AUTISM SPECTRUM DISORDER PHENOMENOLOGY IN PHELAN-MCDERMID SYNDROME

by

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OVERVIEW

This thesis consists of two volumes and is submitted by Caroline Richards for the Clinical Psychology Doctorate at the University of Birmingham. Volume One comprises the research component of the doctorate and contains three papers. The first paper is a meta-analytic review of the prevalence of autism spectrum disorder phenomenology in rare genetic and metabolic syndromes, which will be submitted to *Psychological Bulletin*. The second paper is an empirical study of the behavioural phenotype and prevalence and profile of autism spectrum disorder in Phelan-McDermid syndrome, which will be submitted to *Research in Developmental Disabilities*. The final paper is an executive summary which provides an accessible overview of the two preceding papers. The executive summary will be used to disseminate the findings of the meta-analysis and empirical paper to families and professionals.

Volume Two of the thesis consists of five clinical practice reports that were completed over the course of the doctorate. The first report describes the assessment and formulation of symptoms of low mood which were experienced by a young man. His difficulties were formulated using cognitive-behavioural and systemic models. The second report describes an evaluation of service user satisfaction in a Child and Adolescent Mental Health Service. The third report details the assessment, formulation, intervention and evaluation of cognitive-behavioural therapy for a man experiencing depression and anxiety. The fourth report presents a series of experimental functional analyses, conducted to ascertain the function of self-injury displayed by a young girl with Smith-Magenis syndrome. The final report presents an abstract of an oral presentation case study.

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CHAPTER 1

The Prevalence of Autism Spectrum Disorder Phenomenology in Rare Syndromes: A Meta-Analytic Study

1.1 Abstract

Background: Autism spectrum disorder (ASD) phenomenology is reported to be more common in some genetic and metabolic syndromes, compared to other syndromes. However, despite several systematic reviews, no statistical meta-analysis has yet been conducted, synthesising the prevalence data within and between syndromes.

Methods: A literature search identified research reporting the prevalence of ASD phenomenology in syndromes. Reliable quality criteria were developed and a quality weighting used to weight the prevalence estimates in the most robust studies more heavily. Data from 168 papers across 16 syndromes were included in the meta-analysis. Pooled prevalence estimates were generated and compared between syndromes and to a general population estimate of the prevalence of idiopathic ASD.

Results: Robust estimates for the prevalence of ASD phenomenology were generated for 12 syndromes. ASD phenomenology was evident in all syndromes and significantly more likely in all syndromes compared to the general population (Rett syndrome, prevalence of ASD phenomenology 61%, Odds Ratio compared to general population 104.5; Cohen syndrome, 54%, OR 78.7; Cornelia de Lange syndrome, 43%, OR 50.5; Tuberous Sclerosis Complex, 36%, OR 37.7; Angleman syndrome, 34%, OR 34.5; CHARGE syndrome, 30%, OR 28.7; Fragile X syndrome males only 30%, OR 28.7, Fragile X syndrome mixed gender, 22%, OR 18.9; Neurofibromatosis Type 1, 18%, OR 14.7; Down syndrome, 16%, OR 12.8; Noonan syndrome, 15%, OR 11.8; Williams syndrome, 12%, OR 9.1 and 22q11.2 deletion syndrome, 11%, OR 8.3). Between syndrome variation was also evident. ASD phenomenology was significantly more likely in Rett syndrome, compared to nine other syndromes and in Cohen syndrome, compared to eight other syndromes. ASD phenomenology was significantly less likely in Williams and 22q13.2 deletion syndromes, compared to six other syndromes.

Discussion: Results are discussed in relation to service provision for syndromes, identifying the genetic aetiology of idiopathic ASD and areas for future research.

1.2 Introduction

The term Autism Spectrum Disorder (ASD) is an umbrella term which describes a group of behaviourally defined neurodevelopmental disorders, including Autistic disorder, Childhood autism, Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS), and Asperger syndrome (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, American Psychiatric Association, 1994; International Classification of Diseases, ICD-10, World Health Organization, 1992). Despite diagnostic variation between ASD subcategories, all disorders are defined by the presence of a triad of impairments: abnormalities or impairments in social interaction and communication with accompanying restricted or repetitive behaviours, activities or interests. Given the association between impairments in social interaction and social communication, DSM-V (American Psychiatric Association, 2013) consolidated social and communication difficulties resulting in a dyad of impairments. DSM-V also removed the subcategories of ASD, resulting in a dichotomous distinction between ASD and Social (pragmatic) Communication Disorder[1].

ASD is highly prevalent, with recent total population estimates ranging from 1 in 100 (Baird *et al.*, 2006; Center for Disease Control, 2009) to 1 in 68 (Center for Disease Control, 2014). However, despite the high prevalence of ASD and robust research documenting its heritability (e.g., Ronald *et al.,* 2006), the genetic aetiology of ASD is unknown. This may in part be due to the behavioural heterogeneity present within the spectrum and the associated methodological challenges to delineation of the genetic underpinnings of a vastly heterogeneous population (Bill & Geschwind, 2009).

Whilst the genetic aetiology of idiopathic ASD remains unclear, there is growing evidence that ASD phenomenology is more prevalent in specific rare genetic and metabolic syndromes relative to other syndromes (e.g., Bruining *et al.,* 2014; Oliver, Berg, Moss, Arron & Burbidge, 2011). It is argued that the study of the prevalence and phenomenology of ASD in and across these rare syndromes may illuminate the genetic and biological pathways that underlie idiopathic ASD (Abrahams & Geschwind, 2007; Bill & Geschwind, 2009; Persico & Bourgeron, 2006). It is hypothesised that through the study of relatively homogenous syndromes, models could be developed which establish causal links from genes to

[1] Social (Pragmatic) Communication Disorder is defined by the presence of social communication deficits, without the accompanying restricted and repetitive behaviours.

neuropathology and from these biological markers to specific cognitive deficits which underpin characteristic idiopathic ASD behaviours. An understanding of the variation in the prevalence of ASD phenomenology between syndromes would target these attempts at model building to the syndromes in which ASD phenomenology is most common.

The translation of prevalence findings between syndromes to inform an understanding of the pathways implicated in idiopathic ASD is predicated on an assumption that ASD phenomenology in syndromes is commensurate with idiopathic ASD. However, some authors have argued that ASD phenomenology in certain biologically defined syndromes is a categorically different construct to that seen in behaviourally defined idiopathic ASD (Hall, Lightbody, Hirt, Rezvani & Reiss, 2010). There is emerging evidence in some syndromes of an atypical ASD profile, which may support a categorical distinction between 'syndromic' variants of ASD and idiopathic ASD (see Moss, Howlin & Oliver, 2011 or Moss & Howlin, 2009 for a review of this literature). In order to progress this debate, fine-grained analysis of the phenomenology of ASD behaviours within syndromes is necessary. However, a recent review identified over 100 syndromes that are now documented to evidence an association with ASD (Zafeiriou, Ververi, Dafoulis, Kalyva & Vargiami, 2013). The size and scope of evaluating the profile of ASD in each of these rare syndromes, with the necessary inclusion of appropriate contrast groups with idiopathic ASD, is likely unachievable. A more pragmatic strategy would be to target fine-grained analysis of phenomenology towards those syndromes in which prevalence estimates for ASD are consistently high. However, despite many systematic reviews (Fombonne, 1999; Moss & Howlin, 2009; Moss *et al.*, 2011; Zafeiriou, Ververi & Vargiami, 2007; Zafeiriou *et al.*, 2013) there have been no meta-analytic studies documenting the consistency of prevalence data within syndromes, detailing the variation of prevalence estimates between syndromes or comparing these prevalence estimates to those identified in the general population. Therefore, there is a need to synthesise published prevalence data to provide estimates of the risk of ASD phenomenology within and between syndromes. These data would highlight 'high risk' syndromes and thus provide a useful starting point for structured investigation of ASD phenomenology. This delineation could then answer the wider question of whether ASD phenomenology in syndromes is synonymous to idiopathic ASD

.

An additional motivation for the delineation of ASD phenomenology in syndromes is to aid planning and provision of clinical and educational services. The presence of idiopathic ASD is known to increase risk of inpatient hospital admission (Cowley, Newton, Sturmey, Bouras & Holt, 2005), psychotropic medication use (Tsakanikos, Costello, Holt, Sturmey & Bouras, 2007), mental health disorder (Bradley, Summers, Wood & Bryson, 2004; Brereton, Tonge & Einfeld, 2006) and repetitive, self-injurious and aggressive behaviour (McClintock, Hall & Oliver, 2003; Richards, Oliver, Nelson & Moss, 2012). ASD also has a negative impact upon carer stress and carer mental health (Griffith, Hastings, Nash & Hill, 2009; Olsson & Hwang 2001). The national financial costs associated with idiopathic ASD in the UK are high, estimated at £2.7 and £25 billion a year for children and adults respectively (Knapp, Romeo & Beecham, 2009). It is likely that the human and economic costs of ASD in syndromes would be similar to those identified in idiopathic ASD and thus there is significant clinical incentive to delineate statistically the prevalence and phenomenology of ASD in individual syndromes.

There are a number of methodological challenges to synthesising the prevalence literature for ASD phenomenology across syndromes. First, the diagnosis of ASD in clinical practice requires rigorous multi-component assessment. NICE clinical guidance for autism assessment (NICE, 2011) suggests that this should include: detailed questions about parent's/carer's concerns, and if appropriate the child's concerns; details of the child's experiences of home life, education and social care; a developmental history; assessment through interaction and observation with the child; a medical history; a physical examination and exclusion of numerous differential diagnoses. This depth and breadth of diagnostic assessment is rarely replicated in research, and thus any prevalence estimates may be more accurately described as estimates of the presence of ASD phenomenology, rather than estimates of the presence of diagnostically defined ASD. This caveat must be considered when extrapolating from data in order to inform clinical and educational service provision.

An additional methodological issue concerns the wide variation in the mode and psychometric properties of the assessment measures utilised. Many studies rely solely upon screening measures which confer time and resource advantages when attempting to measure ASD phenomenology across small and geographically widespread samples. However, screening measures often have low levels of specificity and sensitivity (Charman & Gotham, 2013;

Moss *et al.,* 2011) and thus the prevalence data obtained have wide confidence intervals. Diagnostic measures have greater sensitivity and specificity, however, the resultant prevalence data may still be biased as accuracy for ASD assessments is lowest for marginal or unusual cases, such as those with intellectual disability and/or syndromes (Charman & Gotham, 2013). Therefore, the differing limitations of the assessment methodologies must be taken into account when attempting to synthesise prevalence literature within and between syndromes, when varying assessments may have been employed.

Despite the challenges and complexities outlined above, the need to inform service provision for syndromes, address the question of similarities and differences from idiopathic ASD and to contribute to an understanding of the gene, brain, cognition, behaviour pathways implicated in idiopathic ASD remains. The present meta-analysis will describe and evaluate the literature estimating the prevalence of ASD phenomenology in genetic and metabolic syndromes in order to:

i. generate pooled prevalence estimates for ASD phenomenology within each syndrome, weighted by the quantity and quality of the available evidence;
ii. conduct preliminary comparisons of the pooled prevalence estimates across syndromes;
iii. compare pooled prevalence estimates in the syndromes to prevalence estimates of ASD phenomenology in the general population[2].

[2] It could be argued that comparison to the prevalence of ASD phenomenology in populations with intellectual disability would provide a more useful contrast, than the general population. However, it was felt that a comparison to the general population was methodologically and clinically warranted. Estimates of the prevalence of ASD phenomenology in individuals with heterogeneous intellectual disability would inevitably include individuals with the syndromes being investigated in the present study, and thus any statistical comparisons would be compromised by the inadvertent inclusion of these individuals. Additionally, comparison to those with intellectual disability would minimise the purported heightened probability of ASD in these syndromes, which undermines the aim of this paper to inform service provision and planning.

1.3 Methods

1.3.1 Search Strategy

In order to focus the literature search on syndromes that were most likely to be associated with ASD phenomenology, a list of syndromes to be investigated was generated from a recent review of ASD phenomenology in syndromes (Moss & Howlin, 2009[3]). This resulted in 21 syndromes being selected for review.

Literature searches were conducted in Ovid PsycINFO, Ovid MEDLINE, Ovid Embase and PubMed Central. A list of the syndrome groups, search dates, inclusion dates and search terms are displayed in Table 1.1. Searches were conducted by combining all variations of the syndrome search terms with autism search terms. The autism search terms included: Autis*, Autism*, Autistic*, ASD, Autism spectrum disorder*, PDD-NOS, PDDNOS, Unspecified PDD, Pervasive developmental disorder*, Pervasive developmental disorder not otherwise specified, Asperger*, Asperger* syndrome. In addition, a hand search of the references from Moss and Howlin (2009) was conducted and any identified papers were included alongside those from the literature searches.

[3] Moss and Howlin (2009) identified these syndromes through inspection of previous systematic reviews which had noted associations between ASD phenomenology and genetic and metabolic syndromes (Gillberg & Coleman, 2000; Fombonne, 1999). Moss and Howlin (2009) focused their review upon the seven syndromes in which ASD had been most frequently reported or where five or more papers had been published. However, in order to broaden the scope of this review, the full 21 syndromes in which associations with ASD phenomenology had initially been reported, were entered into the literature search.

Table 1.1. Syndrome groups, search details and search terms.

	PsycINFO		MEDLINE		Embase		PubMed Central		
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Search terms**
Fragile X syndrome (FraX)	14/03/14	1967 to March Week 2 2014	14/03/14	1946 to March week 1 2014	14/03/14	1974 to 2014 Week 10	30/03/14	1950 to 30th March 2014	Fragile X; Fragile-X; Fragile X syndrome; FXS; FRAXA syndrome; AFRAX; Martin-Bell* syndrome; Marker X syndrome; fraX syndrome; fra(X) syndrome; X-linked mental retardation; Macroorchidism; Escalante* syndrome; Escalante*
Tuberous Sclerosis Complex (TSC)	15/04/14	1967 to April Week 2 2014	15/04/14	1946 to April week 1 2014	15/04/14	1974 to 2014 Week 15	30/03/14	1950 to 30th March 2014	Tuberous sclerosis; Tuberous sclerosis syndrome; Bourneville* disease; Bourneville* phakomatosis; Cerebral sclerosis; Cerebral sclerosis syndrome; Epiloia; Sclerosis tuberose; Tuberose sclerosis; Tuberose sclerosis syndrome; Tuberous sclerosis complex; TSC; TSS
Rett's syndrome (Rett)	28/04/14	1967 to April Week 4 2014	28/04/14	1946 to April week 3 2014	28/04/14	1974 to 2014 Week 17	30/03/14	1950 to 30th March 2014	Rett*; Rett* syndrome; Rett* disorder; RTS; RTT; Cerebroatrophic hyperammonemia; Autism-dementia-ataxia-loss of purposeful hand use syndrome
Down syndrome (DS)	01/04/14	1967 to March Week 4 2014	01/04/14	1946 to March week 3 2014	01/04/14	1974 to 2014 Week 13	30/03/14	1950 to 30th March 2014	Down*; Down* syndrome; Trisomy 21; Trisomy G; 47,XX,+21; 47,XY,+2

	PsycINFO		MEDLINE		Embase		PubMed Central		
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Search terms**
Phenylketonuria syndrome (PKU)	30/04/14	1967 to April week 4 2014	30/04/14	1946 to April Week 3 2014	30/04/14	1974 to 2014 Week 17	30/03/14	1950 to 30th March 2014	Phenylketonuria; Phenylalanine hydroxylase; Folling* disease; Folling* syndrome; PAH deficiency; PAH deficiency disease; Phenylalanine hydroxylase deficiency disease; Phenylalanine hydroxylase deficiency; PKU; Oligophrenia phenylpyruvica**;** Deficiency Disease, Phenylalanine Hydroxylase
CHARGE syndrome (CHARGE)	11/04/14	1967 to April Week 2 2014	11/04/14	1946 to April week 1 2014	11/04/14	1974 to 2014 Week 14	25/06/14	1950 to 25th June 2014	CHARGE; CHARGE syndrome; CHARGE association; Hall-Hittner* syndrome; Hall* Hittner* syndrome
Angelman syndrome (AS)	30/03/14	1967 to March Week 4 2014	30/03/14	1946 to March week 3 2014	30/03/14	1974 to 2014 Week 13	30/03/14	1950 to 30th March 2014	Angelman*; Angelman* syndrome; AS; Happy puppet syndrome; Happy puppet
Neurofibromatosis Type 1 (NF1)[4]	30/04/14	1967 to April week 4 2014	30/04/14	1946 to April Week 3 2014	30/04/14	1974 to 2014 Week 17	25/04/14	1950 to 25th April 2014	Neurofibromatosis; Neurofibromatosis type 1; Neurofibromatosis 1; NF1; Peripheral Neurofibromatosis; Recklinghausen* disease; Neurofibromatosis type 2; Neurofibromatosis 2; NF2; Central neurofibromatosis; Bilateral acoustic neurofibromatosis; BANF; Familial acoustic neuromas

[4] Both Neurofibromatosis type 1 and type 2 were included in the literature search, however only papers concerning NF1 met the inclusion criteria for review

	PsycINFO		MEDLINE		Embase		PubMed Central		
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Search terms**
Joubert syndrome (JS)	30/03/14	1967 to March Week 4 2014	30/03/14	1946 to March week 3 2014	30/03/14	1974 to 2014 Week 13	09/04/14	1950 to 9th April 2014	Joubert*; Joubert* syndrome; Joubert-Bolthauser* syndrome; JBTS; Cerebello-oculo-renal syndrome; Cerebello-oculo-renal syndrome 1; Cerebellooculorenal syndrome 1; Cerebellooculorenal syndrome; CORS; CORS1; Cerebellar vermis agenesis; Cerebelloparenchymal disorder 4; Cerebelloparenchymal disorder; CPD; CPD4; Familial aplasia of the vermis
William's syndrome (WS)	30/03/14	1967 to March Week 4 2014	30/03/14	1946 to March week 3 2014	30/03/14	1974 to 2014 Week 13	25/06/14	1950 to 25th June 2014	William*; William* syndrome; Beuren* syndrome; Elfin Facies syndrome; Hypercalcemia-Supravalvar Aortic Stenosis; Infantile hypercalcemia; Supravalvar aortic stenosis syndrome; WBS; Williams-Beuren* syndrome; WMS; WS
Goldenhar syndrome (GS)	30/04/14	1967 to April week 4 2014	30/04/14	1946 to April Week 3 2014	30/04/14	1974 to 2014 Week 17	25/04/14	1950 to 25th June 2014	Goldenhar*; Goldenhar* syndrome; Oculoauriculovertebral spectrum; Oculoauriculovertebral syndrome; Oculoauriculovertebral dysplasia; OAV; OAVD; OAVS; Oculo-Auriculo-Vertebral syndrome; Oculo-Auriculo-Vertebral spectrum; Oculo-Auriculo-Vertebral dysplasia; Brachial arch syndrome; Facioauriculovertebral syndrome; FAV; FAVS; Lateral facial dysplasia

	PsycINFO		MEDLINE		Embase		PubMed Central		
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Search terms**
Hypomelanosis of Ito syndrome (HoI)	30/04/14	1967 to April week 4 2014	30/04/14	1946 to April Week 3 2014	30/04/14	1974 to 2014 Week 17	09/04/14	1950 to 9th April 2014	Hypomelanosis of Ito; Ito hypomelanosis; Incontinentia pigmentosa achromians; Ito syndrome; ITO; IPA; HMI
Noonan syndrome (Noonan)	30/04/14	1967 to April week 4 2014	30/04/14	1946 to April Week 3 2014	30/04/14	1974 to 2014 Week 17	25/04/14	1950 to 25th April 2014	Noonan*; Noonan* syndrome; Nunan*; Nunan* syndrome; Familial Turner* syndrome; Female pseudo-Turner syndrome; Male Turner* syndrome; Noonan-Ehmke* syndrome; Nunan-Ehmke* syndrome; Pseudo-Ullrich-Turner* syndrome; Turner-like syndrome; Ullrich-Noonan* syndrome; Ullrich-Nunan* syndrome; Turner* phenotype, karyotype normal; Turner syndrome in female with X chromosome
Sotos syndrome (Sotos)	28/03/14	1967 to March Week 4 2014	28/03/14	1946 to March week 3 2014	28/03/14	1974 to 2014 Week 12	09/04/14	1950 to 9th April 2014	Sotos*; Sotos* syndrome; Cerebral gigantism; Sotos* sequence
Leber's Amaurosis syndrome (Leber's)	12/03/14	1967 to March Week 1 2014	12/03/14	1946 to February Week 4 2014	12/03/14	1974 to 2014 Week 10	05/05/14	1950 to 5th May 2014	Leber* amaurosis; Leber* congenital amaurosis; LCA; Congenital retinal blindness; CRB; Dysgenesis neuroepithelialis retinae; Hereditary epithelial dysplasia of retina; Hereditary retinal aplasia; Heredoretinopathia congenitalis; Leber* abiotrophy; Leber* congenital tapetoretinal degeneration

	PsycINFO		MEDLINE		Embase		PubMed Central		
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Search terms**
22q11.2 deletion syndrome (22q11.2)	24/04/14	1967 to April Week 4 2014	24/04/14	1946 to April week 3 2014	24/04/14	1974 to 2014 Week 17	25/04/14	1950 to 25th April 2014	VCF; VCFS; Velocardiofacial syndrome; CTAF; Velo-cardio-facial syndrome; DiGeorge* syndrome; Conotruncal anomaly face syndrome; CATCH22; Autosomal dominant Opitz G/BBB syndrome; Autosomal dominant Opitz G BBB syndrome; Cayler cardiofacial syndrome; Deletion 22q11/2 syndrome; 22q11/2 deletion syndrome; 22q11/2DS; 22q11 deletion syndrome; Sedlackova* syndrome; Shprintzen* syndrome
Cohen syndrome (Cohen)	27/02/14	1967 to February Week 3 2014	27/02/14	1946 to February Week 3 2014	27/02/14	1974 to 2014 Week 08	09/04/14	1950 to 9th April 2014	Cohen* syndrome; Norio* syndrome; Obesity-hypotonia syndrome; Pepper* syndrome; Prominent incisors-obesity-hypotonia syndrome; Hypotonia obesity and prominent incisors
Cornelia de Lange syndrome (CdLS)	26/02/14	1967 to February Week 3 2014	26/02/14	1946 to February Week 2 2014	26/02/14	1974 to 2014 Week 08	09/04/14	1950 to 9th April 2014	Cornelia de Lange* syndrome; CDLS; De Lange* syndrome; Branchmann-De Lange* syndrome; BDLS; Brachmann* syndrome; Amstelodamensis typus degenerativus; Amsterdam dwarf syndrome; Amsterdam dwarfism

	PsycINFO		MEDLINE		Embase		PubMed Central		
	Date searched	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Date searched**	**Inclusion dates**	**Search terms**
Ehlers-Danlos syndrome (EDS)	11/03/14	1967 to March Week 1 2014	11/03/14	1946 to February Week 4 2014	11/03/14	1974 to 2014 Week 10	05/05/14	1950 to 5th May 2014	Ehlers-Danlos; Ehlers-Danlo*; Ehlers-Danlos syndrome; Ehlers-Danlo* syndrome; EDS; Ehlers-Danlos disease; Ehlers-Danlo* disease; Ehlers Danlos; Ehler* Danlo*; Ehlers Danlos syndrome; Ehler* Danlo* syndrome; Ehlers Danlos disease; Ehler* Danlo* disease; ED syndrome; vascular-Ehler* Danlo* syndrome; vascular ehler* danlo* syndrome; vascular ehler* danlo*; vascular-Ehler* Danlo*; vEDS
Lujan-Fryns syndrome (LFS)	11/03/14	1967 to March Week 1 2014	11/03/14	1946 to February Week 4 2014	11/03/14	1974 to 2014 Week 10	05/05/14	1950 to 5th May 2014	Lujan-Fryns*; Lujan-Fryn*; Lujan-Fryns* syndrome; LFS; Lujan* syndrome; X-linked intellectual deficit with marfanoid habitus; X-linked intellectual deficit with marfanoid features; X-linked mental retardation with marfanoid features; X-linked mental retardation with marfanoid habitus; XLMR with marfanoid features; XLMR with marfanoid habitus
Moebius syndrome (Moebius)	04/03/14	1967 to February Week 3 2014	04/03/14	1946 to February Week 3 2014	04/03/14	1974 to 2014 Week 09	05/05/14	1950 to 5th May 2014	Moebius*; Mobius*; Moebius* syndrome; Mobius* syndrome; Moebius* spectrum; Mobius* spectrum; Moebius* sequence; Mobius* sequence; Congenital facial diplegia; Congenital ophthalmoplegia and facial paresis; Moebius* congenital oculofacial paralysis; Mobius* congenital oculofacial paralysis

1.3.2 Selection Strategy

A total of 32,230 papers were identified by the searches. These papers were assessed for suitability using the following three stages.

