Change Over Time in People with Rare Neurogenetic Syndromes

by

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A thesis submitted to the University of Birmingham in part completion of the degree of
DOCTOR OF CLINICAL PSYCHOLOGY

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May 2024

Thesis Overview

This thesis comprises four chapters. The first chapter contains a meta-analytic review of 154 studies reporting on the prevalence of epilepsy in genetic syndromes associated with intellectual disability. The meta-analysis used a random-effects model to estimate pooled prevalence of epilepsy across 12 genetic syndromes identified in the systematic search. Pooled prevalence estimates ranged from 4% in people with Rubinstein-Taybi syndrome to 96% in people with Wolf-Hirschhorn syndrome. The prevalence estimates varied across syndrome groups, with all estimates exceeding rates reported for the general population. The methodology varied across studies and so prevalence estimates of epilepsy may be impacted by the measurement of epilepsy and the identification of samples.

The second chapter contains an empirical research study evaluating the persistence of behaviours that challenge, specifically self-injury, aggression and destruction of property, in people with genetic syndromes associated with intellectual disability over a period of 16 years. Parents/carers of 81 people with genetic syndromes completed online questionnaires. Overall, the results suggested behaviours that challenge continue to persist over 16 years. The study also evaluated demographic and behavioural characteristics associated with the developmental trajectory of these behaviours. The results revealed that impulsivity and mood predict persistent aggressive behaviours over 16 years, with impulsivity also predicting persistent destructive behaviours. The findings highlight individual characteristics of impulsivity and mood that may support the identification of children at an increased likelihood of developing persistent behaviours that challenge.

The third and fourth chapters comprise of press releases for the meta-analytic review and empirical study, respectively.

Acknowledgements

I would like to thank my supervisors, Professor Caroline Richards and Dr Stacey Bissell, who have been incredibly supportive throughout this project. I am so grateful for all of your guidance, encouragement and expertise. I would also like to thank members of the research team who supported the project, I am so thankful for your help! I would like to thank Dr Christopher Jones and Dr Alice Welham for all their advice, time and support.

I would like to extend a huge thank you to all the families who participate in the research carried out with the Cerebra Network.

Lastly, I would like to thank my Mum, Dad, Lydia, Evie, and Ellie, you are the best, thank you for everything you do.

Contents Listings

List of Illustrations

Chapter 1: Literature and Meta-analytic Review

List of Tables

Chapter 1: Literature and Meta-Analytic Review

Chapter 2: Empirical Research Study

Chapter 1: Systematic Literature Review and Meta-Analysis

Prevalence of Epilepsy in People with Rare Neurogenetic Syndromes Associated with Intellectual Disability: A Systematic Literature Review and Meta-Analysis

Word Count: 6,929

Abstract

Background: The prevalence of epilepsy appears to be higher in people with genetic syndromes associated with intellectual disability compared to those without these syndromes. However, robust prevalence estimates in this population have not been established.

Aims: This meta-analysis aimed to calculate pooled prevalence estimates for epilepsy in people with genetic syndromes associated with intellectual disability, whilst accounting for the methodological quality of the included studies.

Method: A systematic review of literature reporting on the prevalence of epilepsy in people with genetic syndromes was conducted using five databases. Following screening of studies, a total of 154 studies, identifying a total of 12 syndrome groups, were included for meta-analytic review. Pooled prevalence estimates were calculated and heterogeneity investigated.

Results: Pooled prevalence estimates of epilepsy ranged from 4% (95% CI 0-10) in people with Rubinstein-Taybi syndrome to 96% (95% CI 92-100) in people with Wolf-Hirschhorn syndrome. Prevalence estimates may be impacted by the heterogeneity between studies, particularly in relation to the identification of participants and measurement of epilepsy.

Conclusions: Whilst there is variability in prevalence estimates across genetic syndromes, estimates in Wolf-Hirschhorn syndrome, SYNGAP1 syndrome, Angelman syndrome, tuberous sclerosis complex, Rett syndrome, 1p36 deletion syndrome and MECP2 duplication syndrome are strikingly higher than prevalence estimates in people with intellectual disability of heterogenous aetiology, identifying these groups as high-risk for developing epilepsy.

Introduction

Epilepsy refers to a group of conditions characterised by recurrent, unprovoked seizures and is associated with heterogenous aetiologies, ages of onset, seizure types and co-occurring conditions (Berg et al., 2010; Dhinakaran & Mishra, 2019). Epilepsy is one of the most common neurological disorders, affecting approximately 50 million people worldwide (WHO, 2022). Estimates for the prevalence of epilepsy in the general population of high-income countries range from 6 in 1000 people to 12 in 1000 (Christensen et al., 2023; Wigglesworth et al., 2023). It is well reported that epilepsy occurs more frequently in people with intellectual disability (ID) compared to the general population (Liao et al., 2021; Snoeijen-Schouwenaars et al., 2021), with pooled prevalence estimates of approximately 22% (Oeseburg et al., 2011; Robertson et al., 2015). The prevalence of epilepsy is thought to increase with severity of ID, with higher rates of epilepsy in those with more severe ID (Oeseburg et al., 2011; Robertson et al., 2015). In comparison to epilepsy in the general population, epilepsy in people with ID is associated with higher mortality rates (Forsgren et al., 2005), increased resistance to anti-epileptic medication (McGrother et al., 2006; Shankar et al., 2017) and increased risk of misdiagnosis (Deb, 2007). Thus, there is substantial clinical importance in advancing understanding of the relationship between epilepsy and ID.

The prevalence of epilepsy appears to be higher in people with a genetic syndrome associated with ID compared to those without syndromes. For example, tuberous sclerosis complex, Rett syndrome, fragile X syndrome, Down syndrome and Angelman syndrome are commonly associated with epilepsy (Clarke & Deb, 2009). Broad estimates suggest that up to half of those with a neurogenetic syndrome will experience seizures (Depositario-Cabacar & Zelleke, 2010; Sunder, 1997). Specifically, studies estimate that 12.4% of people with Down syndrome, a common genetic cause of ID, have epilepsy

(Robertson et al., 2015), 70% of people with tuberous sclerosis complex (Joinson et al., 2003), and up to 82% of children with Angelman syndrome report a diagnosis of epilepsy (Bindels-de Heus et al., 2020). However, whilst a number of studies report on the presence of epilepsy in cohorts of participants with genetic syndromes, overall estimates of pooled prevalence rates are less well established. Thus, the need for developing pooled prevalence estimates is warranted.

Studies have begun to explore the aetiological relationship between epilepsy and ID through review of research into the genetic and biological pathways across specific genetic syndromes of ID (Leung & Ring, 2013). There may be a range of pathophysiological processes that are likely to lead to an increased risk of both ID and epilepsy, including a number of genetic/chromosomal abnormalities impacting molecular pathways that regulate processes underlying learning and seizure activity (Busch et al., 2014; Kerr & Watkins, 2019). For example, Leung and Ring (2013) describe the role of impaired glial functioning across fragile X syndrome, Rett syndrome and tuberous sclerosis complex in the development of both seizure activity and intellectual functioning. Further to this finding, variations in seizure characteristics (e.g. age of onset, seizure type and severity) within and across syndromes allude to there being a number of causal pathways to developing epilepsy in populations with ID (e.g. see Leung & Ring, 2013). Given the genetic and phenotypic heterogeneities of epilepsy across syndromes, there is a need to establish a better understanding of the mechanisms underpinning both ID and epilepsy to support clinical management of seizures earlier on. Ultimately, collating information on the prevalence of epilepsy across syndromes may promote clinicians' awareness of the possible risk of epilepsy in people with genetic syndromes and improve earlier identification and assessment of seizures.

It is suggested that the aetiology and nature of ID may influence the prognosis and severity of epilepsy (Bowley & Kerr, 2000), whilst in turn, the level of ID may be impacted by the type and severity of epilepsy (Forsgren et al., 1990). For example, those with fragile X syndrome experiencing seizures for longer periods of time have been found to have greater cognitive impairment (Berry-Kravis et al., 2021). In those with tuberous sclerosis complex where ID is present, more severe epilepsies, including drug-resistant epilepsy and early-onset seizures, are seen (Chu-Shore et al., 2010). The severity of seizures and developmental delay also appear to be related to the genetic mutation underlying diagnosis of Angelman syndrome, whereby more severity is associated with 15q11-q13 microdeletion or UBE3A mutation (Leung & Ring, 2013; Lossie et al., 2001; Minassian et al., 1998). Furthermore, research points to an association between more severe and frequent seizure activity and the development of behavioural and emotional difficulties and reduced quality of life in ID populations (Espie et al., 2003; Snoeijen-Schouwenaars et al., 2019; van Ool et al., 2016; van Ool et al., 2018). Thus, clarification on the risk of developing epilepsy in syndromes associated with ID is not only important in understanding underlying causal pathways between epilepsy and ID, but also in informing clinical practice considering the wider impact the presence of epilepsy may have on quality of life and psychosocial wellbeing.

A pragmatic strategy to understanding the aetiology of epilepsy in people with ID would be to delineate the nature of epilepsy across genetic syndromes associated with ID, essentially, building a phenotype of epileptic seizures observed across these syndromes. Bowley and Kerr (2000) suggest the possibility of then linking genetic mechanisms to specific epilepsy phenotypes, which will give clearer indications of clinical outcomes and treatment pathways. Determining the risk of developing epilepsy across a wide range of genetic syndromes can support future research in defining epilepsy phenotypes across

those high-risk groups whereby prevalence estimates are greater. In addition, accurate prevalence estimates will help to identify priority syndromes where epilepsy management and assessment should be targeted. Ensuring support is prioritised for these high-risk groups is particularly important due to the known associations between epilepsy, neurodevelopmental conditions and poorer clinical outcomes, particularly in regards to quality of life (Kerr et al., 2009; Snoeijen-Schouwenaars et al., 2021; Turky et al., 2011; Watkins et al., 2022). Whilst previous studies have reviewed the prevalence of epilepsy in people with ID (Oeseburg et al., 2011) and across more specific genetically determined syndromic ID groups, including tuberous sclerosis complex, fragile X syndrome, Rett syndrome and Angelman syndrome (Leung & Ring, 2013), prevalence data on a wider range of less common specific genetic syndromes associated with ID has yet to be conducted.

In addition to the need for pooled prevalence estimates of epilepsy in syndromes, there are also challenges to developing accurate estimates in populations with ID. Prevalence data for epilepsy is variable in the ID population and can range from 14 to 44% across samples of non-syndromic ID (Bowley & Kerr, 2000; Kerr & Watkins, 2019). Considerable variation in prevalence estimates is also observed across syndromic ID groups. For example, it is reported that anywhere between 60 to 80% of people with Rett syndrome (Operto et al., 2019) and between 66 to 93% of people with tuberous sclerosis complex will develop epilepsy (Hallett et al., 2011). This variation may be partly attributed to differing phenotypes and genotypes within syndromes (e.g. Operto et al., 2019), but variability is also likely attributable to methodological limitations, such as a lack of standardisation in the diagnosis and definition of epilepsy across studies (Beghi, 2020; Fiest et al., 2017; Liu et al., 2022). Therefore, there is a need to synthesise the available

data to generate robust pooled estimates, and to explore empirically potential methodological sources of variability in the estimates.

There are a number of methodological challenges in ascertaining prevalence data for epilepsy within and across syndromes. Firstly, the ever-evolving definitions of epilepsy (Beghi, 2020), coupled with differences in the measurement of epilepsy (Fiest et al., 2017), add to the complexity of teasing apart prevalence estimates. Determining the presence of epilepsy is inconsistent across studies due to the use of various definitions and methods of collecting this information (Robertson et al., 2015). A further challenge to this is the clinical difficulty in diagnosing epilepsy in people with ID and the higher likelihood of misdiagnosis through confusing other clinical manifestations as epileptic seizures (e.g. Guerrini & Parrini, 2012; Operto et al., 2019). Lastly, epidemiological methodologies vary across studies considerably, complicating the synthesis of prevalence data further (Liu et al., 2022). So, any attempt to synthesise this data needs to take these factors into consideration and account for methodological variability potentially impacting estimates of epilepsy prevalence.

The Present Review

Consequently, there is a need to synthesise the available literature to provide a more accurate description of epilepsy across genetic syndromes associated with ID, whilst accounting for the quality of epidemiological methodology across studies. The aim of this meta-analysis therefore was to identify empirical research reporting epilepsy prevalence across genetic syndromes associated with ID and to calculate pooled estimates for prevalence of epilepsy or epileptic seizures within each syndrome, taking into account the methodological quality of studies.

Methods

Identifying Primary Studies

Search Strategy

The review was conducted in accordance with the Preferred Reporting Items for Systematic Review and meta-analysis (PRISMA) guidelines (Moher et al., 2009; Page et al., 2021) and was pre-registered on Prospero, which can be accessed through the following link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023390862.

Five databases were searched: PsychINFO (1967 to January Week 3 2023), MEDLINE (1946 to January 25 2023), Embase (1974 to 2023 January 25), PubMed (all years) and ProQuest (all dates). For full search strategy see Appendix 5. For ID, search terms included: intellectual disability, intellectual disturbance, learning disability, mental retardation, mental handicap, mental deficiency, mental disorder, mental incapacity, mental delay, and further variants of these. ID search terms were based upon a previous literature review of similar methodology (Surtees et al., 2018). For epilepsy, search terms included: epilep*, seizure*, convuls* and infantile spasm. Epilepsy search terms were informed by hand searches of terminology in relevant meta-analyses, systematic reviews, and independent studies and through consulting the most recent International League Against Epilepsy classification (Fisher et al., 2017; Wirrell et al., 2022). Terms for genetic syndromes included: gene*, syndrom*, geno*, genetic syndrom* and chromosome disorder*. Epilepsy, ID and genetic syndrome search terms were combined using the AND operator. Search terms were required to be in the abstract, keywords or title of papers. Medical subject headings (MeSH) terms were used where available.

Study Selection

Initial searches produced 57,416 references. To note, 27,327 references were produced from the search on PubMed, however the database only allows a maximum of 10,000 (either the newest or oldest 10,000 by publication date) to be displayed on the interface and exported from a search. References were exported using the 'Results by Year timeline' tool in sets of less than 10,000 at a time (e.g. 2006-2016 n=9518; 2017-2022 n=9883). The timeline includes all publication dates for a citation, including both print and electronic publication dates, which may span more than one year. Thus, the sum of results shown by the timeline may be greater than the search results count, due to duplicate citations. The total number of references extracted from PubMed was therefore 28,046. The duplicates exported from this process were dealt with during the de-duplication stage of the total 57, 416 references produced. After duplicates were removed, 35,187 articles remained (See Figure 1.1).

Specific inclusion and exclusion criteria were applied at an initial screening phase of titles and abstracts (See Table 1.1 for inclusion and exclusion criteria). The papers were assessed at this stage for inclusion by the author and an independent second rater. Both raters completed a training phase of screening with the first 50 abstracts, whereby any discrepancies were discussed against the inclusion and exclusion criteria and consensus reached. Following this, the author screened 20% (n=7,038) and the second rater screened 100% of the papers (n=35,187). Inter-rater reliability was established using Cohen's Kappa statistic on 20% of the total papers (n=7,038). Using criteria defined by McHugh (2012), an initial assessment of inter-rater reliability suggested fair agreement between the author and second rater (Kappa = .28). Following this, a post-discrepancy resolution process was undertaken. Any disagreements in ratings were discussed and major causes of discrepancy identified. The majority of disagreements were due to differences in defining

a genetic syndrome associated with ID, and thus the inclusion and exclusion criteria were adjusted, and subsequent criteria were established to define the criterion further (see Table 1.1). Assessment of inter-rater reliability following this process indicated substantial agreement between the raters (Kappa = .74).

Table 1.1

Inclusion and Exclusion Criteria at Screening of Titles and Abstracts

Inclusion Criteria	Exclusion Criteria
Empirical peer-reviewed studies	Conference proceedings, magazines and books OR review articles with no novel data
Studies published or available in English	Studies only published or available in a language other than English
Title or abstract indicates that the study reports on epilepsy or presence of seizures within the genetic syndrome group.	Title or abstract does not mention any presence of epilepsy or seizure.
Title or abstract indicates that the study reports on a sample of people with a syndrome defined by a genetic aetiology that is known to be associated with intellectual disability[1]	Title or abstract does not mention presence of a sample of people with a genetic syndrome that is known to be associated with intellectual disability
Sample with genetic syndrome associated with intellectual disability ≥ 10[2]	Sample with genetic syndrome associated with intellectual disability < 10.
Study reporting on a genetic syndrome associated with intellectual disability, not an epilepsy syndrome associated with intellectual disability.	Study reporting on an epilepsy syndrome associated with intellectual disability, e.g. dravet syndrome, lennox-gestaut syndrome[3]
Studies reporting on live human participants	Studies reporting on animal participants, pure genetic or biological studies/biomarkers

[1] Three criterion were used to establish the inclusion of a genetic syndrome group. These were:

1. A number of symptoms or identifying features that tend to occur in conjunction characterise a recognisable group that has one primary name established to identify the condition, or, 'syndrome' is used in the name of the condition.
2. Intellectual disability is considered to be a part of the phenotype or is an identifying feature of the syndrome.
3. The syndrome is of genetic aetiology.

[2] Studies including a participant sample of ten people of more were included as consistent with a previous meta-analytic review of similar methodology (Richards et al., 2015).

[3]Classification of epilepsy syndromes was determined by the 2022 report by the International League Against Epilepsy (Wirrell et al., 2022).

In total, 34,710 papers were manually excluded at abstract and title screening. The three most common reasons for exclusion were: no genetic syndrome was mentioned (n=8,661), case study, case series or $n \leq 10$ (n=7,457) and purely genetic or biological focused studies where no epilepsy data were collected (n=5,346). Following the initial screening, the remaining 477 articles underwent full-text screening for eligibility using additional criteria (see Table 1.2). At full-text screening, moderate inter-rater reliability was found between the author and second rater (Kappa = .63).

Table 1.2

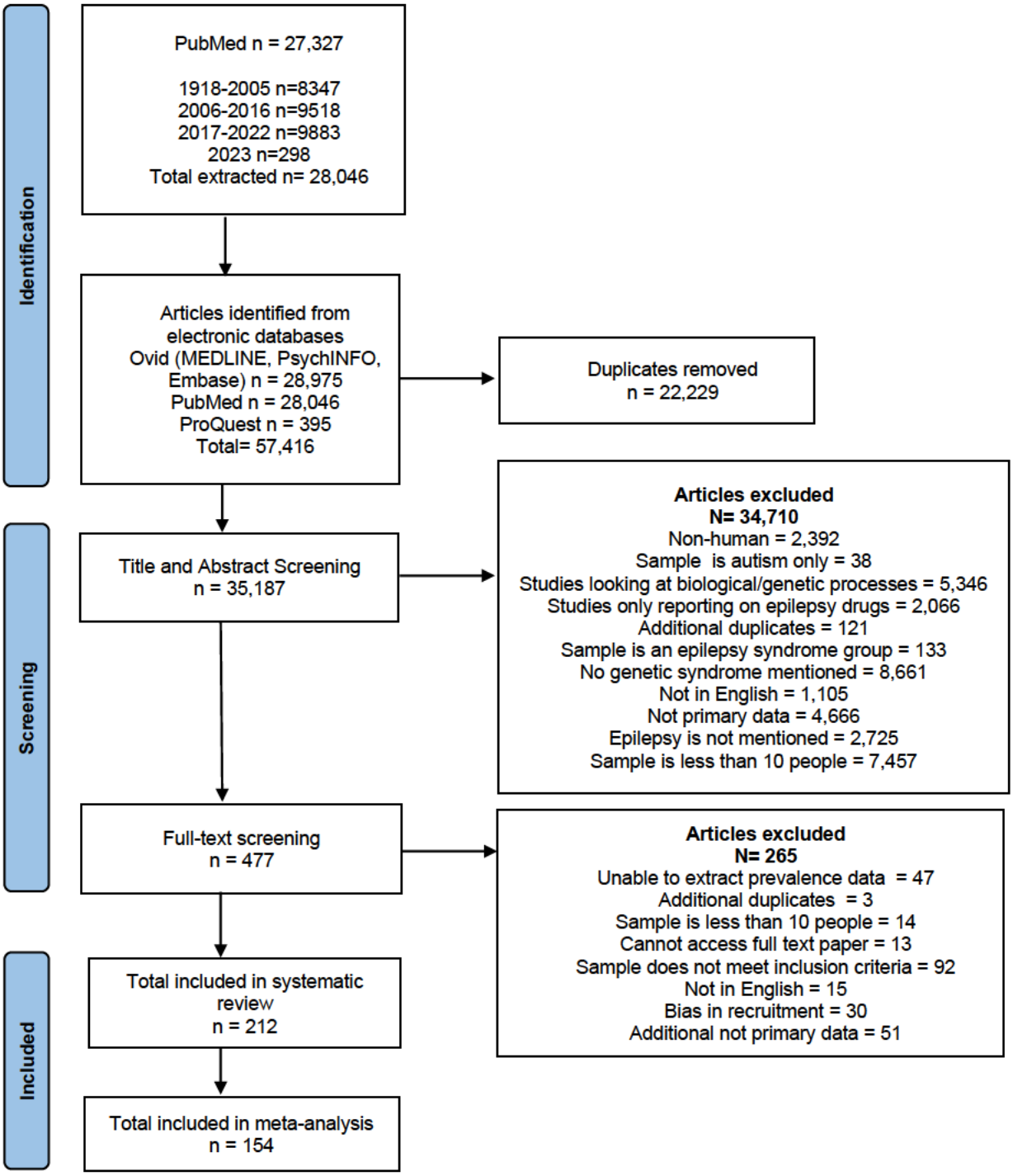
Inclusion and Exclusion Criteria at Screening of Full-Text Articles

Inclusion Criteria	Exclusion Criteria
Study reports on the number of participants with the genetic syndrome who had epilepsy or seizures.	Determining the number of participants with the genetic syndrome with epilepsy or seizures is not possible e.g. study reports only the number of participants who were taking anti-epileptic drugs or reports only reasons for hospitalisation.
Study reports on participants with a genetic syndrome associated intellectual disability.	Study reports on participants with a genetic syndrome not known to be associated with intellectual disability.
Participants recruited without clear bias (e.g., inclusion criteria includes presence of epilepsy or abnormal EEG).	Participants were recruited due to a diagnosis of epilepsy or presence of epileptic seizures.
Study reports on a unique sample or if the sample overlaps with a previously reported sample, the proportion of overlap cannot be determined.	Study reports on the same sample as previously reported in a different study.

After screening the full-text papers, 212 articles met full criteria for inclusion in the review (See Figure 1.1). The main reasons for exclusion at full-text screening were: the sample did not meet criteria for inclusion as a syndrome group as outlined in Table 1.1 (n=92), additional papers without primary data (n=51) and papers where prevalence data could not be ascertained or extracted (n=47).

Figure 1.1

PRISMA Flow Diagram Depicting Study Selection and Numbers of Returned Papers



Data Extraction

From the 212 papers included, data were extracted by the author. Data extraction included the total number of participants with the genetic syndrome, the number of those within the sample who had epilepsy or epileptic seizures, demographic information (including age and sex), country of publication, classification of the genetic syndrome, how the presence of epilepsy or seizures were determined in the study and how participants were recruited.

Quality Criteria

All studies were evaluated against an adapted quality rating tool developed for use in the assessment of prevalence data in genetic syndromes associated with ID (Richards et al., 2015). Each paper was rated by the author on a scale of poor (0) to excellent (3) across three domains: sample identification, confirmation of syndrome diagnosis and classification of epilepsy diagnosis (see Appendix 3.1). The final domain, 'epilepsy classification', was included and adapted for the current study, based on a previous review of similar methodology (Winsor et al., 2021). Studies with a score of 0 did not specify or report on the sample identification, syndrome classification or epilepsy diagnosis, or they reported only on seizures or infantile spasms (e.g. determining if the seizures reported on were epileptic seizures was not possible or clear). Scores of 3 were given to studies that used random or total population samples, established a genetic confirmation of the syndrome group (where required based on diagnostic criteria for each group), or reported on medically validated primary data of epilepsy diagnoses as established in the study. The quality weighting for each paper was calculated by dividing the total scores (between 0 and 9) by the possible maximum score of nine (quality index score). An assessment of

inter-rater reliability of the quality weighting using 20% of the included papers indicated excellent agreement between the raters (Kappa=.97).

Data Analysis

The data analysis was carried out through use of the meta-analysis strategy of the Centre for Applied Psychology, University of Birmingham. The RStudio application using the Metafor package for R (Viechtbauer, 2010), was used to calculate pooled prevalence estimates.

Only syndrome groups with five or more studies were included for synthesis in the meta-analytic review, this threshold is in line with previous meta-analyses (e.g. Thomas et al., 2022). Fifty-eight studies were excluded from the meta-analysis as either less than five papers were identified for the syndrome group (*n*=53; see Appendix 3.2 for a list of the excluded syndrome groups and reported prevalence rates) or the study reported on the point prevalence of seizures or epilepsy as opposed to lifetime prevalence (*n*=5).

