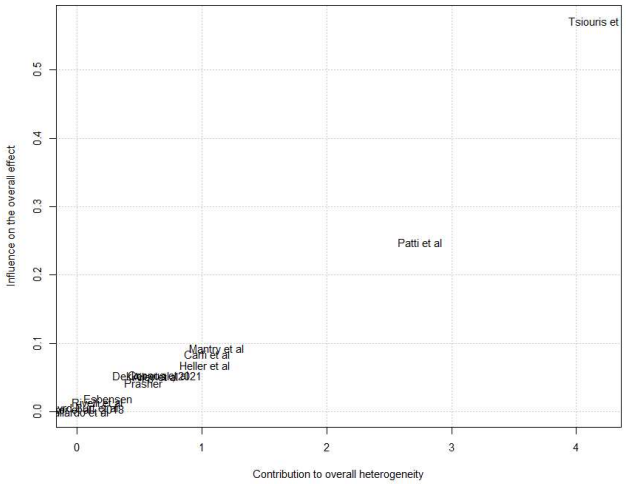


**Appendix 4.4: Forest plot for Down syndrome before the "leave-one-out" analysis**

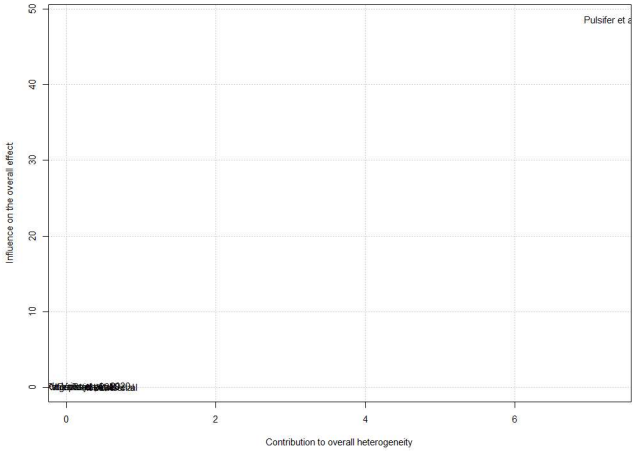


## Appendix 4.5: Baujat plots

Down syndrome




Tuberous sclerosis complex



## Appendix 5: Supplementary tables for the empirical research study

### Appendix 5.1: Kruskal Wallis tests showing group differences between variables

| | Age (year) | Age (months) | MIPQ-S total | ADAMS mood | SEQ | CSHQ | Wessex | HQ | SCQ |
|---|---|---|---|---|---|---|---|---|---|
| Kruskal-Wallis H | 5.399 | 5.357 | 1.153 | .052 | 4.479 | 6.037 | 10.720 | 31.175 | .546 |
| df | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Asymp. Sig. | .067 | .069 | .562 | .974 | .107 | .049 | .005 | <.001 | .761 |

**Appendix 5.2: Mann Whitney tests for gender differences on low mood scores**

| | | Mann-Whitney U | *p* value |
|---|---|---|---|
| **CdLS** | | | |
| | MIPQ-S total scores | 169.5 | .964 |
| | ADAMS mood subscale | 107 | .813 |
| **RTS** | | | |
| | MIPQ-S total scores | 219 | .719 |
| | ADAMS mood subscale | 193 | .890 |

**Appendix 5.3: Spearman's rho correlation analyses for CdLS**

| | | MIPQ-S total | ADAMS mood | Age (months) | Wessex | HQ | SEQ | CSHQ | SCQ |
|---|---|---|---|---|---|---|---|---|---|
| MIPQ-S total score | Correlation Coefficient | 1.000 | -.556*** | -.053 | .252 | -.134 | -.586*** | -.497** | -.543*** |
| | Sig. (2-tailed) | . | .001 | .756 | .150 | .442 | <.001 | .003 | <.001 |
| | N | 37 | 30 | 37 | 34 | 35 | 33 | 33 | 35 |
| ADAMS mood subscale | Correlation Coefficient | -.556*** | 1.000 | .287 | .303 | -.004 | .251 | .510** | .224 |
| | Sig. (2-tailed) | .001 | . | .124 | .103 | .985 | .181 | .004 | .234 |
| | N | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Age (months) | Correlation Coefficient | -.053 | .287 | 1.000 | .440** | .179 | -.369* | .032 | -.257 |
| | Sig. (2-tailed) | .756 | .124 | . | .009 | .303 | .034 | .860 | .136 |
| | N | 37 | 30 | 37 | 34 | 35 | 33 | 33 | 35 |
| Adaptive ability (Wessex) | Correlation Coefficient | .252 | .303 | .440** | 1.000 | -.344 | -.457** | .011 | -.470** |
| | Sig. (2-tailed) | .150 | .103 | .009 | . | .054 | .009 | .952 | .005 |
| | N | 34 | 30 | 34 | 34 | 32 | 32 | 32 | 34 |
| Current health difficulties (HQ) | Correlation Coefficient | -.134 | -.004 | .179 | -.344 | 1.000 | .038 | -.037 | .028 |
| | Sig. (2-tailed) | .442 | .985 | .303 | .054 | . | .834 | .840 | .875 |
| | N | 35 | 30 | 35 | 32 | 35 | 33 | 33 | 33 |
| Sensory processing differences (SEQ) | Correlation Coefficient | -.586*** | .251 | -.369* | -.457** | .038 | 1.000 | .513** | .726*** |
| | Sig. (2-tailed) | <.001 | .181 | .034 | .009 | .834 | . | .002 | <.001 |
| | N | 33 | 30 | 33 | 32 | 33 | 33 | 33 | 33 |
| Sleep difficulties (CSHQ) | Correlation Coefficient | -.497** | .510** | .032 | .011 | -.037 | .513** | 1.000 | .398* |
| | Sig. (2-tailed) | .003 | .004 | .860 | .952 | .840 | .002 | . | .022 |
| | N | 33 | 30 | 33 | 32 | 33 | 33 | 33 | 33 |
| | Correlation Coefficient | -.543*** | .224 | -.257 | -.470** | .028 | .726*** | .398* | 1.000 |
| | Sig. (2-tailed) | <.001 | .234 | .136 | .005 | .875 | <.001 | .022 | . |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Autism characteristic (SCQ) | N | 35 | 30 | 35 | 34 | 33 | 33 | 33 | 35 |