1.3.2.1 Stage 1: Screening

Papers were screened by review of abstracts and titles. Table 1.2 outlines the inclusion and exclusion criteria used at this stage. For any papers where suitability was unclear a second researcher was asked to review the paper and consensus was derived.

Table 1.2. Inclusion and exclusion criteria for screening.

Inclusion Criteria	Exclusion Criteria
Empirical papers	Conference proceedings, magazines, dissertations, review articles and books
Papers published or available in English	Papers published in a language other than English
Abstract indicates that the paper reports on the prevalence of ASD within syndrome group	Participants recruited because of a previous or suspected autism diagnosis
Participant sample N≥10	Participant sample N<10

1.3.2.2 Stage 2: Eligibility

The full texts of the screened papers were then read to assess the eligibility of the data. The same inclusion and exclusion criteria were utilised at screening and eligibility. However, the following additional criteria were specified at the eligibility stage (see Table 1.3 for details).

Table 1.3. Additional inclusion and exclusion criteria for eligibility assessment.

Inclusion Criteria	Exclusion Criteria
The paper reports the number of participants in the syndrome group who met a clinical cut-off for ASD	The paper only reports average scores on a measure of ASD phenomenology
Participants were recruited without any specific bias	Participants were recruited because they showed some additional feature e.g., self-injury, seizures etc.
Study reports on a unique sample (or a potentially overlapping sample, but the proportion of overlap cannot be readily determined)	Study reports on exactly the same sample as reported in a previous study.

1.3.2.3 Stage 3: Quality

The quality of the remaining papers was then assessed according to the quality criteria (see below, Section 1.3.3). Papers were included if they had a minimum quality weighting of 0.33, obtained over at least two of the quality criteria.

Papers which met the criteria at each stage were included in the meta-analysis. However, if at any stage the number of papers remaining in a syndrome group was N<2, the group was removed from the analysis. The table presented below in Table 1.4, adapted from Moher, Liberati, Tetzlaff and Altman (2009) and Liberati *et al.* (2009) utilising the PRISMA model, outlines the number of papers excluded at each stage for each syndrome.

Table 1.4. Number of papers included and excluded at each stage of selection

	Identification			Screening		Eligibility		Quality		Included
	Records identified through database searching	**Records identified through hand searching**	**Records after duplicates removed**	**Number of papers screened**	**Excluded**	**Full text papers assessed for eligibility**	**Excluded with reasons**	**Papers assessed for quality**	**Excluded**	**Papers included in meta-analysis**
FraX	5207	30	5211	5211	5110	101	42[b, c, d, e, i]	59	3	56
TSC	2251	24	2256	2256	2218	38	12[b, d, e, f, i]	26	1	25
22q11.2	1213	0	1213	1213	1195	18	4[e]	14	0	14
CdLS	315	1	315	315	302	13	1[e]	12	0	12
DS	8530	16	8536	8536	8511	25	14[b, c, e]	11	1	10
AS	1898	7	1898	1898	1882	16	9[e, f]	7	0	7
NF1	629	0	629	629	621	8	2[e, f]	6	0	6
WS	4200	0	4200	4200	4189	11	5[b, c, e]	6	1	5
Rett	2352	18	2356	2356	2330	26	21[b, e, f, i]	5	0	5
CHARGE	1086	8	1086	1086	1078	8	3[g, h]	5	1	4
Moebius	63	0	63	63	49	14	10[e, g]	4	0	4
PKU	292	7	292	292	283	9	5[e, f]	4	0	4
Cohen	1944	0	1944	1944	1938	6	4[e, f, i]	2	0	2
Noonan	359	0	359	359	356	2	0	2	0	2
JS	452	0	452	452	448	4	2[b, c]	2	0	2
HoI	532	0	532	532	529	3	0	3	2[a]	---
GS	241	0	241	241	237	4	3[a, g, h]	---	---	---
L-F	97	0	97	97	93	4	3[a, f]	---	---	---
Leber's	254	1	254	254	252	2	1[a, e]	---	---	---
Sotos	149	0	149	149	148[a]	---	---	---	---	---
E-D	147	0	147	147	147[a]	---	---	---	---	---
Total	**32211**	**112**	**32230**	**32230**	**31916**	**312**	**141**	**168**	**9**	**158**

[a] Syndrome group removed at this point as papers remaining in syndrome group was N<2
[b] Sample N<10
[c] Participants recruited or excluded due to a previous or suspected ASD diagnosis
[d] Participants recruited because of additional features e.g., seizures, self-injury, pre-mutation of Fragile X etc.
[e] Study did not report the prevalence of sample meeting clinical cut off for ASD
[f] Paper is a review article and does not present any new data
[g] Paper reported on the same sample as another paper
[h] Study altered the scoring algorithms of the assessments
[i] Unable to obtain access to paper from either University of Birmingham Library or the British Library

1.3.3 Quality Review

A numerical quality weighting for each study was generated through a quality review and the data were used to weight the influence of individual studies in the quality-effects pooled prevalence estimate for each syndrome. As this was the first statistical meta-analysis of ASD phenomenology in syndromes, a pragmatic decision was taken to delineate broad quality criteria that allowed for the maximum inclusion of studies, whilst weighting prevalence estimates more heavily by the most robust of these studies. This was particularly important due to the rarity of some of the genetic syndromes and the scarcity of research with these groups.

The quality criteria were generated through reviewing standardised quality criteria for intervention studies (e.g., Downs & Black, 1998) and prevalence studies (Shamliyan *et al.*, 2011). In order to control for key threats to validity, idiosyncratic quality criteria were devised for: 1) the selection of the samples with syndromes, 2) the confirmation of syndrome and 3) the assessment of ASD. For each of these criteria, literature reviews were conducted and active research experts in the field of autism and rare syndromes were consulted for advice on areas of methodological concern. A full description of this process and justification of the assigned quality ratings is provided in Appendix A.

Table 1.5 presents all three quality criteria. The criteria for each article were coded as red for a score of 0, yellow for a score of 1, amber for a score of 2 and green for a score of 3 to provide a simple visual matrix for the evidence quality for each genetic syndrome. The quality weighting was calculated by dividing the total quality score by the maximum possible total of nine. All studies which met the inclusion criteria were read by the first author and rated for quality using these criteria. In order to establish the reliability of these criteria, 31% (N = 52) of all studies were independently rated by a second researcher. Correlation coefficients for Sample identification ($r(52) = 0.67$, $p < .001$), Confirmation of syndrome ($r(52) = 0.62$, $p < .001$), ASD assessment ($r52) = 0.86$, $p < .001$) and total Quality weighting ($r(52) = 0.78$, $p < .001$) were all good.

Table 1.5. Quality Criteria for sample identification, confirmation of syndrome and ASD assessment.

	Quality Rating			
	0 **Poor**	**1** **Adequate**	**2** **Good**	**3** **Excellent**
Sample Identification	Not specified/reported	Single restricted or non-random sample e.g., a specialist clinic or previous research study[5] Single regional sample e.g., a regional parent support groups	Multiple restricted or non-random samples e.g., 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[6]
ASD assessment	Not specified/reported Clinician judgement only	Screening instrument e.g., SCQ, M-CHAT Clinician judgement against specified diagnostic criteria e.g., DSM-IV or ICD-10	Diagnostic instrument e.g., ADI-R, DISCO, ADOS, 3Di	Consensus from multiple assessments, including at least one diagnostic instrument

[5] For individuals recruited as part of a larger *ongoing* study, if the recruitment strategy is described, it is coded. If not, it is coded as 1, indicating the sample has come from one source (i.e., the larger ongoing study).

[6] For syndromes where genetic causes are only currently identified for a proportion of cases (e.g., in CdLS, the NIP-BL gene deletion is thought to account for only 50% of cases), the study will receive a score of 3 if they tested all participants, even if all participants did not evidence the genetic marker and were subsequently confirmed through clinical assessment of features.

1.3.4 Data analysis

In order to describe the prevalence of ASD phenomenology in each syndrome, the number and percentage of the samples meeting clinical cut-off[7] for ASD phenomenology were extracted from each paper. These data were analysed using MetaXL 2.0 (Barendregt & Doi, 2011) to generate pooled prevalence estimates. Fixed-effects models of pooled prevalence assume that the differences in the prevalence estimates between studies are simply a function of sampling error (Barendregt & Doi, 2011), and that there is a common true effect across studies. Given the significant heterogeneity in the extracted prevalence rates within and between syndromes, a random-effects model was felt to be more appropriate. The random-effects model assumes two sources of variability; one from sampling error and one from study level differences, and controls for these in the weighting assigned to each study. However, the random-effects model does not allow or control for variability that arises due to differences in the quality or execution inherent in the studies. Therefore, a quality-effects model was also generated, in which the quality weighting derived through the quality review process was used to weight the prevalence estimates.

In order to make comparisons across syndromes, the random-effects and quality-effects pooled prevalence estimates for each group were plotted against one another. Relative risk statistics using 99[8]% confidence intervals were then calculated to evaluate the relative likelihood of ASD phenomenology in each syndrome utilising the quality-effects prevalence.

Finally, in order to compare ASD phenomenology in each syndrome with an estimated prevalence in the general population, odds ratios with 95% confidence intervals were generated, comparing the quality-effects pooled prevalence for each syndrome with the most recent total population prevalence estimate for ASD diagnosis (1 in 68; Center for Disease Control, 2014). Whilst this total population prevalence estimate of ASD diagnosis is significantly higher than previous estimates, it was felt to be the most appropriate comparison for meta-analysis, as any identified increased likelihood of ASD phenomenology in the syndrome groups could not be attributed to overly conservative estimates for the general population prevalence.

[7] The clinical cut-off varied for each measure of ASD assessment used. Where an assessment provided multiple cut-offs (e.g., PDD-NOS vs autistic disorder), the most conservative cut off, requiring the highest level of ASD phenomenology was entered into the meta-analysis.

[8] More conservative confidence intervals were selected due to the large number of relative risk calculations performed.

1.4 Results

1.4.1 Identified papers

A total of 168 papers were identified as suitable for review, across 16[9] syndromes. In order to assess the first aim of the meta-analysis, each study was evaluated against the quality criteria, and data describing the study, sample characteristics and prevalence of ASD phenomenology were extracted. These data were then analysed to generate pooled prevalence estimates. The results for each syndrome are presented below with a brief summary of the evidence carrying capacity of each literature. The syndromes are presented in order of the size of the evidence base, beginning with the syndrome with the largest number of included papers, through to the syndrome with the least number of included papers.

Across all syndromes, only nine (5.4%) papers met criteria for the highest quality rating for Sample Identification, whereas 89 (53.0%) obtained the highest quality rating for Syndrome Confirmation and 43 (25.6%) for ASD Assessment. Only one (0.6%) paper met the highest quality rating for all three quality criterion. Nine (5.4%) papers were excluded from the pooled prevalence estimates as they did not meet the required quality inclusion criteria. In total, 54 (32.1%) papers reported on the profile of ASD phenomenology within the syndrome, in addition to reporting the prevalence. The majority of papers (N=91, 54.1%) reported the proportion of the sample that had an intellectual disability.

1.4.2 Fragile X syndrome

The literature search identified 59[10] papers that reported the prevalence of ASD phenomenology in Fragile X syndrome. These are presented in Table 1.6. It is notable that the quantity of research investigating or reporting ASD phenomenology in Fragile X syndrome far outweighs the quantity identified for all other syndrome groups. Whilst the quality of the identified papers was variable (quality weightings ranging from 0.11 to 1.00), the large number of higher quality papers included in the meta-analysis for Fragile X syndrome means that the resultant prevalence estimates can be considered to be relatively robust. Confirmation

[9] Given the large number of identified papers and syndromes, it is beyond the scope of this review to provide a summary of the genetic, clinical and behavioural phenotypes of each syndrome in relation to the ASD phenomenology. Readers are directed towards Moss & Howlin, 2009, Moss *et al.,* 2011, Zafeiriou *et al.,* 2007 and Zafeiriou *et al.,* 2013 for further helpful reviews.

[10] Two further papers met the initial screening criteria; however it was not possible to obtain these papers from either University of Birmingham Library or the British Library.

of Fragile X syndrome was undertaken and reported well across the studies, with 50 papers using genetic testing to confirm the diagnosis. However, only 15 studies obtained the maximum quality rating for ASD assessment, and only one study obtained the maximum for sample identification. A total of 20 papers provided data on the profile of ASD in Fragile X syndrome. These may provide sufficient data for future fine-grained meta-analysis of the profile of ASD phenomenology in the syndrome.

The study by Bailey, Raspa, Olmsted and Holiday (2008) is notable in presenting data on a very large sample with genetically confirmed Fragile X syndrome (N=1235). The sampling strategy used in this study also received a good rating, suggesting that the prevalence data obtained in this large scale study were obtained in a representative sample. The data are limited by reliance on parental report rather than direct assessment. However, this methodological decision is understandable with such a large sample. A number of additional studies with very high quality weightings were identified (Hall *et al.,* 2010; McDuffie, Kover, Abbeduto, Lewis & Brown, 2012; McDuffie, Thurman, Hagerman & Abbeduto, 2014; Philofsky, Hepburn, Hayes, Hagerman & Rogers, 2004; Pierpont, Richmond, Abbeduto, Kover & Brown, 2011; Scambler, Hepburn, Hagerman & Rogers, 2007; Wolff, Hazlett, Lightbody, Reiss & Piven, 2013). All of these studies measured ASD phenomenology using clinical consensus of diagnostic measure and at least one other tool *and* confirmed Fragile X syndrome genetically. The inclusion of these studies further strengthens the pooled prevalence estimates. In total, three papers were excluded from the statistical meta-analysis as they did not meet the pre-defined quality inclusion criteria. The first of these was a very large study conducted by Bailey and colleagues (2012) reporting medication use in Fragile X syndrome. Whilst the sampling strategy employed was good, the study did not report confirmation of Fragile X syndrome, and relied upon parental report of treatment for ASD. Secondly, the study by Partington (1984) was excluded as it did not meet minimum quality ratings on any of the three criteria. However, it is a notable study as it is one of the first descriptions of atypical social interaction and communication in Fragile X syndrome. Additionally, the study by Cohen (1995) was excluded as it did not meet the minimum quality criteria for Sample Identification or Confirmation of Fragile X syndrome.

Table 1.6. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Fragile X syndrome.

	Quality Criteria	*Fragile X Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional[11]**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Alanay *et al.*, 2007		24	100.0	Not reported	79.1	Genetic	DSM-IV	Not reported	No	PDD-NOS: 32.0	32.0 *(7)*	0.56
Bailey *et al.*, 2001		55	100.0	58.5[12] *24.0 – 94.0*	Not reported	DNA analysis	CARS[13]	Trained researchers	No	Severe autism: 3.6 Mild/mod autism: 21.8	3.6 *(2)*	0.67
Bailey *et al.*, 1998		57	100.0	66.7[14] *24.0 - 133*	Not reported	DNA analysis	CARS	Trained researchers	Yes	Severe autism: 3.5 Mild/mod autism: 21.1	3.5 *(2)*	0.44
Bailey *et al.*, 2012		1363	78.1	33.8[15]	Not reported	Parental report	Parental report	N/A	No	Diagnosed or treated for autism:~37.0	37.0 *(504)*	0.22
Bailey *et al.*, 2008		1235	79.0	Not reported	13.0	Genetic	Parental report of diagnosis	N/A	No	Autism: 5.0	5.0 *(62)*	0.56

[11] Where interpretation of clinical criteria (e.g., DSM-III) or assessment results (e.g., ADOS; ADI-R) is necessary, data are reported (where given) on the profession or training of the person interpreting the assessments.
[12] Age in months
[13] Childhood Autism Rating Scale
[14] Age in months
[15] Ability rated as 'poor'

	Quality Criteria		***Fragile X Syndrome Study and Sample Characteristics***								***Outcome Data***	
Authors	**Sample**	**Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional[11]**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Baranek *et al.*, 2005			11	90.9	49.0[16] *(22.0)*	Mild ID[17]	DNA analysis	CARS	Not reported	No	Autism: 27.3	27.3 *(3)*	0.56
Borghgraef *et al.*, 1987			23	100.0	*2.5 – 11.9*	100.0	Cytogenetic	Autiscale	N/A	No	Moderate autism: 30.4 Slight autism: 8.7	30.4 *(7)*	0.56
Bregman *et al.*, 1988			14	100.0	*3.0 – 27.0*	52.0[18]	Cytogenetic	ABC[19] DSM-III	Experienced Child and Adolescent Psychiatrists	No	Infantile autism: 7.1	7.1 *(1)*	0.56
Chonchaiya *et al.*, 2010			61[20] 97	60.7 78.4	9.61 *(5.59)* *1.5 – 24.0* 9.41 *(6.31)* *0.9 – 25.2*	62.75[21] 60.80	Cytogenetic	ADOS[22] ADI-R[23]	Team consensus	No	Autism: 36.1 PDD-NOS: 26.2 Autism: 32.0 PDD-NOS: 25.8	33.5 *(53)*	0.67

[16] Age in months
[17] Average classification for group using the Batelle Developmental Inventory
[18] Mean IQ score
[19] Autism Behavior Checklist
[20] The results of this study were presented in two groups; those whose mother's had experienced an autoimmune disease (top), and those who had not (bottom).
[21] Mean full scale IQ
[22] Autism Diagnostic Observation Schedule
[23] Autism Diagnostic Interview - Revised

Authors	*Quality Criteria* Sample	Syndrome	ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional[11]	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
						Fragile X Syndrome Study and Sample Characteristics							***Outcome Data***	
Cianchetti *et al.*, 1991				36	100.0	36.2 *7.0 – 78.0*	68.5[24]	Cytogenetic	ADI DSM-III-R ICD-10	Examiners	No	Autism: 5.6	5.6 *(2)*	0.78
Clifford *et al.*, 2007				64[25]	51.6	23.2 *5.8 – 60.7*	Not reported for full sample	DNA analysis	SCQ[26] ADOS ADI-R	Not reported	Yes	SCQ ASD: 46.9 ADOS autism: 10.9 ADOS ASD: 15.6 ADI-R autism: 10.9 Consensus autism: 14.1	14.1 *(9)*	0.78
Cohen, 1995				109	100.0	*1.9 - 51*	Not reported	Not reported	DSM-III-R	Not reported	No	Autism: 27.5	27.5 *(30)*	0.11
Cordeiro *et al.*, 2011				97	59.8	12.8 *(5.8)* *5.0 – 33.3*	58.0	DNA analysis	ADOS-G[27] ADI-R DSM-IV	Team consensus; trained clinician	No	Autism: 28.9 ASD: 20.0	28.9 *(28)*	0.78
Demark *et al.*, 2003				15	80.0	11.8 *(2.6)*	100.0	DNA analysis	CARS	Trained assessor	No	Mild/mod autism: 46.7 Severe autism: 6.7	6.7 *(1)*	0.56