As studies differ in methodological details and participant characteristics, it was anticipated there would be considerable heterogeneity between the study-level estimates. The distribution of included study effects is shown in Appendix 4.1. The variance of the true effect (tau^2) was calculated using the Restricted Maximum Likelihood (REML) estimator, as this method is shown to be more robust to skewed distributions of effects (Banks et al., 1985). Across all syndrome groups, there was clear evidence of non-linearity in the distribution of study-level effects when using the fixed-effects model. However, across Rett syndrome, MECP2 duplication syndrome, Wolf-Hirschhorn syndrome, Prader-Willi syndrome, Rubinstein-Taybi syndrome, 1p36 deletion syndrome and SYNGAP1 syndrome, there was no evidence of non-linearity in the distribution of epilepsy within the included studies when using the random-effects model. Within tuberous sclerosis complex,

Down syndrome, fragile X syndrome, Angelman syndrome and DiGeorge syndrome, 95% of the study effects fell within the 95% confidence intervals for the expected values (see Appendix 4.1). This suggests that use of the random-effects model calculated using the REML estimator is appropriate for the analysis of these data. A quality-effects model was also used to calculate prevalence estimates, whereby a weighted average based on the quality index score and sample size was generated.

A degree of variation in the prevalence estimates may result from differing methodology, participant characteristics or other uncontrolled factors. In order to assess the level of heterogeneity in the primary studies and its impact on the prevalence estimates, Higgins I^2 was calculated (Higgins et al., 2003). Higgins I^2 measures the degree of between study variation in the prevalence estimates that cannot be attributed to true variation in the distribution of prevalence estimates in the population. Heterogeneity was reviewed independently by syndrome group. Where an unacceptable level of heterogeneity was indicated, defined as an I^2 value exceeding 75%, review of Baujat plots and subsequent 'leave-one-out' analyses were conducted to explore the impact of influential studies on the effect (Baujat et al., 2002). To conduct the 'leave-one-out' analysis, the overall effect was calculated with each of the primary studies removed one at a time, changes to the prevalence estimate and heterogeneity were reviewed. Where disproportionate influence and discrepancy were identified, papers were critically re-reviewed to establish any possible sources of bias with a view of removing the paper if a substantial reason was identified.

Subgroup analyses and meta-regression were carried out to explore the impact of study-level characteristics on the prevalence estimates. To explore the impact of quality ratings on epilepsy prevalence rates, subgroup analyses were conducted for syndrome groups with 10 or more effects, as is consistent with previous recommendations

(Richardson et al., 2019). The impact of age on the prevalence of epilepsy in each syndrome group was explored by regressing the mean and median age in each sample to the reported prevalence rate where available data allowed (minimum of 10 effects). Similarly, the impact of sex on prevalence estimates was explored by regressing the percentage of males in each sample to the reported prevalence rate. Due to the multiple comparisons, and therefore the increased likelihood of type one errors (inappropriately rejecting the null hypothesis), effects at $p < 0.01$ were reported as significant, however interpretation of the findings should be cautious.

Additionally, the impact of publication and small study bias was reviewed by checking for asymmetry across funnel plots (Egger et al., 1997). As the accuracy of reviewing visual funnel plots is unclear (Terrin et al., 2005), Egger's regression method was also used with the standard error as moderator to the random effects model (Egger et al., 1997). Where Egger's regression test was significant, the effect of bias was simulated using a trim and fill procedure (Duval & Tweedie, 2000), yielding an adjusted effect size. In addition, the fail-safe number was calculated (Rosenthal, 1979). The Orwin method (Orwin, 1983) calculates the number of studies reporting null results (defined in the present study as the average prevalence of epilepsy in persons with ID) that would need to be added to the observed outcomes to reduce the prevalence estimate to general ID population levels.

Results

Prevalence of Epilepsy

There were 154 studies, across 12 syndromes, reporting a total of 56,333 participants. Study characteristics for each paper are presented in Tables 1.3-1.14. The prevalence of epilepsy or epileptic seizures ranged from 4% (95% CI 0-10) in people with Rubinstein-Taybi syndrome to 96% (95% CI 92-100) in people with Wolf-Hirschhorn syndrome. Forest plots depicting the prevalence of epilepsy across each genetic syndrome are presented in Appendix 4.2.

Table 1.3

Tuberous Sclerosis Complex Study and Sample Characteristics

Author (Year)	*N*	% Male	Country of publication	Age			Quality criteria			Quality weighting
				Mean Age (SD)	Median Age (IQR)	Age Range	Sample	Epilepsy	Syndrome	
Aden (2019)	34	44	Qatar	Not reported	8.77	1 - 16y				0.67
Almobarak et al. (2018)	88	63.6	Saudi Arabia	16.56 (14.21)	Not reported	Not reported				0.56
Alsowat et al. (2021)	55	50.9	Canada	8.85	Not reported	Not reported				0.67
Baumer et al. (2015)	17	59	USA	7.2 (4.4)	Not reported	Not reported				0.33
Capal et al. (2017)	130	52.3	USA	0.433 (.28)	Not reported	Not reported				0.67
Cervi et al. (2020)	42	45.2	Italy	11.36 (4.19)	Not reported	Not reported				0.56
Chou et al. (2008)	25	56	Taiwan	11 (7.4)	Not reported	2 - 29y				0.44
Chou and Chang (2004)	35	40	Taiwan	15.9 (12.5)	Not reported	Not reported				0.44
Chung et al. (2017)	70	46	Australia	Not reported	9	Not reported				0.67
Bachour et al. (2022)	181	48.6	Canada	33.6 (13.7)	Not reported	Not reported				0.67
Davis et al. (2017)	130	52	USA	0.43 (.28)	Not reported	Not reported				0.67
De Sautu De Borbon et al. (2021)	57	47.4	Spain	42	Not reported	20 - 86y				0.33
De Vries et al. (2007)	258	42.4	UK	Not reported	Not reported	5 - 18y				0.44
Dedeoğlu et al. (2022)	34	52.9	Turkey	11.2	Not reported	6 - 16y				0.56
Devlin et al. (2006)	73	46.57	Ireland	27.9 (16.8)	Not reported	10m - 69y				0.44
Ding et al. (2021)	124	49.2	China	Not reported	8.5 (3.7)	Not reported				0.33
Gupta et al. (2020)	1319	51.36	USA	Not reported	16	1m - 81y				0.78
Hunt (1993)	300	54	UK	Not reported	Not reported	6m - 74y				0.22
Iscan et al. (2005)	17	58.82	Turkey	Not reported	Not reported	0 - 17y				0.44

Author (Year)	*N*	% Male	Country of publication	Age			Quality criteria			Quality weighting
				Mean Age (SD)	Median Age (IQR)	Age Range	Sample	Epilepsy	Syndrome	
Joinson et al. (2003)	108	51.85	UK	Not reported	25 (26)	4 - 75y				0.44
Jozwiak et al. (1998)	106	44	Poland	Not reported	Not reported	Not reported				0.33
Kingswood et al. (2017)	2093	48.2	UK	Not reported	13	0 - 71y				0.67
Kosac and Jovic (2019)	44	40.9	Serbia	19.4 (11.8)	Not reported	1 - 58y				0.44
Marcinkowska et al. (2022)	100	52	Poland	32.33 (11.29)	Not reported	Not reported				0.33
Nabbout et al. (2019)	2216	47.9	France	Not reported	13	0 - 71y				0.67
Rama Rao et al. (2008)	15	53.3	India	15.9	Not reported	1.5 - 50y				0.33
Rentz et al. (2015)	676	40.8	USA	29.8 (17.7)	Not reported	Not reported				0.22
Vignoli et al. (2021)	257	43.2	Italy	Not reported	37	18 - 87y				0.67
Wilbur et al. (2017)	81	51	Canada	Not reported	10	0.2 - 23.2y				0.56
Yapici et al. (2007)	13	38.5	Turkey	8.43 (5.49)	Not reported	10m - 16.7y				0.33
Yates et al. (2011)	125	49.6	UK	Not reported	2.7	4w - 18y				0.78
Georgieva et al. (2021)	33	NR	Bulgaria	Not reported	Not reported	Not reported				0.44
Kingswood et al. (2016)	334	47	UK	30.3 (18.6)	Not reported	Not reported				0.67
Kothare et al. (2014)	916	49.4	USA	25 (62)	Not reported	Not reported				0.78
Nath et al. (2015)	20	55	India	11.9 (4.8)	Not reported	Not reported				0.44
Toldo et al. (2019)	32	50	Italy	9.75 (5.5)	Not reported	Not reported				0.67
van Eeghen et al. (2012)	66	48.5	USA	5.8	Not reported	0.5 - 20y				0.56
Yang et al. (2017)	117	51.3	China	5.17 (3.6)	Not reported	Not reported				0.33
Hou et al. (1994)	18	61.1	Taiwan	Not reported	Not reported	Not reported				0.33
Shepherd and Stephenson (1992)	104	52.9	UK	Not reported	Not reported	Not reported				0.56
Ebrahimi-Fakhari et al. (2019)	22	59.1	Germany	4	Not reported	Not reported				0.67

Table 1.4

Rett Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Age			Quality Criteria			Quality weighting
				Mean Age (SD)	Median Age (IQR)	Age range	Sample	Epilepsy	Syndrome	
Buoni et al. (2008)	154	0	Italy	Not reported	Not reported	Not reported				0.67
Cardoza et al. (2011)	89	0	Wales	Not reported	Not reported	5 - 43y				0.78
Cass et al. (2003)	87	0	UK	Not reported for whole sample[1]	Not reported	2 - 44y				0.33
Cianfaglione et al. (2015)	91	0	UK	20.5	Not reported	4 - 47y				0.44
Cooper et al. (1998)	171	0	UK	Not reported for the included sample	Not reported	Not reported				0.33
Cutri-French et al. (2020)	535	0.56	USA	Not reported	13.5 (7.2 - 20.9)	Not reported				0.56
Glaze et al. (2010)	602	0	USA	Not reported	Not reported	8m - 64y				0.44
Henriksen et al. (2018)	70	0	Norway	Not reported	21 (14-34)	1 - 66y				0.78
Jian et al. (2006)	275	0	Australia	Not reported	14.6	2.3 - 29.5y				0.56
Kerr et al. (2006)	13	0	UK	22.4 (8.6)	Not reported	Not reported				0.67
Kim et al. (2012)	20	0	South Korea	7.7 (2.6)	Not reported	3.6 - 14.3y				0.78
Nissenkorn et al. (2010)	97	0	Israel	12.3	Not reported	1.5 - 42y				0.44
Peron et al. (2022)	50	0	Italy	Not reported	29	19 - 49y				0.56
Pintaudi et al. (2010)	165	0	Italy	14.9 (8.5)	14	2 - 40y				0.78

Author (year)	*N*	% Male	Country of publication	Age			Quality Criteria			Quality weighting
				Mean Age (SD)	Median Age (IQR)	Age range	Sample	Epilepsy	Syndrome	
Steffenburg et al. (2001)	53	0	Sweden	Not reported	Not reported	5 - 55y				0.56
Megahed et al. (2015)	32	0	Egypt	3.08	Not reported	18 - 56m				0.44
Moser et al. (2007)	11	0	Switzerland	Not reported	Not reported	1 - 33y				0.56
Anderson et al. (2014)	411	0	Australia	Not reported	24.9 (21.5 - 30.7)	18 - 54.3y				0.67
Bao et al. (2013)	685	0	China	11.08 (9.33)	Not reported	Not reported				0.67
Bisgaard et al. (2021)	24	0	Denmark	34.3 (8.1)	Not reported	Not reported				0.56
Boban et al. (2016)	360	0.55	Australia	Not reported	14.5	2.1 - 57.2y				0.67
Buoni et al. (2010)	16	0	Italy	19.4 (8.4)	Not reported	8 - 38y				0.78

[1] The study reported "Twenty-six participants (29.9%) were aged between 2 and 4 years (mean age 3 years 2 months, SD 8 months), 28 (32.2%) were aged between 5 and 9 years (mean age 7 years 6 months, SD 1 year 10 months); 13 participants (14.9%) were aged between 10 and 19 years (mean age 13 years 8 months, SD 2 years 2 months), and 20 (23%) were adults aged between 20 and 44 years (mean age 27 years, SD 7 years 6 months)." (Cass et al., 2003).

Table 1.5

Down Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Age			Quality Criteria			Quality weighting
				Mean Age (SD)	Median Age	Age Range	Sample	Epilepsy	Syndrome	
Aparicio et al. (2023)	28716	58.2	Spain	41 (13)	Not reported	18 -96y				0.44
Athale et al. (2018)	38	45	USA and Canada	Not reported	5.6	1.3 -16.9				0.33
Barca et al. (2014)	39	33	Romania	Not reported	Not reported	Not reported				0.56
Bayen et al. (2018)	353	51	USA	58.7 (7.1)	Not reported	Not reported				0.44
Bayen et al. (2018)	525	52	USA	55.9 (7.5)	Not reported	Not reported				0.44
Belton et al. (2018)	141	45.1	Ireland	50.1 (6.5)	Not reported	Not reported				0.44
Breia et al. (2014)	176.47	59.8	Spain	36.25 (8.35)	Not reported	20 -58y				0.78
Collacott (1993)	344	NR	UK	Not reported[1]	Not reported	Not reported				0.33
Esbensen et al. (2022)	108	57.4	USA	12.3 (3.2)	Not reported	6 - 18y				0.22
Goldberg-Stern et al. (2001)	350	60.71	USA	Not reported	Not reported	0 - 20y				0.78
Johannsen et al. (1996)	72	75	Denmark	31.67	Not reported	14 - 60 y				0.89
Kinnear et al. (2018)	186	48.9	Scotland	41.1	Not reported	Not reported				0.44
Kwong and Wong (1996)	124	62.1	China	2.3	Not reported	12w - 18y				0.22
McVicker et al. (1994)	191	NR	Ireland	Not reported[2]	Not reported	Not reported				0.56
Molloy et al. (2009)	20	75	USA	10 (3.67)	Not reported	4 - 16y				0.78
Real de Asua et al. (2015)	144	51	Spain	35 (12)	Not reported	17 - 65y				0.33
Roizen et al. (2014)	440	51.7	USA	7.5 (3.1)	Not reported	3 - 13y				0.67
Romano et al. (1990)	113	46.9	Italy	Not reported	Not reported	5m - 51y				0.44

Author (year)	*N*	% Male	Country of publication	Age			Quality Criteria			Quality weighting
				Mean Age (SD)	Median Age	Age Range	Sample	Epilepsy	Syndrome	
Seppalainen and Kivalo (1967)	92	60.9	Finland	Not reported	Not reported	0 - 41y				0.44
Smigielska-Kuzia et al. (2009)	252	61.5	Poland	9.6[c]	Not reported	1 - 20y				0.78
Tatsuno et al. (1984)	844	54.98	Japan	Not reported	Not reported	0-15y				0.33

[1]Of those with seizures, 14 people were <30 years old, 11 were between 30-39 years, four were between 40-49 years, three were between 50-59 years, four were over 60 years.
[2]Of the sample with Down syndrome 37% were between 19 and 29 years, 33% were between 30 and 39 years, 22% were between 40 and 49 years and 8% were over 50 years.
[3]The mean age of boys was 9.17 (6.3) and of girls was 10.12 (5.5).

Table 1.6

Fragile X Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Age		Quality Criteria			Quality weighting
				Mean Age (SD)	Age Range	Sample	Epilepsy	Syndrome	
Alanay et al. (2007)	24	100	Turkey	8.5 (4)	2 - 17y				0.67
Bailey et al. (2008)	1235	79	USA	Not reported[1]	Not reported				0.56
Berry-Kravis (2002)	136	83	USA	Not reported	2 - 15y				0.67
Berry-Kravis et al. (2021)	1607	77	USA	13.8	Not reported				0.78
Berry-Kravis et al. (2010)	1394	78.2	USA	Not reported	1 - 62y[2]				0.67
Chonchaiya et al. (2010)	60	60.7	USA	9.61 (5.59)	Not reported				0.78
Chonchaiya et al. (2010)	95	78.4	USA	9.41 (6.31)	Not reported				0.78
Guerreiro et al. (1998)	11	81.82	Brasil	Not reported	8 - 19y				0.67
Heard et al. (2014)	135	94.74	USA	5.94	15m - 13y				0.78
Incorpora et al. (2002)	30	100	Italy	Not reported	Not reported				0.78
Musumeci et al. (1999)	192	100	USA and Italy	Not reported	1 - 67y[3]				0.89
Sabaratnam et al. (2001)	24	100	UK	Not reported	13 - 63y				0.78
Wisniewski et al. (1991)	62	88.7	USA	Not reported[4]	Not reported				0.56
García-Nonell et al. (2008)	57	100	USA	9.8 (5.74)	Not reported				0.44
García-Nonell et al. (2008)	33	100	USA	7.75 (3.74)	Not reported				0.44
Wisniewski et al. (1985)	28	89.3	USA	21.3	8m - 60y				0.67

[1] The age at study enrollment of the children with the full mutation was varied, with 11% between the ages of birth and four years, 34% between five and 11 years, 24% between 12 and 18 years, 10% between 19 and 22 years, 10% between 23 and 30 years, and 11% who were 30 years or older.
[2] Individuals with a seizure history ranged in age from less than one to 55, whereas individuals who did not have seizures ranged in age from less than one to 62 years.

[3] The first group of 168 male patients: Age range 1-67 years, mean age at the last visit was 16.3 years, SD 12, median age 12 years. The second group of 24 male patients recruited: Age range at first visit, 3-25 years, mean age 10.62, SD 6.23, median age 9.58. Age range at last visit, 6-28 years, mean age 15.59, SD 6.54, median age 14.09.

[4] Males participants: Mean age 23.1, SD 14.3, range 2-70 years. Female participants: Mean age 15.7, SD 3.5, range 10-20 years.

Table 1.7

Angelman Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Age			Quality Criteria			Quality weighting
				Mean Age (SD)	Median Age	Age Range	Sample	Epilepsy	Syndrome	
Bakke et al. (2021)	42	59.5	Norway	18.5	Not reported	2 - 57y				0.78
Belghiti et al. (2022)	20	36.84	Morrocco	5.47	Not reported	1 - 12y				0.67
Bindels-de Heus et al. (2020)	100	50	Netherlands	8.8 (5.3)	Not reported	Not reported				0.78
Clayton-Smith (2001)	28	42.9	UK	Not reported	Not reported	16 - 40y				0.44
den Besten et al. (2021)	94	50.5	Netherlands	31.6 (12.6)	29	18 - 83y				0.78
Duca et al. (2013)	15	33.3	Romania	3.19 (3.04)	Not reported	10m - 11y				0.78
Guerrini et al. (1996)	11	45.5	Italy	17	18	3 - 28y				0.67
Laan et al. (1997)	36	55.5	Netherlands	11	Not reported	1.5 - 39y				0.78
Leitner and Smith (1996)	24	45.83	Australia	Not reported	Not reported	3 - 30y				0.67
Miano et al. (2005)	10	50	Italy	5.8	Not reported	2 - 16y				0.67
Ohtsuka et al. (2005)	11	54.5	Japan	8.82 (4.9)	Not reported	Not reported				0.67
Galvan-Manso et al. (2005)	37	48.65	Spain	13.3 (5.2)	Not reported	3.2 - 23y				0.67

Table 1.8

MECP2 Duplication Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Age			Quality Criteria			Quality weighting
				Mean Age (SD)	Median Age (IQR)	Age Range	Sample	Epilepsy	Syndrome	
Cutri-French et al. (2020)	49	89.8	USA	Not reported	7.4 (4.1-12.1)	Not reported				0.56
Ak et al. (2022)	101	100	USA	10 (8.9)	7	1 - 51y				0.56
Lim et al. (2017)	55	87.5	Singapore	Not reported	7.9	1.2 - 37.6y				0.22
Lugtenberg et al. (2009)	13	100	Netherlands	12.15 (6.01)	Not reported	Not reported				0.56
Marafi et al. (2019)	47	87.5	USA	10 (7)	Not reported	1 - 27y				0.78
Miguet et al. (2018)	59	90.1	France	11.7	Not reported	2m - 48y				0.67
Peters et al. (2021)	69	89.9	USA	9.45 (7.78)	Not reported	Not reported				0.67
Ta et al. (2022)	148	87	Australia	Not reported	9.16 (.94- 51.6)	Not reported				0.56

Table 1.9

Di George Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Age			Quality Criteria			Quality weighting
				Mean Age (SD)	Median Age (IQR)	Age Range	Sample	Epilepsy	Syndrome	
AlKalaf et al. (2020)	28	100	Saudi Arabia	10.92 (8.7)	Not reported	Not reported				0.67
Bohm et al. (2017)	24	58.33	USA	2.08	Not reported	7d - 8y				0.44
Boot et al. (2018)	45	71.1	Canada	Not reported	Not reported	Not reported				0.44
Butcher et al. (2018)	13	30.77	USA	30.9 (13.3)	Not reported	Not reported				0.44
Cunningham et al. (2018)	70	58.6	UK	11.2 (2.2)	Not reported	Not reported				0.67
Zhang et al. (2021)	37	NR	China	Not reported	Not reported	11d - 27y				0.56
Eaton et al. (2019)	108	57.4	UK	13.6 (3.3)	Not reported	6.2 - 20.5y				0.67
Kim et al. (2016)	145	49.7	Korea	Not reported	6.6 (2.5-12.1)	Not reported				0.67

Table 1.10

Wolf-Hirschhorn Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Age		Quality Criteria			Quality weighting
				Mean Age (SD)	Age Range	Sample	Epilepsy	Syndrome	
Battaglia et al. (1999)	15	20	Italy	7.23 (5.2)	Not reported				0.56
Battaglia, Filippi, et al. (2008)	87	37.93	Italy	Not reported	0 - 17y[1]				0.67
A. Battaglia et al. (2021)	35	25.71	Italy	31.74 (7.8)	Not reported				0.56
Kagitani-Shimono et al. (2005)	11	27.27	Japan	10 (7.2)	2 - 25y				0.78
Wieczorek et al. (2000)	13	38.46	Germany	Not reported	6m - 13y				0.44
Shimizu et al. (2014)	21	18.2	Japan	7.16 (5.7)	Not reported				0.56
Yang et al. (2016)	10	40	China	2.6 (2.08)	Not reported				0.67

[1]Age at first observation

Table 1.11

Prader-Willi Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Age			Quality Criteria			Quality weighting
				Mean Age	Median Age	Age Range	Sample	Epilepsy	Syndrome	
Elia et al. (2021)	74	52.7	Italy	Not reported	Not reported	2 - 42y				0.78
Gilboa and Gross-Tsur (2013)	126	50	Israel	13	Not reported	1m - 48y				0.67
Takeshita et al. (2013)	142	57.7	Japan	Not reported	9	2m - 40y				0.67
Vendrame et al. (2010)	92	37.5	USA	11.1	Not reported	Not reported				0.78
Sanjeeva et al. (2017)	34	67.6	India	Not reported	8	1 - 24y				0.44
Shelkowitz et al. (2022)	893	49.7	USA	Not reported	14	8 - 23y				0.56

Table 1.12

Rubinstein-Taybi Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Age			Quality Criteria			Quality weighting
				Mean Age	Median Age	Age Range	Sample	Epilepsy	Syndrome	
Giacobbe et al. (2016)	23	52.17	Italy	7.08	Not reported	18m - 20y				0.89
Kumar et al. (2012)	11	81.8	India	4.3	Not reported	4m - 15y				0.33
Martins et al. (2022)	13	38.46	Brazil	Not reported	11.58	1 - 20y				0.33
Lee et al. (2015)	16	56	Korea	7.4	Not reported	1 - 20y				0.56
Yu et al. (2019)	18	44.4	China	2.67	Not reported	2m - 12y				0.67
Hou (2005)	10	60	Taiwan	Not reported	Not reported	Not reported				0.56

Table 1.13

1p36 Deletion Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Mean Age (SD)	Age Range	Quality Criteria			Quality weighting
						Sample	Epilepsy	Syndrome	
Battaglia, Hoyme, et al. (2008)	60	31.67	USA	Not reported	0 - 24y				0.56
Brazil et al. (2014)	40	27.5	USA	19.65	Not reported				0.67
Carter et al. (2019)	47 (term) [1]	NR	USA	10d (14.8)[2]	Not reported				0.00
Carter et al. (2019)	11 (preterm) [1]	NR	USA	9d (9.5)[2]	Not reported				0.00
Kurosawa et al. (2005)	11	36.4	Japan	8.05 (4.82)	6m - 17y				0.67
Jacquin et al. (2023)	68	42.5	France	Not reported	Not reported				0.78

[1]Patients were divided into term and preterm groups, with term defined as 37-weeks of gestation or more completed.
[2]Mean age at discharge.

Table 1.14

SYNGAP1 Syndrome Study and Sample Characteristics

Author (year)	*N*	% Male	Country of publication	Mean Age (SD)	Median Age	Age Range	Quality Criteria			Quality weighting
							Sample	Epilepsy	Syndrome	
Wright et al. (2022)	27	40.7	UK	8.4 (6.8)	Not reported	Not reported				0.22
Jimenez-Gomez et al. (2019)	15	53	USA	Not reported	Not reported	Not reported				0.67
Mignot et al. (2016)	17	47.1	France	10.3	Not reported	3 - 29y				0.78
Parker et al. (2015)	10	30	UK	8.6	Not reported	Not reported				0.67
Vlaskamp et al. (2019)	57	53	Australia	Not reported	8	Not reported				0.67

A high level of heterogeneity (see Table 1.15) was observed in estimates for nine syndromes (tuberous sclerosis complex, Rett syndrome, Down syndrome, fragile X syndrome, Angelman syndrome, Prader-Willi syndrome, DiGeorge syndrome, 1p36 deletion syndrome and SYNGAP1 syndrome), suggesting that these prevalence estimates may be biased by uncontrolled or confounding factors. Therefore, subsequent analyses were conducted to identify sources of heterogeneity between the estimates of prevalence in the primary studies for each syndrome group.