*Note.* *** significant at $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

**Appendix 5.4: Spearman's rho correlations for FXS**

| | | MIPQ-S total | ADAMS mood | Age (months) | Wessex | HQ | SEQ | CSHQ | SCQ |
|---|---|---|---|---|---|---|---|---|---|
| MIPQ-S total score | Correlation Coefficient | 1.000 | -.542*** | -.010 | .188 | -.119 | -.343* | .489*** | 414** |
| | Sig. (2-tailed) | . | <.001 | .940 | .150 | .382 | .012 | <.001 | .002 |
| | N | 60 | 50 | 59 | 60 | 56 | 53 | 56 | 54 |
| ADAMS mood subscale | Correlation Coefficient | -.542*** | 1.000 | -.073 | -.065 | .249 | .419** | .409** | .262 |
| | Sig. (2-tailed) | <.001 | . | .617 | .656 | .081 | .002 | .003 | .069 |
| | N | 50 | 50 | 49 | 50 | 50 | 50 | 49 | 49 |
| Age (months) | Correlation Coefficient | -.010 | -.073 | 1.000 | .448*** | -.045 | -.274* | -.345** | -.062 |
| | Sig. (2-tailed) | .940 | .617 | . | <.001 | .746 | .049 | .010 | .654 |
| | N | 59 | 49 | 59 | 59 | 55 | 52 | 55 | 54 |
| Adaptive ability | Correlation Coefficient | .188 | -.065 | .448*** | 1.000 | -.057 | -.460*** | -.410** | 417** |
| | Sig. (2-tailed) | .150 | .656 | <.001 | . | .675 | <.001 | .002 | .002 |
| | N | 60 | 50 | 59 | 60 | 56 | 53 | 56 | 54 |
| Current health difficulties (HQ) | Correlation Coefficient | -.119 | .249 | -.045 | -.057 | 1.000 | .058 | .234 | .115 |
| | Sig. (2-tailed) | .382 | .081 | .746 | .675 | . | .678 | .088 | .417 |
| | N | 56 | 50 | 55 | 56 | 56 | 53 | 54 | 52 |
| Sensory processing differences (SEQ) | Correlation Coefficient | -.343* | .419** | -.274* | -.460*** | .058 | 1.000 | .529** | .563*** |
| | Sig. (2-tailed) | .012 | .002 | .049 | <.001 | .678 | . | <.001 | <.001 |
| | N | 53 | 50 | 52 | 53 | 53 | 53 | 51 | 51 |
| Sleep difficulties (CSHQ) | Correlation Coefficient | -.489*** | .409** | -.345** | -.410** | .234 | .529*** | 1.000 | .276* |
| | Sig. (2-tailed) | <.001 | .003 | .010 | .002 | .088 | <.001 | . | .048 |
| | N | 56 | 49 | 55 | 56 | 54 | 51 | 56 | 52 |
| | Correlation Coefficient | -.414** | .262 | -.062 | -.417** | .115 | .563*** | .276* | 1.000 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Autism characteristics (SCQ) | Sig. (2-tailed) | .002 | .069 | .654 | .002 | .417 | <.001 | .048 | . |
| | N | 54 | 49 | 54 | 54 | 52 | 51 | 52 | 54 |

*Note.* *** significant at $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