[24] Mean IQ score
[25] Study also presented data on permutation carriers; only data on cases with full mutation presented here.
[26] Social Communication Questionnaire
[27] Autism Diagnostic Observation Schedule - Generic

	Quality Criteria		***Fragile X Syndrome Study and Sample Characteristics***								***Outcome Data***	
Authors	**Sample**	**Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional[11]**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Einfeld *et al.*, 1989			45	80.0	12.6 *2.0 – 42.0*	56.0[28]	Cytogenetic	DSM-III-R	Child Psychiatrist	Yes	Autism: 8.9	8.9 *(4)*	0.67
Flenthrope & Brady, 2010			25	84.0	27.0[29] *(7.1)* *15.0 – 40.0*	Not reported	Not reported	CARS	Not reported	No	Mild/mod autism: 64.0	64.0 *(16)*	0.33
Frankland *et al.*, 2004			10	100.0	13.2	50.2[30]	Not reported	ASQ[31]	N/A	No	Autism: 40.0	40.0 *(4)*	0.33
Fryns *et al.*, 1984			21	100.0	*2.0 – 21.0*	100.0	Human genetics department	Not reported	Not reported	No	Autism: 14.3	14.3 *(3)*	0.33
Gabis *et al.*, 2011			28	82.1	14.2	Not reported	DNA analysis	Screening Measure[32]	N/A	No	Autism/schizoid personality: 31.8	31.8 *(7)*	0.67

[28] Mean IQ score
[29] Age in months
[30] Mean IQ score
[31] Autism Screening Questionnaire
[32] Early Childhood Inventory-4 Screening Manual, Child Symptom Inventory-4 Screening and Norms Manual, or Adolescent Symptom Inventory-4 Screening Manual (Screening measure selected dependent on age; all measures were translated into Hebrew)

Authors	*Quality Criteria* Sample	Syndrome	ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional[11]	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
	Fragile X Syndrome Study and Sample Characteristics												***Outcome Data***	
Hagerman *et al.*, 1986				50	100.0	*4.11 – 34.9*	Not reported	Cytogenetic testing and clinical features	DSM-III ABC	N/A	Yes	DSM-III Infantile autism: 16.0 ABC autism: 30.0	16.0 *(8)*	0.56
Hall *et al.*, 2010				120	60.8	13.2[33] 13.5 *(3.3)* *(4.6)* *5.0 – 24.0*	45.7 76.8 [34]	DNA analysis	SCQ ADOS	Trained researcher or clinician	Yes	SCQ ASD: 44.2 ADOS autism: 21.7 Consensus autism: 13.3	13.3 *(16)*	0.89
Hall *et al.*,2008				60	51.7	13.2[35] 13.1 *(3.2)* *(3.9)* *5.0 – 20.0*	46.3 70.8 [36]	DNA analysis	ADOS-G	Trained experimenters	Yes	Autism: 36.7 ASD: 60.0	36.7 *(22)*	0.56
Harris *et al.*, 2008				63	100.0	7.9 *(4.3)* *2.8 – 19.5*	56.0[37]	DNA analysis	ADOS ADI-R DSM-IV	Trained researchers; team consensus	Yes	Autistic disorder: 30.2 PDD-NOS: 30.2 ASD: 60.3	30.2 *(9)*	0.67
Hatton *et al.*, 2006				179	82.1	54.4[38] *(33.9)*	Not reported	DNA analysis	CARS	Trained data collectors	No	Mild/mod autism: 21.2	21.2 *(38)*	0.56

[33] Mean age and SD are presented separately for male (left) and female (right) participants.
[34] Mean IQ scores are presented separately for male (left) and female (right) participants
[35] Mean age and SD are presented separately for male (left) and female (right) participants
[36] Mean IQ scores are presented separately for male (left) and female (right) participants
[37] Mean IQ score
[38] Age in months

Authors	*Quality Criteria* Sample	Syndrome	ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional[11]	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
	Fragile X Syndrome Study and Sample Characteristics												*Outcome Data*	
Hatton *et al.*, 2003				70	85.7	75.7[39] *(33.5)* *12.0 – 143.0*	Not reported	DNA analysis	CARS	Not reported	No	Mild/mod autism: 64.3	64.3 *(45)*	0.67
Kaufmann *et al.*, 2004				56	100.0	57.1[40]	55.2[41]	DNA analysis	ADI-R DSM-IV	Two trained interviewers	Yes	Autistic disorder: 25.0 PDD-NOS: 17.9 ASD: 42.9	25 *(14)*	0.78
Ke *et al.*, 2005				12	83.0	*2.0 – 7.0*	Not reported	Chromosome studies	CARS	Not reported	Yes	Severe autism: ~ 8.0	8.3 *(1)*	0.44
Largo & Schinzel, 1985				13	100.0	*2.6 – 12.5*	100.0	Cytogenetic testing	Develop-mental and behavioural history	Not reported	No	Autistic features: 69.2	69.2 *(9)*	0.56
Maes *et al.*, 1993				58	100.0	41.0 *(13.1)* *21.0 – 67.0*	100.0	Genetic testing	ABC	N/A	Yes	Autism: 6.9	6.9 *(4)*	0.67
Mazzocco *et al.*, 1997				30	0.0	10.7 *(3.2)* *6.1 – 16.2*	33.3	DNA analysis	NDI[42] DSM-III	Not reported	Yes	Autistic disorder: 3.3 PDD-NOS: 17.0	3.3 *(1)*	0.56

[39] Age in months
[40] Age in months
[41] Mean IQ score
[42] Neuropsychicatric Developmental Interview

	Quality Criteria			*Fragile X Syndrome Study and Sample Characteristics*								*Outcome Data*	
Authors	**Sample**	**Syndrome**	**ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional[11]**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
McDuffie *et al.*, 2010				51	68.6	*10.0 – 16.0*	Not reported	Molecular genetic testing	ADI-R	Research-reliable examiners	Yes	Autism: 47.1	47.1 *(24)*	0.78
McDuffie *et al.*, 2012				34	100.0	13.0 *(1.7)*	45.6[43]	Molecular genetic testing	ADI-R ADOS	Research-reliable examiners	No	Both Autism: 47.1	47.1 *(16)*	0.89
McDuffie *et al.*, 2014				49	100.0	7.5 *(2.0)*	57.9[44]	Genetic testing	ADI-R ADOS	Research reliable staff	Yes	Both autism: 81.6	81.6 *(40)*	0.89
Moss *et al.*, 2013a				177	100.0	16.9 *(8.8)* *4.0 – 40.0*	Not reported	Physician/ Paediatrician/ Geneticist	SCQ	N/A	Yes	Autism: 45.6 ASD: 83.6	48.6 *(86)*	0.44
Oliver *et al.*, 2011				191	100.0	16.6 *(8.8)* *4.0 – 47.0*	9.9[45]	Physician/ Paediatrician/ Geneticist	SCQ	N/A	Yes	Autism: 46.3 ASD: 83.6	46.3 *(82)*	0.44
Ornstein *et al.*, 2008				42	100.0	129.3 *(18.7)*	53.4[46]	DNA analysis	CARS	Not reported	No	Mild/mod autism: 23.8	23.8 *(10)*	0.56

[43] Mean IQ score
[44] Mean non-verbal IQ
[45] Defined as not able on the Wessex
[46] Mean IQ score

	Quality Criteria		***Fragile X Syndrome Study and Sample Characteristics***								***Outcome Data***	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional[11]**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Partington, 1984		61	100.0	*2.0 – 59.0*	100.0	Not reported	Clinical examination	Psychiatrists	No	Autism: 4.9	4.9 *(3)*	0.00
Philofsky *et al.*, 2004		18	100.0	*26.0 – 45.0*[47]	Not reported	Molecular genetic testing	DSM-IV ADOS ADI-R	Psychologist with expertise in autism	Yes	Consensus autism: 44.4	44.4 *(8)*	0.89
Pierpont *et al.*, 2011		44	68.2	12.6 *(1.8)* *10.0 – 16.0*	46.0[48] 66.9	Molecular genetic testing	ADOS ADI-R	Research reliable examiner	No	Both autism: 25.0	25.0 *(11)*	0.89
Reiss & Freund, 1990		17	100.0	11.0 *3.0 – 24.0*	50.0[49]	Cytogenetic testing	NDI DSM-III-R	Trained research assistant or Child Psychiatrist	Yes	Autistic disorder: 17.6 PDD-NOS: 41.2	17.6 *(3)*	0.56
Roberts *et al.*, 2009a		55	100.0	*8.0 – 48.0*	Not reported	Genetic report	CARS	Consensus of two examiners	No	Mild-severe autism:~31	30.9 *(~17)*	0.56

[47] Age range in months
[48] Non-verbal mean IQ, reported separately for males (left) and females (right)
[49] Mean IQ score

	Quality Criteria				***Fragile X Syndrome Study and Sample Characteristics***							***Outcome Data***	
Authors	**Sample**	**Syndrome**	**ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional[11]**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Roberts *et al.*, 2009b				51	100.0	4.0[50] 8.1	Not reported	DNA analysis	CARS	Examiner consensus	No	Mild/Mod autism: 35.3	35.3 *(18)*	0.67
Roberts *et al.*, 2001				39	100.0	57.3[51] *(15.9)* *20.6 – 86.1*	Not reported	DNA analysis	CARS	Examiner	No	Mild/Mod autism: 20.5	20.5 *(8)*	0.67
Roberts *et al.*, 2007				86	100.0[52]	79.4[53] *(52.11)*	53.37[54]	DNA analysis	CARS	Examiner consensus	No	Mild/mod autism: 32.6	32.6 *(28)*	0.56
Rogers *et al.*, 2001				24	95.8	35.1[55] *(7.1)*	Not reported	DNA testing	ADI-R ADOS-G DSM-IV	Reliable trained raters	Yes	Autism: 33.3 PDD: 16.7	33.3 *(8)*	0.89

[50] Age reported in two groups; those who scored below the CARS threshold (left) and those who scored above the threshold (right)
[51] Age in months
[52] The study also presents data on a sample of females with Fragile X syndrome; however, the data regarding the prevalence of ASD phenomenology in the female sample is not reported, therefore only data on the male sample is presented here.
[53] Age in months
[54] Mean non-verbal IQ
[55] Age in months

Authors	*Quality Criteria* Sample	Syndrome	ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional[11]	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
						Fragile X Syndrome Study and Sample Characteristics							***Outcome Data***	
Sabaratnam *et al.*, 2003				23	95.7	37.5 *(22.2)* *6.0 – 76.0*	Not reported	Cytogenetic	DSM-III B-DAS[56] HBS[57]	Not reported	No	Autistic disorder: 0.0[58] PDD-NOS: 17.4	0.0 *(0)*	0.78
Scambler *et al.*, 2007				17	88.2	*24.0 – 47.0*[59]	Not reported	DNA analysis	ADOS-G ADI-R DSM-IV	Clinician with expertise in ASD	No	Autism: 23.5	23.5 *(4)*	0.89
Shanahan *et al.*, 2008				25	100.0	34.8[60] *(2.2)* *30.0 – 37.0*	Not reported	Not reported	CARS	Not reported	No	Mild/mod autism: 28.0	28.0 *(7)*	0.33
Shaw & Porter, 2013				16	25.0	Not reported	64.0[61]	Genetic	ABC	N/A	No	Autism: 6.3	6.3 *(1)*	0.67
Simko *et al.*, 1989				20	90.0	$\leq$ 7.5	100.0	Chromosomal analysis	Parental report	N/A	No	Autistic-like behaviour: 55.0	55.0 *(11)*	0.44

[56] Brief Disability Assessment Scale
[57] Handicaps, Behaviours and Skills Schedule
[58] This longitudinal study presented ASD prevalence data for two time points; however, there were no differences in prevalence between the time points.
[59] Age in months
[60] Age in months
[61] Mean IQ score

	Quality Criteria				*Fragile X Syndrome Study and Sample Characteristics*							*Outcome Data*	
Authors	**Sample**	**Syndrome**	**ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional[11]**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Smith *et al.*, 2012				136	84.6	≥ 12.0	Not reported	Genetic confirmation	Parental report Case review SCQ	Consensus review by authors	Yes	Autistic disorder: 22.0	22.0 *(30)*	0.67
Tawfik *et al.*, 2009				16	100.0	10.8 *(3.6)* *6.0 – 18.0*	61.0[62]	Molecular Genetic testing	CARS	Not reported	No	Mild/mod autism: 43.8	43.8 *(7)*	0.56
Turk & Graham, 1997				49	100.0	*4.0 – 16.0*	Not reported	Cytogenetic	HBS	Researcher	Yes	Autism: 28.6 PDD-NOS: 30.6	28.6 *(14)*	0.56
Warren *et al.*, 2010				55	80.0	*11.0 – 48.0*[63]	Not reported	Genetic	CARS	Examiners	No	Mild/mod autism: 32.7[64]	32.7 *(18)*	0.67
Wheeler *et al.*, 2010				46	76.1	61.6[65] *(8.2)* *42.4 – 72.4*	Not reported	Genetic	CARS	Consensus of two trained researchers	No	Mild/mod autism: 32.6	32.6 *(15)*	0.67
Wisniewski *et al.*, 1985				28	89.3	21.3 *0.8 – 60.0*	100.0	Participants had the 'Fragile X chromosome'	DSM-III	Not reported	No	Infantile autism: 25.0	25.0 *(7)*	0.56

[62] Mean IQ score
[63] Age in months at first of three time points
[64] Mean CARS scores were calculated by the authors based on the final two time points in the study.
[65] Age in months

	Quality Criteria			***Fragile X Syndrome Study and Sample Characteristics***							***Outcome Data***	
Authors	**Sample**	**Syndrome**	**ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional[11]**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Wisniewski *et al.*, 1991				62	88.7	23.1[66] 15.7 *(14.3)* *(3.5)* *2-70* *10-20*	100.0	Cytogenetic	DSM-III-R	Not reported	No	Autistic stigmata: 16.1	16.1 *(10)*	0.33
Wolff *et al.*, 2013				41	100.0	4.6 *(0.8)*	55.7[67]	Genetic	ADOS ADI-R	Trained clinicians	No	Autism: 39.0	39.0 *(16)*	0.89
Zingerevich *et al.*, 2009				48	75.0	41.3[68] *(16.0)* *12.0 – 76.0*	Not reported	DNA analysis	ADOS ADI-R DSM-IV	Experienced clinicians Team consensus	No	Autism: 27.1 PDD-NOS: 33.3	27.1 *(13)*	0.78

[66] Age presented for males (left) and females (right) separately
[67] Mean IQ score
[68] Age in months

Random and quality-effects pooled prevalence estimates were generated based on the 56 papers that met the quality inclusion criteria. These are presented in Figures 1.1 and 1.2.

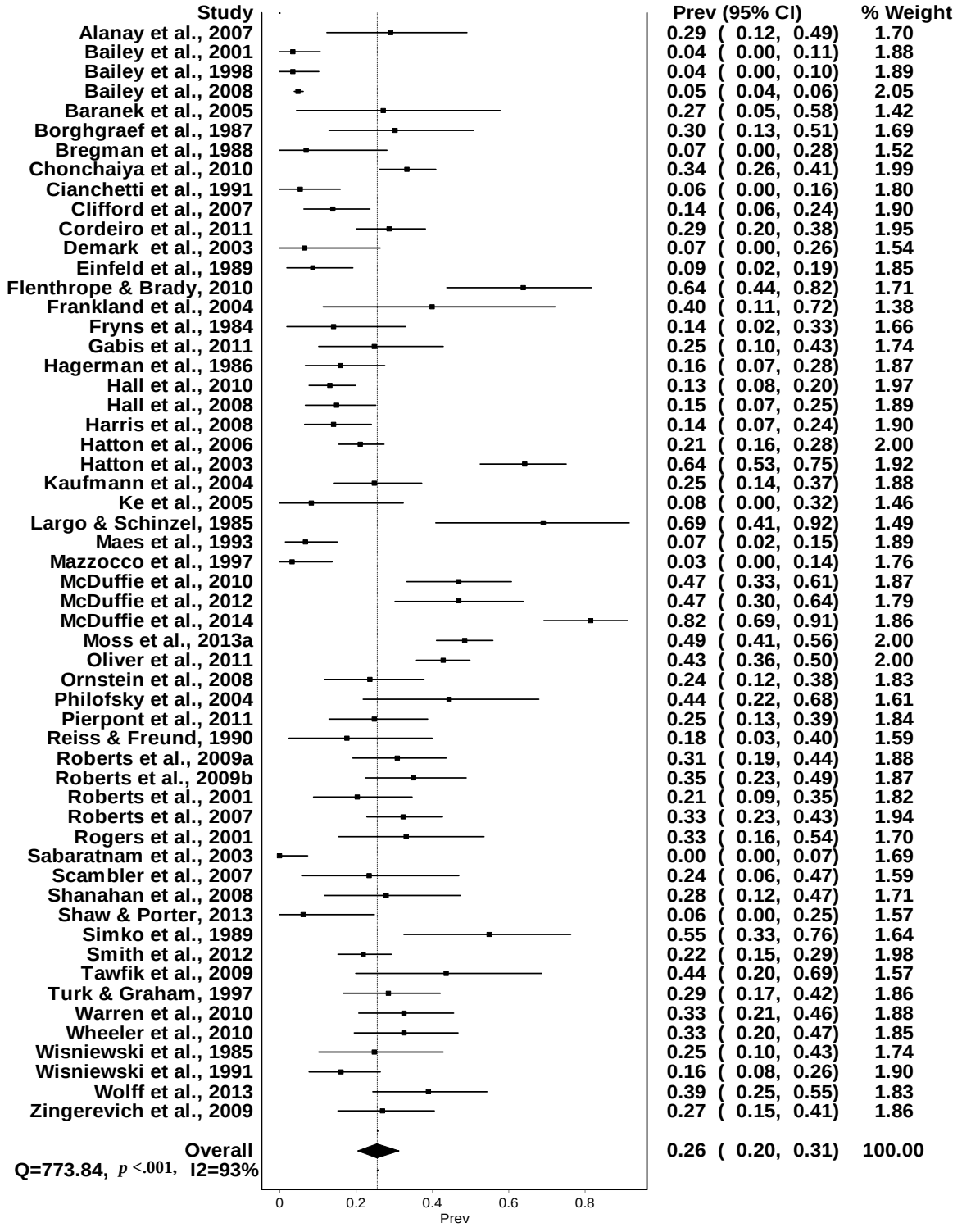

Figure 1.1. Pooled prevalence estimates for ASD phenomenology in Fragile X syndrome using a random-effects model.

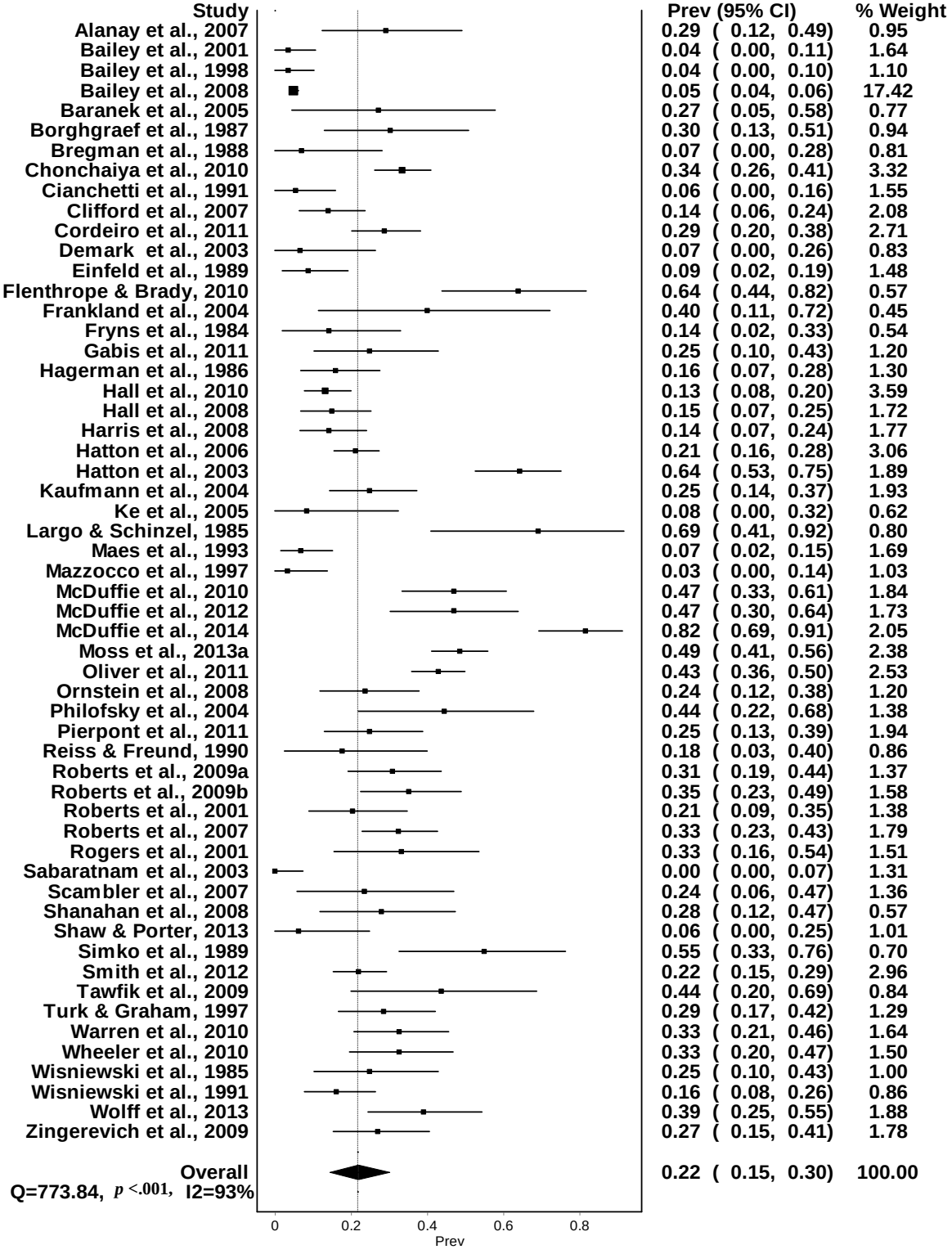

Figure 1.2. Pooled prevalence estimates for ASD phenomenology in Fragile X syndrome using a quality-effects model.