Table 1.15

Mean Quality Ratings, Pooled Prevalence Estimates for Epilepsy and Heterogeneity for all Syndrome Groups Included in the Meta-Analysis

	Studies	Effects[1]	Patients (n)	Mean quality weighting (SD)	Individual quality scores			Prevalence of Epilepsy		I^2
					Obtained score of 3 for sample	Obtained score of 3 for syndrome	Obtained score of 3 for epilepsy	Random-effects pooled prevalence (CI)	Quality-effects pooled prevalence (CI)	
Tuberous sclerosis complex	41	41	10,485	0.51 (0.16)	0 (0%)	11 (26.8%)	1 (2.4%)	79% (75-84)	80% (75-84)	99%
Rett syndrome	22	22	4,011	0.59 (0.14)	1 (4.5%)	12 (55%)	2 (9.1%)	67% (60-74)	67% (60-74)	96%
Down syndrome	20	21	33,268	0.51 (0.20)	1 (5%)	6 (30%)	4 (20%)	13% (9-17)	13% (9-18)	98%
Fragile X syndrome	14	16	5123	0.68 (0.13)	0 (0%)	14 (100%)	7 (46.7%)	15% (11-18)	14% (11-18)	79%
Angelman syndrome	12	12	428	0.69 (0.1)	0 (0%)	12 (100%)	4 (33.3%)	83% (74-91)	84% (75-92)	91%
MECP2 duplication syndrome	8	8	541	0.57 (0.16)	0 (0%)	5 (62.5%)	0 (0%)	52% (46-58)	52% (46-58)	49%
DiGeorge syndrome	7	7	470	0.59 (0.11)	0 (0%)	7 (100%)	0 (0%)	17% (12-21)	16% (12-21)	39%[2]
Wolf-Hirschhorn syndrome	7	7	192	0.60 (0.1)	0 (0%)	7 (100%)	0 (0%)	96% (92-100)	96% (92-100)	62%
Prader-Willi syndrome	6	6	1411	0.65 (0.13)	0 (0%)	6 (100%)	0 (0%)	12% (5-18)	11% (5-18)	90%
Rubinstein–Taybi syndrome	6	6	91	0.56 (0.21)	0 (0%)	1 (16.7%)	3 (50%)	5% (0-11)	4% (0-10%)	49%
1p36 deletion syndrome	5	6	237	0.53 (0.31)	0 (0%)	4 (80%)	0 (0%)	57% (42-71)	54% (37-71)	81%
SYNGAP1 syndrome	5	5	126	0.60 (0.22)	0 (0%)	4 (80%)	0 (0%)	90% (79-100)	93% (81-100)	77%

[1]In some cases the number of effects exceeds the number of studies; where studies reported on a sample of participants separated into more than one group (e.g. participants born term and participants born preterm as in Carter et al. (2019)), data for each sample was extracted individually where appropriate

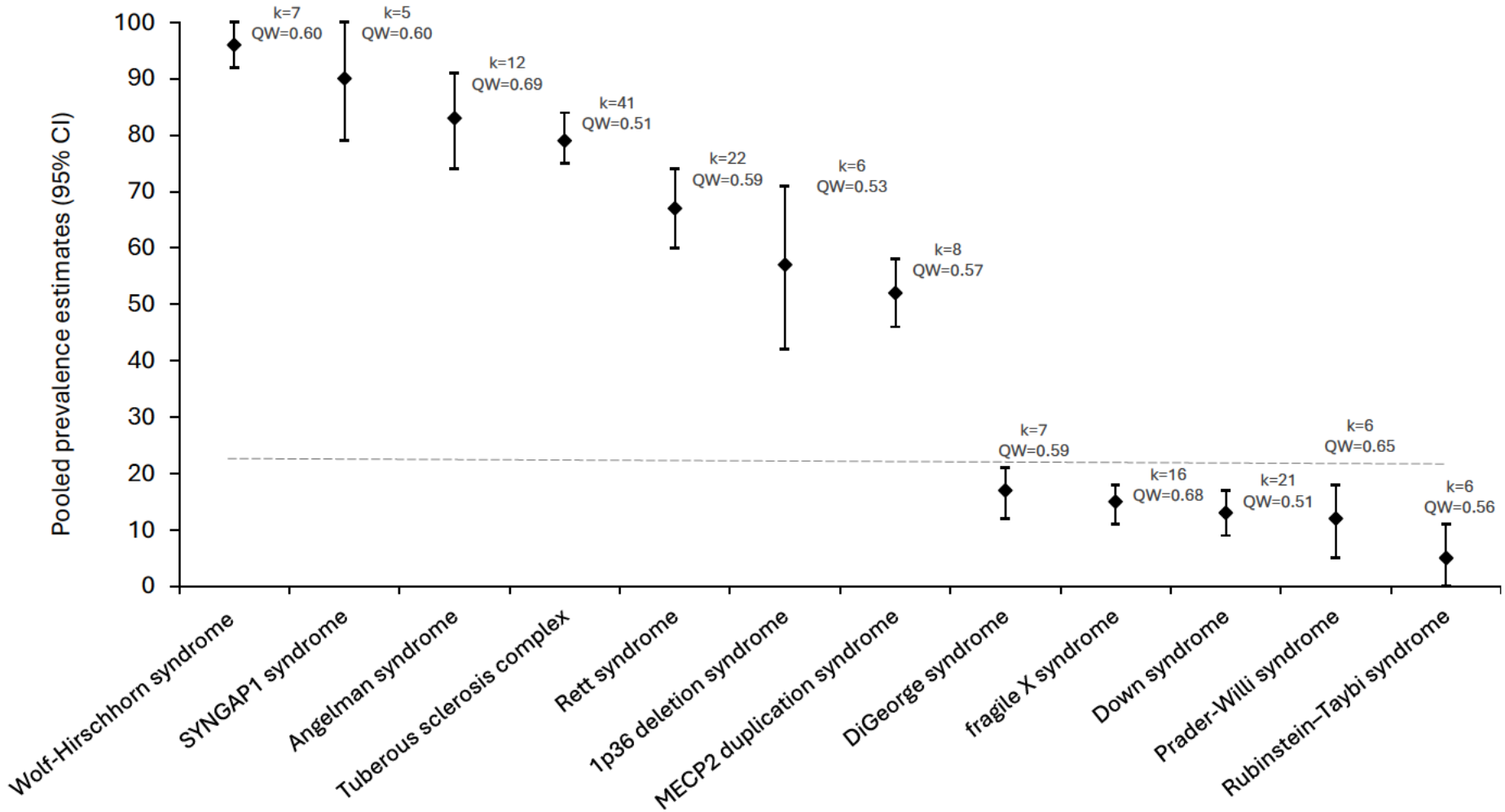
[2]Corrected estimate and I^2 value following the leave-one-out procedure (see page 36)

The Impact of Influential Primary Studies

Following the ‘leave-one-out’ analysis, one study (Butcher et al., 2018) was identified to have a disproportionate effect on the pooled prevalence estimates of epilepsy for DiGeorge syndrome, and thus the study was re-examined to determine whether any substantive reason for the discrepancy could be identified. Within the study, medical records were reviewed for participants with DiGeorge syndrome where the term catatonia or symptoms of catatonia were detailed. Whilst participants were not recruited due to a diagnosis of epilepsy (see Table 1.2 for exclusion criteria), epileptic seizures are a secondary cause of catatonia (Gadelho & Marques, 2022), and thus a substantial bias in the identification of participants was determined. The study was subsequently removed from the final analysis due to the identified bias in the participant sample. The random-effects model was recalculated with the remaining seven studies. The corrected model reported prevalence of epilepsy for DiGeorge syndrome as 17% (95% CI 12-21). The corrected estimate is approximately an 11% decrease relative to the uncorrected estimate (28%, 95% CI 9-46). The heterogeneity decreased from 94 to 39%. The final corrected estimates of pooled prevalence rates for epilepsy and 95% CI are depicted for each syndrome group in Figure 1.2.

Figure 1.2

Pooled Prevalence Estimates of Epilepsy Using the Random-Effects Model with Number of Effects (K), Mean Quality Weighting (QW) and a Reference Line of the Pooled Prevalence Estimate of Epilepsy in People with ID of Mixed Aetiology (22%)



The Impact of Study-Level Characteristics

Across all syndromes included in the meta-analysis, only two studies obtained the highest quality rating for sample identification (1%) and, 21 (14%) for epilepsy confirmation, whereas 89 (58%) achieved the highest quality rating for syndrome confirmation. For syndrome groups with 10 or more effects, a series of subgroup analyses were conducted on the quality ratings to assess the impact of possible methodological bias on prevalence estimates (see Appendix 3.3).

No significant differences between the quality ratings for sample identification, syndrome confirmation or epilepsy confirmation were found for tuberous sclerosis complex, Rett syndrome or fragile X syndrome, suggesting the obtained prevalence estimates for these syndromes are robust to these methodological biases. In Down syndrome, studies rated as 'adequate' on sample identification reported significantly lower epilepsy prevalence (6%) than papers rated as 'good' (15%; $\chi^2 = 7.96$, $p = .0048$) or 'excellent' (20%; $\chi^2 = 14.2$, $p = .0002$). In Angelman syndrome, studies rated as 'poor' on sample identification reported significantly higher prevalence (100%) than studies rated as 'adequate' (77%; $\chi^2 = 10.46$, $p = .0012$) or 'good' (85%; $\chi^2 = 11.64$, $p = .0006$). Also, in Angelman syndrome, studies rated as 'poor' on epilepsy confirmation reported significantly lower epilepsy prevalence (39%) than studies rated as 'good' (86%; $\chi^2 = 23.6$, $p < .0001$) or 'excellent' (89%; $\chi^2 = 20.4$, $p < .0001$).

The Impact of Participant-Level Characteristics

To further explore the impact of participant-level characteristics upon prevalence of epilepsy for each syndrome group, a series of meta-regressions were conducted for

syndrome groups with 10 or more effects for either the mean or median age of the participant sample (Table 1.16).

Age

The association between mean age and reported prevalence of epilepsy did not reach statistical significance for tuberous sclerosis complex or Angelman syndrome. However, for Down syndrome, the prevalence of epilepsy increased by .004 for each year of age (reported mean age; z = 3.8, p = .0001). Additionally, the prevalence rates of epilepsy for tuberous sclerosis complex decreased by -.006 for each year of age (reported median age; z = -4.3, p = <.0001).

Table 1.16

Meta-Regression for the Impact of Participant Age on Prevalence Estimates for Syndrome Groups with 10 or more Effects (K)

	k	Coefficient	SE	Z	*p*
Tuberous sclerosis complex - mean age	24	-0.004	0.003	-1.349	.177
Tuberous sclerosis complex - median age	10	-0.0056	0.0013	-4.3036	**<.0001***
Down syndrome – mean age	13	0.004	0.0011	3.813	**.0001***
Angelman syndrome – mean age	10	0.001	0.004	0.257	.797

*significant at $p < .01$ level

Sex

The association between proportion of male participants in each sample, and prevalence of epilepsy did not reach statistical significance for any of the syndrome groups included in the meta-regression analyses. See Appendix 3.3 for the results.

The Impact of Publication and Small Study Biases

When exploring the impact of publication bias for syndrome groups with 10 or more effects, the high heterogeneity in the prevalence rates of epilepsy, may contribute to asymmetry in the funnel plots and lead to false significance when testing for publication

bias (Peters et al., 2006). However, for completeness, funnel plots were reviewed and tests of publication bias were carried out. Funnel plots for each syndrome group are included in Appendix 4.3.

Egger's regression tests were not significant for Rett syndrome, Down syndrome or fragile X syndrome, indicating no funnel plot asymmetry for these syndrome groups.

Tuberous sclerosis complex

Due to the large heterogeneity previously described, the funnel plot was difficult to interpret. There was evidence of small study bias in the distribution of epilepsy prevalence, whereby small studies tended to produce lower estimates of epilepsy prevalence than studies with larger sample sizes. However, this mitigates against publication bias when comparing to a base rate of epilepsy prevalence in people with ID (22%). Egger's regression test was significant (β = -6.49, t = -5.63, p = <.0001). Therefore, the trim and fill procedure was conducted. The trim and fill procedure yielded a corrected prevalence estimate of 77% (95% CI 72-81), evidencing approximately a 2% decrease relative to the uncorrected estimate of 79%.

In addition to the Trim and Fill procedure, Owrin's (1983) failsafe number was calculated. Orwin's algorithm indicated that 974 studies reporting an average consistent with the general ID population would be required to reduce the uncorrected estimate of 79% to baseline levels (defined as the prevalence estimate of the general ID population), suggesting that the observed prevalence estimate of 79% is robust to studies missing due to publication bias.

Angelman syndrome

There was evidence of publication bias in the distribution of prevalence of epilepsy for Angelman syndrome. Egger's regression test was significant ($\beta = -2.93$, $t = -5.88$, $p = .0002$), and so the trim and fill procedure was carried out. The Trim and Fill procedure however, did not impute any studies and therefore did not result in an adjustment to prevalence estimates. Orwin's failsafe number was also calculated. Orwin's algorithm indicated that 715 studies reporting an average consistent with the general ID population would be required to reduce the uncorrected estimate of 83% to baseline levels, suggesting that the observed prevalence estimate of 83% is robust to studies missing due to publication bias.

Discussion

The current meta-analysis provided the first pooled prevalence estimates of epilepsy and/or epileptic seizures in genetic syndromes associated with ID, whilst accounting for the quality of methodology across studies. The prevalence of epilepsy was notably high in Wolf-Hirschhorn syndrome (96%), SYNGAP1 syndrome (93%), Angelman syndrome (84%), tuberous sclerosis complex (80%), Rett syndrome (67%), 1p36 deletion syndrome (54%) and MECP2 duplication syndrome (52%). These estimates are strikingly higher than those reported for epilepsy prevalence in people with ID of heterogenous aetiology (22%; Robertson et al., 2015). The lowest prevalence estimate was found in people with Rubinstein-Taybi syndrome (4%), with DiGeorge (16%), fragile X syndrome (14%), Down syndrome (13%) and Prader-Willi syndrome (11%) also showing prevalence estimates lower than reports for estimates in people with ID (Robertson et al., 2015).

The prevalence estimates of the current study are largely consistent with previously reported prevalence estimates cited by systematic reviews and individual empirical studies conducted with specific syndromes. For example, Robertson et al. (2015) reported prevalence of epilepsy in people with Down syndrome (12.4%) to be lower than in the general population of people with ID (22%), this estimate is consistent with the findings of the current meta-analysis (13%). The estimate of 52% for MECP2 duplication syndrome was consistent with the 52% incidence rate of epilepsy reported by Ramocki et al. (2010) for 110 people described in the literature. Additionally, the high prevalence estimate of 96% for Wolf-Hirschhorn syndrome is congruous with a systematic review reporting seizures to occur in over 90% of people with Wolf-Hirschhorn syndrome (Paprocka et al., 2022). The similarities in prevalence estimates between the present meta-analytic review and those previously reported in systematic reviews of single syndrome groups improves confidence in these estimates; they should be used to guide clinical assessment of epilepsy and seizures in these syndrome groups.

Whilst the prevalence estimates were mostly consistent with past estimate ranges cited in systematic reviews, slight differences were observed. Firstly, whilst the high estimate of 80% found for tuberous sclerosis complex is at the very mid-point of the range reported by Hallett et al. (2011; 66-93%), it fell just slightly below more recent estimates reported by Zöllner et al. (2020; 84-88%). However, both systematic reviews reported on far fewer studies than the estimates of this study, suggesting that the pooled prevalence obtained in this meta-analysis is robust. Secondly, Raspa et al. (2017) reported rates of epilepsy to be between 10 to 20% for boys with fragile X syndrome and slightly lower for girls; the estimate of 14% for this study is toward the low end of the range. The more conservative estimate may be due to the inclusion of data from a mixed sex sample of people with fragile X syndrome. Similarly, the prevalence estimates generated in the

current study for Rett (67%), Angelman (84%), Prader-Willi (11%), and 1p36 deletion syndromes (54%) were at the low end of previously reported prevalence range estimates in systematic reviews (Rett syndrome; 60-80% reported by Operto et al. (2019), Angelman syndrome; 80-95% reported by Wheeler et al. (2017), Prader-Willi syndrome; 4-26% reported by Verrotti et al. (2014), and 1p36 deletion syndrome; 44-70% reported by Jacquin et al. (2023)). Large confidence intervals were found across these syndrome groups, suggesting uncertainty in the estimates and the need for further research. However, the more conservative estimates of the current meta-analysis are based on a larger number of studies than previous reviews and additionally, are weighted for methodological quality, strengthening the robustness of estimates.

The analysis in the present study attempted to understand the heterogeneity identified in the literature across many of the syndrome groups. In particular, very high heterogeneity (≥90%) in epilepsy prevalence estimates was found for tuberous sclerosis complex, Rett syndrome, Down syndrome, Angelman syndrome and Prader-Willi syndrome, limiting confidence in the estimates for these groups. The leave-one-out analysis for Angelman syndrome found that heterogeneity decreased from 91 to 73% when Ohtsuka et al. (2005) was removed from the analysis; however this did not impact the prevalence estimate (84% vs 80%) and no substantive reason for removing the paper was identified. Nonetheless, this may help us to understand the high heterogeneity for this syndrome group. Additionally, research was sparse for a number of the included syndrome groups whereby heterogeneity was high, including Prader-Willi syndrome, Angelman syndrome, 1p36 deletion syndrome and SYNGAP1 syndrome. A lack of studies can impact the accuracy of prevalence estimates due to the enhanced effect of heterogeneity between studies. Further research focused on these syndrome groups would be needed to strengthen the robustness of the estimates where a sparsity of literature has been found.

Further subgroup analyses were conducted to understand the high heterogeneity identified and specifically whether age and sex moderated prevalence rates. The prevalence of epilepsy increased with age for Down syndrome and decreased with age for tuberous sclerosis complex. The finding that the prevalence of epilepsy increases with age in people with Down syndrome is consistent with the well-established observation in literature indicating an increased risk for epilepsy particularly after 40 years of age, which coincides with the development of Alzheimer's disease (Altuna et al., 2021; Bösebeck, 2022; Carfì et al., 2014; McVicker et al., 1994). The significant decrease in epilepsy prevalence across the lifespan indicated in tuberous sclerosis complex is also consistent with previous literature reporting that epilepsy is more commonly reported in younger people with tuberous sclerosis complex (Chu-Shore et al., 2010; Nabbout et al., 2021). This finding may be related to the advancements in understanding of epilepsy treatment pathways for people with tuberous sclerosis complex (e.g. Nouri et al., 2022; Schubert-Bast & Strzelczyk, 2021), for example the use of preventative epilepsy management and pre-seizure monitoring (e.g. Jozwiak et al., 2019; Kotulska et al., 2021; Słowińska et al., 2021). Furthermore, research points to a number of syndrome specific associations between age and epilepsy, which may relate to other aspects of the phenotypes of these syndromes. For example, the mean age of seizure onset in fragile X syndrome has been reported to be 6.4 years (Berry-Kravis et al., 2021), whereas in Angelman syndrome and Down syndrome seizures are likely to begin in the first year of life (Pueschel et al., 1991; Samanta, 2021, respectively). The between-syndrome variations in epilepsy characteristics highlights the need for epilepsy monitoring to be syndrome sensitive. The percentage of male participants was not found to moderate prevalence rates across any of the included syndrome groups. This may be unexpected for certain syndrome groups, for example, previous prevalence data shows higher prevalence rates of epilepsy for males with fragile

X syndrome compared to females (Berry-Kravis et al., 2021; Raspa et al., 2017). However, whilst only groups with 10 or more effects were included in the subgroup analyses, the low number of effects may mean that further research is needed to confirm this null finding.

A final aim of the study was to consider the methodological quality of the literature and to ascertain the impact of methodological variability on generated prevalence estimates. For Down syndrome, papers that were rated higher for quality on sample identification reported significantly higher epilepsy prevalence. These higher estimates were closer to previously reported prevalence rates (e.g. Robertson et al., 2015) than those reported by the studies rated as adequate on sample identification, increasing confidence in the estimates. This finding suggests that where samples were more representative, evidenced through the use of multiple samples or national sampling, prevalence of epilepsy was higher. However, for Angelman syndrome, two studies rated as poor for sample identification reported significantly higher prevalence of epilepsy (Guerrini et al., 1996; Ohtsuka et al., 2005). Both studies evaluated EEG profiles of seizure activity. Thus, an interpretation of this finding may be related to research that suggests studies reviewing EEG activity tend to report higher prevalence estimates of epilepsy (e.g. Akman et al., 2009; Paprocka et al., 2022). Additionally, for Angelman syndrome, studies that were rated higher for quality on epilepsy confirmation, such as those reviewing EEG data, reported significantly higher prevalence estimates, adding weight to this interpretation. It is important to note here, that the low number of effects in the subgroup analyses mean caution should be taken in these interpretations. Overall, the differences between prevalence estimates and quality ratings suggest the need for more robust and clear reporting of methodology, particularly with regard to the assessment of epilepsy and recruitment of participants.

The current meta-analysis was broad in its search strategy, allowing for a comprehensive synthesis of the relevant literature and an evaluation of its methodological quality. This gave light to a number of key areas of improvement for future research. Firstly, the high heterogeneity may be understood in part by the wide variation of methodological approaches implemented between studies to assess the prevalence of epilepsy. Study designs typically varied between small n studies evaluating EEG profiles of seizure activity, parent/caregiver-report questionnaire studies and larger scale retrospective chart reviews. There are both strengths and limitations to the various study designs observed, for example, there may be an overall under-reporting of epileptic seizures in caregiver-reported studies when compared to studies monitoring EEG-video results (e.g. Akman et al., 2009; Paprocka et al., 2022). The variability in establishing the presence or diagnosis of epilepsy between studies, may therefore limit the findings of the meta-analysis. Future research striving to establish the prevalence or profile of epilepsy in single syndrome groups should consider the methodological approach to confirming epilepsy as a possible moderator of prevalence estimates.

In addition, the definition of epilepsy varied across the included studies or in many instances was not specified. Definitions ranged from studies stating a diagnosis or history of epilepsy, to reporting a definition of epilepsy in accordance with standard definitions from the International League Against Epilepsy criteria, to specifying the proportion of those with various types of epileptic seizures. Whilst the quality assessment of the present study suggested that prevalence estimates were largely unaffected by the confirmation of epilepsy, ideally, to allow for accurate prevalence estimates, the same definition of epilepsy should be adopted across studies. Empirical research should therefore strive to report a clear definition of epilepsy and where possible, meta-analytic reviews can

investigate the impact of epilepsy definitions on prevalence estimates in those syndrome groups whereby estimates appear high.

The description of epilepsy characteristics, for example, onset of seizures, seizure type and severity, as well as reporting on the sample and study characteristics was often unclear or varied largely between studies. Description of the level of ID in participant samples was under-reported and challenging to extract. Similarly, information on the type and severity of seizures was also not always reported. Given the associations between level of ID and epilepsy profile, acquiring this information would support the understanding of underlying pathways linking genetic syndromes, ID, and epilepsy. Empirical research investigating epilepsy in genetic syndromes should ensure comprehensive reporting of epilepsy profiles and description of ID, alongside gaining genetic confirmation of syndromes where possible, to support linking genetic mechanisms to specific epilepsy phenotypes. Alongside this, single syndrome meta-analytic review exploring the impact of ID on the prevalence of epilepsy is needed. Overall, clearer reporting of epilepsy characteristics as well as participant and study characteristics, will allow more comprehensive moderator analyses within future meta-analytic review. This will enable research to progress understanding of the underlying mechanisms between genetic factors, intellectual functioning and epilepsy profiles. This will further inform clinicians as to the risk, type and severity of epilepsy for specific syndrome groups and in turn, identify appropriate treatment pathways.

A substantial number of syndrome groups were identified through the literature search but excluded from the analysis due to a scarcity of studies reporting on the prevalence of epilepsy in these groups. In addition, a number of the included groups lacked enough effects to allow for further interpretation through subgroup analysis. Thus, further

research reporting the prevalence and profile of epilepsy in these groups is needed to allow robust prevalence estimates to be established.

The meta-analysis has identified a number of priority syndrome groups at an increased risk of developing epilepsy, whereby prevalence estimates appear notably high. Furthermore, all syndrome groups included in the review showed prevalence estimates higher than those reported for the general population (.76%; World Health Organization, 2019). For some of these syndrome groups, for example, tuberous sclerosis complex, epilepsy is well characterised and understood as part of the phenotype of the syndrome and therefore clinical recommendations for epilepsy management are better established (e.g. Curatolo et al., 2018; Schubert-Bast & Strzelczyk, 2021). This is not the case across all included groups and thus for syndrome groups at risk of developing epilepsy, epilepsy assessment and management should be targeted. Treatment recommendations in tuberous sclerosis complex may serve a useful tool for guiding pathways for other genetic syndromes. Establishing possible treatment pathways most effective in reducing seizure severity and frequency, whilst also optimising quality of life, should therefore be a key focus of clinicians and professionals supporting people with genetic syndromes (e.g. see Watkins et al., 2022). In syndrome groups with an increased risk of epilepsy, early monitoring of seizure activity should be prioritised following syndrome diagnosis. Those working with people with these syndromes should also support families in their understanding and recognition of seizures to support early epilepsy assessment and management.