**Appendix 5.5: Spearman's rho correlation analyses for RTS**

| | | MIPQ-S total | ADAMS mood | Age (months) | Wessex | HQ | SEQ | CSHQ | SCQ |
|---|---|---|---|---|---|---|---|---|---|
| MIPQ-S total score | Correlation Coefficient | 1.000 | -.442** | -.190 | -.097 | -.263 | -.253 | -.181 | -.271 |
| | Sig. (2-tailed) | . | .004 | .217 | .534 | .085 | .097 | .244 | .075 |
| | N | 44 | 40 | 44 | 43 | 44 | 44 | 43 | 44 |
| ADAM mood subscale | Correlation Coefficient | -.442** | 1.000 | .081 | -.008 | .510*** | .391* | .010 | .087 |
| | Sig. (2-tailed) | .004 | . | .619 | .961 | <.001 | .013 | .950 | .595 |
| | N | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Age (months) | Correlation Coefficient | -.190 | .081 | 1.000 | .257 | -.136 | -.408** | -.192 | .049 |
| | Sig. (2-tailed) | .217 | .619 | . | .097 | .378 | .006 | .217 | .754 |
| | N | 44 | 40 | 44 | 43 | 44 | 44 | 43 | 44 |
| Adaptive ability (Wessex) | Correlation Coefficient | -.097 | -.008 | .257 | 1.000 | -.305* | -.288 | -.305* | -.305* |
| | Sig. (2-tailed) | .534 | .961 | .097 | . | .047 | .061 | .050 | .046 |
| | N | 43 | 40 | 43 | 43 | 43 | 43 | 42 | 43 |
| Current health difficulties (HQ) | Correlation Coefficient | -.263 | .510*** | -.136 | -.305* | 1.000 | .295 | .216 | .264 |
| | Sig. (2-tailed) | .085 | <.001 | .378 | .047 | . | .052 | .165 | .083 |
| | N | 44 | 40 | 44 | 43 | 44 | 44 | 43 | 44 |
| Sensory processing differences (SEQ) | Correlation Coefficient | -.253 | .391* | -.408** | -.288 | .295 | 1.000 | .386* | .516*** |
| | Sig. (2-tailed) | .097 | .013 | .006 | .061 | .052 | . | .011 | <.001 |
| | N | 44 | 40 | 44 | 43 | 44 | 44 | 43 | 44 |
| Sleep difficulties (CSHQ) | Correlation Coefficient | -.181 | .010 | -.192 | -.305* | .216 | .386* | 1.000 | .312* |
| | Sig. (2-tailed) | .244 | .950 | .217 | .050 | .165 | .011 | . | .041 |
| | N | 43 | 40 | 43 | 42 | 43 | 43 | 43 | 43 |
| | Correlation Coefficient | -.271 | .087 | .049 | -.305* | .264 | .516*** | .312* | 1.000 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Autism characteristics (SCQ) | Sig. (2-tailed) | .075 | .595 | .754 | .046 | .083 | <.001 | .041 | . |
| | N | 44 | 40 | 44 | 43 | 44 | 44 | 43 | 44 |

*Note.* *** significant at $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

**Appendix 5.6: Multiple regression models showing the influence of each predictor on each outcome variable.**

| | MIPQ-S total scores | | | | ADAMS depressed mood subscale square root | | | |
|---|---|---|---|---|---|---|---|---|
| | Unstandardised B | Standardised Coefficients Beta | t | p | Unstandardised B | Standardised Coefficients Beta | t | p |
| **CDLS**[2] | | | | | | | | |
| Age (months) | -.02 | -.36 | -2.35 | .026* | .00 | .23 | 1.27 | .216 |
| SEQ | -.24 | -.47 | -2.11 | .044* | -.00 | -.03 | -0.11 | .917 |
| CSHQ | -.15 | -.17 | -1.00 | .326 | .08 | .55 | 2.85 | .009** |
| SCQ | -.21 | -.20 | -1.07 | .294 | .02 | .13 | 0.61 | .549 |
| **FXS**[3] | | | | | | | | |
| Age (months) | -.01 | -.33 | -2.7 | .009** | .00 | .05 | 0.38 | .704 |
| SEQ | .04 | .01 | 0.57 | .955 | .02 | .29 | 1.62 | .114 |
| CSHQ | -.36 | -.48 | -3.69 | < .001*** | .05 | .37 | 2.47 | .017* |
| SCQ | -.28 | -.32 | -2.16 | .036* | -.00 | -.01 | -0.04 | .967 |
| **RTS**[4] | | | | | | | | |
| Age (months) | -.01 | -.38 | -2.55 | .015* | .00 | .24 | 1.66 | .105 |
| SEQ | -.15 | -.43 | -2.76 | .009** | .02 | .33 | 2.24 | .031* |
| HQ | -.63 | -.21 | -1.48 | .146 | .22 | .43 | 3.13 | .003** |

*Note.* *** significant at $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

[2] n = 33 for MIPQ-S, n = 30 for ADAMS subscale
[3] n = 49 for MIPQ-S, n = 48 for ADAMS subscale
[4] n = 44 for MIPQ-S, n = 40 for ADAMS subscale