The results revealed that the random-effects model generated a prevalence estimate for ASD phenomenology in Fragile X syndrome of 26% (CI 20 – 31%). The quality-effects model generated a more conservative estimate of 22% (CI 15 – 30%).

ASD phenomenology is reported to vary by gender in Fragile X syndrome (Moss & Howlin, 2009). Therefore, additional prevalence estimates were generated from the 28 papers that reported on solely male samples. The forest plots for these analyses are presented in Appendix B. The results revealed that the random-effects model generated a prevalence estimate for males with Fragile X syndrome of 28% (CI 21 – 36%). The quality-effects model generated a less conservative estimate of 30% (CI 22 – 38%). In order to provide equivalent comparisons to the other syndrome groups, in which gender was not controlled for, the Fragile X male only prevalence estimates will not be used in between group comparisons.

1.4.3 Tuberous Sclerosis Complex

The literature search identified 26[69] papers that reported the prevalence of ASD phenomenology in Tuberous Sclerosis Complex. These are presented in Table 1.7. The quality of the identified papers was variable, with quality weightings ranging from 0.33 to 0.78. Only one study in Tuberous Sclerosis Complex achieved the highest quality rating for more than one criterion (Peters *et al.,* 2013), and no studies obtained a quality rating of three in all three areas. One paper was excluded from the pooled prevalence estimate due to poor quality (Smalley, Smith & Tanguay, 1991). A total of two studies obtained the highest quality rating for sample identification, five for confirmation of Tuberous Sclerosis complex and eight for ASD assessment. Four studies presented data describing the profile of ASD in Tuberous Sclerosis Complex.

The majority of the studies obtained small samples of less than 100 participants, however two large scale studies investigating ASD phenomenology in Tuberous Sclerosis Complex were identified (De Vries, Hunt & Bolton, 2007; Muzykewicz, Newberry, Danforth, Halpern & Thiele, 2007). These studies provide useful robust estimates of ASD phenomenology. However, both studies failed to reach an adequate rating of quality in all three areas, demonstrating the innate difficulties in conducting rigorous study of ASD phenomenology in large samples with rare syndromes.

[69] A further two papers met the initial screening criteria; however it was not possible to obtain these papers from either University of Birmingham Library or the British Library.

Table 1.7. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Tuberous Sclerosis Complex.

	Quality Criteria	*Tuberous Sclerosis Complex Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Baker *et al.*, 1998		20	25.0	13.8 *4.0 – 30.0*	Not reported for full sample	Paediatric neuro-radiologist	ABC ADI DSM-IV	Experienced psychiatrist	No	ABC autism: 60.0 ABC+ADI autism: 40.0 Consensus autism: 20.0	20.0 *(4)*	0.67
Bolton & Griffiths, 1997		18	Not reported	*3.0 – 25.0*	61.1	Multi-disciplinary experienced clinic	ICD-10	Psychiatrist	No	Autism: 22.2 Atypical autism: 27.8	22.2 *(4)*	0.44
Bolton *et al.*, 2002		60	Not reported	Not reported	Not reported	Participants met criteria for TSC	ADI-R ADOS-G ICD-10	Two Psychiatrists	No	Autism: 23.3 Atypical autism: 6.7 PDD-NOS: 1.7	23.3 *(14)*	0.67
Bruining *et al.*, 2014		50	38.0	126.2[70] *(74.0)*	69.3[71]	Cytogenetic	ADI-R	Not reported	Yes	ASD: 44.0	44.0 *(22)*	0.78
Chopra *et al.*, 2011		45	48.9	14.8 *0.5 – 47.0*	60.0	Clinical, Radiological and Genetic	Neuro-psychological tests[72]	Neurologist Clinical Geneticist	No	ASD: 33.3	33.3 *(15)*	0.56

[70] Age in months
[71] Mean IQ score
[72] Tests were only completed for some of the participants – the study does not report which tests, or for what proportion of the sample

	Quality Criteria		*Tuberous Sclerosis Complex Study and Sample Characteristics*								*Outcome Data*	
Authors	**Sample**	**Syndrome**	**ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Chung *et al.*, 2011				62	56.5	15.4 *(9.5)* *3.0 – 48.0*	69.4	Clinical or genetic criteria by specialist	DSM-IV	Psychiatrist	No	ASD: 37.1	37.1 *(23)*	0.44
De Vries *et al.*, 2007				265	40.0	<18	56.6	Parental report of diagnostic features	Parental report of ICD-10 or DSM-IV[73]	Diagnosis by a clinician	No	ASD: 44.9	44.9 *(119)*	0.33
Gillberg *et al.*, 1994				28	39.3	*2.0 – 20.0*	64.3	Clinical criteria Psychiatric examination	CARS ABC DSM-III-R	Psychiatric examination	No	Autistic disorder: 60.7 Autistic like conditions: 21.4 Asperger syndrome: 3.6	60.7 *(17)*	0.56
Granader *et al.*, 2010				21	57.1	10.1 *(4.3)* *5.0 – 18.0*	73.6[74]	Clinical criteria and chart review	SRS[75] SCQ	N/A	No	SRS ASD: 52.4 SCQ ASD: 42.9	52.4 *(11)*	0.33
Gutierrez, 1998				28	39.3	Not reported for full sample	60.7	Medical geneticist	ADI-R ADOS ICD-10 DSM-IV	Trained researchers	Yes	Autism: 28.6 PDD-NOS: 14.3	28.6 *(8)*	0.78

[73] The study further qualified these by establishing 90% agreement between ADOS/ADI-R diagnosis and parent report in a subset of 8% of the sample (N=21). Therefore, this study is given a quality rating of 1 for quality criterion 3.
[74] Mean IQ score for 15 (71%) of participants
[75] Social Responsiveness Scale

Authors	*Quality Criteria* Sample	Syndrome	ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
	Tuberous Sclerosis Complex Study and Sample Characteristics												*Outcome Data*	
Hunt, 1998				23	43.5	*18.0 –24.0*	100.0	Case note review	HBS Screening questions[76]	N/A	No	Autistic traits: 43.5	43.5 *(10)*	0.44
Hunt & Dennis, 1987				90	Not reported	Not reported	Not reported	'Confirmed diagnosis' Case note review	Rutter criteria[77] Screening questions[78]	Authors	No	Autistic behaviour: 50.0	50.0 *(45)*	0.44
Hunt & Shephard, 1993				21	47.6	*3.0 – 11.0*	57.1	At least one clinical feature	HBS DSM-III-R	Not reported	No	Autistic: 23.8 PDD-NOS: 19.0	23.8 *(5)*	0.44
Jeste *et al.*, 2008				14	Not reported	60.0[79]	Not reported	'Satisfied diagnostic criteria'	ADOS	Not reported	No	Autism: 28.6 ASD: 21.4	28.6 *(4)*	0.33
Jeste *et al.*, 2013				28	63.2[80]	23.1[81] *3.0 – 46.0*	Not reported	Paediatric neuro-radiologist	ADOS or AOSI[82]	Child neurologist	No	Autism: 35.7	35.7 *(10)*	0.44

[76] Developed from Wing & Gould, 1979.
[77] Developed from Rutter & Hersov, 1977
[78] Criteria proposed by Rendle-Short (Bruce, 1967)
[79] Age in months. This study was longitudinal and presents ADOS classifications at four time points. The oldest time point is reported here as the authors suggest that ASD phenomenology would be most stable at this point in development.
[80] Gender only report for 19 (68%) of the sample
[81] Age in months
[82] Autism Observation Scale of Infancy; as not all children were assessed using a diagnostic assessment, the study was given a quality rating of '1' for quality criterion ASD

Authors	*Quality Criteria* Sample	Syndrome	ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
	Tuberous Sclerosis Complex Study and Sample Characteristics												*Outcome Data*	
Lewis *et al.*, 2013				42	66.7	9.9 *1.0 – 27.0*	Not reported	Clinical criteria multi-disciplinary team	DSM-IV ADOS	Paediatric neurologist	No	ASD: 28.6	28.6 *(12)*	0.67
Muzykewicz *et al.*, 2007				241	49.0	20.0 *0.8 – 63.4*	67.0[83]	Clinical criteria Neurologist[84]	Not reported	Neuro-psychologist or Neurologist	No	Autism: 35.7	35.7 *(86)*	0.33
Numis *et al.*, 2011				103	Not reported	*3.0 – 55.0*	Not reported	Clinical criteria and genetic	DSM-IV GADS[85] CSI-4[86] BASC-2[87]	Neuro-psychologist	No	ASD: 9.1	9.1 *(41)*	0.56
Park & Bolton, 2001				43	55.8	110.0[88] *(49.0)* *30.0 – 192.0*	Not reported	Clinical criteria Child Psychiatrist	ADOS-G ADI-R ICD-10	Trained Child Psychiatrist	Yes	ASD: 32.6	32.6 *(14)*	0.78

[83] Mean IQ score for 112 (46%) of sample
[84] Mutational analysis was conducted for 191 (79%) of sample
[85] Gilliam Asperger's Disorder Scale
[86] Child Symptom Inventory – 4 Parent Checklist
[87] Behavioural Assessment System for Children - 2
[88] Age in months

	Quality Criteria		***Tuberous Sclerosis Complex Study and Sample Characteristics***								***Outcome Data***	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Peters *et al.*, 2012a		40	60.0	7.2 *0.5 – 25.0*	60.0	Clinical criteria neurological examination Paediatric Neuro-radiologist	DSM-IV ADOS	Paediatric neurologist	No	ASD: 20.0	20.0 *(12)*	0.56
Peters *et al.*, 2013		43	62.7	6.9 *0.7 – 25.6*	Not reported	Clinical criteria and genetic	DSM-IV ADOS	Paediatric neurologist Trained examiners	No	ASD: 32.6	32.6 *(14)*	0.78
Smalley *et al.*, 1991		24	Not reported	Not reported	Not reported	Not reported	ABC DSM-III-R	Author	No	Autism: 20.8	20.8 *(5)*	0.11
Smalley *et al.*, 1992		13	38.5	10.1 *(7.4)*	53.8	Medical geneticist	ADI ICD-10	Not reported	Yes	Autism: 53.8	53.8 *(7)*	0.67
van Eeghen *et al.*, 2013		64	42.2	22.0 *4.0 – 62.0*	46.9	Genetic mutation analysis	SRS	N/A	No	Autism: 37.5 ASD: 56.3	37.5 *(24)*	0.56
Walz *et al.*, 2002		50	54.0	Not reported	Not reported	Clinical criteria Paediatric Neuro-radiologist	DSM-IV	Paediatric Neuro-psychologist	No	Autism: 30.0	30.0 *(15)*	0.44

Authors	*Quality Criteria* Sample	Syndrome	ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
						Tuberous Sclerosis Complex Study and Sample Characteristics							***Outcome Data***	
Wong & Khong, 2006				22	45.5	Not reported	86.4	Neuro-radiologist	DSM-IV ADI-R	Not reported	No	Autism: 31.8	31.8 *(7)*	0.67

The study conducted by Bruining and colleagues (2014) is notable, as a recent, methodologically robust study. The authors investigated ASD phenomenology using a diagnostic measure, across a variety of genetically confirmed syndromes. They then conducted novel statistical analysis to delineate the profiles of ASD phenomenology in each of the syndromes, relative to one another and relative to idiopathic ASD. This methodology could be usefully replicated and applied in other syndrome groups.

Random and quality-effects pooled prevalence estimates were generated based on the 25 papers that met the quality inclusion criteria. These are presented in Figures 1.3 and 1.4. The results revealed that the random-effects model generated a prevalence estimate for ASD phenomenology in Tuberous Sclerosis Complex of 37% (CI 33 – 40%). The quality-effects model generated a similar prevalence figure of 36% (CI 33 – 40%). There were no significant outliers in the data.

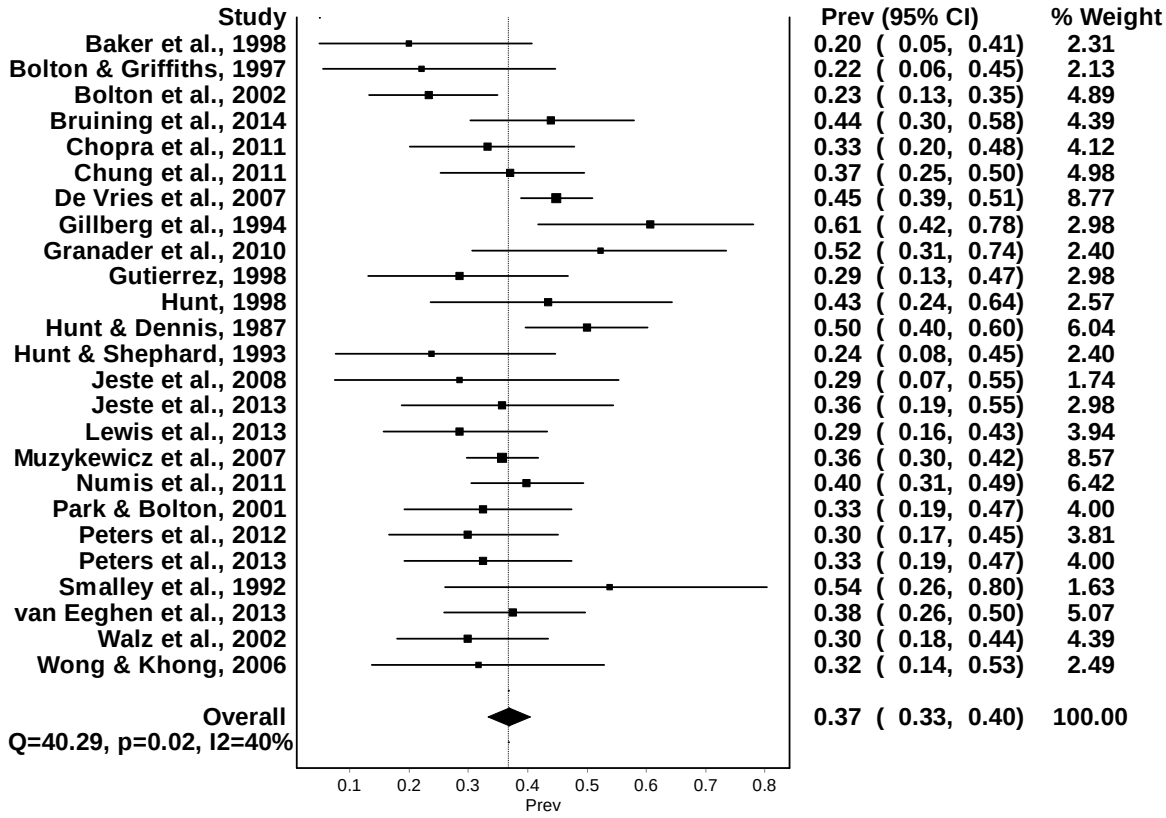

Figure 1.3. Pooled prevalence estimates for ASD phenomenology in Tuberous Sclerosis Complex using a random-effects model.

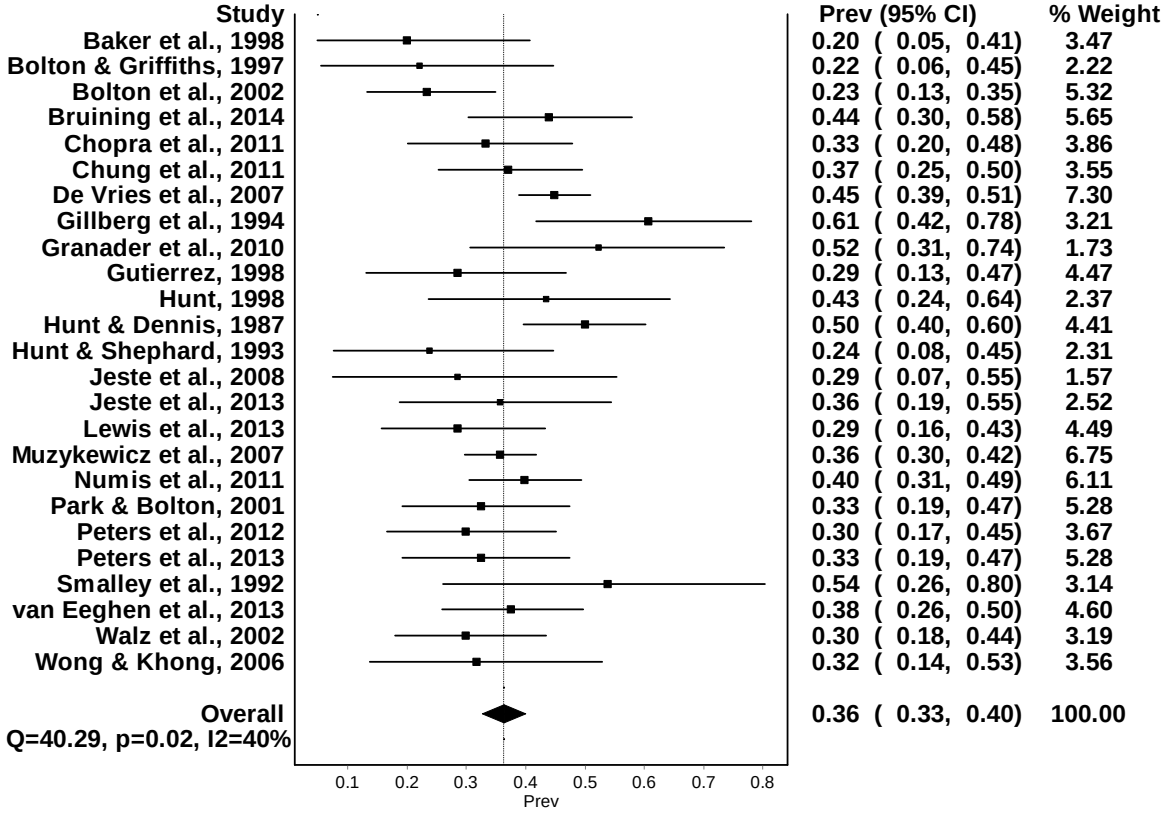

Figure 1.4. Pooled prevalence estimates for ASD phenomenology in Tuberous Sclerosis Complex using a quality-effects model.

1.4.4 22q11.2 Deletion Syndrome

The literature search identified 14 papers that reported the prevalence of ASD phenomenology in 22q11.2 deletion syndrome. These are presented in Table 1.8. The papers were all of good quality, with quality weightings ranging from 0.44 to 0.89. All 14 papers received the maximum quality rating for confirmation of syndrome, six studies received the maximum quality rating for ASD assessment and three studies presented data on the profile of ASD phenomenology in the sample. No studies were excluded on the basis of quality and 11 studies presented data on the proportion of their sample with an intellectual disability. The overall quality of the literature in 22q11.2 deletion syndrome suggests that the generated prevalence estimates will be robust. One notable limitation of the data is that the meta-analysis may have inadvertently included individual samples multiple times, as studies by Niklasson and colleagues (2001; 2002; 2005; 2009) and Vorstman and colleagues (2006; 2013) appear to have used similar samples across multiple studies; however, this was not definitively identifiable from the reporting in the papers.

Table 1.8. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in 22q11.2 deletion syndrome.