Clinicians should be cognisant of the risk for developing epilepsy across genetic syndrome groups, and support for individuals affected by epilepsy and their families should be prioritised. This is particularly pertinent due to evidence showing people with

epilepsy are likely to experience co-occurring anxiety and depression, social exclusion and a poorer quality of life (World Health Organization, 2019). Additionally, in the management of epilepsy in people with ID, careful consideration should be given to the impact of anti-epileptic medication on behaviour and mental health (Dussaule & Bouilleret, 2018; Snoeijen-Schouwenaars et al., 2021). Therefore, multidisciplinary team working should be considered to support a holistic approach towards supporting people with genetic syndromes who experience epilepsy, whereby consideration is given to wider factors complicating treatment pathways, such as co-occurring mental health difficulties and side effects of medication.

In summary, the current meta-analysis reports prevalence estimates for epilepsy across 12 genetic syndromes. The findings demonstrated the variability in prevalence estimates across genetic syndromes associated with ID, establishing syndromes whereby the risk of developing epilepsy is likely, whilst also highlighting groups that are currently under-researched. The variation in estimates across groups supports the notion of exploring underlying mechanisms that may drive presentations of epilepsy and intellectual functioning. It should be noted that prevalence estimates may be impacted by the heterogeneity between studies, with varied approaches used to establish the presence of epilepsy, and thus estimates should be interpreted with caution. Future research should aim to extend the meta-analytic findings, through clear and comprehensive reporting of epilepsy prevalence rates in genetic syndrome groups. Providing description of how epilepsy has been defined, as well as detailing epilepsy characteristics and level of intellectual functioning will enable future reviews to elucidate more robust prevalence estimates. In turn, this may support the identification of priority syndrome groups whereby epilepsy support and management needs to be targeted.

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Chapter 2: Empirical Research Paper

Persistence and Predictors of Self-Injurious, Aggressive, and Destructive Behaviour in People with Genetic Syndromes Associated with Intellectual Disability

Word Count: 6,711

Abstract

Background: Self-injurious, aggressive and destructive behaviours have been found to be elevated in genetic syndromes associated with intellectual disability. Yet few studies have explored the developmental trajectory of these behaviours over time in genetic syndromes.

Aims: The study aimed to evaluate the persistence of self-injurious, aggressive and destructive behaviours in a cohort of people with genetic syndromes over 16 years. Additionally, demographic and behavioural characteristics associated with the developmental trajectory of these behaviours was investigated.

Method: Parents/carers of 81 people with genetic syndromes completed an online survey. Analysis assessed the persistence of behaviours over 16 years and evaluated possible behavioural risk markers associated with the persistence of self-injury, aggression and destruction of property. The value of the identified risk markers in predicting persistence of behaviours was also assessed.

Results: Self-injurious, aggressive and destructive behaviours were persistent in 63.2%, 62.5% and 63.2% of participants, respectively. Self-injurious and destructive behaviours were stable over the 16-year period, whilst the proportion of those showing aggressive behaviours significantly changed over time. Baseline levels of impulsivity and mood predicted persistent aggressive behaviours, and impulsivity predicted persistent destruction of property.

Conclusions: The findings suggest that self-injurious and destructive behaviours, in particular, continue to persist in people with genetic syndromes over a 16-year period. Impulsivity and mood may be useful predictors able to support identification of those at an increased risk of developing persistent behaviours that challenge.

Introduction

'Behaviours that challenge' (BtC) is a socially constructed umbrella term used to refer to behaviours of an intensity, frequency or duration that they substantially impact upon a person's and/or other's quality of life, physical safety and may result in aversive or restrictive responses (Banks et al., 2007; Emerson & Bromley, 1995). Self-injurious behaviour, aggression and property destruction are considered severe forms of BtC and are common in people with intellectual disability (ID). Importantly, the presence of these behaviours in people with ID is associated with poorer quality of life (Beadle-Brown et al., 2009), increased use of psychotropic medication (Tsiouris et al., 2013) and restrictive practices (Allen et al., 2009), and can considerably impact on carer emotional wellbeing and levels of stress (Adams et al., 2018). BtC are reported to be elevated across genetic syndromes associated with ID (Arron et al., 2011; Powis & Oliver, 2014), with estimates of 55.8% of those with ID and genetic syndromes showing self-injury and 52.8% displaying physical aggression (Arron et al., 2011). Whilst BtC appear to impact a large proportion of people with genetic syndromes, there is a paucity of research delineating how these behaviours change over time in this population. As such, there is an imperative need to further understand the developmental trajectory of BtC in people with genetic syndromes associated with ID, to inform early intervention practices.

Research has highlighted the persistence of BtC across the lifespan among a wider population of people with ID of heterogenous aetiology, whereby the cause or origin of ID may be due to a number of different factors such as complications during pregnancy or birth, developmental disabilities, and genetic or chromosomal conditions (Harris, 2006). Self-injurious and aggressive behaviours typically occur in childhood with prevalence estimates increasing into early adulthood before subsiding (Davies & Oliver, 2013). In a

longitudinal study, self-injurious, aggressive and destructive behaviours were found to persist over two years in children with ID in 58%, 69% and 57%, respectively (Davies & Oliver, 2016). A recent systematic review suggests estimates for the persistence of self-injurious behaviours range from 19 (Dimian et al., 2017) to 95% (Nøttestad & Linaker, 2001) in populations with intellectual and developmental disabilities (Dimian & Symons, 2022), with estimates increasing with older age. Furthermore, in autism, estimates for the persistence of self-injurious behaviour suggest 44% persistence over 10 years (Laverty et al., 2020) and 77.8% over three years (Richards et al., 2016). Lower estimates of aggressive behaviours have been reported in autistic people, with behaviours persisting in 30% of people over 10 years (Laverty et al., 2023). Less attention has been given to establishing the persistence of aggression and destruction of property. Defining different types of behaviour with specificity, such as exploring self-injurious, aggressive and destructive behaviours, is important as there may be different trajectories for different behaviours (Beavers et al., 2013; Oliver, 2017). Therefore, it is important for research to delineate longitudinal trajectories across different forms of behaviours in populations with ID, in particular across genetic syndrome groups where limited data exist.

Despite the elevated prevalence of BtC in people with genetic syndromes associated with ID, research is relatively limited in its delineation of the persistence of these behaviours over time. Single syndrome studies have begun to explore the developmental trajectory of these behaviours. For example, estimates of persistence in people with tuberous sclerosis complex vary from 67% for aggression and destruction of property to 85% for self-injury over a three-year period (Wilde et al., 2018). In people with fragile X syndrome, self-injurious behaviours and aggression persisted in 77% and 69% over eight years, respectively (Crawford et al., 2019). Again, these studies point to the highly persistent nature of self-injurious, aggressive, and destructive behaviours in single

syndromes. However, this cannot be extrapolated to wider populations with genetic syndromes, where the persistence of BtC has not been described. Thus, longitudinal cohort studies detailing the prevalence and persistence of self-injurious, aggressive and destructive behaviours in genetic syndromes associated with ID are needed.

Cross-syndrome comparative research is important in highlighting both characteristics that are common across different syndromes as well as behavioural phenotypes associated with or elevated in certain syndromes. For example, the behavioural phenotype, defined as a set of characteristics more commonly occurring in those with a given syndrome than those without it (Dykens, 1995; Waite et al., 2014), associated with Cornelia de Lange syndrome indicates a higher prevalence of self-injury, whilst higher prevalence estimates of aggression are associated with Angelman syndrome (Arron et al., 2011). However, whilst there are differences in topographies of BtC between and within distinct syndromes, it is also evident that BtC are elevated across all syndrome groups (Arron et al., 2011). As such, a pragmatic strategy to advance understanding of the developmental trajectory of these behaviours in a high-risk population would be to incorporate a transdiagnostic approach, investigating change into adulthood in a heterogenous group of people with genetic syndromes associated with ID (see Astle et al., 2022). There is a need to investigate persistence on a larger scale in order to enhance power in the analysis, alongside reporting findings from smaller cohorts of single syndrome groups (e.g. Kingswood et al., 2014). For example, open patient registries have begun to strategically group genetic syndromes by overlapping aetiology or phenotype, such as the GenIDA registry which is focused on characterising populations with ID of genetic cause with a focus on autism and epilepsy (Burger et al., 2023). These registries aim to improve statistical evidence and understanding of genotype-phenotype correlations through grouping large cohorts of conditions with common features (Sernadela et al.,

2017). In addition, this approach mitigates the risk that by focusing research on just single syndromes, the majority of people with genetic syndromes may go unstudied, particularly rare syndrome groups that have less well-established behavioural phenotypes, such as PTEN-related syndromes where BtC appear highly prevalent (e.g. Cummings et al., 2024). Therefore, describing longitudinal data in a heterogenous group of genetic syndromes associated with ID may enhance confidence in findings regarding the developmental trajectory of BtC.

A number of demographic and behavioural characteristics are associated with the presence of self-injury, aggression and property destruction, with emerging evidence of risk markers associated with, and predicting the persistence of, BtC. In populations with heterogenous ID, characteristics found to predict the persistence of self-injury include lower ability level, attention deficit hyperactivity disorder (ADHD), visual impairment, younger age, and site and topography of self-injury (Cooper et al., 2009; Danquah et al., 2009; Emerson et al., 2001). In autism, risk markers including impulsivity, overactivity, stereotyped behaviour, lower adaptive functioning and difficulties with social interaction and communication are associated with the persistence of self-injury and aggression over time (Laverty et al., 2023; Laverty et al., 2020; Richards et al., 2016). Understanding of risk markers associated with the prevalence and persistence of BtC is less well developed in genetic syndromes associated with ID. Emerging single syndrome research identified repetitive behaviour as a predictor of persistent self-injury in fragile X syndrome, and age, impulsivity and overactivity are associated with persistent aggression (Crawford et al., 2019). Similarly, overactivity and impulsivity are associated with persistent self-injury and aggression in people with tuberous sclerosis complex (Wilde et al., 2018). There is a need to explore whether these findings extend over a longer period of time across genetic syndromes and in turn, suggest at-risk characteristics that may identify people with the

greatest risk of experiencing persistent BtC. Function-based interventions aimed at reducing BtC may lead to better outcomes for people with ID when implemented earlier due to behaviours being less well established through reinforcement processes (Davies & Oliver, 2016; Oliver, 1995; Oliver et al., 2005). Furthermore, National Institute for Health and Care Excellence guidance (NICE, 2015) for BtC suggest that proactive interventions aimed at reducing the risk of BtC should be employed. Therefore, identifying risk markers predicting the persistence of BtC may support a more effective targeted intervention approach aimed at improving outcomes and support for high-risk groups at an earlier stage.

There are a number of behavioural correlates and risk markers, such as impulsivity and overactivity, difficulties with social interaction/communication and repetitive behaviours that are consistently reported to be associated with BtC across populations (Crawford et al., 2019; Laverty et al., 2020; Richards et al., 2017; Richards et al., 2016; Shelley et al., 2023; Wilde et al., 2018), implicating these as possible transdiagnostic risk markers. Identifying predictors that span across genetic syndromes may allude to causal mechanisms underlying the persistence of BtC, that may be relevant to a broader group of people with syndromic ID. So, whilst there are likely specific syndrome-associated pathways to behavioural outcomes, it may also be possible to identify processes that are common across syndromes. For example, it has been theorised that high levels of repetitive behaviour and impulsivity found to be associated with the presence of BtC can be understood through models of compromised executive functioning and behavioural inhibition that are likely to give rise to more frequent or severe BtC (Oliver & Richards, 2015; Turner, 1997). Whilst this has been hypothesised more often in populations of autistic people (Laverty et al., 2023; Laverty et al., 2020; Richards et al., 2016), the cognitive mechanism underlying the association between impulsivity and the presence of

BtC has more recently been considered in rare genetic syndrome research as well (e.g. Shelley et al., 2023). Findings such as these may have substantial clinical importance in contributing to existing interventions through including strategies aimed at targeting individual characteristics such as impulsivity, regardless of aetiology of neurodevelopmental condition.

In summary, the prevalence of BtC is elevated in people with genetic syndromes associated with ID (Arron et al., 2011). Despite this, there is a lack of research delineating the developmental trajectory of severe forms of BtC, including self-injury, aggression and destruction of property in this population. Evidence suggests BtC are persistent in people with ID, though this is less well evaluated in people with genetic syndromes. There is, however, emerging evidence of the persistence of self-injury, aggression and property destruction in single syndrome groups, reporting comparable persistence rates to populations with ID of heterogenous aetiology and other neurodevelopmental conditions (Crawford et al., 2019; Wilde et al., 2018). To the author's knowledge, no data exist investigating the persistence of BtC in a heterogenous group of people with genetic syndromes associated with ID. Therefore, data were collected to calculate the persistence of, and behavioural risk markers for self-injury, aggression and property destruction in genetic syndromes associated with ID over a span of 10 to 20 years. The aims of the present study were as follows:

1. To evaluate the persistence of self-injury, aggression and destruction of property across two time points in people with genetic syndromes associated with ID.

2. To investigate possible demographic and behavioural risk markers associated with the persistence of self-injury, aggression and destruction of property at T_2.

3. To establish the value of behavioural and demographic variables at T_1 in predicting the persistence of self-injury, aggression and destruction of property at T_2.

Methods

Recruitment

The present study was part of a larger project: Behavioural and Emotional Outcomes in individuals with Neurodevelopmental Disorders (BEOND). The project was pre-registered on Open Science Framework, which can be accessed through the following link: https://osf.io/n89x7. The BEOND study was a longitudinal survey expanding on a previous survey conducted by the Cerebra Centre for Neurodevelopment Disorders which commenced in 2003. Participants at Time 1 (T_1) were recruited in the original study through syndrome support groups and digital platforms between 2003 to 2012. At Time 2 (BEOND; T_2), families were recruited from the existing cross-syndrome database held by the Cerebra Network of parents/carers from the T_1 sample that had consented to being contacted about future research. Families were invited to take part through email or letter. The mean follow-up time was 16.2 years (range = 10.7-19.8 years).

Participants

Three participants that completed the measure of self-injury, aggression and destruction of property at T_2 were excluded as they had incomplete data on this measure at

T_1. A final sample of 81 participants were included. Demographic characteristics of the 81 participants at each time point are presented in Table 2.1. Genetic syndrome groups included in the sample comprised of fragile X syndrome (n = 25), Angelman syndrome (n = 18), Rubinstein-Taybi syndrome (n = 13), tuberous sclerosis complex (n = 9), Smith Magenis syndrome (n = 5), 8p23 syndrome (n = 3), Cornelia de Lange syndrome (n = 3), Cri du Chat syndrome (n = 1), Prader-Willi syndrome (n = 1), Lowe syndrome (n = 1), Kleefstra syndrome (n = 1) and Phelan-Mcdermid syndrome (n = 1). Informants comprised of parents/guardians (n = 77) and carers (n = 4). Informant-report confirmed genetic syndrome diagnosis was from a relevant professional (GP, clinical geneticist, or paediatrician).

Table 2.1

Demographic Characteristics of Participants at T_1 and T_2

		Time 1 (n = 81)	Time 2 (n = 81)
Age in years	Mean (SD)	14.5 (8.8)	31.6 (9.5)
	Range	2-42	14-53
Sex	% male	69.1[3]	67.9[4]
Wessex self-help	% partly able/able	64.2	61.7
Wessex mobility[1]	% mobile	87.7	81.5
Wessex speech[2]	% verbal	60.5	65.4
Wessex vision	% normal	85.2	75.3
Wessex hearing	% normal	91.4	88.9

[1]Able to walk unaided, derived from the Wessex Questionnaire (Kushlick et al., 1973)
[2]Speak/sign more than 30 words, derived from the Wessex Questionnaire (Kushlick et al., 1973)
[3] n=3 missing
[4] 30.9% (n=25) female, 1.2% (n=1) prefer to self-describe

Procedure

Carers were invited to complete an online survey containing an information sheet, consent forms, a background questionnaire and questionnaire pack of measures assessing behaviour and development. Hard paper copies of the survey were available upon request.

The BEOND project obtained ethical approval from the Wales Research Ethics Committee 1 Cardiff (ref: 22/WA/0086; see Appendix 1).

Measures

The following informant-report questionnaires were included in the questionnaire pack and were appropriate for people with intellectual disabilities.

The background questionnaire obtained demographic information on sex, age, mobility, verbal ability and genetic syndrome diagnosis, and was included at both time points. A sub-section was included at T_2 to obtain information on clinical services accessed in the past two years. Informants were asked to retrospectively report on service use. Inclusion of these service receipt items allowed exploration of service use and associations with BtC. All other measures were included at both time points.

The Wessex Questionnaire (WQ; Kushlick et al., 1973) was used in this study to measure self-help adaptive functioning. The scale contains the following subscales: continence, mobility, self-help skills, speech and literacy. The scale has good inter-rater reliability at the subscale level and is appropriate for use in large scale questionnaire studies (mean reliability coefficients of .62 for overall classification and .54 for item level; Palmer & Jenkins, 1982).

The Challenging Behaviour Questionnaire (CBQ; Hyman et al., 2002) assesses the presence of self-injury, aggression, destruction of property and stereotyped behaviour within the past month and was developed from the Challenging Behaviour Interview (Oliver et al., 2003). The questionnaire also evaluates topographies of self-injury and severity of each type of behaviour. The scale has good inter-rater reliability (reliability coefficients ranging from α=.61-.89; Hyman et al., 2002).

The Activity Questionnaire (TAQ; Burbidge et al., 2010) measures overactivity and impulsivity. The scale consists of 18 items across three subscales, including overactivity, impulsive speech and impulsivity. The scale has been shown to have good item level inter-rater reliability (mean of .56) and test-retest reliability (mean of .75). Internal consistency for subscale scores has also been shown to be good.

The Mood, Interest and Pleasure Questionnaire (MIPQ; Ross & Oliver, 2003) assesses two subscales of mood and interest and pleasure. The short form comprises 12 items (six per subscale) and has good internal consistency (total $\alpha = .88$, Mood $\alpha = .79$, Interest and Pleasure $\alpha = .87$), test-retest (.97), and inter-rater reliability (.85).

The Repetitive Behaviour Questionnaire (RBQ; Moss et al., 2009) comprises 19 items measuring the frequency of repetitive behaviours within the past month across five subscales: stereotyped behaviour, compulsive behaviour, insistence on sameness, restricted preferences, and repetitive speech. The scale has been shown to have good item-level inter-rater (range .46-.80) and test-retest reliability coefficients (range .61-.93). Concurrent and content validity has also been shown to be good between the RBQ and the Autism Screening Questionnaire (.60; Berument et al., 1999).

The Social Communication Questionnaire (SCQ; Berument et al., 1999) measures behaviours associated with autism. The scale comprises 40 items across three subscales including communication, social interaction, and repetitive and stereotyped behaviour. A cut off total score of 15 is suggestive of possible autism spectrum disorder and a total score of 22 or above is indicative of possible autism. The scale has been shown to have good internal consistency ($\alpha = .90$ for the total scale) and good concurrent validity with the Autism Diagnostic Interview and with the Autism Diagnostic Observation Schedule (Howlin & Karpf, 2004).

Data Analysis

Normality of data were tested using Kolmogorov-Smirnov tests. As the data significantly deviated from normal distributions ($p < 0.05$), non-parametric tests were used.

Chi-square analyses were conducted to assess difference between those that took part at T_2 and those who did not, in order to explore how representative the sample at T_2 was of the original T_1 sample.

To describe the developmental trajectory of BtC, participants were split into the following groups: absent (behaviour absent at both time points), remission (behaviour present at T_1 and absent at T_2), incidence (behaviour absent at T_1 and present at T_2) and persistent (present at both time points). Percentages (n) for self-injury, aggression and destruction of property were presented for each group. McNemar analyses were calculated to assess the persistence of behaviours from T_1 to T_2.

To explore correlates of BtC, participants were then re-categorised into absent, transient and persistent groups, whereby transient included both incidence and remission groups (i.e. behaviour absent at either time point) to increase power. Chi-square analyses were used to evaluate service use between participants presenting with self-injury, aggressive behaviour or destruction of property at T_2 and those who did not. A series of Kruskal-Wallis analyses, corrected for multiple comparisons, were conducted to evaluate differences in T_1 demographic and behavioural risk markers between absent, transient and persistent groups at T_2. Chi-Square analyses were carried out to assess categorical data. Where significant differences were found between groups, post-hoc Mann-Whitney *U* analyses were conducted. Effect size estimates (*r)* were calculated using z-scores, as

recommended for non-parametric tests (Fritz et al., 2012), and interpreted according to guidelines by Cohen (1988) for *r* estimates where 0.1 to 0.3 indicates a small effect, 0.3 to 0.5 a medium effect and 0.5 or greater a large effect.

To explore the relative contribution of identified risk markers to the persistence of BtC, regression analyses were undertaken. Data were tested to ensure assumptions for binary logistic regressions were met. Multicollinearity of data were tested using variation inflation factors, indicating acceptable levels of correlation between the predictor variables. The Box-Tidwell procedure (Box & Tidwell, 1962) was used to test for linearity between the predictors and the logit transformation, indicating linearity between predictors and log odds. Binary logistic regressions were then conducted to evaluate the predictive value of the T_1 variables found to be associated with persistence of behaviours.

In order to optimise power, a pairwise deletion approach was used throughout the analysis, whereby participants were included in the analysis if they had the required data and excluded from each analysis if data were missing. The number of participants included in each analysis is presented in the corresponding table of the results. For the SCQ, three participants under the age of four years at T_1 were excluded from the analysis of the SCQ, as recommended by the SCQ authors. To reduce the likelihood of Type 1 errors (incorrectly rejecting the null hypothesis), Holm-Bonferroni corrections were applied to all analyses and *p* values were adjusted accordingly (Abdi, 2007).

Results

Demographic and Behavioural Characteristics of the Sample

To assess how representative the BEOND T_2 sample was of the original T_1 cross-syndrome sample, and to increase confidence that the sample was not biased by participants that did not take part at T_2, comparisons were made across a range of demographic and behavioural characteristics between those that declined to take part at T_2 and those that took part (see Table 2.2). Those who took part at T_2 did not significantly differ from those that declined to take part at T_2 on any of the demographic or behavioural characteristics collected at T_1. Additionally, the sample was not significantly different regarding the presence of self-injury, aggression or destruction of property, suggesting the final sample was broadly representative of the original sample.

Table 2.2

Demographic and Behavioural Characteristics of Participants Who Took Part at T_2 and Those Who Declined to Take Part at T_2

		Took part at T_2 $N = 84$[1]	Declined to take part at T_2 $N = 2033$	Mann-Whitney U/χ^2	*p* value
Age	Median (IQR)	12 (11)	13 (12)	83211.5	.79
Sex	% male	70.4	64.4	1.20	.27
Self help	% partially able/able	64.3	72.2	2.47	.12
Mobility	% mobile	86.9	86	0.05	.82
Speech	% verbal	60.7	70.4	3.57	.94[+]
Self-injury	% with behaviour	47.6	47.8	0.00	.96
Aggression	% with behaviour	60.8	50.4	3.26	.07
Destruction of property	% with behaviour	47.5	45	0.20	.66
TAQ impulsivity	Median (IQR)	17.5 (11.6)	16 (12.6)	78602	.22
TAQ overactivity	Median (IQR)	15 (13.9)	13 (17)	79392	.44
RBQ compulsive behaviour	Median (IQR)	1 (6)	3.4 (9)	68664	.20[+]
RBQ insistence on sameness	Median (IQR)	1 (4)	3 (5)	70414.5	.85[+]
RBQ stereotyped behaviour	Median (IQR)	5.5 (6.5)	6 (7.9)	80063.5	.55
MIPQ mood	Median (IQR)	21 (3)	20 (4)	79234.5	.26
MIPQ interest & pleasure	Median (IQR)	18 (7)	17 (7)	82635.5	.62
SCQ communication	Median (IQR)	7 (3)	6 (4)	66221.5	.77
SCQ social interaction	Median (IQR)	8 (5)	7 (7)	67018.5	.79
SCQ repetitive behaviour	Median (IQR)	4 (3)	4 (4)	80641	.63

[1]Total N includes the three participants that were excluded due to missing CBQ data at T_1

[+]*P* value adjusted following Holm-Bonferroni correction. Non-adjusted *p* values were as follows: $p = .06$ for speech, $p = .01$ for compulsive behaviour, $p = .05$ for insistence on sameness

Persistence of Self-injury, Aggression and Property Destruction

The point prevalence of self-injury, aggressive behaviour and destruction of property at T_1 was 46.9%, 61.5% and 48.1% and at T_2 was 42.0%, 43.2% and 40.7%, respectively, suggesting a decline in point prevalence between the two time points. To assess the persistence, incidence and remission of self-injury, aggression and destruction of property from T_1 to T_2, the percentage of those who showed these behaviours, alongside McNemar analyses, were calculated (see Table 2.3). McNemar analyses indicated that there were no statistically significant changes in the presence of self-injury or destruction of property between T_1 and T_2, suggesting that self-injury and destruction of property were relatively stable across time (Table 2.3). However, a significant change in aggressive behaviours was observed between the two time points (p = .03), whereby aggressive behaviours remitted in 37.5% and persisted in 62.5% of participants.

Table 2.3

Percentage (N) of Participants Showing Remission, Incidence, Persistent or Absent Self-Injurious Behaviour, Aggression and Destruction of Property Between T_1 and T_2

Behaviour	Absent	Remission	Incidence	Persistent			
	Absent T_1 Absent T_2	Present T_1 Absent T_2	Absent T_1 Present T_2	Present T_1 Present T_2	*p* value (2 tailed)	Remission in participants with behaviour at T_1	Persistence in participants with behaviour at T_1
Self-injury (n=81)	40.7% (33)	17.3% (14)	12.3% (10)	29.6% (24)	.57[+]	36.8% (14)	63.2% (24)
Aggression (n=78)	32.1% (25)	23.1% (18)	6.4% (5)	38.5% (30)	**.03*[+]**	37.5% (18)	62.5% (30)
Destruction of property (n=79)	41.8% (33)	17.7% (14)	10.1% (8)	30.4% (24)	.57[+]	36.8% (14)	63.2% (24)

[+]*P* value adjusted following Holm-Bonferroni correction. Non-adjusted *p* values were as follows: $p = .54$ for self-injury, $p = .01$ for aggression, $p = .29$ for destruction of property

*significant at $p<.05$

In order to investigate the impact of service use on change in self-injury, aggressive behaviours and destruction of property between T_1 and T_2, Fisher's exact tests were calculated (Tables 2.4 - 2.6). There were no significant differences between groups for self-injury, aggressive behaviours, or property destruction regarding service access.

Table 2.4

Number and Percentage of Participants Accessing Services and Chi-Square Analysis for Self-Injury

	Self-injury			Chi-square test		
	Absent (*N*=32)	Transient (N=23)	Persistent (N=24)	$\chi 2$	df	*p* value
GP	2 (6.3%)	2 (8.7%)	1 (4.2%)	0.591	2	.86
Psychiatrist	3 (9.4%)	4 (17.4%)	5 (20.8%)	1.636	2	.46
Clinical psychologist	2 (6.3%)	5 (21.7%)	4 (16.7%)	3.019	2	.24
Occupational therapist	0 (0%)	0 (0%)	3 (12.5%)	4.864	2	.91[+]
Speech and Language therapist	2 (6.3%)	1 (4.3%)	3 (12.5%)	1.204	2	.65
Support group	0 (0%)	0 (0%)	0 (0%)	N/A		
Social Worker	0 (0%)	2 (8.7%)	4 (16.7%)	5.505	2	.76[+]
Nurse	0 (0%)	1 (4.3%)	1 (4.2%)	1.757	2	.51
Paediatrician	0 (0%)	2 (8.7%)	0 (0%)	3.318	2	.08

Fishers exact *p* value reported as 50% had an expected count <5
[+]*P* value adjusted following Holm-Bonferroni correction. Non-adjusted *p* values were as follows: *p* = .05 for occupational therapist, and *p* = .04 for social worker

Table 2.5

Number and Percentage of Participants Accessing Services and Chi-Square Analysis for Aggressive Behaviour

	Aggression			Chi-square test		
	Absent (*N*=25)	Transient (N=21)	Persistent (N=30)	$\chi 2$	df	*p* value
GP	0 (0%)	1 (4.8%)	4 (13.3%)	3.507	2	.14
Psychiatrist	0 (0%)	2 (9.5%)	9 (30%)	10.274	2	.09[+]
Clinical psychologist	0 (0%)	4 (19%)	6 (20%)	6.515	2	.67[+]
Occupational therapist	0 (0%)	0 (0%)	3 (10%)	3.238	2	.11
Speech and Language therapist	0 (0%)	1 (4.8%)	5 (16.7%)	4.815	2	.07
Support group	0 (0%)	0 (0%)	0 (0%)	N/A		
Social Worker	0 (0%)	0 (0%)	5 (16.7%)	6.299	2	.26[+]
Nurse	0 (0%)	0 (0%)	2 (6.7%)	2.078	2	.33
Paediatrician	0 (0%)	1 (4.8%)	1 (3.3%)	1.338	2	.74

Fishers exact *p* value reported as 50% had an expected count <5

[+]*P* value adjusted following Holm-Bonferroni correction. Non-adjusted *p* values were as follows: *p* = .004 for psychiatrist, *p* = .03 for clinical psychologist and *p* = .01 for social worker

Table 2.6

Number and Percentage of Participants Accessing Services and Chi-Square Analysis for Destruction of Property

	Destruction of property			Chi-square test		
	Absent (*N*=32)	Transient (N=21)	Persistent (N=24)	$\chi 2$	df	*p* value
GP	3 (9.4%)	0 (0%)	2 (8.3%)	1.922	2	.51
Psychiatrist	2 (6.3%)	2 (9.5%)	7 (29.2%)	5.624	2	.06
Clinical psychologist	2 (6.3%)	2 (9.5%)	6 (25%)	4.06	2	.13
Occupational therapist	2 (6.3%)	0 (0%)	1 (4.2%)	1.181	2	.78
Speech and Language therapist	2 (6.3%)	2 (9.5%)	2 (8.3%)	0.466	2	1
Support group	0 (0%)	0 (0%)	0 (0%)	N/A		
Social Worker	0 (0%)	0 (0%)	5 (20.8%)	8.866	2	.07^{+}
Nurse	0 (0%)	0 (0%)	2 (8.3%)	3.056	2	.17
Paediatrician	0 (0%)	1 (4.8%)	1 (4.2%)	1.851	2	.51

Fishers exact *p* value reported as 50% had an expected count <5
$^{+}$*P* value adjusted following Holm-Bonferroni correction. The non-adjusted *p* value for social worker was $p = .003$

Longitudinal Risk Markers for the Presence of Self-Injury, Aggressive Behaviours and Property Destruction

To evaluate risk markers for self-injury, aggressive behaviours and property destruction, Kruskal-Wallis and chi-square analyses were calculated to explore demographic and behavioural variables associated with the presence of behaviours over time (Tables 2.7 - 2.8). No significant differences were found between groups regarding the length of time between completion of T_1 data and T_2 data or on any of the demographic

variables (see Table 2.7). In terms of behavioural characteristics, there were significant differences between groups on measures of impulsivity (H (2) =16.32, p = .04) and mood (H (2) =14.28, p = .04) for aggressive behaviours and on measures of impulsivity for destruction of property (H (2) =19.21, p = .04).

Post hoc analyses indicated that those in the persistent aggressive behaviour group had significantly higher scores on impulsivity than those in the absent aggressive behaviour group (U = 129, p = .01, r = -.56, large effect size). Those in the persistent (U= 182, p = .01, r = -.45, medium effect size) and transient (U = 133, p = .01, r = -.47, medium effect size) aggressive behaviour groups also had significantly lower scores on mood than those in the absent aggressive behaviour group. Those in the persistent destruction group had significantly higher scores on impulsivity than those in the absent group (U = 118.5, p = .01, r = -.58, large effect size) and those in the transient group (U = 139, p = .03, r = -.41, medium effect size).

Table 2.7

Kruskal-Wallis and Chi-Square Analyses for Demographic and Behavioural Variables Between Absent, Persistent and Transient Self-Injury, Aggressive Behaviours and Destruction of Property

	Self-injury			Aggression			Destruction of property		
	Kruskal-Wallis/ $\chi 2$	df	*p* value	Kruskal-Wallis/ $\chi 2$	df	*p* value	Kruskal-Wallis/ $\chi 2$	df	*p* value
Age	4.4	2	.11	1.18	2	.56	3.92	2	.14
Sex	0.54	2	.76	0.52	2	.77	0.06	2	.97
Wessex self-help score	0.88	2	.65	2.88	2	.24	0.38	2	.83
TAQ impulsivity	4.73	2	.09	16.32	2	**.04***$^{+}$	19.21	2	**.04***$^{+}$
TAQ overactivity	8.48	2	.37^{+}	5.71	2	.06	11.45	2	.12^{+}
RBQ compulsive behaviour	0.87	2	.65	0.16	2	.92	3.45	2	.18
RBQ insistence on sameness	0.88	2	.65	0.13	2	.94	5.65	2	.06
RBQ stereotyped behaviour	1.69	2	.43	5.17	2	.08	1.62	2	.44
MIPQ mood	2.48	2	.29	14.28	2	**.04***$^{+}$	10.74	2	.19^{+}
MIPQ interest & pleasure	1.23	2	.54	4.75	2	.09	2.17	2	.34
SCQ communication	0.16	2	.92	3.33	2	.19	0.17	2	.92
SCQ social interaction	0.16	2	.92	8.72	2	.37^{+}	0.33	2	.85
SCQ repetitive behaviour	0.31	2	.86	6.98	2	.96^{+}	3.66	2	.16
Time between T_1 and T_2	2.72	2	.26	0.42	2	.81	1.24	2	.54

$^{+}$*P* value adjusted following Holm-Bonferroni correction. Non-adjusted *p* values for self-injury were $p = .01$ for overactivity. For aggression, $p < .001$ for impulsivity, $p < .001$ for mood, $p = .01$ for social interaction, $p = .03$ for repetitive behaviour. For destruction of property, $p < .001$ for impulsivity, $p = .003$ for overactivity, $p = .005$ for mood

*significant at $p<.05$

Table 2.8

Post Hoc Comparison for Significant Behavioural Variables Between Absent, Persistent and Transient Aggressive Behaviours and Destruction of Property for TAQ Impulsivity and MIPQ Mood

						Post hoc Mann-Whitney U			
		Persistent	Transient	Absent		U	Z	*p* value	*r*
Aggressive behaviour									
TAQ impulsivity	Median (IQR)	19 (6)	17.5 (13.75)	13 (11.5)	Persistent > Absent	129	-4.17	**.01***	-0.56
					Transient ~ Absent	161.5	-2.43	.06	
					Persistent ~ Transient	291	-0.73	.94	
MIPQ mood	Median (IQR)	21 (3)	20 (4)	22 (2)	Absent > Persistent	182	-3.31	**.01***	-0.45
					Absent > Transient	133	-3.24	**.01***	-0.47
					Persistent ~ Transient	326	-0.35	.94	
Destruction of property									
TAQ impulsivity	Median (IQR)	22 (5.75)	16.5 (11.75)	13.5 (12)	Persistent > Absent	118.5	-4.32	**.01***	-0.58
					Persistent > Transient	139	-2.77	**.03***	-0.41
					Absent ~ Transient	266	-1.36	.54	

All *p* values were adjusted following Holm-Bonferroni correction. Non-adjusted *p* values were as follows: $p < .001$, $p = .02$, $p = .47$, $p < .001$, $p < .001$, $p = .73$, $p < .001$, $p = .01$, $p = .18$, respectively.
*significant at $p < .05$

Predictors of Persistent Aggressive and Destructive Behaviours

A binary logistic regression was calculated with aggressive behaviours (persistent n = 30 or absent n = 25) as the dependent variable and impulsivity and mood as the predictor variables, as these variables were found to differentiate between persistent, transient and absent aggressive behaviour groups. The logistic regression model was statistically significant (χ^2 (2) = 27.432, p = <.001). The model explained 52.5% (NagelKerke R^2) of the variance in persistent aggressive behaviour and correctly classified 78.2% of cases. Specifically, the model correctly classified 76% of absent cases and 80% of persistent cases. Both impulsivity (Wald = 9.756, df(1), p = .002) and mood (Wald = 8.173, df(1), p = .004) significantly contributed to the prediction of persistent aggressive behaviour. Increasing impulsivity and decreasing mood scores were associated with an increased likelihood of exhibiting persistent aggression.

A second binary logistic regression was calculated with destructive behaviours (persistent n = 24 or absent n = 31) as the dependent variable and impulsivity as the predictor variable. The logistic regression model was statistically significant (χ^2 (2) = 20.043, p = <.001). The model explained 41% (NagelKerke R^2) of the variance in persistent destructive behaviour and correctly classified 74.5% of cases. Specifically, the model correctly classified 71% of absent cases and 79.2% of persistent cases. Impulsivity significantly contributed to the prediction of persistent destructive behaviour (Wald = 11.453, df(1), p = <.001). Increasing impulsivity was associated with an increased likelihood of exhibiting persistent destructive behaviour.

Table 2.9

Logistic Regression Models for T_1 Predictors of T_2 Persistence or Absence of Aggressive and Destructive Behaviours

	T2 persistent aggressive behaviours (n = 30)				T2 persistent destructive behaviours (n = 24)			
			95% Confidence Interval for Exp (β)				95% Confidence Interval for Exp (β)	
T1 predictors	β (SE)	Exp (β)[1]	Lower	Upper	β (SE)	Exp (β)	Lower	Upper
Impulsivity	**0.184 (.059)***	1.203	1.07	1.35	**0.225 (.067)***	1.253	1.099	1.427
Mood	**-0.695 (.243)***	0.499	0.31	0.8				

[1]Exp(β)/Odds Ratio indicates the probability of persistent aggressive/destructive behaviour based on a one unit change in the T_1 predictor variable. An Exp (β) exceeding 1 would lead to an increase in the odds of persistent behaviour occurring, and below 1 indicate that an increase in the predictor score would lead to a decrease in the odds of persistent behaviour occurring.
*significant at $p<.05$

Discussion

The present study evaluated the persistence of self-injurious, aggressive and destructive behaviours in people with genetic syndromes associated with ID over an average period of 16 years. In addition, the value of identified behavioural risk markers in predicting the persistence of these behaviours was assessed. This is the first study delineating the persistence of various forms of BtC in a heterogenous group of people with genetic syndromes, as well as exploring the predictive value of behavioural risk markers, and thus the findings have considerable clinical utility. The use of standardised measures with established psychometric properties across both time points add to the reliability and validity of the conclusions. Additionally, a demographically and behaviourally representative sample at follow-up enhances the internal validity of the findings. The study found self-injurious and destructive behaviours to be stable and persistent in people with genetic syndromes, whereas the proportions of those showing aggressive behaviours significantly changed over time. Behavioural risk markers of impulsivity and mood predicted persistent aggression, with the former also predicting persistent destructive behaviours over a 16-year period.

The results of the current study demonstrated that self-injurious and destructive behaviours were both stable over time, whereby the majority of the sample either continued to display the behaviour or continued to not exhibit it at follow-up. Broadly, this is in line with existing literature demonstrating stability in BtC over time in populations with ID (Davies & Oliver, 2016; Wilde et al., 2018). However, the proportion of those showing aggressive behaviour significantly changed over the 16-year period, demonstrating less stability and persistence than for self-injurious and destructive behaviours. This may suggest that the natural trajectory of aggressive behaviours from

childhood/adolescence (T_1, mean age 14.5 years) to adulthood (T_2 mean age 31.6 years) diverges from that of self-injurious and destructive behaviours, that appear more stable across time. This is similar to previous studies finding that self-injurious behaviours were more persistent than aggressive behaviours in people with genetic syndromes (Crawford et al., 2019; Wilde et al., 2018). The results indicated that 61.5% of participants showed aggressive behaviours at T_1, which declined to 42% at follow-up, suggesting an age-related decline in these behaviours. A similar trajectory in aggressive behaviours has been shown in autistic populations over a comparable period of 10 years (Laverty et al., 2023). Overall, the current study suggests that BtC continue to persist over 16 years, as children and adolescence with genetic syndromes transition into adulthood. This is particularly concerning due to evidence highlighting the adverse effects of BtC on quality of life for people with genetic syndromes and their families (Adams et al., 2018; Beadle-Brown et al., 2009). Thus, there is substantial need for proactive interventions targeting behaviours at an earlier stage of their development, in order to mitigate their persistence overtime.

The results showed self-injury, aggression and destructive behaviours were persistent over approximately 16 years in 63.2%, 62.5% and 63.2% of people with genetic syndromes, respectively. The persistence rates in this sample are comparable to those previously reported for people with ID of heterogenous aetiology (58%, 69%, 57%, respectively; Davies & Oliver, 2016). Additionally, the persistence rates for aggressive and destructive behaviours were similar to those reported previously for single syndrome groups; ranging between 66 to 69% for tuberous sclerosis complex over three years (Wilde et al., 2018) and fragile X syndrome over eight years (Crawford et al., 2019). However, more conservative persistence rates were observed in this sample for self-injurious behaviours (63.2%) in comparison to those reported for tuberous sclerosis complex

(84.6%; Wilde et al., 2018) and fragile X syndrome (77%; Crawford et al., 2019). The more conservative estimates may be due to the longer follow-up period in the current study, or possibly the inclusion of a number of genetic syndrome groups. For example, self-injurious behaviour has been found to be particularly prevalent in people with Cri du Chat, Cornelia de Lange and Smith-Magenis syndromes, of which were less represented in this sample, compared to syndrome groups such as Angelman syndrome (Arron et al., 2011), which made up 22% of the sample. Overall, the findings of the current study continued to demonstrate that self-injurious behaviours were persistent in the majority of participants. Therefore, future research should extend the current findings through exploring the developmental trajectory of self-injurious behaviours in large, collective samples of people with genetic syndromes, and where possible, investigate the impact of genetic syndrome diagnosis on the trajectory of behaviours.

Whilst the results revealed no significant differences in the access of professional services between persistent, absent and transient BtC, this analysis may be underpowered due to the low numbers of those accessing services overall. Furthermore, the low service access numbers reflect a wider concern consistent with existing literature that access to services for support with BtC is poor in populations with rare genetic syndromes, ID of heterogenous aetiology and autism (Awan et al., 2020; Laverty et al., 2020; Ruddick et al., 2015). Despite the persistence of self-injurious, aggressive and destructive behaviours, and thus the increased need for support to reduce these behaviours (NICE, 2015), there is a discrepancy between service need and service receipt (Awan et al., 2020). The difference between need and services provided, often referred to as the assessment and treatment gap, is frequently found for rare genetic syndromes, including tuberous sclerosis complex (de Vries et al., 2015; Leclezio & de Vries, 2016). Additionally, the lack of professional input

for BtC is likely to strengthen the persistence of these behaviours (Awan et al., 2020). To ensure needs are better met for people displaying BtC and their carers, research should endeavour to understand the discrepancy between need and receipt, with a view to improving access to services in populations where these needs are largely unmet.

The present study identified impulsivity to be a risk marker differentiating those who showed persistent aggressive and destructive behaviours from those who never displayed these behaviours. This finding is consistent with existing literature establishing impulsivity as a putative risk marker for BtC across populations including, ID, autism and rare genetic syndromes (Arron et al., 2011; Crawford et al., 2019; Davies & Oliver, 2016; Laverty et al., 2020; Wilde et al., 2018). Furthermore, the results found higher scores on impulsivity significantly predicted the persistence of aggressive and destructive behaviours, extending prior evidence whereby impulsivity predicted persistent aggression in fragile X syndrome (Crawford et al., 2019). Replicating these findings in a larger, heterogenous sample of genetic syndromes over 16 years lends support to a transdiagnostic approach, whereby the individual characteristic of impulsivity continues to predict persistent aggression when evaluated across a number of genetic syndromes (e.g. Astle et al., 2022). This highlights impulsivity as a sensitive predictor that may span across syndromes, suggesting that impulsivity could be used as a marker to identify children at risk of developing persistent aggressive and destructive behaviours across populations. The predictive value found for impulsivity in this sample was not unexpected. Impulsivity has been consistently found to be an important behavioural correlate associated with aggression (e.g. Davies & Oliver, 2016), with growing evidence for causal models exploring the indirect pathways between impulsivity and aggression in which underlying cognitive mechanisms, particularly in terms of impaired behaviour inhibition, are

associated with the development and maintenance of aggression (Oliver et al., 2013; Oliver & Richards, 2015). The finding that impulsivity may be a useful risk marker of persistent BtC highlights the importance of risk-informed services, whereby those with increased risk are identified and supported earlier on, and intervention strategies take into account individual characteristics, such as impulsivity, in their approach.

The results also showed mood to be a risk marker differentiating those who showed persistent and transient aggressive behaviours from those who never displayed aggression. In addition, lower mood at T_1 predicted persistent aggression, strengthening this association. Whilst low mood has previously been found to be associated with aggression in autism, as well as in some genetic syndromes including, tuberous sclerosis complex, Cri du Chat and Smith-Magenis syndromes (Arron et al., 2011; Eden et al., 2014; Laverty et al., 2023), it has been more commonly observed as a correlate of self-injurious behaviour (Arron et al., 2011; Oliver & Richards, 2015; Richards et al., 2016). Although, a recent systematic review found aggression, self-injurious and disruptive behaviours to be commonly reported in people with severe ID and depression (Eaton et al., 2021). An explanation for this association may be that aggression serves a communicative function for people with ID experiencing low mood, as a way of expressing emotions or needs (e.g. Bowring et al., 2019; Hayes et al., 2011). In populations of typically developing children, expressions of anger may also be understood as indicative of underlying low mood (Kerr & Schneider, 2008). Furthermore, low mood as a predictor of persistent aggression could be understood through a third variable, such as painful health conditions (Eaton et al., 2021; Eden et al., 2014; Oliver & Richards, 2015), which are shown to often be either overlooked or untreated across genetic syndromes and ID as a result of diagnostic overshadowing (Hughes-McCormack et al., 2017). Furthermore, children with genetic

syndromes showing aggressive behaviours often exhibit a greater number of behavioural indicators of pain, adding weight to this explanation (Eden et al., 2014). Just over half (53%) of the current sample comprised of people with either fragile X or Angelman syndromes, both of which are associated with common painful conditions, such as recurrent ear infections, epilepsy and gastroesophageal reflux disease (Bindels-de Heus et al., 2020; Khan et al., 2023; Kidd et al., 2014; Lozano et al., 2016). Future research should continue to delineate the predictive value of mood in relation to different forms of BtC in samples of people with genetic syndromes, and extend the results of this study by accounting for pain or health-related quality of life.

The analysis found none of the demographic or behavioural characteristics were associated with the developmental trajectory of self-injurious behaviours. This finding is somewhat surprising based on existing literature identifying a number of behavioural correlates of self-injurious behaviour, particularly overactivity, impulsivity and repetitive behaviour (Crawford et al., 2019; Laverty et al., 2020; Richards et al., 2016; Wilde et al., 2018). There may be a number of plausible explanations for this null finding, for example, the more stringent correction employed for multiple comparisons, as well as the analysis perhaps being underpowered, which may have led to small effects being overlooked. Additionally, through grouping genetic syndromes together, the analysis was likely unable to detect syndrome-specific associations, a number of which have been demonstrated in relation to correlates of self-injurious behaviour. For example, there are associations between self-injury and sleep problems in Smith-Magenis syndrome (Bouras et al., 1998), as well as between repetitive and compulsive behaviours and self-injury displayed by those with Prader-Willi and Cornelia de Lange syndromes (Didden et al., 2007; Hyman et al., 2002; Srivastava et al., 2021). Therefore, it may be possible that generalised behavioural

risk markers and predictors, regardless of aetiology, are important for aggressive and destructive behaviours, whereas correlates of self-injurious behaviours may be syndrome specific. This highlights the value of syndrome sensitivity in behavioural interventions for self-injurious behaviours. Given the clinical importance of the findings, cross-syndrome study in relation to the predictors of persistent self-injury warrants attention in future research, in order to expand understanding of the trajectory of self-injury in people with rare genetic syndromes.

The present study was limited by a modest sample size at follow-up, with a low return rate for the original sample at T_2. However, analyses between those who participated and those who declined at follow-up indicated no difference in demographic or behavioural variables, strengthening the internal validity of the findings. Furthermore, the study aimed to overcome challenges inherent in rare genetic syndrome research by evaluating the trajectory of BtC in a larger, collective sample of people with genetic syndromes. Whilst this allowed inclusion of syndrome groups that are often under-researched, a number of groups were under-represented in the analysis, including 8p23, Cornelia de Lange, Cri du Chat, Prader-Willi, Lowe, Kleefstra and Phelan-Mcdermid syndromes (individually $n < 5$). This may have biased the persistence estimates and predictor variables, impacting the external validity of the results, and so should be considered when interpreting the findings. The analysis however did detect models predicting the persistence of aggressive and destructive behaviours that may be applicable to a number of genetic syndromes. Therefore, future research may wish to further explore drivers of BtC in large-scale samples of people with genetic syndromes associated with ID to confirm the current study's findings.

A strength of the study was the use of specific definitions of behaviour, as opposed to grouping self-injurious, aggressive and destructive behaviours into 'BtC' or 'problem behaviours', a common approach taken (Oliver, 2017). The differing risk markers identified between behaviours indicates the importance of this approach. Additionally, a recent meta-analysis highlighted the importance of specificity in the measurement of BtC, particularly as different interventions may be effective for different topographies of behaviour (Groves et al., 2023). Further specificity in the measurement of behaviours may have enhanced the study's ability to evaluate causal pathways to the development and maintenance of BtC, for example, exploring specific topographies of self-injurious behaviours. However, the analysis was restricted by the multiple comparisons carried out, and thus it was appropriate to limit analysis to self-injurious, aggressive and destructive behaviours, as the most severe forms of BtC. The multiple comparisons allowed explorative analysis of valuable theoretical models, and furthermore, stringent Bonferroni corrections were applied to reduce the likelihood of type one errors (Abdi, 2007). Additionally, attention should be given to effect sizes in the interpretation of the results; the medium to large effects suggest that the associations between impulsivity and mood, with the developmental trajectory of BtC were notable. The study was also limited in its ability to investigate relationships between physical health problems, pain and BtC. Given the established associations between pain and BtC (Hastings et al., 2013), measurement of health difficulties may have contributed to understanding of the relationship between mood as a predictor of persistent aggression. Future research should strive to include measurement of health conditions, pain or behavioural correlates of pain in order to develop causal models of BtC more fully.