	Quality Criteria	*22q11.2 Deletion Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Angkustsiri *et al.*, 2014		100	55.0	10.7 *(2.1)* *7.0 – 14.0*	74.6[89]	Molecular	SCQ BASC-2 ADOS	Not reported	Yes	SCQ ASD: 6.9[90] BASC-2 ASD: 44.0 ADOS ASD: 13.8 ADOS autism: 3.4 SCQ & ADOS: 0.0	0.0 *(0)*	0.89
Antshel *et al.*, 2007		41	52.5	10.6 *(2.4)* *6.5 – 15.8*	Not reported	Genetic	ADI-R DSM-IV	Research reliable clinician	No	Both autism: 19.5 Both ASD: 41.5	19.5 *(8)*	0.78
Briegel *et al.*, 2008		77	55.8	8.0 *4.0 –16.11*	61.0[91]	Genetic	VSK[92]	N/A	Not reported	ASD: 14.3	14.3 *(11)*	0.67
Bruining *et al.*, 2014		90	53.3	162.5[93] *33.6*	67.0[94]	Cytogenetic	ADI-R	Not reported	Yes	ASD: 44.4	44.4 *(40)*	0.78

[89] Mean IQ score
[90] For SCQ and ADOS assessments, a smalls subsample of 29 were assessed.
[91] Parents' estimates of child's intelligence as 'below the average', or 'mentally disabled'.
[92] A German adaption of the SCQ, titled the Behaviour and Social Communication Questionnaire
[93] Age in months
[94] Mean IQ score

	Quality Criteria	*22q11.2 Deletion Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Fine *et al.*, 2005		98	57.1	*22.0-153.0*	Mild global dev. delay[95]	Molecular	M-CHAT or SCQ[96] ADI-R	Trained interviewer	No	Screening ASD: 22.4 Consensus autism: 11.2 Consensus ASD: 13.3	11.2 *(11)*	0.78
Ho *et al.*, 2012		63	47.6	13.7 17.1[97] *(5.5) (1.9)*	80.5 74.5[98]	Genetic	ADOS ADI-R	AID-R and ADOS assessors	Yes	Both autistic disorder: 7.9 Both ASD: 25.4	7.9 *(5)*	0.89
Niklasson *et al.*, 2001		32	40.6	5.0 – 33.0	53.1	Clinical and genetic	DSM-IV ASSQ	Experienced Psychiatrists	No	Autistic disorder: 3.1 PDD-NOS: 28.1	3.1 *(1)*	0.56
Niklasson *et al.*, 2002		20	40.0	5.0 – 33.0	50.0	Genetic	DSM-IV ASSQ[99]	Two Neuro-psychiatrists	No	Autistic syndrome: 30.0 PDD-NOS: 5.0	30.0 *(6)*	0.56
Niklasson *et al.*, 2005		30	46.7	7.0 – 13.0	72.1[100]	Clinical and genetic	DSM-IV ASSQ	Psychiatrists	No	Autistic disorder: 3.3 PDD-NOS: 23.3	3.3 *(1)*	0.56

[95] Average category obtained on the Vineland Adaptive Behavior Scales
[96] Dependent upon age of child; M-CHAT = Modified Checklist for Autism in Toddlers, Revised
[97] Data collected from two research sites; age data presented for both sites
[98] Data collected from two research sites: mean IQ score presented for both sites
[99] Asperger Syndrome Screening Questionnaire
[100] Mean IQ score

	Quality Criteria			*22q11.2 Deletion Syndrome Study and Sample Characteristics*								*Outcome Data*	
Authors	**Sample**	**Syndrome**	**ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Niklasson *et al.*, 2009				100	42.0	1.0 – 35.0	51.0	Genetic	DSM-IV ASSQ	Neuro-psychiatrists	No	Autistic disorder: 5.0 PDD-NOS: 18.0	5.0 *(5)*	0.56
Ousley *et al.*, 2013				31	45.2	19.3 *(4.1)* *14.0 –29.0*	Not reported	Genetic	ADI-R ADOS CPEA[101] DSM-IV	Psychiatrist and Psychologist	No	CPEA ASD: 16.1 DSM-IV only: 32.2	16.1 *(5)*	0.78
Van Campenhout *et al.*, 2012				11	54.5	*3.0 – 13.0*	63.7	Genetic	CBC[102] Clinical assessment	Not reported	No	Severe autistic disorder: 9.1 ASD: 9.1	9.1 *(1)*	0.44
Vorstman *et al.*, 2013				77	50.6	5.9[103] 6.4 *(2.0) (2.0)*	69.7[104] 75.7	Genetic	SRS SCQ	N/A	No	SRS probable ASD: 76.6[105] SCQ probable ASD: 16.9	16.9 *(13)*	0.56
Vorstman *et al.*, 2006				60	38.3	*9.0 – 18.0*	65.2[106]	Genetic	DSM-IV ADI-R	Child Psychiatrist	No	Consensus autism: 5.0 Consensus PDD-NOS: 45.0 ADI-R autism: 33.3	5.0 *(3)*	0.89

[101] Collaborative Program for Excellence in Autism criteria – scoring on both ADI-R, ADOS and meeting DSM-IV criteria
[102] Child Behavior Checklist
[103] Data collected from two subgroups; those with a history of psychosis (left) and those without (right)
[104] Data collected from two subgroups; those with a history of psychosis (left) and those without (right)
[105] Data were obtained retrospectively by parents, scoring the measures on behalf of their adult children
[106] Mean IQ score

Random and quality-effects pooled prevalence estimates were generated based on the 14 papers that met the quality inclusion criteria. These are presented in Figures 1.5 and 1.6.

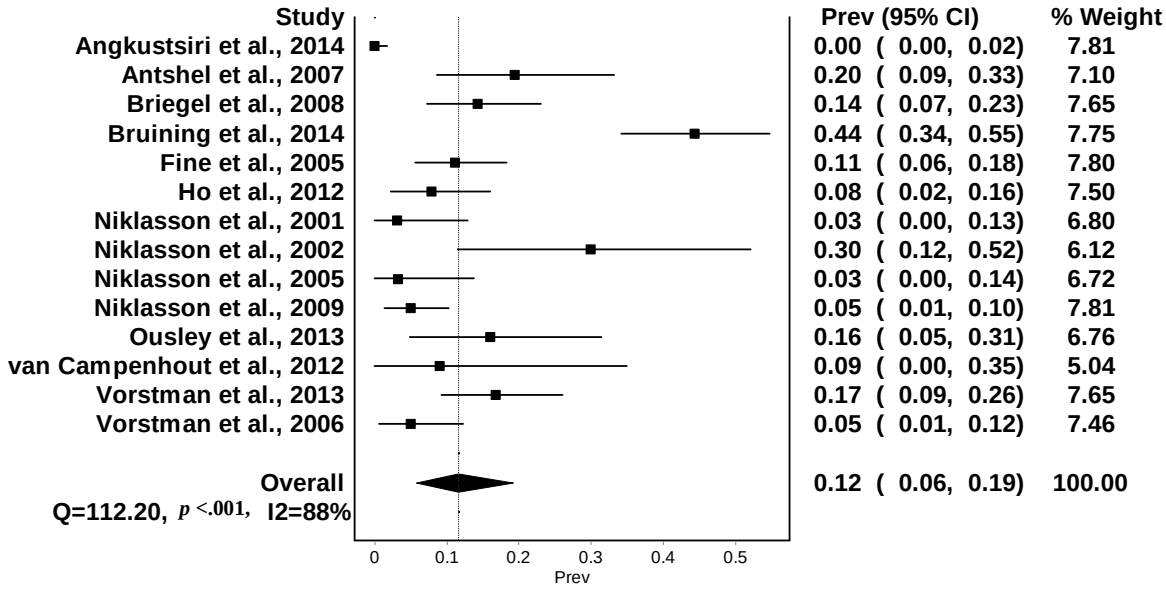

Figure 1.5. Pooled prevalence estimates for ASD phenomenology in 22q11.2 deletion syndrome using a random-effects model.

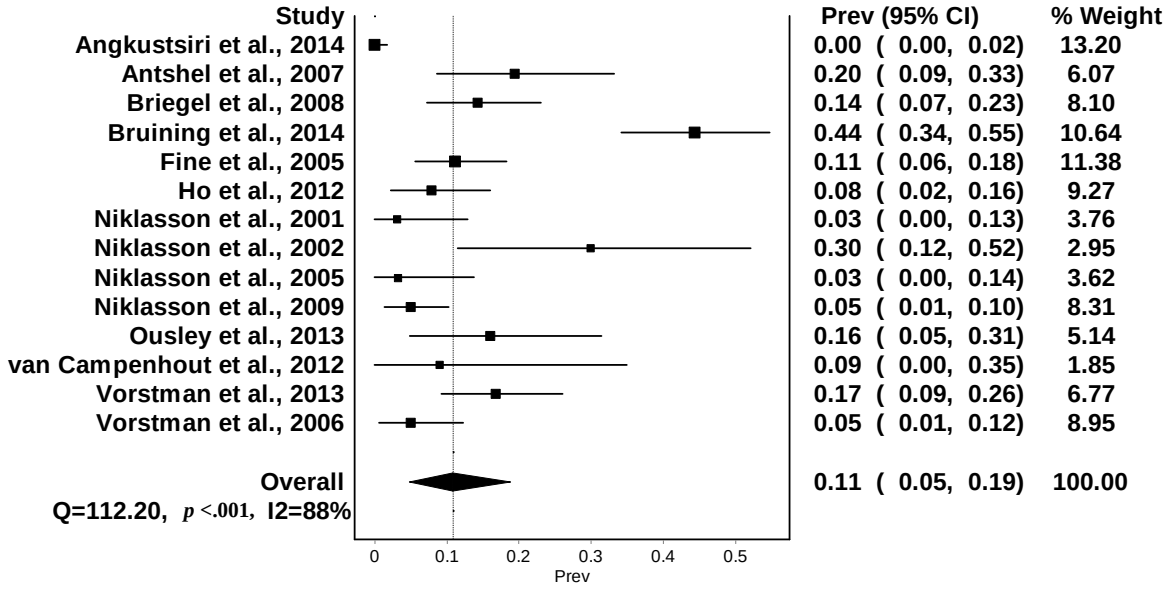

Figure 1.6. Pooled prevalence estimates for ASD phenomenology in 22q11.2 deletion syndrome using a quality-effects model.

The results revealed that the random-effects model generated a prevalence estimate for ASD phenomenology in 22q11.2 deletion syndrome of 12% (CI 6 – 19%). The prevalence estimate generated by the quality-effects model of 11% (CI 5 – 19%) was very similar to that obtained through the random-effects model.

1.4.5 Cornelia de Lange Syndrome

The literature search identified 12 papers that reported the prevalence of ASD phenomenology in Cornelia de Lange syndrome. These are presented in Table 1.9. All 12 papers reached an adequate standard of quality for sample selection, confirmation of Cornelia de Lange diagnosis *and* assessment of ASD phenomenology. This is evidenced in the relatively homogeneous quality weightings, ranging from 0.44 to 0.78, indicating that the pooled prevalence estimates are generated from data of robust quality. Given the genetic heterogeneity in Cornelia de Lange syndrome, it is unsurprising that only one study included a genetic analysis of the Cornelia de Lange syndrome sample (Bhuiyan *et al.,* 2006). Whilst only two studies received the highest quality rating for ASD assessment, five studies presented data on the profile of ASD phenomenology in the syndrome. Nine of the twelve studies reported the proportion of the sample with an intellectual disability.

Similarly with other syndrome groups, it is possible that the meta-analysis may have included individual samples multiple times (e.g., Moss *et al.,* 2013b & Oliver *et al.,* 2011). Whilst papers reporting on identical samples were excluded from the meta-analysis, it was not possible to exclude or account for overlapping samples, as authors did not report the proportion of overlap between studies. The potential overlap between samples marginally limits confidence in the generated pooled prevalence estimates, as individual cases with Cornelia de Lange syndrome may be counted more than once within the meta-analysis.

Table 1.9. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Cornelia de Lange syndrome.

	Quality Criteria	*Cornelia de Lange Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Basile *et al.*, 2007		56	51.8	10.7 *(8.6)* *1.0 – 31.0*	96.4	Expert Geneticist /Paediatrician	ABC CARS	2 independent clinicians	No	Autism:22.0[107] Severe autism: 7.3 Mild/mod autism: 29.3	7.3 *(3)*	0.56
Berney *et al.*, 1999		49	42.9	10.2 *(7.8)*	100.0	General Clinician	Modified ABC ICD-10	1 clinician	No	Autistic disorder: 53.0	53.0 *(26)*	0.44
Bhuiyan *et al.*, 2006		39	48.7	Not reported	92.3	2 Clinical Geneticists	DBC[108] DISCO[109]	Not reported	No	Autism: 56.4 Autism: 61.5	61.5 *(24)*	0.78
Moss *et al.*, 2013a		15	60.0	12.4 *(3.7)* *6.1 – 18.5*	Not reported	Physician/ Paediatrician/ Geneticist	SCQ	N/A	Yes	Autism: 46.2 ASD: 100.0	46.2 *(6)*	0.44
Moss *et al.*, 2012		20	35.0	11.34 *6.0 – 13.0*	43.45[110] (*22.25*)	Physician/ Paediatrician/ Geneticist	ADOS	Not reported	Yes	Autism: 65.0 ASD: 85.0	65.0 *(13)*	0.56

[107] ABC and CARS data only available for 41 of the 56 participants
[108] Developmental Behaviour Checklist (Dutch Version)
[109] Diagnostic Interview for Social and Communication Disorders
[110] British Picture Vocabulary Scales age equivalent score (*SD*)

	Quality Criteria	*Cornelia de Lange Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Moss *et al.*, 2013b		103	41.8	17.2 *(8.8)* *4.0 – 40.0*	Not reported	Physician/ Paediatrician/ Geneticist	SCQ	N/A	Yes	Autism: 45.6 ASD: 78.6	45.6 *(47)*	0.44
Moss *et al.*, 2008		34	47.2	12.4 *(3.8)* *5.0 – 18.96*	100.0	Paediatrician/ Geneticist	SCQ ADOS	N/A Researcher Inter-rater reliability	Yes	SCQ Autism: 23.5 SCQ ASD: 41.2 ADOS Autism: 61.8 ADOS ASD: 73.5	61.8 *(21)*	0.44
Nakanishi *et al.*, 2012		49	47.0	15.2 *4.0 – 44.0*	80.0	Clinical Geneticist	SCQ ADI-R	Trained Investigators supervised by Psychologist	No	SCQ ASD: 49.0 ADI-R Autism: 42.9 Both Autism: 34.7	34.7 *(17)*	0.67
Oliver *et al.*, 2008		54	46.0	13.9 *(8.6)* *3.2 – 37.9*	87.0[111]	Medical Professional	CARS	Not reported	No	Severe autism 32.1 Mild/Mod autism: 15.1	32.1 *(17)*	0.44
Oliver *et al.*, 2011		101	40.6	17.5 *(9.87)* *4.0 – 40.0*	46.5[112]	Physician/ Paediatrician/ Geneticist	SCQ	N/A	Yes	Autism: 45.9 ASD: 78.8	45.9 *(39)*	0.44
Srivastava *et al.*, 2014		41	43.9	11.4 *(3.8)* *5.0 – 18.0*	Not reported	Clinical Geneticist	CARS	Not reported	Yes	Severe autism: 41.4 Mild autism: 41.4	41.4 *(17)*	0.56

[111] Defined as partly able/not able on the Wessex
[112] Defined as not able on the Wessex

Authors	*Quality Criteria* Sample	Syndrome	ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
						Cornelia de Lange Syndrome Study and Sample Characteristics							***Outcome Data***	
Wulffaert *et al.*, 2009a				37	56.8	18.1 *(13.0)* *1.4 – 46.2*	97.3	Clinical Geneticist	DBC-P[113] DISCO	Not reported	No	Autistic Disorder: 54.1 Possible autistic disorder: 16.2	54.1 *(20)*	0.78

[113] Developmental Behaviour Checklist – Parent/carer (Dutch version)

Random and quality-effects pooled prevalence estimates were generated based on the 12 papers that met the quality inclusion criteria. These are presented in Figures 1.7 and 1.8.

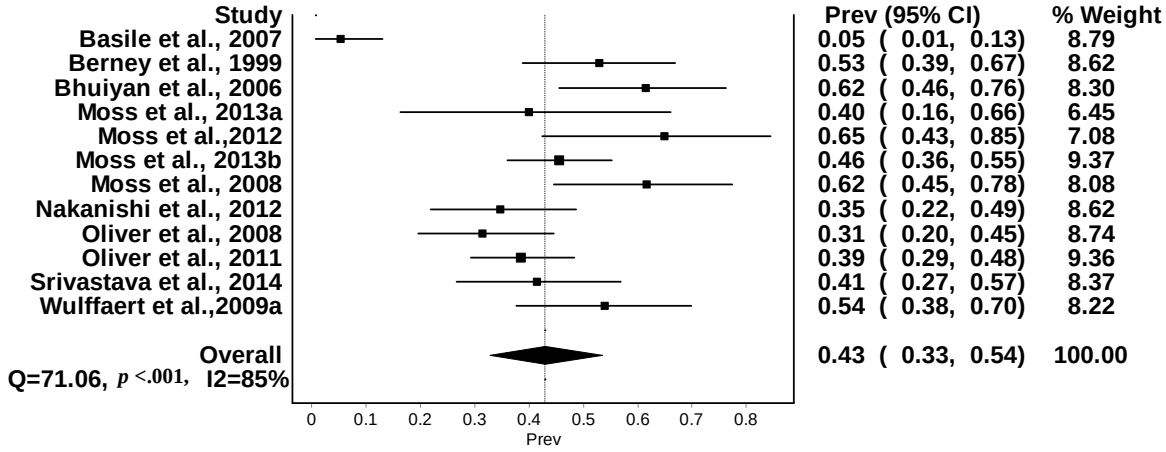

Figure 1.7. Pooled prevalence estimates for ASD phenomenology in Cornelia de Lange syndrome using a random-effects model.

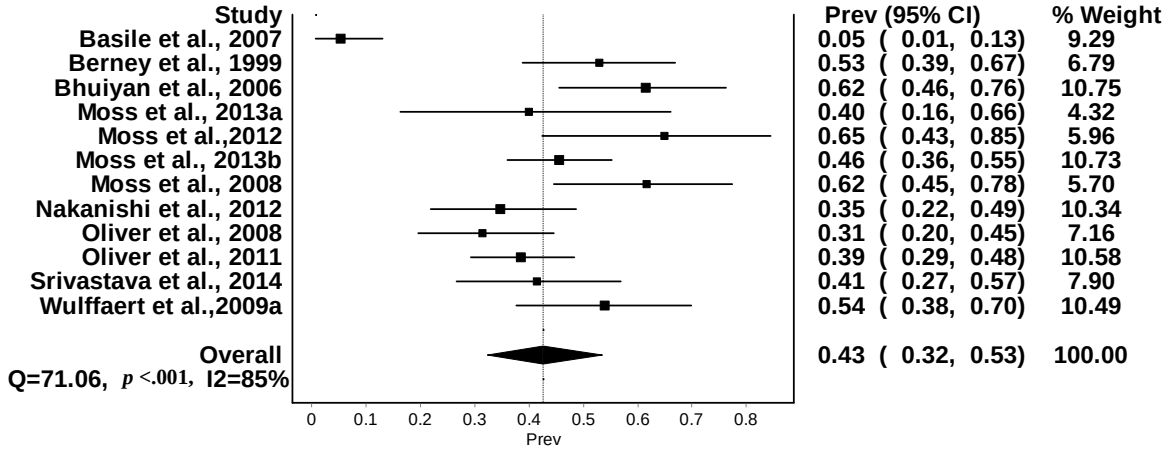

Figure 1.8. Pooled prevalence estimates for ASD phenomenology in Cornelia de Lange syndrome using a quality-effects model.

The results revealed that both the random and quality-effects models generated a prevalence estimate for ASD phenomenology in Cornelia de Lange syndrome of 43%. The confidence intervals were similar in both the random and quality-effects models, ranging from 33 – 54% for random-effects and 32 – 53% for quality-effects. The study conducted by Basile, Villa, Selicorni & Molteni (2007) was an outlier, but removal of this study did not have a substantial impact upon the pooled prevalence estimates (both random and quality-effects estimates increased to 47%). Additionally, the study evidenced a good quality weighting of 0.56 and thus there is a pragmatic argument for including the data from this study.

1.4.6 Down Syndrome

The literature search identified 11 papers that reported the prevalence of ASD phenomenology in Down syndrome. These are presented in Table 1.10. The quality of the identified papers was found to be variable, with quality weightings ranging from 0.11 to 1.00. All studies, apart from Skotko, Davidson and Weintraub (2013) provided an adequate assessment of ASD phenomenology; however, only one of the eleven studies assessed ASD phenomenology with sufficient rigour to obtain a quality rating of three (DiGuiseppi *et al.,* 2010). The study conducted by DiGuiseppi *et al.,* (2010) was notable in that it obtained the highest quality rating for all three criteria. Additionally, the authors reported the prevalence data clearly, allowing for visual inspection of the differing prevalence data generated by each assessment method. Three of the eleven studies used total population recruitment strategies (DiGuiseppi *et al.*, 2010; Kent, Evans, Paul & Sharp, 1999; Lowenthal, Paula, Schwartzman, Brunoni & Mercadante, 2007), which is unusual in comparison to the other syndrome groups where few population studies have been conducted. Seven of the studies also reported on the profile of ASD phenomenology in Down syndrome, in addition to reporting the prevalence.

Despite the relatively clear clinical and genetic markers used for diagnosis in Down syndrome, five of the eleven papers did not report how Down syndrome diagnosis was established in their samples (Kent *et al.*, 1999; Lowenthal *et al.*, 2007; Povee, Roberts, Bourke & Leonard, 2012; Skotko *et al.,* 2013; Starr, Berument, Tomlins, Papanikolaou & Rutter, 2005). In some cases, this was likely due to the competing demand of establishing large enough samples; however in other cases this was due to a lack of descriptive information in the paper. The lack of clarity regarding the diagnostic status of some of the samples does somewhat limit confidence in the generated pooled prevalence estimates. However, all eleven studies provided an adequate sampling strategy, and described this well in the papers. On the basis of quality, one paper (Skotko *et al.,* 2013) was excluded from the quantitative analysis.

Table 1.10. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Down syndrome.