The findings of the current study offer important clinical insight into behavioural risk markers predicting the maintenance of aggressive and destructive behaviours over approximately 16 years. Additionally, these predictors may be applicable to a number of genetic syndrome groups, and so are particularly pertinent for rare, under-researched syndromes. Identifying characteristics that may differentiate children with genetic syndromes at risk of developing persistent aggressive or destructive behaviours, regardless of aetiology, is useful in developing causal models of BtC and in turn, can inform targeted early intervention strategies. Despite the substantial service need, there is a clear gap in those accessing support for BtC (Awan et al., 2020; Ruddick et al., 2015). This is particularly concerning due to the deleterious impact BtC may have on a person's quality of life, as well as on family members and those around them (Beadle-Brown et al., 2009; McIntyre et al., 2002). Furthermore, early proactive interventions are found to improve long term outcomes in children with BtC (Barnes, 2003; Beqiraj et al., 2022; Chu, 2015; Davies et al., 2013; Scott et al., 2001), with emerging research investigating the utility of early parent-focused programmes (Farris et al., 2020). Thus, it is imperative these interventions reach children likely of developing persistent BtC. Clinicians should be aware of individual characteristics, such as impulsivity and mood, that may identify those who are most likely to experience poor behavioural outcomes, above and beyond specific neurodevelopmental diagnoses.

In summary, the findings of the current study demonstrate that BtC persist for the majority of people with genetic syndromes associated with ID over a period of 16 years. In addition, the value of impulsivity and mood in predicting persistent aggressive and destructive behaviours was demonstrated. Future research should aim to extend the current findings through evaluating predictors of BtC in large samples of people with genetic

syndromes associated with ID, in order to further increase power in the analyses and develop more accurate models of the developmental trajectory of behaviours in this population. Importantly, identifying robust predictors may support targeted early intervention approaches, with a view to improving access to services supporting people most at risk of developing persistent BtC.

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Chapter 3: Press Release for Meta-Analytic Review

Word Count: 668

Epilepsy Rates Among People with Genetic Syndromes Associated with Intellectual Disability Exceed Global Rates for the General Population

Epilepsy is highly prevalent among genetic syndromes associated with intellectual disability, indicating the need for epilepsy support and management for these populations.

The recent review of 153 studies, carried out by the University of Birmingham, evaluated how prevalent epilepsy is among people with genetic syndromes. The review found rates varied across syndrome groups, however, all estimates exceeded rates reported for the general population (0.6 - 1.2%; Christensen et al., 2023; Wigglesworth et al., 2023) and many exceeded those reported for people with intellectual disability (22%; Oeseburg et al., 2011; Robertson et al., 2015).

The highest rates were found for people with Wolf-Hirschhorn syndrome, the authors estimated that up to 96% of people with this syndrome will experience epilepsy in their lifetime. In comparison, the lowest rates were found for Rubinstein-Taybi syndrome, with around 4% of people experiencing epilepsy.

The prevalence of epilepsy was also notably high in SYNGAP1 syndrome (93%), Angelman syndrome (84%), tuberous sclerosis complex (80%), Rett syndrome (67%), 1p36 deletion syndrome (54%) and MECP2 duplication syndrome (52%). The lower rates in DiGeorge (16%), fragile X syndrome (14%), Down syndrome (13%) and Prader-Willi syndrome (11%) were still considerably high in comparison to the general population rates.

The lead author said: “The variability in the estimates has given light to a number of syndrome groups whereby the risk of epilepsy is strikingly high, and thus epilepsy treatment and management should target these at-risk groups. Additionally, the review highlighted syndrome groups that are currently under-researched, whereby few studies were found reporting on the rates of epilepsy for these groups.”

The authors also evaluated the association between age and epilepsy estimates. Epilepsy rates for people with Down syndrome increased with age, which is consistent with previous literature indicating an increased risk of epilepsy after the age of 40, coinciding with the development of Alzheimer’s disease (Altuna et al., 2021). Additionally, rates of epilepsy decreased with age in tuberous sclerosis complex, again this finding is largely consistent with previous reports of epilepsy being more common in younger people with this syndrome (Nabbout et al., 2021). The authors suggested this may be related to advancements in epilepsy treatment pathways for this population.

The author continued: “The differences identified between syndromes, for example in the association between age and epilepsy, suggest the need for epilepsy management to be syndrome sensitive. However, it could be useful to refer to clinical recommendations for syndrome groups where epilepsy is well-characterised, such as tuberous sclerosis complex, as a guide for developing treatment pathways for groups where the characteristics and trajectory of epilepsy is currently less well understood”.

The study also evaluated the association between study methods and epilepsy estimates. The results found that for studies reporting on Down syndrome, those considered as better quality in their sample identification reported higher epilepsy prevalence. This suggests higher estimates are reported where samples are more representative and based on multiple samples or national sampling. However, for Angelman syndrome, studies considered of poorer quality (n = 2) in their sample identification reported significantly higher estimates of epilepsy. The authors report these studies both evaluated EEG profiles of seizure activity, and thus, interpreted this finding as more likely being a result of the strategy used to assess epilepsy, as studies reviewing EEG activity tend to report high prevalence estimates (e.g. Akman et al., 2009; Paprocka et al., 2022).

The authors conclude that future research should focus on clear reporting of the assessment of epilepsy and recruitment of participants. This is particularly important in groups where estimates were high, but there was considerable variation in the prevalence rates reported, for example, Prader-Willi syndrome, Angelman syndrome, 1p36 deletion syndrome and SYNGAP1 syndrome. Finally, in syndromes with an increased risk of epilepsy, early monitoring of seizures should be prioritised, and families supported in recognising seizures to support early assessment and management.

ENDS.

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Chapter 4: Press Release for Empirical Study

Word Count: 625

Impulsivity and Low Mood can be Used to Predict Which Children with Genetic Syndromes are Most at Risk of Developing Persistent Aggressive and Destructive Behaviours

People with genetic syndromes associated with intellectual disability that experience low mood and high impulsivity are more likely to develop aggressive behaviour that continues to persist over 16 years. Also, those with high impulsivity are more likely to develop persistent destructive behaviours.

Researchers at the University of Birmingham evaluated longitudinal data on 81 people with genetic syndromes who were followed across an average of 16 years, from the mean ages of 15 to 32 years. The study revealed that self-injurious, aggressive, and destructive behaviours continue to persist across this period for the majority (approximately 63%) of people with these syndromes.

These behaviours fall under the umbrella term that psychologists call 'behaviours that challenge': this refers to behaviours that occur with an intensity, frequency or duration that they substantially impact upon a person's physical safety and quality of life (Banks et al., 2007; Emerson & Bromley, 1995).

The lead author said: "Behaviours that challenge are associated with a number of negative outcomes, in terms of a person's quality of life, and substantially impact upon family members or carers stress levels. It is important to understand factors that may contribute to their development and maintenance, in order to improve early preventative interventions for those most at risk of developing these behaviours."

People with genetic syndromes are at an elevated risk of developing behaviours that challenge, and research has begun to explore how these behaviours change over time into adulthood. Previous studies have begun to suggest these behaviours are persistent in genetic syndromes, including fragile X syndrome and tuberous sclerosis complex (Crawford et al., 2019; Wilde et al., 2018).

The study collected data on a range of parent/carer-reported demographic and behavioural characteristics across two time points, including information on the presence of self-injury, aggression and destruction of property. At the first time point, these behaviours were present in 46.9%, 61.5% and 48.1% of participants, respectively. Both self-injurious and destructive behaviours were stable and persistent across time, with a slight decline in the number of those showing these behaviours at follow-up. However, aggressive behaviours substantially declined across the 16 years, whereby 43.2% reported aggression at follow-up.

The researchers also demonstrated models that were able to predict who was most likely to develop behaviours that persisted over this period. Specifically, those with high impulsivity and low mood at the first time point were at risk of developing persistent aggression, and high impulsivity also predicted persistent destructive behaviours.

No characteristics were associated with or able to predict persistent self-injury. This was somewhat surprising, given previous research on populations with intellectual disability

suggesting a number of characteristics associated with self-injury, including impulsivity. An explanation was suggested that this may be because the study grouped together genetic syndromes, rather than looking at a single group. It may be that characteristics associated with self-injury are specific to certain syndrome groups, whereas findings for aggressive and destructive behaviours may be generalisable across syndromes.

The study was the first to look at the persistence of these behaviours over a period of around 16 years in a group of 12 genetic syndromes. The author concluded: “The findings suggest that impulsivity is a sensitive predictor that spans across syndromes, and may apply to different forms of behaviours that challenge. Research should continue to develop understanding into how these behaviours change over time in people with genetic syndromes to inform interventions aimed at reducing such behaviours”. The results of the study could inform early intervention practices by targeting those at the greatest risk of persistent behaviours that challenge.

ENDS.

For media enquiries please contact Alice Watkins, School of Psychology, University of Birmingham, email:

References

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Chapter 5: Appendices

Appendix 1: Letter from ethics committee granting full ethical approval for the research

Appendix 2: Questionnaires used for the Empirical Research Paper

- 2.1. The Background Questionnaire
- 2.2. The Medication and Service Use Scale
- 2.3. The Wessex Questionnaire
- 2.4. The Challenging Behaviour Questionnaire
- 2.5. The Activity Questionnaire
- 2.6. The Mood, Interest and Pleasure Questionnaire
- 2.7. The Repetitive Behaviour Questionnaire
- 2.8. The Social Communication Questionnaire

Appendix 3: Supplementary Tables for the Meta-analytic Review

- 3.1. Quality criteria for epilepsy confirmation, sample identification and syndrome confirmation
- 3.2. Reported prevalence of epilepsy for excluded syndrome groups with less than five study effects
- 3.3. Subgroup Analyses

Appendix 4: Supplementary Figures for the Meta-analytic Review

- 4.1. QQ plots of the distribution of epilepsy prevalence across syndrome groups
- 4.2. Forest plots for epilepsy prevalence rates across syndrome groups using a random-effects model
- 4.3. Funnel plots of epilepsy prevalence estimates for Tuberous sclerosis complex, Rett syndrome, Down syndrome, Fragile X syndrome and Angelman syndrome

Appendix 5: Full details of Search

Appendix 1: Letter From Ethics Committee Granting Full Ethical Approval for the Research

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: Questionnaires used for the Empirical Research Paper

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

☐ Not listed: _____

7. What is the genetic mechanism causing your child/the person you care for's syndrome?

☐ Uni-Parental Disomy	☐ Translocation
☐ Deletion	☐ Unknown
☐ Sequence repetition	

☐ Not listed: _____

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

Please check your answers and move on to the next questionnaire

SECTION 3

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

Appendix 2.2: The Medication and Service Use Scale

The MASS-P

1. In the past 2 years, has your child/the person you care for received support from services/professionals for any of their physical, emotional and/or behavioural needs?

   ☐ Yes

   ☐ No **(Please skip to question 7)**

2. Which of the following professionals did your child/the person you care for see in order to address their specific physical, emotional and/or behavioural needs?
   (*Please tick where applicable*)

Professional/Service	***Challenging behaviour***	***Sleep***	***Mental Health***	***Medical concerns****
General Practitioner (GP)				
Psychiatrist				
Clinical Psychologist				
Educational Psychologist				
Occupational Therapist				
Speech and Language Therapist				
Syndrome-specific Support Group				
Social Worker				
Nurse				
General Paediatrician				
Teacher /Teaching Assistant				
Dietician/ Nutritionist				
Specialist medical professional *e.g. neurologist, gastroenterologist (Please specify)* _____				
Other *(Please specify)*: _____				

*Please briefly outline your child / the person you care for's medical concerns:

3. Following access to the following professionals, have you noticed a change in your child/the person you care for's **challenging behaviour**?
Please tick where applicable.

CHALLENGING BEHAVIOUR ***Professional/Service***	***Major worsening***	***Slight worsening***	***No change***	***Slight improvement***	***Major improvement***
General Practitioner (GP)					
Psychiatrist					
Clinical Psychologist					
Educational Psychologist					
Occupational Therapist					
Speech and Language Therapist					
Syndrome-specific Support Group					
Social Worker					
Nurse					
General Paediatrician					
Teacher /Teaching Assistant					
Dietician/ Nutritionist					
Specialist medical professional *e.g. neurologist, gastroenterologist* *(Please specify)* _____					
Other *(Please specify)*: _____					

4. Following access to the following professionals, have you noticed a change in your child/the person you care for's **sleep**?
Please tick where applicable.

SLEEP ***Professional/Service***	***Major worsening***	***Slight worsening***	***No change***	***Slight improvement***	***Major improvement***
General Practitioner (GP)					
Psychiatrist					
Clinical Psychologist					
Educational Psychologist					
Occupational Therapist					
Speech and Language Therapist					
Syndrome-specific Support Group					
Social Worker					
Nurse					
General Paediatrician					
Teacher /Teaching Assistant					
Dietician/ Nutritionist					
Specialist medical professional *e.g. neurologist, gastroenterologist* *(Please specify)* _____					
Other *(Please specify)*: _____					

5. Following access to the following professionals, have you noticed a change in your child/the person you care for's **mental health?**
   Please tick where applicable.

MENTAL HEALTH ***Professional/Service***	***Major worsening***	***Slight worsening***	***No change***	***Slight improvement***	***Major improvement***
General Practitioner (GP)					

Psychiatrist					
Clinical Psychologist					
Educational Psychologist					
Occupational Therapist					
Speech and Language Therapist					
Syndrome-specific Support Group					
Social Worker					
Nurse					
General Paediatrician					
Teacher /Teaching Assistant					
Dietician/ Nutritionist					
Specialist medical professional *e.g. neurologist, gastroenterologist* *(Please specify)* _____					
Other *(Please specify)*: _____					

6. Following access to the following professionals, have you noticed a change in your child/the person you care for's **medical needs**?
   Please tick where applicable.

MEDICAL CONCERNS ***Professional/Service***	***Major worsening***	***Slight worsening***	***No change***	***Slight improvement***	***Major improvement***
General Practitioner (GP)					
Psychiatrist					
Clinical Psychologist					
Educational Psychologist					
Occupational Therapist					

Speech and Language Therapist					
Syndrome-specific Support Group					
Social Worker					
Nurse					
General Paediatrician					
Teacher /Teaching Assistant					
Dietician/ Nutritionist					
Specialist medical professional *e.g. neurologist, gastroenterologist* *(Please specify)* _____					
Other *(Please specify)*: _____					

7. Does your child/ the person you care for currently take prescribed medication for their specific physical/medical, emotional and/or behavioural needs?

   ☐ Yes

   ☐ No (**Please skip to question 9)**

8. Please list current medication, dose and primary reason for prescription.

Name of medication	***Dose***	***Primary reason for prescription***

9. Do you consider that your child/the person you care for's physical, emotional and behavioural needs have been met by your local services?

   ☐ Yes (**Please skip to end of form)**

   ☐ No

   ☐ Partially met

   ☐ Not sure

☐ My child/the person I care for does not have any specific physical, emotional, or behavioural needs

10. What are the reasons for the unmet needs?
(Tick all that apply)

☐ A lack of service provision in your local area
☐ A lack of appropriate services for your child/the person you care for's needs
☐ Long waiting lists
☐ Covid-19-related restrictions to service access
☐ Financial/personal reasons
☐ Accessibility reasons
☐ Other
(*please specify*): _____

Appendix 2.3: 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 2.4: The Challenging Behaviour Questionnaire

The CBQ

Section A – Self-injurious Behaviour

Has the person ever shown self-injurious behaviour (e.g. head banging, head-punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing)?

☐ Yes ☐ No

Has the person shown self-injurious behaviour in the last month (e.g. head banging, head-punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing)?

☐ Yes ☐ No

If the behaviour has not occurred, please go to section B.
If the behaviour occurred in the past month, please answer questions 1a to 1d:

1a) Place a tick next to the item for any of the following list of behaviours which the person displays in a repetitive manner (repeats the same movement/ behaviour twice or more in succession):

Hits self with body part (e.g. slaps head or face)	☐
Hits self against surface or object (e.g. bangs head on floor or table)	☐
Hits self with object	☐
Bites self (e.g. bites hand on wrist or arm)	☐
Pulls (e.g. pulls hair or skin)	☐
Rubs or scratches self (e.g. rub marks on arm or leg)	☐
Inserts finger or objects (e.g. eye poking)	☐
Other form of self-injury, (please specify): _____	☐

1b) In the last month, for how long did the **longest** episode or burst of this behaviour last? *(Please circle one number)*

1	**2**	**3**	**4**	**5**
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

1c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	**1**	**2**	**3**	**4**
Never	At least once a month	At least once a week	At least once a day	At least once an hour

1d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	**2**	**3**	**4**	**5**

By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

Section B – Aggression

Has the person ever shown aggression (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing)?

☐ Yes ☐ No

Has the person shown aggression in the last month (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing)?

☐ Yes ☐ No

If the behaviour has not occurred, please go to section C.
If the behaviour occurred in the past month, please answer questions 2a to 2d.

2a) Place a tick next to the item for any of the following list of behaviours which the person displays:

Hits other with body part (e.g. slapping, punching, kicking, head-butting)	☐
Hits other with an object (e.g. throwing object or using a weapon)	☐
Bites other	☐
Pulls or grabs other (e.g. hair-pulling, grabbing clothing)	☐
Rubs, pinches or scratches other	☐
Spits at other	☐
Verbal aggression (e.g. threatening, swearing)	☐
Other form of aggression, (please specify): _____	☐

2b) In the last month, for how long did the **longest** episode or burst of this behaviour last? *(Please circle one number)*

1 Less than a minute	**2** Less than 5 minutes	**3** Less than 15 minutes	**4** Less than an hour	**5** More than an hour

2c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0 Never	**1** At least once a month	**2** At least once a week	**3** At least once a day	**4** At least once an hour

2d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1 By this time next month	**2** By this time next week	**3** By this time tomorrow	**4** In the next hour	**5** In the next 15 minutes

Section C – Disruption and Destruction of Property

Has the person ever shown disruption and destruction of property or the environment (e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal)?

☐ Yes ☐ No

Has the person shown disruption and destruction of property or the environment in the last month? (e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal)?

☐ Yes ☐ No

If the behaviour has not occurred, please go to section D.
If the behaviour occurred in the past month, please answer questions 3a to 3d.

3a) Place a tick next to the item for any of the following list of behaviours which the person displays:

Biting or chewing small objects (e.g. books, clothing)	☐
Tearing or ripping small items (e.g. books, clothing)	☐
Throwing, kicking or smashing small items (e.g. cups, mobile phones)	☐
Slamming, hitting, or kicking doors, walls or windows	☐
Tipping, smashing or throwing large items (e.g. furniture, televisions)	☐
Pulling items from walls or shelves	☐
Verbal aggression (e.g. threatening, swearing)	☐
Other form of disruption (please specify): _____	☐

3b) In the last month, for how long did the **longest** episode or burst of his behaviour last? *(Please circle one number)*

1	**2**	**3**	**4**	**5**
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

3c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	**1**	**2**	**3**	**4**
Never	At least once a month	At least once a week	At least once a day	At least once an hour

3d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	**2**	**3**	**4**	**5**

By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

Section D – Stereotyped Behaviours

Has the person ever shown stereotyped behaviours? (e.g. rocking, twiddling objects, patting or tapping part of the body, constant hand movements, eye pressing)?

☐ Yes ☐ No

Has the person shown stereotyped behaviours in the last month? (e.g. rocking, twiddling objects, patting or tapping part of the body, constant hand movements, eye pressing)?

☐ Yes ☐ No

If the behaviour has not occurred, please go to section E.
If the behaviour occurred in the past month, please answer questions 4a to 4d:

4a) Place a tick next to the item for any of the following list of behaviours which the person displays:

Full body movements (e.g. rocking, bouncing)	☐
Movement of an object (e.g. twiddling or spinning object)	☐
Movement of isolated body part (e.g. hand flapping, head shaking)	☐
Eye-pressing or visual regard of movement (e.g. strobing, spinning object)	☐
Mouthing or sucking on body part or object	☐
Other form of disruption, (please specify): _____	☐

4b) In the last month, for how long did the **longest** episode or burst of his behaviour last? *(Please circle one number)*

1	**2**	**3**	**4**	**5**
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

4c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	**1**	**2**	**3**	**4**
Never	At least once a month	At least once a week	At least once a day	At least once an hour

4d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	**2**	**3**	**4**	**5**
By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

Section E – Other forms of challenging behaviour

Has the person ever shown any other form of challenging behaviour?

☐ Yes ☐ No

Has the person shown any other form of challenging behaviour in the last month?

☐ Yes ☐ No

If the behaviour has not occurred, please skip to the end of this form
If the behaviour occurred in the past month, please answer questions 5a to 5d:

5a) Place a tick next to the item for any of the following list of behaviours which the person displays:

Pica (e.g. eating paper, leaves, discarded food)	☐
Inappropriate vocalisations (e.g. screaming, shouting)	☐
Removal of clothing (not for purpose of washing changing or toileting)	☐
Sexual behaviour (e.g. public masturbation, inappropriate sexual contact)	☐
Anal poking	☐
Smearing of bodily substance (non-accidental)	☐
Stealing	☐
Self-induced vomiting	☐
Other form of challenging behaviour (please specify): _____	☐

5b) In the last month, for how long did the **longest** episode or burst of his behaviour last? *(Please circle one number)*

1	**2**	**3**	**4**	**5**
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

5c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	**1**	**2**	**3**	**4**
Never	At least once a month	At least once a week	At least once a day	At least once an hour

5d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	**2**	**3**	**4**	**5**
By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

Appendix 2.5: The Activity Questionnaire

The TAQ

- Please read each item carefully and circle the appropriate number on the scale, for the person you care for.
- Please ensure that you indicate a response for every item. If the particular behaviour does not apply, for example, if the person is not verbal or not mobile, please circle 0 on the scale.

		Never/ almost never	Some of the time	Half of the time	A lot of the time
1.	Does the person wriggle or squirm about when seated or lying down?	0	1	2	3
2.	Does the person fidget or play with their hands and/or feet when seated or lying down?	0	1	2	3
3.	Does the person find it difficult holding still?	0	1	2	3
4.	Does the person find it difficult to remain in their seat even when in situations where it would be expected?	0	1	2	3
5.	Does the person prefer to be moving around or become frustrated if left in one position for too long?	0	1	2	3
6.	When the person is involved in a leisure activity (e.g. watching TV, playing a game etc.) do they make a lot of noise?	0	1	2	3
7.	When the person is involved in an activity, are they boisterous and/or rough?	0	1	2	3
8.	Does the person act as if they are "driven by a motor" (i.e. often very active)?	0	1	2	3
9.	Does the person seem like they need very little rest to recharge their battery?	0	1	2	3
10.	Does the person often talk excessively?	0	1	2	3
11.	Does the person's behaviour seem difficult to manage/contain whilst out and about (e.g. in town, in supermarkets etc.)?	0	1	2	3
12.	Do you feel that you need to "keep an eye" on the person at all imes?	0	1	2	3
13.	Does the person you care for seem to act/do things without stopping to think first?	0	1	2	3
14.	Does the person blurt out answers before questions have been completed?	0	1	2	3
15.	Does the person start to respond to instructions before they have been fully given or without seeming to understand them?	0	1	2	3
16.	Does the person want things immediately?	0	1	2	3
17.	Does the person find it difficult to wait?	0	1	2	3
18.	Does the person disturb others because they have difficulty waiting for things or waiting their turn?	0	1	2	3

Appendix 2.6: The Mood, Interest and Pleasure Questionnaire

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.

Appendix 2.7: The Repetitive Behaviour Questionnaire

The RBQ

Instructions:

1. The questionnaire asks about 19 different behaviours.
2. Each behaviour is accompanied by a brief definition and examples. The examples given for each behaviour are not necessarily a complete list but may help you to understand the definitions more fully.
3. Please read the definitions and examples carefully and circle the appropriate number on the scale to indicate how frequently the person you care for has engaged in each of the behaviours **within the last month**
4. If a particular behaviour does not apply to the person you care for because they are not mobile or verbal, please circle the number 0 on the scale.

		Never	Once a month	Once a Week	Once a day	More than once a day
1.	**Object stereotypy:** Repetitive, seemingly purposeless movement of objects in an unusual way *E.g., twirling or twiddling objects, twisting or shaking objects, banging or slapping objects.*	0	1	2	3	4
2.	**Body stereotypy:** Repetitive, seemingly purposeless movement of whole body or part of body (other than hands) in an unusual way. *E.g., body rocking, or swaying or spinning, bouncing, head shaking, body posturing.* Does not include self-injurious behaviour)	0	1	2	3	4
3.	**Hand stereotypy:** Repetitive, seemingly purposeless movement of hands in an unusual way. *E.g., finger twiddling, hand flapping, wiggling or flicking fingers, hand posturing.* Does not include self-injurious behaviour.	0	1	2	3	4
4.	**Cleaning:** Excessive cleaning, washing or polishing of objects or parts of the body *E.g., polishes windows and surfaces excessively, washes hands and face excessively.*	0	1	2	3	4
5.	**Tidying up:** Tidying away any objects that have been left out. This may occur in situations when it is inappropriate to put the objects away. Objects may be put away into inappropriate places. *E.g., putting cutlery left out for dinner in the bin, removes all objects from surfaces.*	0	1	2	3	4
6.	**Hoarding:** Collecting, storing or hiding objects to excess, including rubbish, bits of paper, and pieces of string or any other unusual items.	0	1	2	3	4
7.	**Organising objects:** Organising objects into categories according to various characteristics such as colour, size, or function. *E.g., ordering magazines according to size, ordering toy cars according to colour, ordering books according to topic.*	0	1	2	3	4
		Never	Once a month	Once a Week	Once a day	More than once a day
8.	**Repetitive questions**: Asking specific questions over and over. *E.g., always asking people what their favourite colour is, asking who is taking them to school the next day over and over.*	0	1	2	3	4

9.	**Attachment to objects:** Strong preference for a particular object to be present at all times. *E.g., carrying a particular piece of string everywhere, taking a particular red toy car everywhere, attachment to soft toy or particular blanket.*	**0**	**1**	**2**	**3**	**4**
10.	**Repetitive phrases/signing:** Repeating particular sounds, phrases or signs that are unrelated to the situation over and over. *E.g., repeatedly signing the word telephone'.*	**0**	**1**	**2**	**3**	**4**
11.	**Rituals:** Carrying out a sequence of unusual or bizarre actions before, during or after a task. The sequence will always be carried out when performing this task and will always occur in the same way. *E.g., turning round three times before sitting down, turning lights on and off twice before leaving a room, tapping door frame twice when passing through it.*	**0**	**1**	**2**	**3**	**4**
12.	**Restricted conversation:** Repeatedly talks about specific, unusual topics in great detail. *E.g., conversation restricted to trains, buses, dinosaurs, particular film, country or sport.*	**0**	**1**	**2**	**3**	**4**
13.	**Echolalia:** Repetition of speech that has either just been heard or has been heard more than a minute earlier. *E.g., Mum Jack don't do that' Jack Jack don't do that'.*	**0**	**1**	**2**	**3**	**4**
14.	**Preference for routine:** Insists on having the same household, school or work schedule every day. *E.g., likes to have the same activities on the same day at the same time each week, prefers to eat lunch at exactly the same time every day, wearing the same jumper every day.*	**0**	**1**	**2**	**3**	**4**
15.	**Lining up or arranging objects:** Arrangement of objects into lines or patterns. *E.g., placing toy cars in a symmetrical pattern, precisely lining up story books.*	**0**	**1**	**2**	**3**	**4**
16.	**Just right behaviour:** Strong insistence that objects, furniture and toys always remain in the same place. *E.g., all chairs, pictures and toys have a very specific place that cannot be changed.*	**0**	**1**	**2**	**3**	**4**
17.	**Completing behaviour:** Insists on having objects or activities 'complete' or 'whole'. *E.g., must have doors open or closed not in between, story must be read from beginning to end, not left halfway through.*	**0**	**1**	**2**	**3**	**4**
18.	**Spotless behaviour:** Removing small, almost unnoticeable pieces of lint, fluff, crumbs or dirt from surfaces, clothes and objects. *E.g., picking fluff off a jumper, removing crumbs from the kitchen table.*	**0**	**1**	**2**	**3**	**4**

Appendix 2.8: The Social Communication Questionnaire

The Social Communication Questionnaire was omitted due to copyright.

Appendix 3: Supplementary Tables for Meta-Analytic Review

Appendix 3.1: Quality Criteria for Epilepsy Confirmation, Sample Identification and Syndrome Confirmation

	0 – Poor (Red)	1 – Adequate (Orange)	2 – Good (Yellow)	3 – Excellent (Green)
Epilepsy diagnosis	Not specified/reported e.g. reports 'seizures'	Epilepsy or epileptic seizures are specified Parent/caregiver reported	Epilepsy diagnosis supported by secondary clinical data e.g. validated through medical records Seizure type is provided e.g. focal, generalised, partial or unknown	Epilepsy diagnosis supported by primary clinical data e.g. diagnosis supported by reviewing EEG data
Sample Identification	Not specified/reported	Single restricted or non-random sample (e.g., specialist clinic or previous research study) Single regional sample e.g., a regional parent support groups	Multiple restricted or non-random samples (multi-region specialist clinics) National non-random sampling e.g., national parent support groups	Random or total population sample
Confirmation of syndrome	Not confirmed/reported Clinical diagnosis only suspected	Clinical diagnosis by 'generalist' e.g., General Practitioner or Paediatrician	Clinical diagnosis by 'expert' e.g., Clinical Geneticist or Specialist Paediatrician	Molecular/Cytogentic/ Metabolic confirmation of diagnosis[a]

Appendix 3.2: Reported Prevalence of Epilepsy for Excluded Syndrome Groups with Less Than Five Study Effects

Author (Year)	N	Syndrome Group	Prevalence
Shinawi et al. (2010)	16	16p11.2 deletion syndrome	31%
D'Angelo et al. (2016)	31 7	16p11.2 deletion syndrome	22%
El Achkar et al. (2022)	12 9	16p11.2 deletion syndrome	18%
Shinawi et al. (2010)	10	16p11.2 duplication	30%
D'Angelo et al. (2016)	18 0	16p11.2 duplication	19%
El Achkar et al. (2022)	10 6	16p11.2 duplication	11%
Pollak et al. (2020)	31	3q29 duplication syndrome	26%
Remerand et al. (2019)	24	Allan-Herndon-Dudley syndrome	29%
Mierlo et al. (2022)	37	ATR-X syndrome	30%
Cutri-French et al. (2020)	39	Atypical Rett	41%
Chen et al. (2016)	20	BBSOAS	40%
Rech et al. (2020)	46	BBSOAS	52%
Harion et al. (2022)	52	CC2D2A-related Joubert syndrome	13%
Bachmann-Gagescu et al. (2012)	20	CC2D2A-related Joubert syndrome	25%
Berney et al. (1999)	49	CdLS	29%
Mariani et al. (2016)	73	CdLS	22%
D. I. Battaglia et al. (2021)	34	CFCS	65%
Pierpont et al. (2022)	13 8	CFCS	55%
Honjo et al. (2018)	73	Cri du Chat	11%
Fenster et al. (2022)	24	DYRK1A syndrome	58%
Ji et al. (2015)	14	DYRK1A syndrome	64%
Carter et al. (2009)	63	Emmanuel syndrome	48%
Battaglia et al. (2006)	25	FG syndrome	20%
Romano et al. (1994)	10	FG syndrome	60%
Cutri-French et al. (2020)	43	FOXG1 disorder	70%
Seltzer et al. (2014)	30	FOXG1 disorder	87%
Schwartz et al. (2007)	77	Hunter syndrome	13%
Cutri-French et al. (2020)	44	MECP2 mutations	30%
Courgeon et al. (2022)	13	MECP2 mutations	54%
Adam et al. (2006)	12	Mowat-Wilson	75%
Dagorno et al. (2020)	23	Mowat-Wilson	100%

Author (Year)	N	Syndrome Group	Prevalence
Hofmeister et al. (2021)	25	Nicolaides-Baraitser syndrome	92%
Abdul-Rahman et al. (2014)	61	Nicolaides-Baraitser syndrome	64%
Velmans et al. (2022)	18	O'Donnell-Luria-Rodan syndrome	11%
Giordano et al. (2012)	13	Pallister Killian	100%
Wilkens et al. (2012)	47	Pallister Killian	49%
Blyth et al. (2015)	22	Pallister Killian	73%
Candee et al. (2012)	51	Pallister Killian	53%
Boudreau et al. (2005)	40	Pallister-Hall	10%
Reierson et al. (2017)	35	Phelan-Mcdermid syndrome	63%
Holder and Quach (2016)	24	Phelan-Mcdermid syndrome	46%
Khan et al. (2018)	16	Phelan-Mcdermid syndrome	44%
Sarasua et al. (2014)	151	Phelan-Mcdermid syndrome	27%
Zweier et al. (2008)	16	Pitt-Hopkins	38%
de Winter et al. (2016)	101	Pitt-Hopkins	38%
Lee et al. (2018)	18	PURA syndrome	50%
Reijnders et al. (2018)	32	PURA syndrome	50%
Elhassanien and Alghaiaty (2013)	24	Sanjad-Sakati	100%
Lewis et al. (2020)	41	SATB2 syndrome	41%
Rive Le Gouard et al. (2021)	47	Smith-Magenis syndrome	2%
Goldman et al. (2006)	60	Smith-Magenis syndrome	18%
Al Rashed et al. (1999)	14	Sotos	43%
Alrakaf et al. (2018)	56	Temtamy syndrome	73%
Segel et al. (2006)	16	Trisomy 12p	50%
Byrne et al. (2016)	34	Vici syndrome	59%
Saad et al. (2013)	17	Williams syndrome	29%

Appendix 3.3: Subgroup Analyses

Table 3.3a

Subgroup analyses on the impact of quality ratings on epilepsy prevalence for Tuberous sclerosis complex.

	Prevalence					
	Poor (k)	Adaquate (k)	Good (k)	Excellent (k)	χ^2	P
Confirmation of epilepsy	63% (3)	83% (10)	80% (27)	73% (1)	4.71	0.19
Sample identification	100% (4)	80% (23)	83% (14)	N/A	1.23	0.54
Confirmation of syndrome	70% (2)	77% (17)	82% (11)	81% (11)	0.93	0.82

Table 3.3b

Subgroup analyses on the impact of quality ratings on epilepsy prevalence for Rett syndrome.

	Prevalence					
	Poor (k)	Adaquate (k)	Good (k)	Excellent (k)	χ^2	P
Confirmation of epilepsy	76% (2)	58% (9)	77% (9)	54% (2)	8.58	0.04
Sample identification	75% (1)	70% (9)	64% (11)	69% (1)	1.28	0.73
Confirmation of syndrome	N/A	69% (6)	72% (4)	65% (12)	0.54	0.76

Table 3.3c

Subgroup analyses on the impact of quality ratings on epilepsy prevalence for Down syndrome.

	Prevalence					
	Poor (k)	Adaquate (k)	Good (k)	Excellent (k)	χ^2	P
Confirmation of epilepsy	8% (2)	16% (8)	8% (7)	11% (4)	2.97	0.4
Sample identification	N/A	6% (7)	15% (13)	20% (1)	18.84	<.0001
Confirmation of syndrome	8% (7)	18% (8)	N/A	8% (6)	7.46	0.02

Table 3.3d

Subgroup analyses on the impact of quality ratings on epilepsy prevalence for Fragile X syndrome.

	Prevalence					
	Poor (k)	Adaquate (k)	Good (k)	Excellent (k)	χ^2	P
Confirmation of epilepsy	18% (3)	12% (1)	15% (5)	14% (7)	2.5	0.47
Sample identification	24% (2)	14% (10)	14% (4)	N/A	4.04	0.13
Confirmation of syndrome	N/A	N/A	N/A	15% (16)	N/A	

Table 3.3e

Subgroup analyses on the impact of quality ratings on epilepsy prevalence for Angelman syndrome.

	Prevalence					
	Poor (k)	Adaquate (k)	Good (k)	Excellent (k)	χ^2	P
Confirmation of epilepsy	39% (1)	N/A	86% (7)	89% (4)	24.64	<.0001
Sample identification	100% (2)	77% (7)	85% (3)	N/A	19.77	<.0001
Confirmation of syndrome	N/A	N/A	N/A	83% (12)	N/A	

Table 3.3f

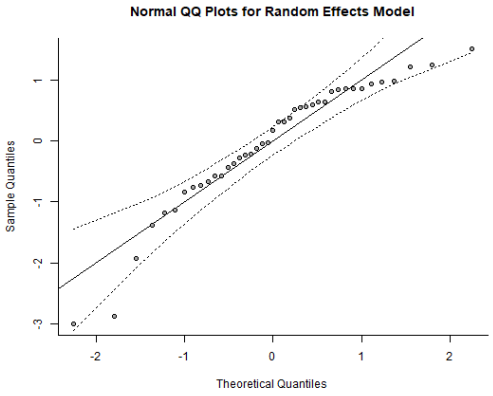
Subgroup analyses on the proportion of male participants on epilepsy prevalence across syndrome groups with 10 or more effects.

	k	Coefficient	SE	Z	p
Tuberous sclerosis complex	40	-0.007	0.0042	-1.5814	0.1138
Rett syndrome	22	-0.3572	0.204	-1.7513	0.0799
Down syndrome	19	-0.0021	0.0026	-0.818	0.4134
Fragile X syndrome	16	0.0018	0.0016	1.1374	0.2554
Angelman syndrome	12	0.0062	0.0061	1.0232	0.3062

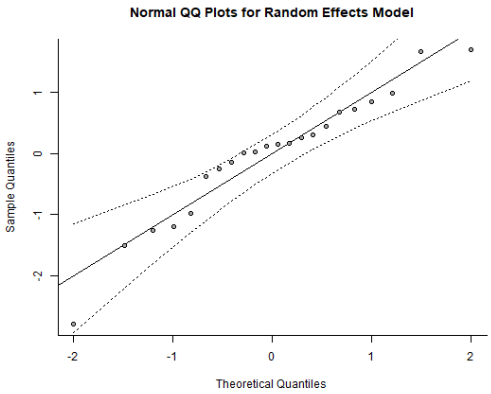
Appendix 4: Supplementary Figures for Meta-Analytic Review

Appendix 4.1: QQ Plots of the Distribution of Epilepsy Prevalence Across Syndrome Groups