	Quality Criteria	*Down Syndrome Study and Sample Characteristics*								*Outcome Data*		
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Bruining *et al.*, 2014		21	23.8	169.1[114] *(32.6)*	49.5[115]	Cytogenetic	ADI-R	Not reported	Yes	ASD: 28.6	28.6 *(6)*	0.78
DiGuiseppi *et al.*, 2010		123	65.0	73.4[116] *(28.0)* 31–142	100.0	Chromosomal analysis	M-CHAT SCQ ADOS-G ADI-R DSM-IV	Expert Psychologists	No	Autistic disorder: 6.4 PDD-NOS:11.8 SCQ/M-CHAT ASD: 42.3	6.4 *(8)*	1.00
Ji *et al.*, 2011		293	76.0	Not reported	Not reported	Cytogenetic[117]	DSM-IV	Not reported	Yes	Autism: 27.3 PDD-NOS: 11.6	27.3 (80)	0.56
Kent *et al.*, 1999		33	54.5	7.2 *2.0-15.0*	Not reported	Not reported	ASSQ CARS ICD-10	N/A Not reported Not reported	Yes No No	Aspergers: 18.2 Atypical autism: 15.2 ASD: 12.1	12.1 *(4)*	0.44
Lund, 1988		44	Not reported	Not reported	Not reported	Clinical or chromosomal	HBS	Not reported	No	Infantile autism: 11.4	11.4 *(5)*	0.44

[114] Age in months
[115] Mean IQ score
[116] Age in months
[117] Genetic confirmation was available for all except 8.5% of the sample who had clinical features consistent with Down syndromes

Authors	*Quality Criteria* Sample	Syndrome	ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
	Down Syndrome Study and Sample Characteristics												***Outcome Data***	
Lowenthal *et al.*, 2007				180	41.3	Not reported	Not reported	Not reported	ASQ History Qs	N/A	No	Autism: 5.6 PDD-NOS: 10.0	5.6 *(10)*	0.44
Moss *et al.*, 2013c				108	42.6	22.16 *(12.51)* *4.0 – 62.0*	Not reported	Physician/ Paediatrician/ Geneticist	SCQ	N/A	Yes	Autism: 8.3 ASD: 19.4	8.3 *(9)*	0.44
Povee *et al.*, 2012				224	Not reported	4.0 – 25.0	Not reported	Not reported	SCQ	N/A	Yes	ASD: 26.8[118]	26.8 *(60)*	0.33
Skotko *et al.*, 2013				105	63.8	9.5 *(3.8)* *3.2 – 20.9*	Not reported	Not reported	Not reported	N/A	Not reported	ASD: 10.5	10.5 *(11)*	0.11
Starr *et al.*, 2005				13	46.2	14.6 7.8 – 31.9	100.0	N/A	A-PL-ADOS[119] ADI-R	Not reported	Yes	ASD: 38.5	38.5 *(5)*	0.44
Turk & Graham, 1997				45	100.0	Not reported	Not reported	Cytogenetic	HBS ADDC[120] DSM-III	Not reported	Yes	Autism: 11.1 PDD-NOS: 17.8	11.1 *(5)*	0.56

[118] This study did not report the more stringent autism cut off for the SCQ. Thus the less conservative ASD cut off is used.
[119] Pre-linguistic ADOS
[120] Autistic Disorders Diagnostic Checklist

Random and quality-effects pooled prevalence estimates were generated based on the ten papers that met the quality inclusion criteria. These are presented in Figures 1.9 and 1.10.

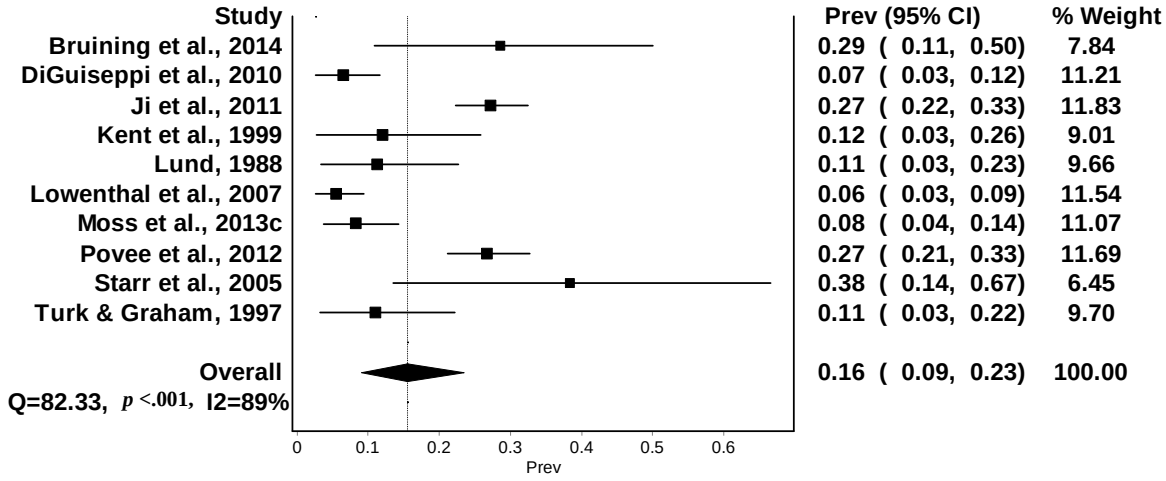

Figure 1.9. Pooled prevalence estimates for ASD phenomenology in Down syndrome using a random-effects model.

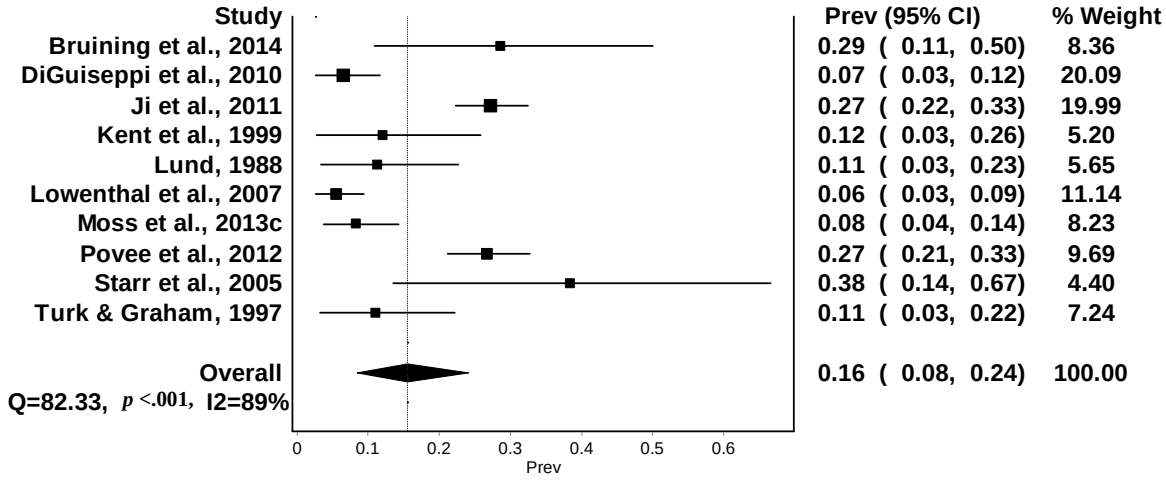

Figure 1.10. Pooled prevalence estimates for ASD phenomenology in Down syndrome using a quality-effects model.

The results revealed that both the random and quality-effects models generated a prevalence estimate for ASD phenomenology in Down syndrome of 16%. The confidence intervals were similar in both the random and quality-effects models, ranging from 9 – 23% for random-effects and 8 – 24% for quality-effects. There were no significant outliers in the data.

1.4.7 Angelman Syndrome

The literature search identified seven papers that reported the prevalence of ASD phenomenology in Angelman syndrome. These are presented in Table 1.11. Six of the seven papers reached an adequate standard of quality for sample selection, confirmation of Angelman diagnosis *and* assessment of ASD phenomenology. The only exception was Sahoo *et al.* (2006) who did not report how their sample were recruited, but did however report an interesting analysis of the associations between deletion size and ASD phenomenology.

Confirmation of Angelman syndrome was well reported, with five of the seven studies utilising genetic analysis. Similarly, assessment of ASD phenomenology was good, with five studies using diagnostic measures. Importantly, five of the seven studies also progressed beyond simply reporting prevalence, and presented data describing the profile of ASD phenomenology in the syndrome. Overall, the quality weightings were good, ranging from 0.44 to 0.89. However, it should be noted that the sample sizes across the studies were relatively small, with the exception of Oliver *et al.* (2011).

Table 1.11. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Angelman syndrome.

	Quality Criteria		***Angelman Syndrome Study and Sample Characteristics***								***Outcome Data***		
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Bonati *et al.*, 2007		23	60.9	*2 - 37*	Not reported	Molecular testing	ADOS ADI-R	Not reported	Yes	Autism: 34.8 ASD: 26.1	34.8 *(8)*	0.89
Moss *et al.*, 2013b		19	52.6	10.4 *(4.8)* *3.0 – 18.5*	Not reported	Physician/ Paediatrician/ Geneticist	SCQ	N/A	Yes	Autism: 40.0 ASD: 93.3	40.0 *(6)*	0.44
Oliver *et al.*, 2011		104	55.8	13.4 *(8.0)* *4.0 – 45.0*	67.0[121]	Physician/ Paediatrician/ Geneticist	SCQ	N/A	Yes	Autism: 17.8 ASD: 66.3	17.8 *(18)*	0.44
Peters *et al.*, 2004		19	57.9	3.8 *(2.5)*	Not reported	Molecular testing	ADOS ADI-R DSM-IV	Reliability trained clinician	No	All autism: 42.1	42.1 *(8)*	0.78
Peters *et al.*, 2012b		42	57.1	5.5 *(4.8)* *2.0 – 25.0*	Not reported	Molecular testing	ADOS	Research reliable Psychologists	Yes	Autism: 28.6[122] ASD: 16.7	28.6 *(12)*	0.78
Sahoo *et al.*, 2006		22	59.1	*1.5 – 17.0*	Not reported	Molecular testing	ADOS ADI-R	Not reported	No	Autism: 45.5	45.5 *(10)*	0.67

[121] Defined as not able on the Wessex
[122] This is a longitudinal study and therefore data in the paper are presented at two time points. Only data from the first time point are reported here,

Authors	*Quality Criteria* Sample Syndrome ASD	N	% Male	Mean Age *(SD)* *Range*	% with ID	Syndrome Diagnosis	ASD Measure	ASD Measure Professional	ASD Profile	%ASD categories	% ASD (*N*)	Quality Weighting
	Angelman Syndrome Study and Sample Characteristics										*Outcome Data*	
Trillingsgaard & Østergaard, 2004		16	43.8	*5.0 – 15.0*	Not reported	Molecular testing	ADOS-G	Trained psychologist	Yes	Autism: 62.5 PDD-NOS: 18.8	62.5 *(10)*	0.78

Random and quality-effects pooled prevalence estimates were generated based on the 7 papers that met the quality inclusion criteria. These are presented in Figures 1.11 and 1.12.

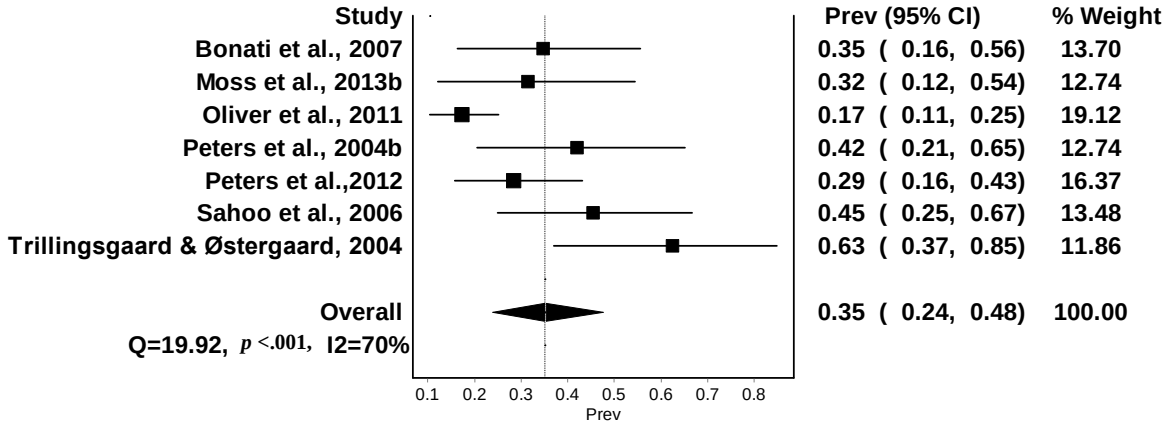

Figure 1.11. Pooled prevalence estimates for ASD phenomenology in Angelman syndrome using a random-effects model.

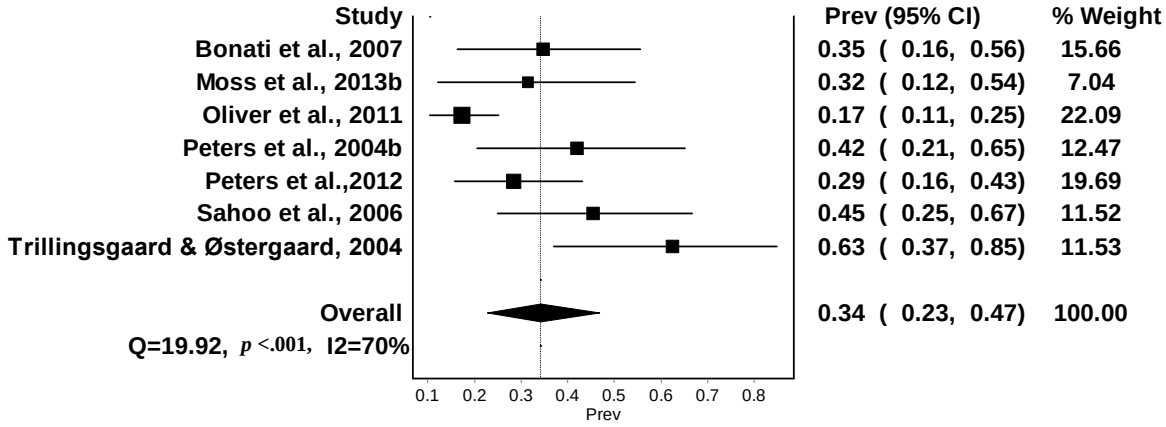

Figure 1.12. Pooled prevalence estimates for ASD phenomenology in Angelman syndrome using a quality-effects model.

The results revealed that the random-effects model generated a prevalence estimate of 35% (CI 24 – 48%). The quality-effects model generated a slightly more conservative estimate of 34% (CI 23 – 47%).

1.4.8 Neurofibromatosis Type 1

The literature search identified six papers that reported the prevalence of ASD phenomenology in Neurofibromatosis Type 1[123]. These are presented in Table 1.12. All of the papers reached an adequate standard of quality for sample selection, confirmation of Neurofibromatosis Type 1 diagnosis *and* assessment of ASD phenomenology.

[123] Although the literature search included terms for Neurofibromatosis Type 2, papers were only identified reporting the prevalence of ASD phenomenology in Neurofibromatosis Type 1.

Table 1.12. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Neurofibromatosis Type 1.

	Quality Criteria	***Neurofibromatosis Type 1 Study and Sample Characteristics***									***Outcome Data***	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Adviento *et al.*, 2014		66	39.4	Not reported	Not reported	Medical geneticist or neurologist[124]	SCQ	N/A	No	SCQ ASD: 11.0	10.6 *(~7)*	0.56
Garg *et al.*, 2013a		47	Not reported	11.7 *(2.9)* *7.2 – 18.4*	95.7[125]	Clinical features by geneticists	ADI-R ADOS CPEA	Blind inter-rater reliability obtained	Yes	ASD: 29.8 Broad ASD: 27.7	29.8 *(14)*	0.89
Garg *et al.*, 2013b		109	45.9	9.11 *(3.3)*	Not reported	Review of medical notes by specialists	SRS	N/A	No	Severe autism: 29.4 Mild/mod autism: 26.6	29.4 *(32)*	0.67
van Eeghen *et al.*, 2013		50	62.0	25.0 *4.0 – 63.0*	6.0	Clinical features by specialists	SRS	N/A	No	Autism: 18.0 ASD: 40.0	18.0 *(9)*	0.44
Walsh *et al.*, 2013		66	63.6	10.11 *(5.4)*	Not reported	Clinical features by specialists	SRS	N/A	No	ASD: 10.6 Clinically raised symptoms: 48.4	10.6 *(7)*	0.44

[124] Molecular confirmation reported for a subset of 11%
[125] Mean verbal IQ

	Quality Criteria				*Neurofibromatosis Type 1 Study and Sample Characteristics*							*Outcome Data*	
Authors	**Sample**	**Syndrome**	**ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Williams & Hersch, 1998				74	55.4	9.6 *0.4 – 31.0*	Not reported	Clinical features by geneticist	DSM-III DSM-IV	Not reported	No	Autism: 4.1	4.1 *(3)*	0.44

The study by Garg *et al.,* (2013a) is particularly notable as it is the only study that used diagnostic, rather than screening, measures for ASD phenomenology. The authors also conducted a population based epidemiological study in order to recruit their sample, resulting in a representative and robustly assessed group. It was also the only study to progress beyond reporting simple prevalence of ASD phenomenology, to describe the profile of ASD phenomenology in Neurofibromatosis Type 1. The quality weightings for all studies conducted in Neurofibromatosis Type 1 were relatively homogenous, ranging from 0.44 to 0.89. This suggests that the generated pooled prevalence estimates are drawn from a robust data set.

Random and quality-effects pooled prevalence estimates were generated based on the 6 papers that met the quality inclusion criteria. These are presented in Figures 1.13 and 1.14.

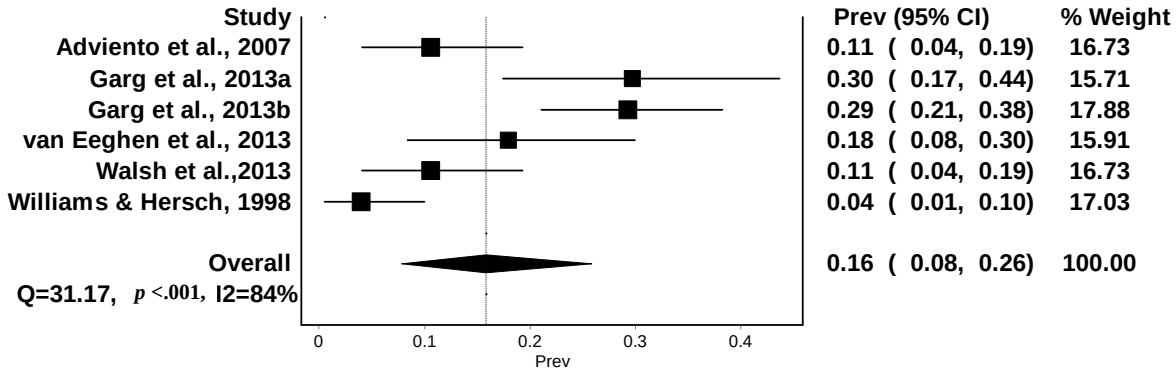

Figure 1.13. Pooled prevalence estimates for ASD phenomenology in Neurofibromatosis Type 1 using a random-effects model.

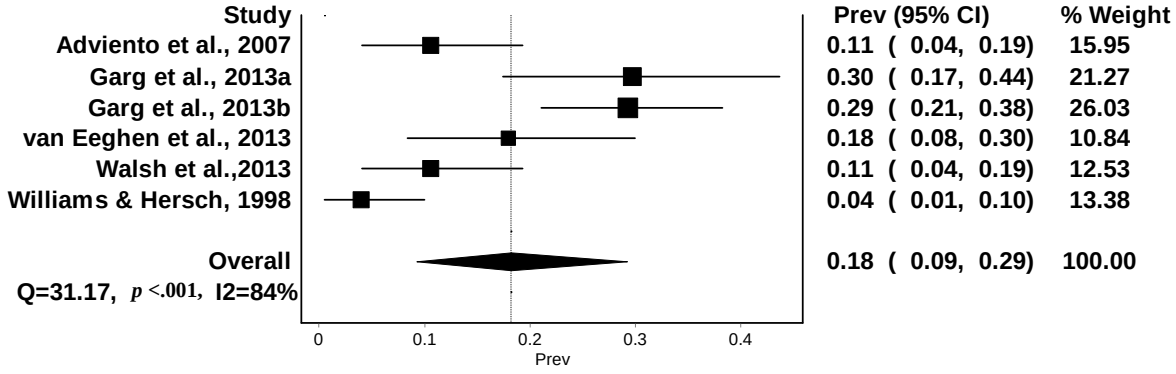

Figure 1.14. Pooled prevalence estimates for ASD phenomenology in Neurofibromatosis Type 1 using a quality-effects model.

The results revealed that the random-effects model generated a prevalence estimate of 16% (CI 8 – 26%). The quality-effects model generated a less conservative estimate of 18% (CI 9 – 29%). There were no significant outliers noted.

1.4.9 Williams Syndrome

The literature search identified six papers that reported the prevalence of ASD phenomenology in Williams syndrome. These are presented in Table 1.13. The quality weightings of the included studies were moderate to good, ranging from 0.33 to 0.78, and thus whilst the literature reporting the prevalence of ASD phenomenology in Williams syndrome is relatively small, it is also quite robust.

One study was excluded from the statistical meta-analysis as it did not meet the pre-defined quality inclusion criteria (Van der Aa *et al.,* 2009). Four of the five included studies confirmed the diagnosis of Williams syndrome with genetic testing. The paper published by Lincoln, Searcy, Jones and Lord (2007) is notable as both syndrome confirmation and ASD assessment received the highest quality weighting. In addition to reporting the prevalence of ASD phenomenology in Williams syndrome, three studies also reported on the profile of these behaviours (Klein-Tasman, Mervis, Lord & Phillips, 2007; Klein-Tasman, Phillips, Lord, Mervis & Gallo, 2009; Lincoln *et al.,* 2007). As in other syndrome groups, it is possible that the two papers by Klein-Tasman and colleagues report on similar samples, and thus some individuals with Williams syndrome may be counted twice within the meta-analysis. However, it was not possible to obtain whether this was the case, or the proportion of overlapping samples from the papers, and thus both studies were included in the meta-analysis.

Table 1.13. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Williams syndrome.

	Quality Criteria	*Williams Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Klein-Tasman *et al.*, 2007		29	65.5	41.6[126] *(8.9)* *30.0 –63.0*	Not reported	Genetically confirmed	ADOS	Certified examiners	Yes	Autism: 10.3 ASD: 37.9	10.3 *(3)*	0.78
Klein-Tasman *et al.*, 2009		30	63.3	41.2[127] *30.0 –63.0*	Not reported	Genetically confirmed	ADOS	Certified examiners	Yes	Autism: 10.0 ASD: 40.0	10.0 *(3)*	0.78
Lincoln *et al.*, 2007		20	45.0	41.6[128] *(11.3)* *27.0 –58.0*	60.5[129]	Genetically confirmed[130]	ADOS DSM-IV	Trained reliable clinicians and Clinical Psychologist	Yes	Autistic disorder: 10.0 PDD-NOS: 10.0	10.0 *(2)*	0.78
Saad *et al.*, 2013		16	62.5	60.4 *(20.2)* *26.0– 100.0*	68.8	Genetic analysis	DSM-IV CARS	Not reported	No	Autism: 6.3	6.4 *(1)*	0.56
Van der Aa *et al.*, 2009		14	Not reported	Not reported	85.7	Genetic analysis	Not reported	Not reported	No	Autism: 14.3 Autistic features: 14.3	14.3 *(2)*	0.33

[126] Age in months
[127] Age reported in months
[128] Age in months
[129] Mean developmental quotient ratio
[130] Confirmed genetically for 19 participants. The remaining 1 participant was diagnosed by a clinical geneticist.