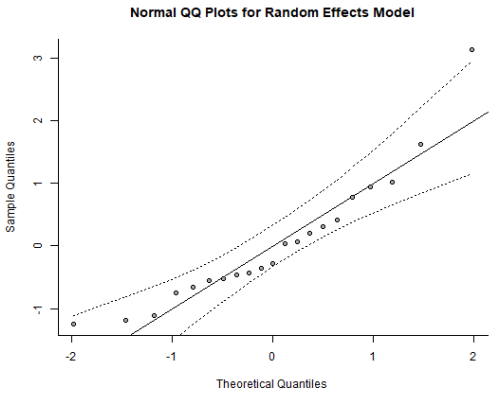
Tuberous Sclerosis Complex



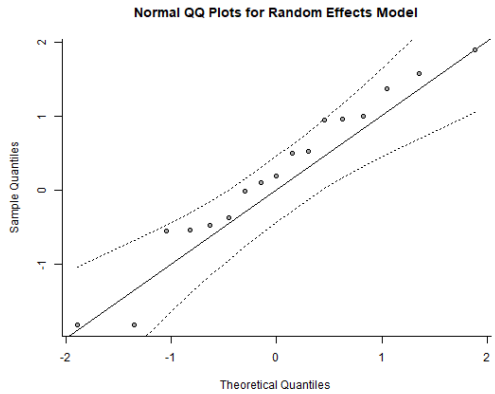
Rett syndrome



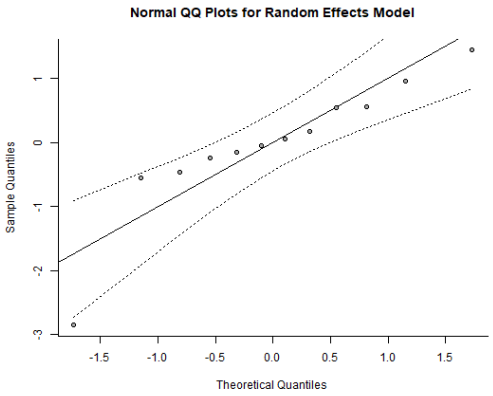
Down syndrome



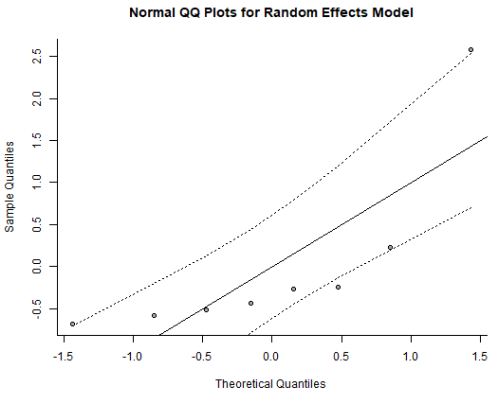
Fragile X syndrome



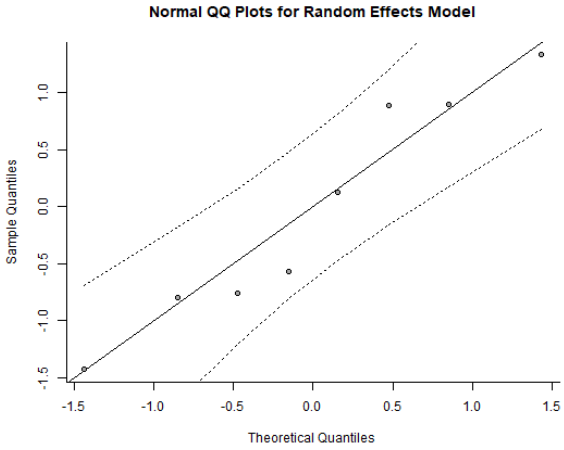
Angelman syndrome



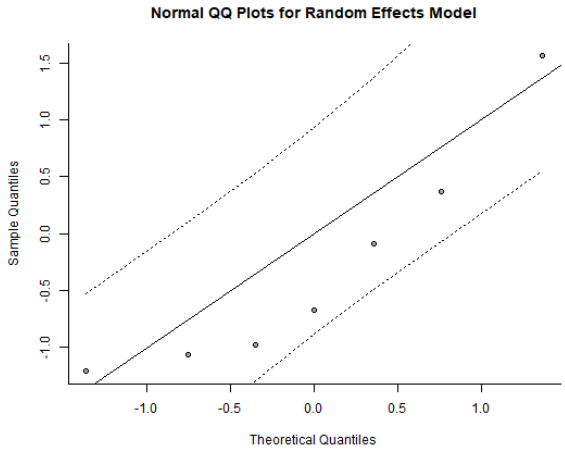
Di George syndrome



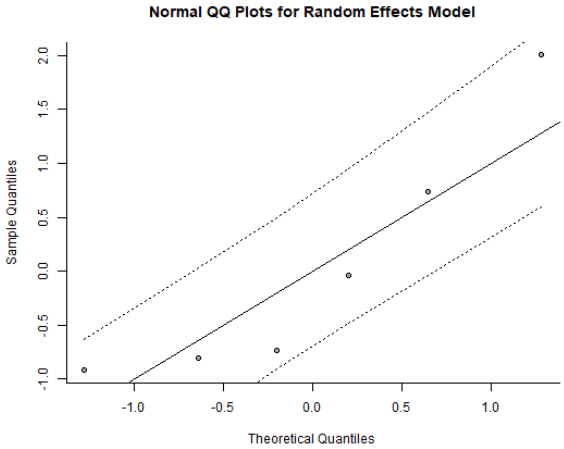
MECP2 duplication syndrome



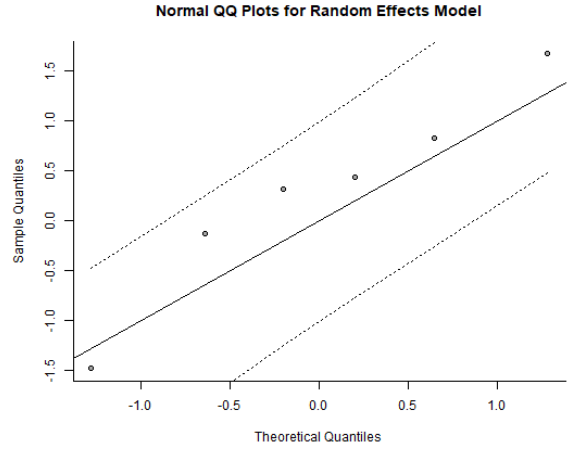
Wolf-Hirschhorn syndrome



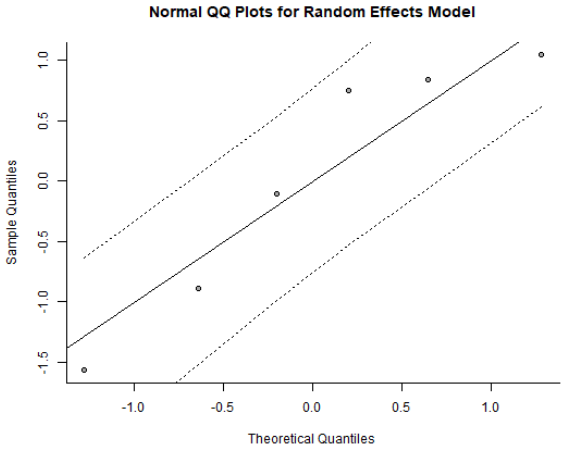
Prader-Willi syndrome



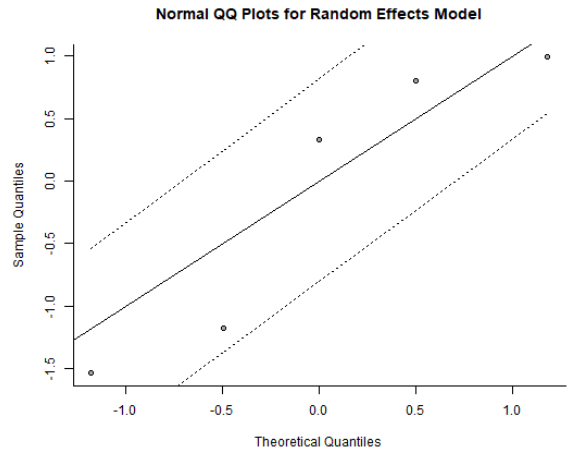
Rubinstein-Taybi syndrome



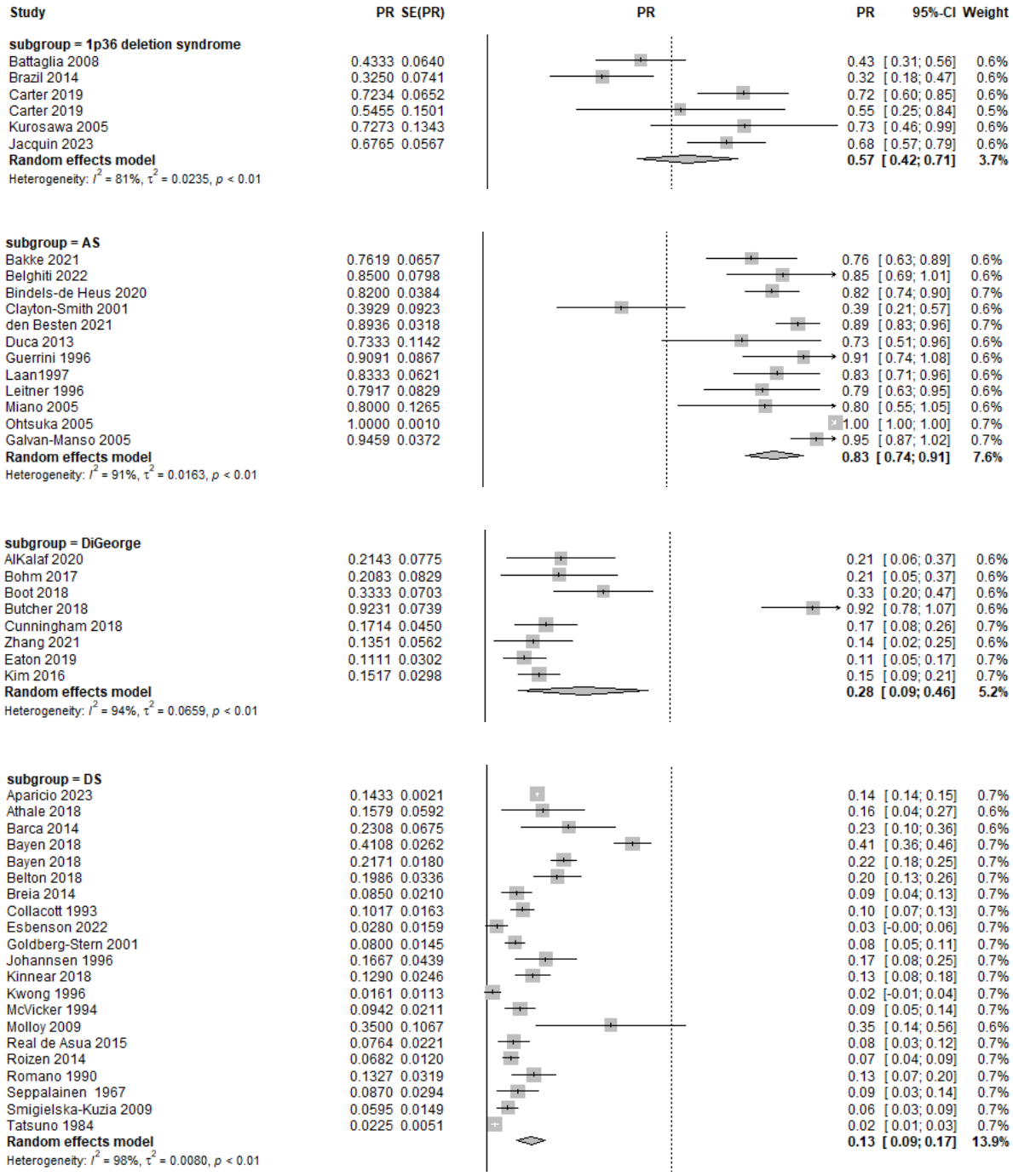
1p36 deletion syndrome

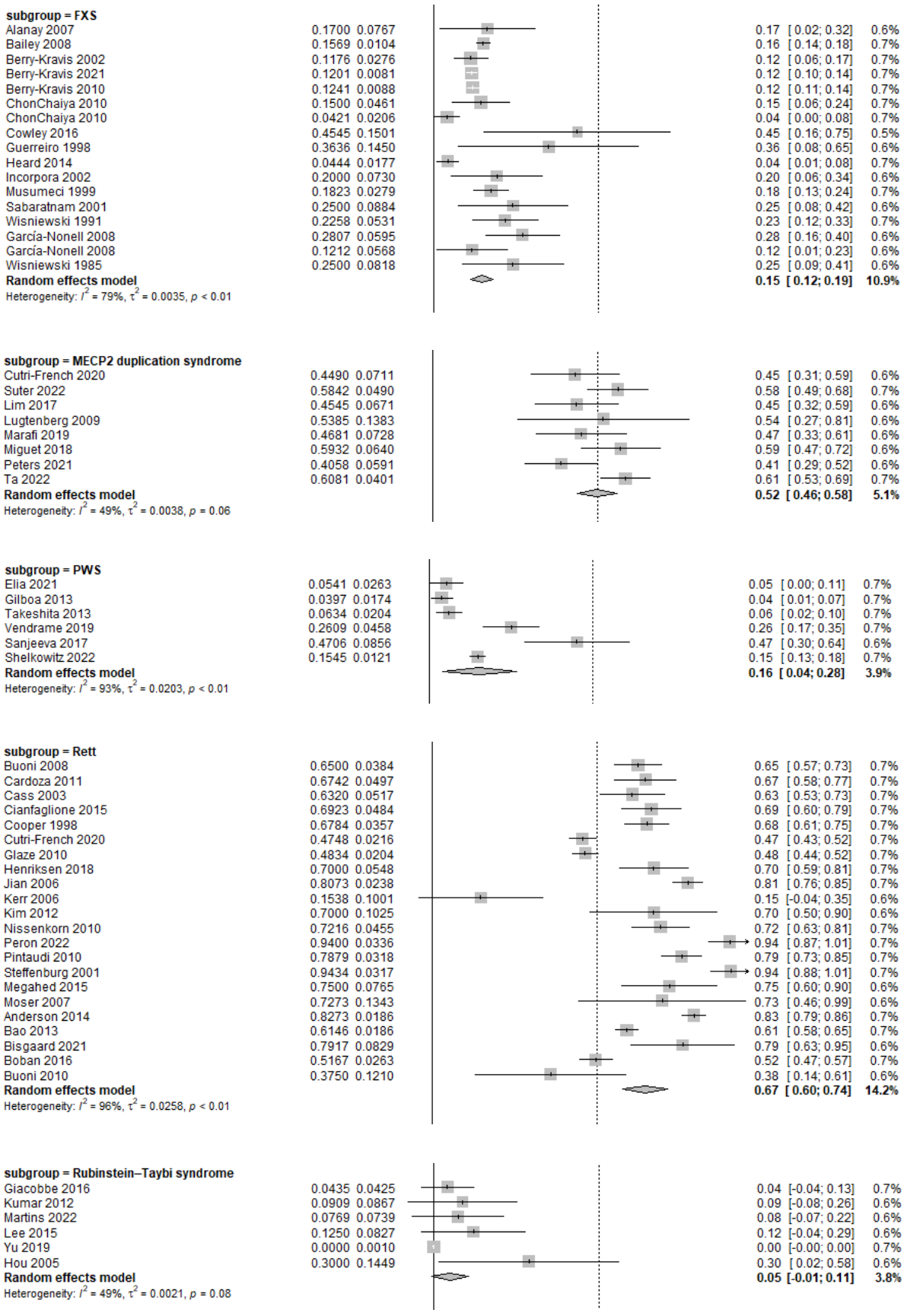


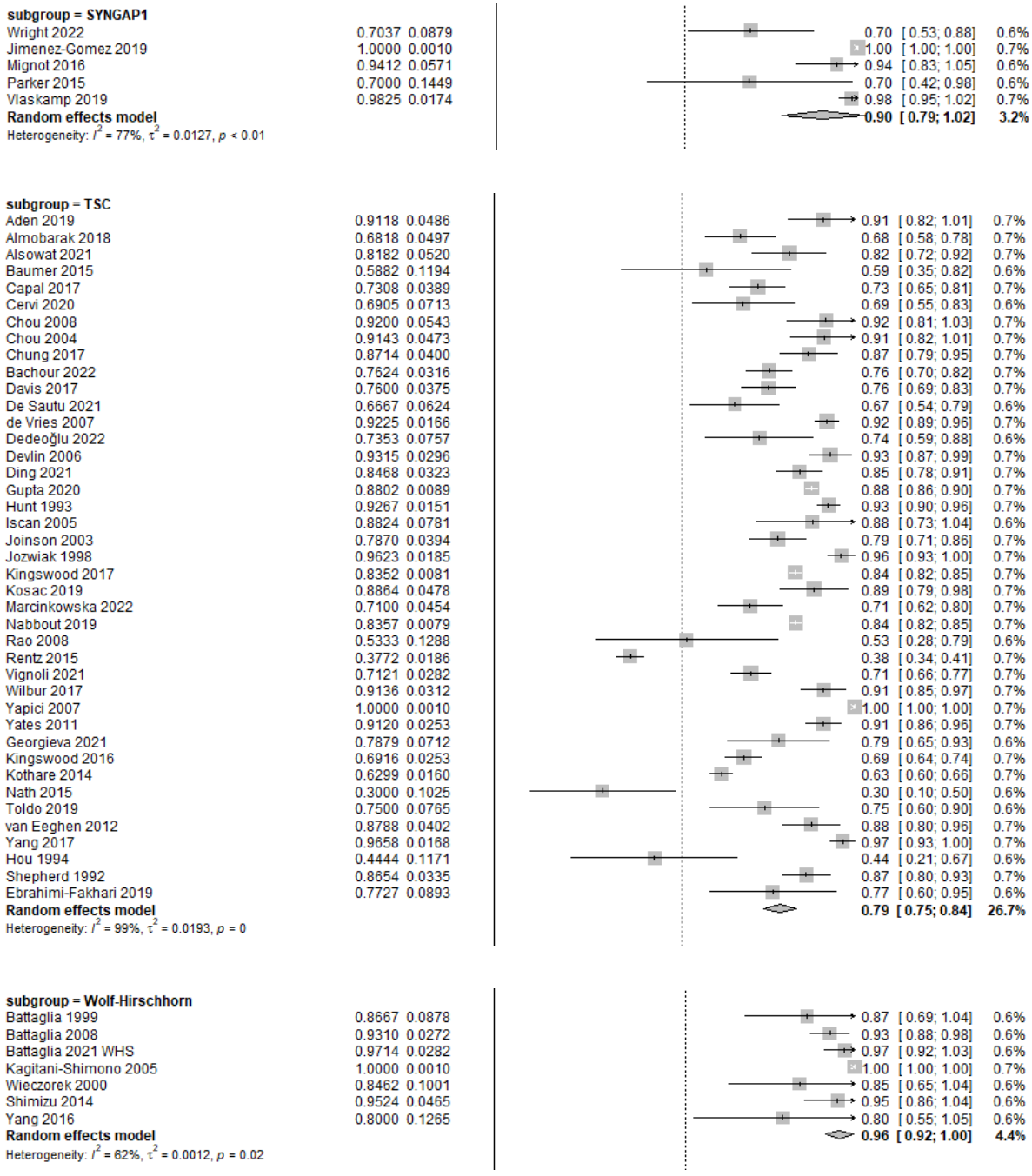
SYNGAP1 syndrome



Appendix 4.2: Forest Plots for Epilepsy Prevalence Rates Across Syndrome Groups Using A Random-Effects Model

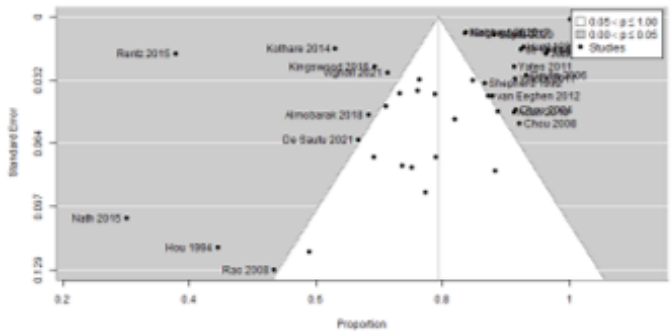



subgroup = FXS
Alanay 2007 0.1700 0.0767 0.17 [0.02; 0.32] 0.6%
Bailey 2008 0.1569 0.0104 0.16 [0.14; 0.18] 0.7%
Berry-Kravis 2002 0.1176 0.0276 0.12 [0.06; 0.17] 0.7%
Berry-Kravis 2021 0.1201 0.0081 0.12 [0.10; 0.14] 0.7%
Berry-Kravis 2010 0.1241 0.0088 0.12 [0.11; 0.14] 0.7%
ChonChaiya 2010 0.1500 0.0461 0.15 [0.06; 0.24] 0.7%
ChonChaiya 2010 0.0421 0.0206 0.04 [0.00; 0.08] 0.7%
Cowley 2016 0.4545 0.1501 0.45 [0.16; 0.75] 0.5%
Guerreiro 1998 0.3636 0.1450 0.36 [0.08; 0.65] 0.6%
Heard 2014 0.0444 0.0177 0.04 [0.01; 0.08] 0.7%
Incorpora 2002 0.2000 0.0730 0.20 [0.06; 0.34] 0.6%
Musumeci 1999 0.1823 0.0279 0.18 [0.13; 0.24] 0.7%
Sabaratnam 2001 0.2500 0.0884 0.25 [0.08; 0.42] 0.6%
Wisniewski 1991 0.2258 0.0531 0.23 [0.12; 0.33] 0.7%
García-Nonell 2008 0.2807 0.0595 0.28 [0.16; 0.40] 0.6%
García-Nonell 2008 0.1212 0.0568 0.12 [0.01; 0.23] 0.6%
Wisniewski 1985 0.2500 0.0818 0.25 [0.09; 0.41] 0.6%
Random effects model 0.15 [0.12; 0.19] 10.9%
Heterogeneity: I^2 = 79%, τ^2 = 0.0035, p < 0.01
subgroup = MECP2 duplication syndrome
Cutri-French 2020 0.4490 0.0711 0.45 [0.31; 0.59] 0.6%
Suter 2022 0.5842 0.0490 0.58 [0.49; 0.68] 0.7%
Lim 2017 0.4545 0.0671 0.45 [0.32; 0.59] 0.6%
Lugtenberg 2009 0.5385 0.1383 0.54 [0.27; 0.81] 0.6%
Marafi 2019 0.4681 0.0728 0.47 [0.33; 0.61] 0.6%
Miguet 2018 0.5932 0.0640 0.59 [0.47; 0.72] 0.6%
Peters 2021 0.4058 0.0591 0.41 [0.29; 0.52] 0.6%
Ta 2022 0.6081 0.0401 0.61 [0.53; 0.69] 0.7%
Random effects model 0.52 [0.46; 0.58] 5.1%
Heterogeneity: I^2 = 49%, τ^2 = 0.0038, p = 0.06
subgroup = PWS
Elia 2021 0.0541 0.0263 0.05 [0.00; 0.11] 0.7%
Gilboa 2013 0.0397 0.0174 0.04 [0.01; 0.07] 0.7%
Takeshita 2013 0.0634 0.0204 0.06 [0.02; 0.10] 0.7%
Vendrame 2019 0.2609 0.0458 0.26 [0.17; 0.35] 0.7%
Sanjeeva 2017 0.4706 0.0856 0.47 [0.30; 0.64] 0.6%
Shelkowitz 2022 0.1545 0.0121 0.15 [0.13; 0.18] 0.7%
Random effects model 0.16 [0.04; 0.28] 3.9%
Heterogeneity: I^2 = 93%, τ^2 = 0.0203, p < 0.01
subgroup = Rett
Buoni 2008 0.6500 0.0384 0.65 [0.57; 0.73] 0.7%
Cardoza 2011 0.6742 0.0497 0.67 [0.58; 0.77] 0.7%
Cass 2003 0.6320 0.0517 0.63 [0.53; 0.73] 0.7%
Cianfaglione 2015 0.6923 0.0484 0.69 [0.60; 0.79] 0.7%
Cooper 1998 0.6784 0.0357 0.68 [0.61; 0.75] 0.7%
Cutri-French 2020 0.4748 0.0216 0.47 [0.43; 0.52] 0.7%
Glaze 2010 0.4834 0.0204 0.48 [0.44; 0.52] 0.7%
Henriksen 2018 0.7000 0.0548 0.70 [0.59; 0.81] 0.7%
Jian 2006 0.8073 0.0238 0.81 [0.76; 0.85] 0.7%
Kerr 2006 0.1538 0.1001 0.15 [-0.04; 0.35] 0.6%
Kim 2012 0.7000 0.1025 0.70 [0.50; 0.90] 0.6%
Nissenkorn 2010 0.7216 0.0455 0.72 [0.63; 0.81] 0.7%
Peron 2022 0.9400 0.0336 0.94 [0.87; 1.01] 0.7%
Pintaudi 2010 0.7879 0.0318 0.79 [0.73; 0.85] 0.7%
Steffenburg 2001 0.9434 0.0317 0.94 [0.88; 1.01] 0.7%
Megahed 2015 0.7500 0.0765 0.75 [0.60; 0.90] 0.6%
Moser 2007 0.7273 0.1343 0.73 [0.46; 0.99] 0.6%
Anderson 2014 0.8273 0.0186 0.83 [0.79; 0.86] 0.7%
Bao 2013 0.6146 0.0186 0.61 [0.58; 0.65] 0.7%
Bisgaard 2021 0.7917 0.0829 0.79 [0.63; 0.95] 0.6%
Boban 2016 0.5167 0.0263 0.52 [0.47; 0.57] 0.7%
Buoni 2010 0.3750 0.1210 0.38 [0.14; 0.61] 0.6%
Random effects model 0.67 [0.60; 0.74] 14.2%
Heterogeneity: I^2 = 96%, τ^2 = 0.0258, p < 0.01
subgroup = Rubinstein–Taybi syndrome
Giacobbe 2016 0.0435 0.0425 0.04 [-0.04; 0.13] 0.7%
Kumar 2012 0.0909 0.0867 0.09 [-0.08; 0.26] 0.6%
Martins 2022 0.0769 0.0739 0.08 [-0.07; 0.22] 0.6%
Lee 2015 0.1250 0.0827 0.12 [-0.04; 0.29] 0.6%
Yu 2019 0.0000 0.0010 0.00 [-0.00; 0.00] 0.7%
Hou 2005 0.3000 0.1449 0.30 [0.02; 0.58] 0.6%
Random effects model 0.05 [-0.01; 0.11] 3.8%
Heterogeneity: I^2 = 49%, τ^2 = 0.0021, p = 0.08

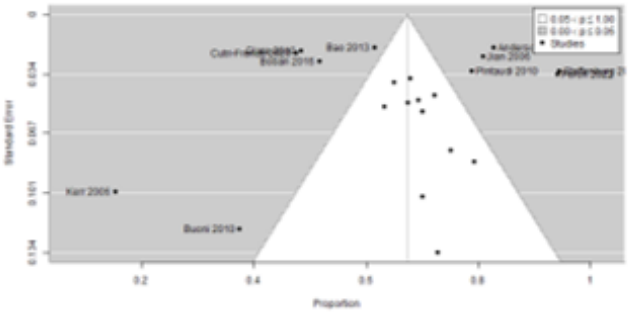

subgroup = SYNGAP1
Wright 2022 0.7037 0.0879 0.70 [0.53; 0.88] 0.6%
Jimenez-Gomez 2019 1.0000 0.0010 1.00 [1.00; 1.00] 0.7%
Mignot 2016 0.9412 0.0571 0.94 [0.83; 1.05] 0.6%
Parker 2015 0.7000 0.1449 0.70 [0.42; 0.98] 0.6%
Vlaskamp 2019 0.9825 0.0174 0.98 [0.95; 1.02] 0.7%
Random effects model 0.90 [0.79; 1.02] 3.2%
Heterogeneity: I^2 = 77%, τ^2 = 0.0127, p < 0.01
subgroup = TSC
Aden 2019 0.9118 0.0486 0.91 [0.82; 1.01] 0.7%
Almobarak 2018 0.6818 0.0497 0.68 [0.58; 0.78] 0.7%
Alsowat 2021 0.8182 0.0520 0.82 [0.72; 0.92] 0.7%
Baumer 2015 0.5882 0.1194 0.59 [0.35; 0.82] 0.6%
Capal 2017 0.7308 0.0389 0.73 [0.65; 0.81] 0.7%
Cervi 2020 0.6905 0.0713 0.69 [0.55; 0.83] 0.6%
Chou 2008 0.9200 0.0543 0.92 [0.81; 1.03] 0.7%
Chou 2004 0.9143 0.0473 0.91 [0.82; 1.01] 0.7%
Chung 2017 0.8714 0.0400 0.87 [0.79; 0.95] 0.7%
Bachour 2022 0.7624 0.0316 0.76 [0.70; 0.82] 0.7%
Davis 2017 0.7600 0.0375 0.76 [0.69; 0.83] 0.7%
De Sautu 2021 0.6667 0.0624 0.67 [0.54; 0.79] 0.6%
de Vries 2007 0.9225 0.0166 0.92 [0.89; 0.96] 0.7%
Dedeoğlu 2022 0.7353 0.0757 0.74 [0.59; 0.88] 0.6%
Devlin 2006 0.9315 0.0296 0.93 [0.87; 0.99] 0.7%
Ding 2021 0.8468 0.0323 0.85 [0.78; 0.91] 0.7%
Gupta 2020 0.8802 0.0089 0.88 [0.86; 0.90] 0.7%
Hunt 1993 0.9267 0.0151 0.93 [0.90; 0.96] 0.7%
Iscan 2005 0.8824 0.0781 0.88 [0.73; 1.04] 0.6%
Joinson 2003 0.7870 0.0394 0.79 [0.71; 0.86] 0.7%
Jozwiak 1998 0.9623 0.0185 0.96 [0.93; 1.00] 0.7%
Kingswood 2017 0.8352 0.0081 0.84 [0.82; 0.85] 0.7%
Kosac 2019 0.8864 0.0478 0.89 [0.79; 0.98] 0.7%
Marcinkowska 2022 0.7100 0.0454 0.71 [0.62; 0.80] 0.7%
Nabbout 2019 0.8357 0.0079 0.84 [0.82; 0.85] 0.7%
Rao 2008 0.5333 0.1288 0.53 [0.28; 0.79] 0.6%
Rentz 2015 0.3772 0.0186 0.38 [0.34; 0.41] 0.7%
Vignoli 2021 0.7121 0.0282 0.71 [0.66; 0.77] 0.7%
Wilbur 2017 0.9136 0.0312 0.91 [0.85; 0.97] 0.7%
Yapici 2007 1.0000 0.0010 1.00 [1.00; 1.00] 0.7%
Yates 2011 0.9120 0.0253 0.91 [0.86; 0.96] 0.7%
Georgieva 2021 0.7879 0.0712 0.79 [0.65; 0.93] 0.6%
Kingswood 2016 0.6916 0.0253 0.69 [0.64; 0.74] 0.7%
Kothare 2014 0.6299 0.0160 0.63 [0.60; 0.66] 0.7%
Nath 2015 0.3000 0.1025 0.30 [0.10; 0.50] 0.6%
Toldo 2019 0.7500 0.0765 0.75 [0.60; 0.90] 0.6%
van Eeghen 2012 0.8788 0.0402 0.88 [0.80; 0.96] 0.7%
Yang 2017 0.9658 0.0168 0.97 [0.93; 1.00] 0.7%
Hou 1994 0.4444 0.1171 0.44 [0.21; 0.67] 0.6%
Shepherd 1992 0.8654 0.0335 0.87 [0.80; 0.93] 0.7%
Ebrahimi-Fakhari 2019 0.7727 0.0893 0.77 [0.60; 0.95] 0.6%
Random effects model 0.79 [0.75; 0.84] 26.7%
Heterogeneity: I^2 = 99%, τ^2 = 0.0193, p = 0
subgroup = Wolf-Hirschhorn
Battaglia 1999 0.8667 0.0878 0.87 [0.69; 1.04] 0.6%
Battaglia 2008 0.9310 0.0272 0.93 [0.88; 0.98] 0.6%
Battaglia 2021 WHS 0.9714 0.0282 0.97 [0.92; 1.03] 0.6%
Kagitani-Shimono 2005 1.0000 0.0010 1.00 [1.00; 1.00] 0.7%
Wieczorek 2000 0.8462 0.1001 0.85 [0.65; 1.04] 0.6%
Shimizu 2014 0.9524 0.0465 0.95 [0.86; 1.04] 0.6%
Yang 2016 0.8000 0.1265 0.80 [0.55; 1.05] 0.6%
Random effects model 0.96 [0.92; 1.00] 4.4%
Heterogeneity: I^2 = 62%, τ^2 = 0.0012, p = 0.02

Appendix 4.3: Funnel Plots of Epilepsy Prevalence Estimates for Tuberous Sclerosis Complex, Rett Syndrome, Down Syndrome, Fragile X Syndrome and Angelman Syndrome

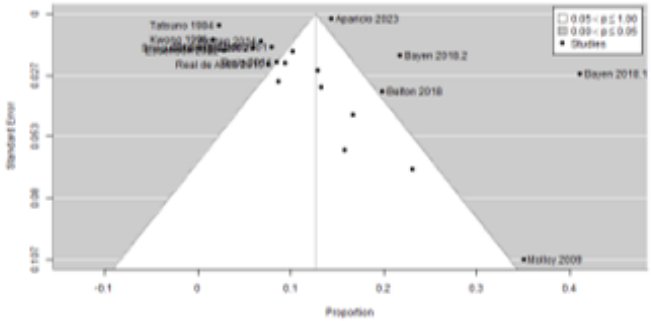
Tuberous sclerosis complex



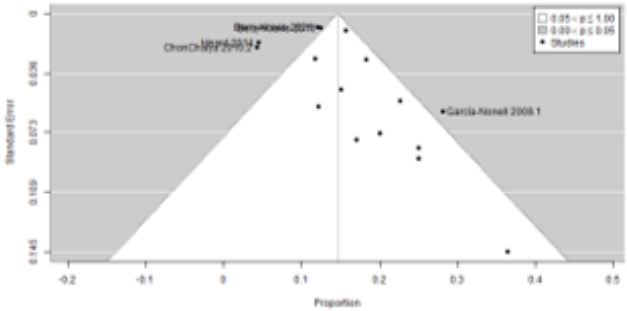
Rett syndrome



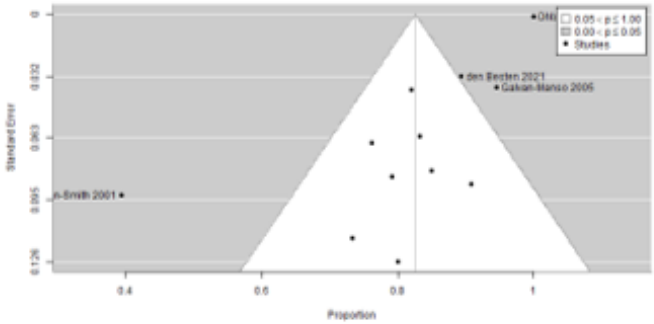
Down syndrome



Fragile X syndrome



Angelman syndrome



Appendix 5: Full Details of Search

Searches were made in OVID Medline, OVID Embase and OVID Psychinfo, with the following steps. In all cases .ab,kw,ti, refers to search being conducted within abstracts, keywords and titles. Adj. requires that the word appears near to the "adjacent" word.

Search Terms for Intellectual Disability

1. ((intellectual* or learning or development* or mental) adj (handicap* or retard* or disabilit* or deficien* or disturb* or disord* or incapac* or delay)).ab,kw,ti.

Search terms for epilepsy/seizures

2. (Epilep* or seizure* or convuls* or infantile spasm).ab,kw,ti.

Search terms for genetic syndromes

3. (gene* or syndrom* or geno* or genetic syndrom* or chromosom* disorder*).ab,kw,ti.

4. 1 AND 2 AND 3

The following search was made in PubMed using relevant Medical subject headings (MeSH) terms.

(("Genetic Diseases, Inborn"[Mesh] OR gene* OR syndrom* OR geno* OR genetic syndrom* OR chromosom* disorder*) AND ("Intellectual Disability"[Mesh] OR ((intellectual* or learning or development* or mental) AND (handicap* OR retard* OR disabilit* OR deficien* OR disturb* OR disord* OR incapac* OR delay)))) AND ("Epilepsy"[Mesh] OR "Seizures"[Mesh] OR Epilep* OR seizure* OR convuls* OR infantile spasm)

A search was also carried out in ProQuest (all dates). This search was limited to the English Language and Dissertations and Theses were the selected source.

Search Terms for Intellectual Disability

1. ((intellectual* or learning or development* or mental) near (handicap* or retard* or disabilit* or deficien* or disturb* or disord* or incapac* or delay))

Search terms for epilepsy/seizures

2. Epilep* or seizure* or convuls* or infantile spasm

Search terms for genetic syndromes

3. gene* or syndrom* or geno* or genetic syndrom* or chromosom* disorder*

4. 1 AND 2 AND 3