	Quality Criteria				*Williams Syndrome Study and Sample Characteristics*							*Outcome Data*	
Authors	**Sample**	**Syndrome**	**ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Van der Fluit *et al.*, 2012				24	50.0	12.5 *(2.8)* *8.1 – 15.9*	65.7[131]	Not reported	SCQ	N/A	No	ASD: 29.2	29.2 *(7)*	0.33

[131] Mean IQ score

Random and quality-effects pooled prevalence estimates were generated based on the five papers that met the quality inclusion criteria. These are presented in Figures 1.15 and 1.16.

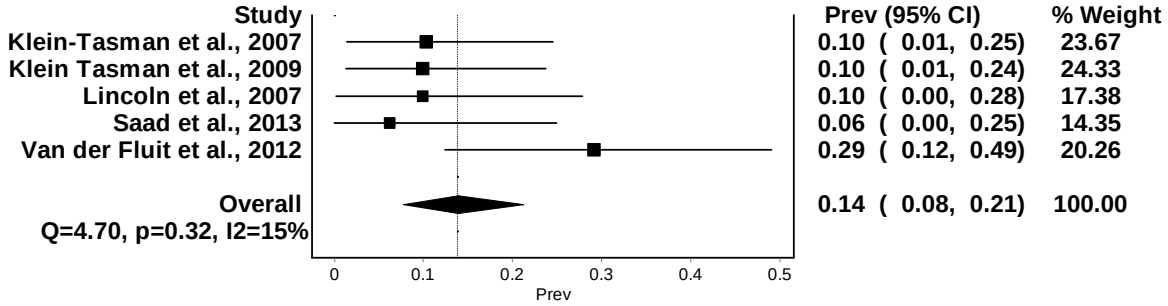

Figure 1.15. Pooled prevalence estimates for ASD phenomenology in Williams syndrome using a random-effects model.

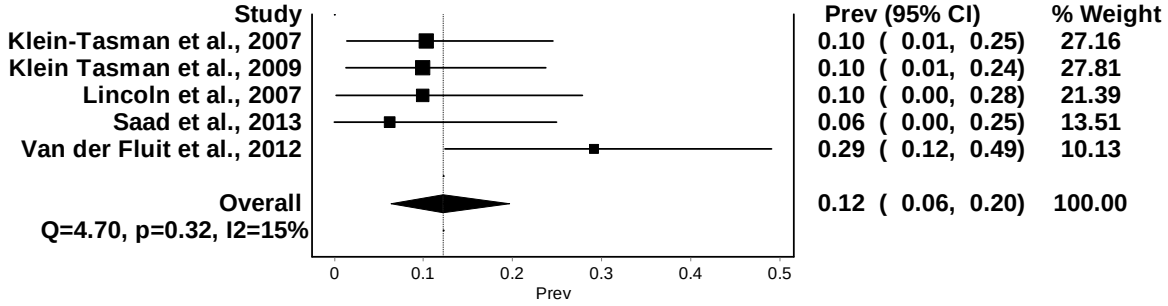

Figure 1.16. Pooled prevalence estimates for ASD phenomenology in Williams syndrome using a quality-effects model.

The results revealed that the random-effects model generated a prevalence estimate of 14% (CI 8 – 21%). The quality-effects model generated a more conservative estimate of 12% (CI 6 – 20%).

1.4.10 Rett syndrome

The literature search identified five[132] papers that reported the prevalence of ASD phenomenology in Rett syndrome. These are presented in Table 1.14. The overall quality of research conducted in Rett syndrome was relatively poor, with only one study obtaining a quality weighting greater than 0.56 (range 0.44 – 0.78). Two studies confirmed the presence of Rett syndrome with genetic testing, but no studies undertook sufficiently robust ASD assessments to obtain the highest quality rating. Two studies did however present data on the profile of ASD phenomenology in the syndrome.

[132] A further paper met the initial screening criteria; however it was not possible to obtain this paper from either University of Birmingham Library or the British Library.

Table 1.14. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Rett syndrome.

	Quality Criteria	*Rett Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Coleman *et al.*, 1988		63	0.0	*2.0 – 20.0*	Not reported	Experienced Paediatricians Paediatric neurologists	Parental report	N/A	No	Autistic withdrawal: 73.0	73.0 *(46)*	0.44
Hagberg *et al.*, 1983		35	0.0	Not reported	Not reported	Child neurologists and authors of paper	Not reported	Not reported	No	Pronounced autistic behaviour:80.0	80.0 *(28)*	0.44
Mount *et al.*, 2003		15	0.0	13.6 *(2.1)*	Not reported	Experienced paediatrician	ABC	N/A	Yes	High probability autism: 40.0	40.0 *(6)*	0.44
Renieri *et al.*, 2009		29	0.0	*5.0 – 37.0*	Not reported for full sample	Genetic and Child Neuro-psychiatrist	DSM-IV ABC[133]	Child Neuro-psychiatrist	No	Autism: 44.8	44.8 *(13)*	0.56
Wulffaert *et al.*, 2009b		52	0.0	16.5 *(11.8)* *2.4 – 49.3*	100.0	Genetic testing and clinical features	DBC DISCO	Trained interviewers	Yes	DBC Autistic disorder: 42.3 DISCO autistic disorder: 57.8	57.8 *(30)*	0.78

[133] Only used in some cases – study does not report the proportion of cases where this was used.

The overall lower quality of evidence obtained in Rett syndrome does somewhat limit the validity of the generated pooled prevalence estimates. However, all studies obtained a good rating for confirmation of Rett syndrome and an adequate rating for sample identification, so key aspects of internal and external validity were appropriately controlled.

Random and quality-effects pooled prevalence estimates were generated based on the five papers that met the quality inclusion criteria. These are presented in Figures 1.17 and 1.18.

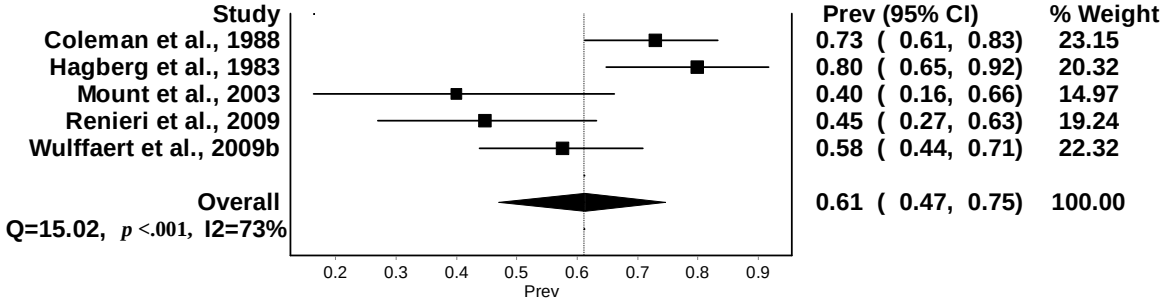

Figure 1.17. Pooled prevalence estimates for ASD phenomenology in Rett syndrome using a random-effects model.

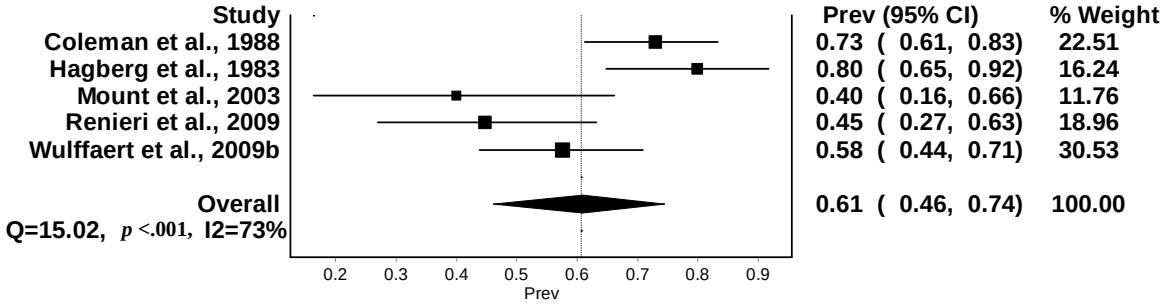

Figure 1.18. Pooled prevalence estimates for ASD phenomenology in Rett syndrome using a quality-effects model.

The results revealed that both the random and quality-effects models generated a prevalence estimate for ASD phenomenology in Rett syndrome of 61%. The confidence intervals were similar in both the random and quality-effects models, ranging from 47– 75% for random-effects and 46 – 74% for quality-effects.

1.4.11 CHARGE Syndrome

The literature search identified five papers that reported the prevalence of ASD phenomenology in CHARGE syndrome. These are presented in Table 1.15.

Table 1.15. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in CHARGE syndrome.

	Quality Criteria	*CHARGE syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Hartshorne *et al.*, 2005		160	53.1	10.9 *(5.6)* *3.0 – 33.0*	Not reported	Not reported	ABC	N/A	Yes	Autism: 27.5	27.5 *(44)*	0.33
Johansson *et al.*, 2006		28	48.4[134]	8.11[135]	78.6	Multi-disciplinary specialist team Clinical features	ADI-R CARS ABC DSM-III DSM-IV	Independent investigators	Yes	Autism: 60.7	60.7 *(17)*	0.78
Miller *et al.*, 2004		31	Not reported	Not reported	38.7[136]	Multi-disciplinary specialist team Clinical features	ADI-R CARS ABC DSM-IV	Not reported	No	Autistic disorder: 16.1 ASD: 16.1	16.1 *(5)*	0.78
Smith *et al.*, 2005		13	61.5	9.0 *2.9 – 24.0*	Not reported	Multi-disciplinary specialist team Clinical features	SCQ	N/A	No	Autism: 15.4 ASD: 23.1	15.4 *(2)*	0.67
Wachtel *et al.*, 2007		87	59.3	11.1 *(3.7)* *6.0 – 18.0*	Not reported	Parental report	Parental report	N/A	No	Autism: 9.2 Asperger's: 2.3 PDD: 6.9	9.2 *(8)*	0.11

[134] Percentage of males presented for total sample of 31; however only 28 participants completed the ASD assessments
[135] Mean age presented for total sample of 31; however, only 28 participants completed the ASD assessments
[136] Severe developmental delay

The quality of the studies was varied, with quality ratings ranging from 0.33 to 0.78. One study (Wachtel, Hartshorne & Dailor, 2007) was excluded as it did not meet the pre-defined quality inclusion criteria. Of the four included studies, two papers assessed ASD very robustly, using consensus of a diagnostic measure and an additional ASD assessment (Johansson *et al.,* 2006; Miller, Stromland, Ventura, Johansson, Bandim & Gillberg, 2004), and two studies presented data on the profile of ASD phenomenology in the syndrome (Hartshorne, Grialou & Parker, 2005; Johansson *et al.,* 2006). The paper conducted by Hartshorne and colleagues (2005) was notable, as they recruited a large sample with CHARGE syndrome, although they did not report how the syndrome was confirmed. All three other studies reported 'expert' clinical confirmation of CHARGE syndrome.

Random and quality-effects pooled prevalence estimates were generated based on the four papers that met the quality inclusion criteria. These are presented in Figures 1.19 and 1.20.

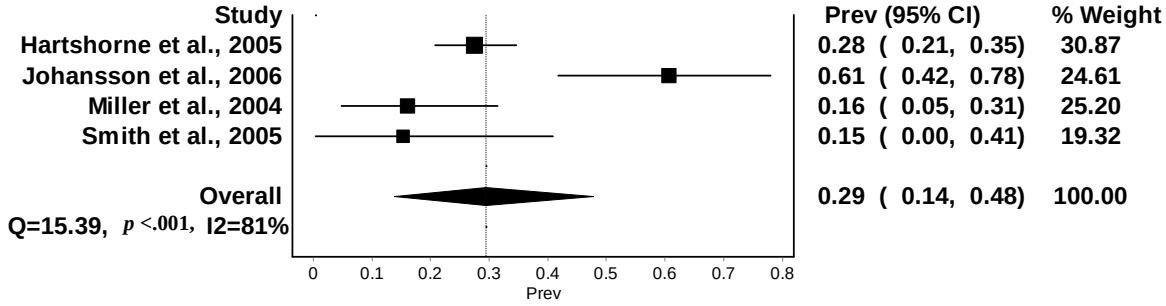

Figure 1.19. Pooled prevalence estimates for ASD phenomenology in CHARGE syndrome using a random-effects model.

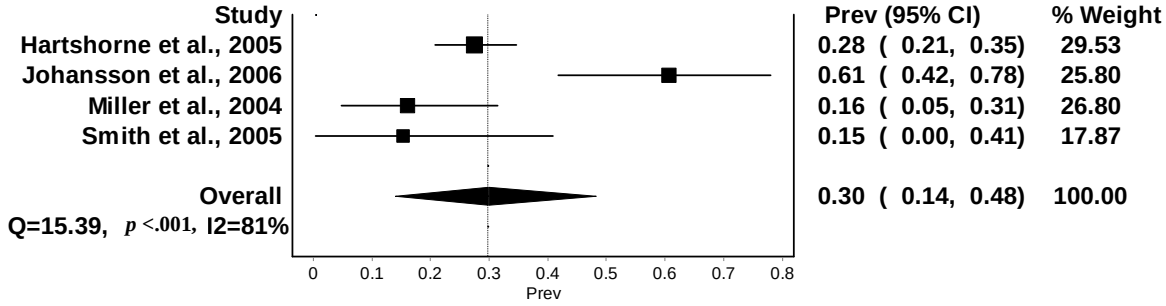

Figure 1.20. Pooled prevalence estimates for ASD phenomenology in CHARGE syndrome using a quality-effects model

The results revealed that the random-effects model generated a prevalence estimate of 29% (CI 14 – 48%). The quality-effects model generated a similar estimate of 30% (CI 14 – 48%).

1.4.12 Moebuis Syndrome

The literature search identified four papers that reported the prevalence of ASD phenomenology in Moebuis syndrome. These are presented in Table 1.16. All four papers reached an adequate standard of quality for sample selection, confirmation of Moebuis diagnosis *and* assessment of ASD phenomenology. This is evidenced in the relatively homogeneous quality weightings, ranging from 0.44 to 0.67, indicating that the pooled prevalence estimates are generated from data of robust quality. As no specific genetic cause has been identified for Moebuis syndrome, it is unsurprising that none of the studies employed genetic testing to confirm the diagnosis; however, only one study utilised 'experts' to confirm a clinical diagnosis of Moebuis, with the remaining three studies utilising 'generalists'. Two papers provided very robust assessment of ASD phenomenology, and one study presented data on the profile of ASD in Moebuis as well as the prevalence. Whilst the key indicators for the quality ratings were well reported across the studies, two of the studies did not report the sample characteristics of their participants very clearly (Gillberg & Steffenburg, 1989; Miller *et al.,* 2004). Additionally, although the quality weightings of the studies were robust, the generated pooled prevalence estimates may be biased by the inadvertent inclusion of participants in multiple studies (Briegel *et al.,* 2009; Briegel *et al.,* 2010). Similarly to other syndrome groups, it was not possible to confirm the proportion of overlapping samples from the papers, and thus both studies were included in the meta-analysis.

Table 1.16. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Moebuis syndrome.

	Quality Criteria	*Moebuis Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Briegel *et al.*, 2010		22	54.5	11.3 *6.0 – 16.0*	9.1	Geneticist or paediatrician	VSK MBAS[137] ADI-R ADOS Kinder-DIPS	Clinical consensus conference	No	Possibly autistic: 13.6 Autistic: 0.0	0.0 *(0)*	0.67
Briegel *et al.*, 2009		27	44.4	11.6 *(2.11)* *6.9 – 17.0*	0.0	Geneticist or paediatrician	VSK MBAS ADI-R ADOS Kinder-DIPS	Not reported	Yes	Possibly autistic: 7.4 Autistic: 0.0	0.0 *(0)*	0.67
Gillberg & Steffenburg, 1989		17	Not reported	*2.0 – 34.0*	Not reported	Clinical criteria Medical case records Paediatrician or Child Psychiatrist	DSM-III-R	Authors	No	Autistic disorder: 29.4	29.4 *(5)*	0.44
Miller *et al.*, 2004		28	Not reported	Not reported	Not reported	Multi-disciplinary specialist team Clinical features	CARS DSM-IV	Not reported	No	Autistic disorder: 17.9 Autistic-like condition: 7.1	17.9 *(5)*	0.56

[137] Marburger Asperger's Syndrome Rating Scale

Random and quality-effects pooled prevalence estimates were generated based on the four papers that met the quality inclusion criteria. These are presented in Figures 1.21 and 1.22.

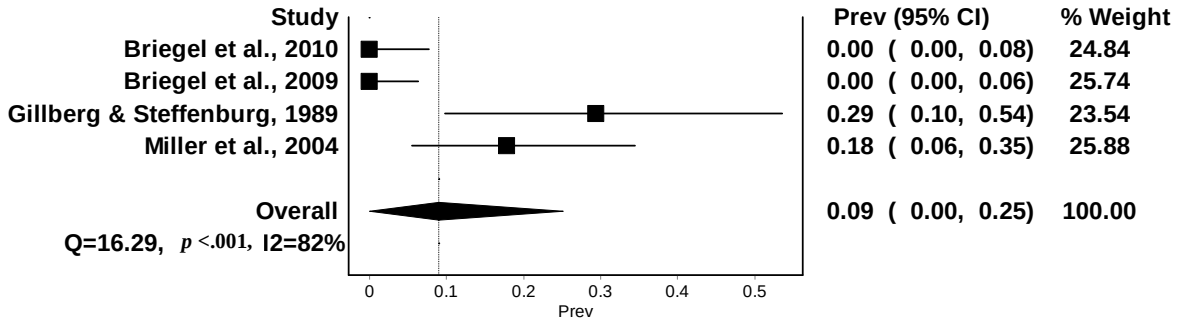

Figure 1.21. Pooled prevalence estimates for ASD phenomenology in Moebuis syndrome using a random-effects model.

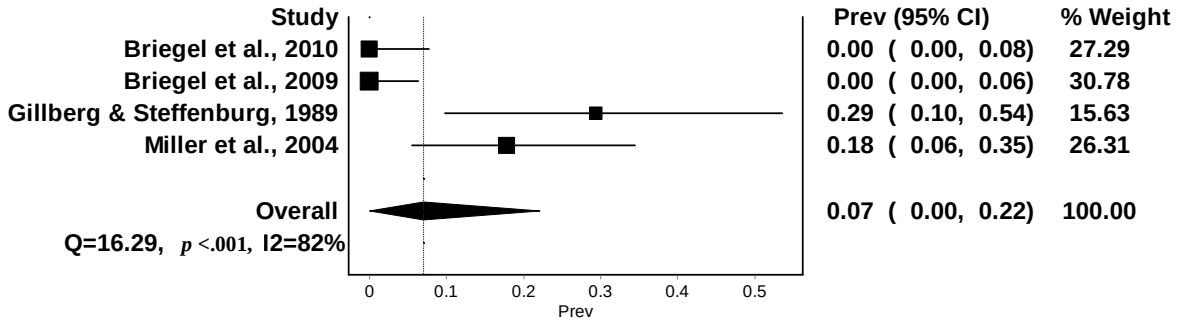

Figure 1.22. Pooled prevalence estimates for ASD phenomenology in Moebuis syndrome using a quality-effects model.

The results revealed that the random-effects model generated a prevalence estimate of 9% (CI 0 – 25%). The quality-effects model generated a more conservative estimate of 7% (CI 0 – 22%). However, given the heterogeneity between the prevalence estimates in the papers, the pooled prevalence estimates need to be interpreted with caution. This caution is supported by the confidence intervals for both the random and quality-effects models' including zero. Therefore, the pooled prevalence estimates for Moebuis syndrome are not included in any further between syndrome comparisons.

1.4.13 Phenylketonuria

The literature search identified four papers that reported the prevalence of ASD phenomenology in Phenylketonuria. These are presented in Table 1.17. Three of the four papers reached an adequate standard of quality for sample selection, confirmation of Phenylketonuria diagnosis *and* assessment of ASD phenomenology.

Table 1.17. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Phenylketonuria.

	Quality Criteria	***Phenylketonuria Study and Sample Characteristics***									***Outcome Data***	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Baieli *et al.*, 2003		97[138]	63.9	5.7[139] 18.5 *(2.5)* *(2.4)* *2-10* *12-24*	94.4[140] 45.5	Metabolic testing	ADI-R CARS	Not reported	No	Autism: 2.1[141]	2.1 *(2)*	0.78
Hackney *et al.*, 1968		22[142]	Not reported	Not reported	100.0	Various[143]	Not reported	Psychologist	No	Autistic behaviour patterns: 40.9	40.9 *(9)*	0.22
Sadek *et al.*, 2013		24[144]	62.5	3.4 *(3)* *0.08 –11.0*	66.7	Metabolic testing	CARS DSM-IV	Not reported	No	Autistic features: 33.3	33.3 *(8)*	0.56
Yalaz *et al.*, 2006		146[145]	Not reported	Not reported	89.0	Paediatric neurologist[146]	CARS ABC	Not reported	No	Autism: 10.3[147]	10.3 *(15)*	0.44

[138] Includes 62 diagnosed by neonatal screening and 35 were identified later as they were born after the introduction of screening, and thus had gone untreated
[139] Data presented separately for the early diagnosed (left) and late diagnosed groups (right)
[140] Mean IQ score – early diagnosed group top, late diagnosed group bottom
[141] Both cases were identified in the late diagnosed group
[142] All untreated cases
[143] Some underwent metabolic testing, or screening, but not all
[144] This sample were untreated as they were newly diagnosed
[145] This sample were untreated as they were recruited from rural areas where screening had not taken place; all participants were then commenced upon treatment and some results in the study are presented stratified based upon the length of treatment the participant had received.
[146] Genotyping conducted for 84.2% of cases
[147] All cases were identified in the late treated sample

The study by Hackney, Hanley, Davidson and Lindsao (1968) is the earliest study identified in the literature search, across all of the syndromes, and as such should be highlighted as one of the first attempts to quantify and describe the phenomenology of ASD in a syndrome. However, the assessment of ASD phenomenology in this study was inadequate, and as the quality rating of the other two criteria was low, the study was not included in the statistical pooled prevalence estimation.

Of the remaining three papers reporting the prevalence of ASD phenomenology in Phenylketonuria, the quality was broadly good, with quality weightings ranging from 0.44 to 0.78. Importantly, all three studies clearly reported the proportion of their samples that evidenced untreated Phenylketonuria, which is an important moderating variable when interpreting the prevalence estimates in this syndrome (Baieli, Pavone, Meli, Fiumara & Coleman, 2003, 36% untreated; Sadek, Emam & Alhaggagy, 2013, 100% untreated; Yalaz, Vanli, Yilmaz, Tokatli & Anlar, 2006, 100% untreated). Similarly, all four studies provided information on the proportion of their sample with an intellectual disability, enabling further understanding of the nature of ASD phenomenology in the group. However, none of the three included studies provided any analysis on the profile of ASD behaviours in the syndrome, and thus would not be possible to ascertain how similar or different the profile is from idiopathic ASD. Two of the studies provided metabolic confirmation of Phenylketonuria, and one provided a very robust assessment of ASD phenomenology and obtained the highest quality rating on this criteria.

Random and quality-effects pooled prevalence estimates were generated based on the three papers that met the quality inclusion criteria. These are presented in Figures 1.23 and 1.24.

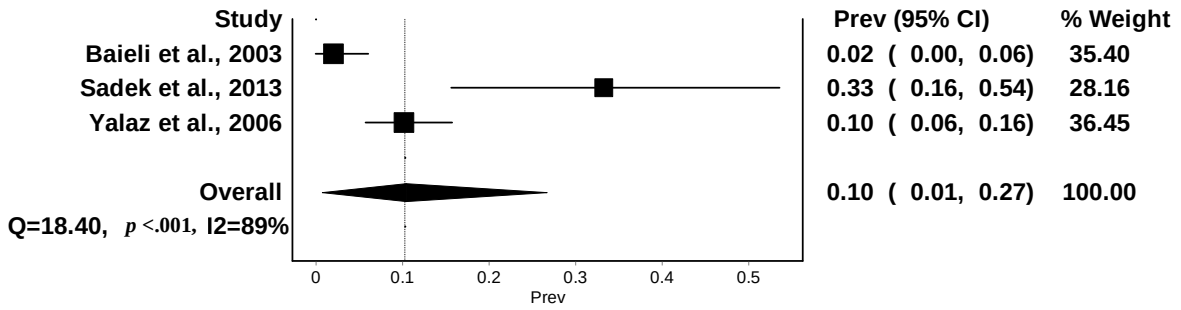

Figure 1.23. Pooled prevalence estimates for ASD phenomenology in Phenylketonuria using a random-effects model.

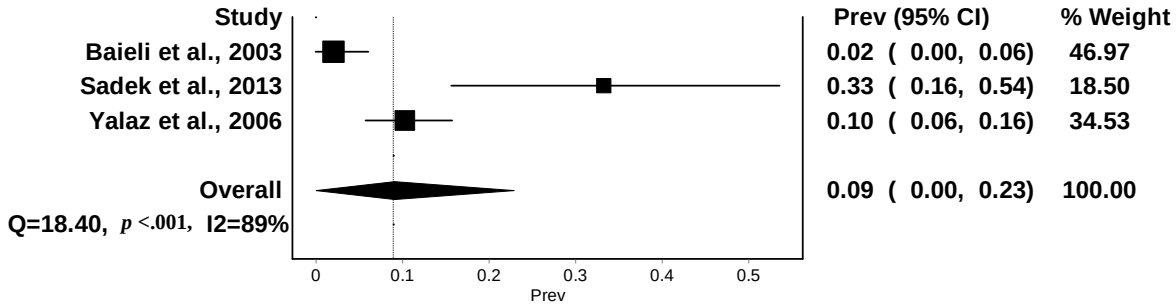

Figure 1.24. Pooled prevalence estimates for ASD phenomenology in Phenylketonuria using a quality-effects model.

The results revealed that the random-effects model generated a prevalence estimate of 10% (CI 1 – 27%). The quality-effects model generated a more conservative estimate of 9% (CI 0 – 23%).

However, given the small number of papers and significant heterogeneity between the prevalence estimates in the papers, the pooled prevalence estimates need to be interpreted with caution. This caution is supported by the confidence intervals for the quality-effects model including zero. Therefore, the pooled prevalence estimates for Phenylketonuria are not included in any further between syndrome comparisons.

1.4.14 Cohen syndrome

The literature search identified two[148] papers that reported the prevalence of ASD phenomenology in Cohen syndrome. These are presented in Table 1.18. The quality of the identified papers was good, with both obtaining quality weightings of 0.67. Both studies provided excellent assessment of ASD phenomenology (Howlin & Karpf, 2004; Howlin, Karpf & Turk, 2005), with one study progressing beyond prevalence data to report the profile of ASD phenomenology in the syndrome (Howlin *et al.,* 2005). However, whilst the generated pooled prevalence data are likely to be robust, they are limited by the small number of identified papers and the relatively limited confirmation of Cohen syndrome by 'generalists' in each study.

[148] A further paper met the initial screening criteria; however it was not possible to obtain this paper from either University of Birmingham Library or the British Library.

Table 1.18. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Cohen syndrome

	Quality Criteria	*Cohen Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Howlin & Karpf, 2004		51	~43.1	16.7 *(8.9)* *4.8 – 49.0*	80.4	Geneticist, Paediatrician or Ophthamologist	SCQ ADI-R ADOS	Trained examiner attending consensus meetings	No	SCQ ASD: 49.0 ADOS autism: 58.8 ADOS ASD: 15.7 ADI-R autism: 78.4 Consensus ASD: 58.8	58.8 *(30)*	0.67
Howlin *et al.*, 2005		45	42.2	16.5 *(9.3)* *4.8 – 48.9*	80.0	Geneticist, Paediatrician or Ophthamologist	ADOS ADI-R	Trained examiner attending consensus meetings	Yes	ADOS autism: 51.1 ADOS ASD: 75.5 ADI-R autism: 75.5 Consensus autism: 48.9 Consensus ASD: 68.9	48.9 *(22)*	0.67

Random and quality-effects pooled prevalence estimates were generated based on the two papers that met the quality inclusion criteria. These are presented in Figures 1.25 and 1.26.

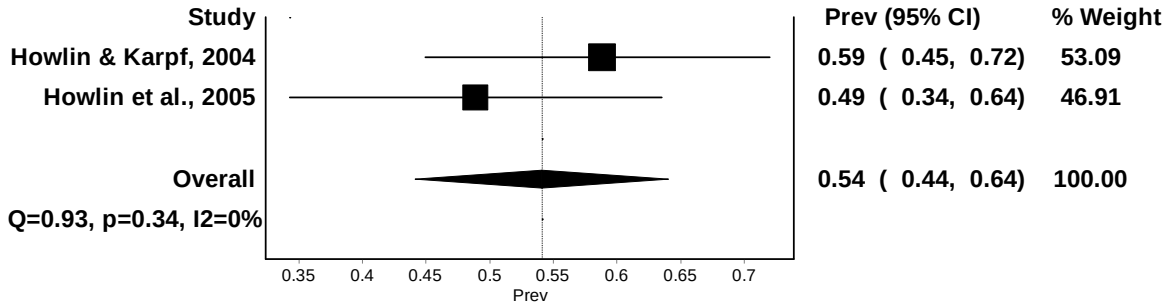

Figure 1.25. Pooled prevalence estimates for ASD phenomenology in Cohen syndrome using a random-effects model.

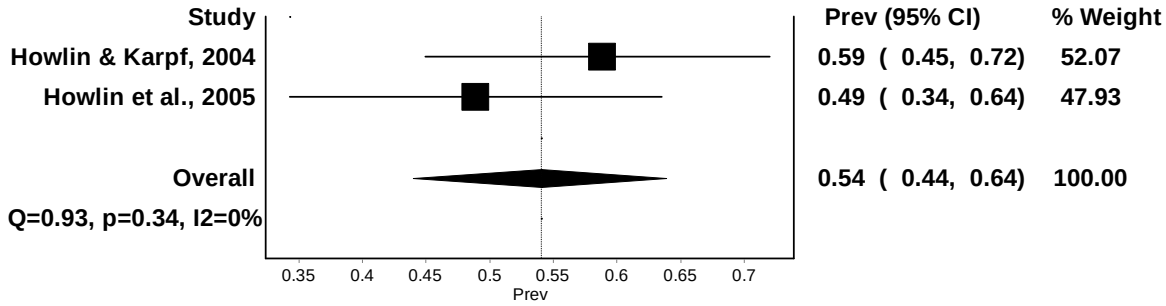

Figure 1.26. Pooled prevalence estimates for ASD phenomenology in Cohen syndrome using a quality-effects model.

The results revealed that the random and quality-effects models generated the same prevalence estimate of 54% (CIs 44 – 64%).

1.4.15 Noonan syndrome

Following the literature search, two recent papers were identified that reported the prevalence of ASD phenomenology in Noonan syndrome. These are presented in Table 1.19. Both papers reached an adequate standard of quality for sample selection, confirmation of Noonan diagnosis *and* assessment of ASD phenomenology, although both studies are limited by reliance upon screening tools to assess ASD phenomenology. Whilst the quality weightings for both studies were good, as only two studies were included in the meta-analysis, the pooled prevalence estimates should be interpreted with caution.

Table 1.19. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Noonan syndrome.

	Quality Criteria		*Noonan Syndrome Study and Sample Characteristics*									*Outcome Data*	
Authors	**Sample**	**Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Adviento *et al.*, 2014			48	54.2	Not reported	Not reported	Clinical criteria by Geneticist[149]	SCQ	N/A	No	SCQ ASD: 21	20.8 *(~10)*	0.56
Alfieri *et al.*, 2014			38	57.9	9.5[150] *2.9 – 21.9*	85.5[151]	Genetic confirmation	SCQ or M-CHAT DSM-IV	N/A Not reported	No	ASD: 10.5	10.5 *(4)*	0.67

[149] Molecular confirmation occurred for 56% of cases
[150] Median age
[151] Median IQ score

Random and quality-effects pooled prevalence estimates were generated based on the 2 papers that met the quality inclusion criteria. These are presented in Figures 1.27 and 1.28.

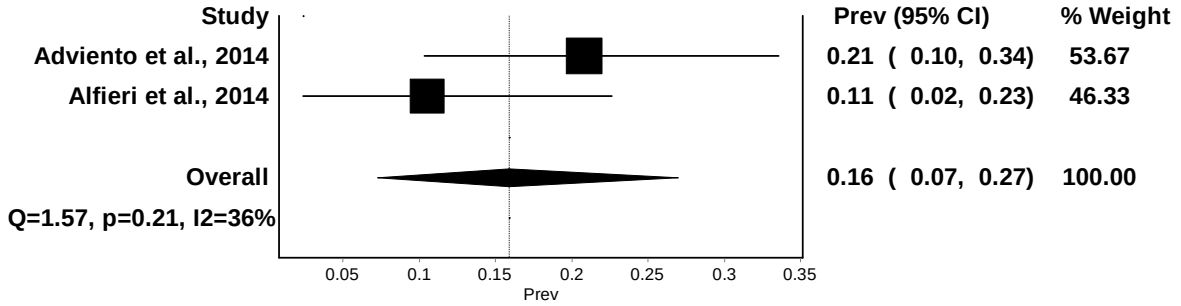

Figure 1.27. Pooled prevalence estimates for ASD phenomenology in Noonan syndrome using a random-effects model.

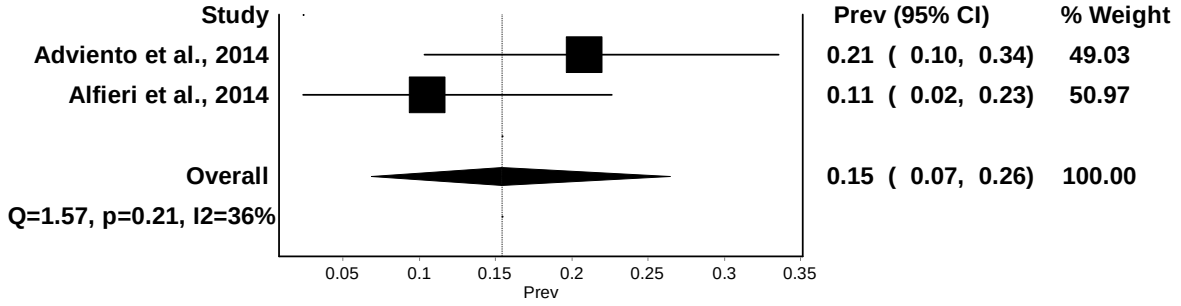

Figure 1.28. Pooled prevalence estimates for ASD phenomenology in Noonan syndrome using a quality-effects model.

The results revealed that the random-effects model generated a prevalence estimate of 16% (CI 7 – 27%). The quality-effects model generated a slightly more conservative estimate of 15% (CI 7 – 26%).

1.4.16 Joubert syndrome

Following the literature search, two papers were identified that reported the prevalence of ASD phenomenology in Joubert syndrome. These are presented in Table 1.20 Both papers reached an adequate standard of quality for sample selection, confirmation of Joubert diagnosis *and* assessment of ASD phenomenology. The study by Ozonoff, Williams, Gale and Miller (1995) is notable as the authors included multiple diagnostic measures of ASD phenomenology; however, the study did not obtain the highest quality rating for ASD assessment, as no consensus was derived from the multiple measures. Additionally, the sample size for the study was small. Whilst the quality weightings for both studies were good, as only two studies were included in the meta-analysis, the pooled prevalence estimates should be interpreted with caution.

Table 1.20. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Joubert syndrome.

	Quality Criteria		*Joubert Syndrome Study and Sample Characteristics*								*Outcome Data*		
Authors	**Sample**	**Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Ozonoff *et al.*, 1995			11	63.6	7.9 *(4.0)* *2.3 – 15.1*	Not reported	Neurologist or geneticist	ADI-R ADOS-G DSM-IV[152]	Independent raters	Yes	Autistic disorder: 27.3 PDD-NOS: 9.1	27.3 *(3)*	0.67
Takahashi *et al.*, 2005			43	67.4	6.6 *(5.3)* *0.4 – 16.2*	Not reported	Medical	ABC Family history interview	Authors of paper	No	Autism: 0.0 Borderline autism symptoms: 9.3	0.0 *(0)*	0.44

[152] Although the study used multiple diagnostic tools, they did not obtain a consensus from the tools. Therefore the study can only obtain a rating of 2 on the third quality criterion.

Random and quality-effects pooled prevalence estimates were generated based on the 2 papers that met the quality inclusion criteria. These are presented in Figures 1.29 and 1.30.

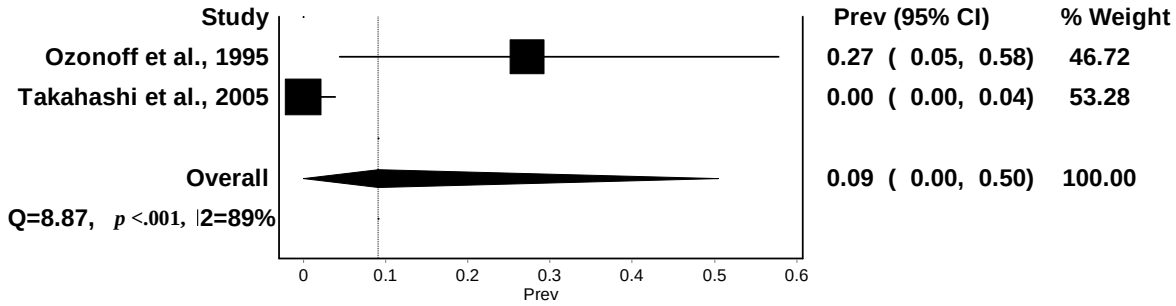

Figure 1.29. Pooled prevalence estimates for ASD phenomenology in Joubert syndrome using a random-effects model.

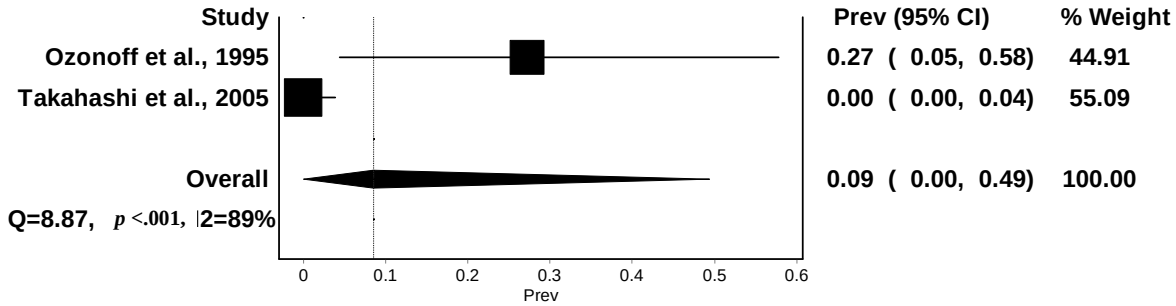

Figure 1.30. Pooled prevalence estimates for ASD phenomenology in Joubert syndrome using a quality-effects model.

The results revealed that both the random and quality-effects models generated a prevalence estimate of 9%. The confidence intervals were similar in both the random and quality-effects models, ranging from 0 – 50% for random-effects and 0 – 49% for quality-effects. However, given the significant heterogeneity between the prevalence estimates in the papers, the pooled prevalence estimates need to be interpreted with caution. This caution is supported by the confidence intervals for the random-effects and quality-effects models' including zero. Therefore, the pooled prevalence estimates for Joubert syndrome are not included in any further between syndrome comparisons.

1.4.17 Hypomelanosis of Ito

The literature search identified three papers that reported the prevalence of ASD phenomenology in Hypomelanosis of Ito. These are presented in Table 1.21.

Whilst all three of these papers provided an estimation of the prevalence of ASD phenomenology in Hypomelanosis of Ito, two of them were judged not to be of sufficient quality to include in the meta-analysis (Pascual-Castroviejo *et al.,* 1988; Pascual-Castroviejo *et al.,* 1998). Importantly, neither study provided any information about how ASD phenomenology was assessed or confirmed. Thus, as there was only one paper from which to generate a prevalence estimate for Hypomelanosis of Ito, no calculations were made and the syndrome was not included in any further between syndrome comparisons.

Table 1.21. Quality criteria, study and sample characteristics and outcome data for studies reporting the prevalence of ASD in Hypomelanosis of Ito.

	Quality Criteria		*Hypomelanosis of Ito Study and Sample Characteristics*								*Outcome Data*	
Authors	**Sample**	**Syndrome ASD**	**N**	**% Male**	**Mean Age *(SD)* *Range***	**% with ID**	**Syndrome Diagnosis**	**ASD Measure**	**ASD Measure Professional**	**ASD Profile**	**%ASD categories**	**% ASD (*N*)**	**Quality Weighting**
Pascual-Castroviejo *et al.*, 1998			76	46.1	*Newborn - 10*	56.6	Clinical confirmation	Not reported	Not reported	No	Autism: ~5.3	5.3 *(~4)*	0.22
Pascual-Castroviejo *et al.*, 1988			34	58.8	*0.2 – 10.0*	64.7	Clinical confirmation	Not reported	Not reported	No	Autistic behaviour:11.8	11.8 *(4)*	0.22
Zappella, 1992			25	64.0	*2.0 – 17.0*	96.0	Clinical features	ABC DSM-III-R	Not reported	No	Autistic disorder: 40.0 Autistic like conditions:12.0	40.0 *(10)*	0.33

1.4.18 Comparisons across syndromes

In order to explore the second aim of the meta-analysis, comparisons between the prevalence estimates of ASD phenomenology in each syndrome were made. Syndromes were only included in these analyses if the pooled prevalence estimates were robust (i.e., confidence intervals > 0) and the quality of the papers met the minimum inclusion criteria. Thus, the random-effects and quality-effects pooled prevalence estimates for 12 of the 16 syndromes are presented below in Figure 1.31. The data revealed that ASD phenomenology was most prevalent in Rett syndrome (random-effects and quality-effects 61%) and least prevalent in 22q11.2 deletion syndrome (random-effects 12%, quality-effects 11%).

These comparisons were explored further by conducting relative risks analyses between each syndrome. Table 1.22 presents the relative risk statistics and 99% confidence intervals. The results revealed that ASD phenomenology was significantly more likely in Rett and Cohen syndrome compared to nearly all other syndromes. The associations for Tuberous Sclerosis Complex, Cornelia de Lange, CHARGE and Angelman syndrome were mixed; ASD phenomenology was significantly more likely in each of these groups, in comparison to four to six other syndromes, but ASD phenomenology was also significantly less likely in comparison to one or two other syndromes. ASD phenomenology was significantly less likely in Fragile X syndrome and Neurofibramatosis Type 1 compared to three or four other syndromes. ASD phenomenology was significantly less likely in Noonan, 22q11.2 deletion, William and Down syndromes in comparison to five or six other groups.

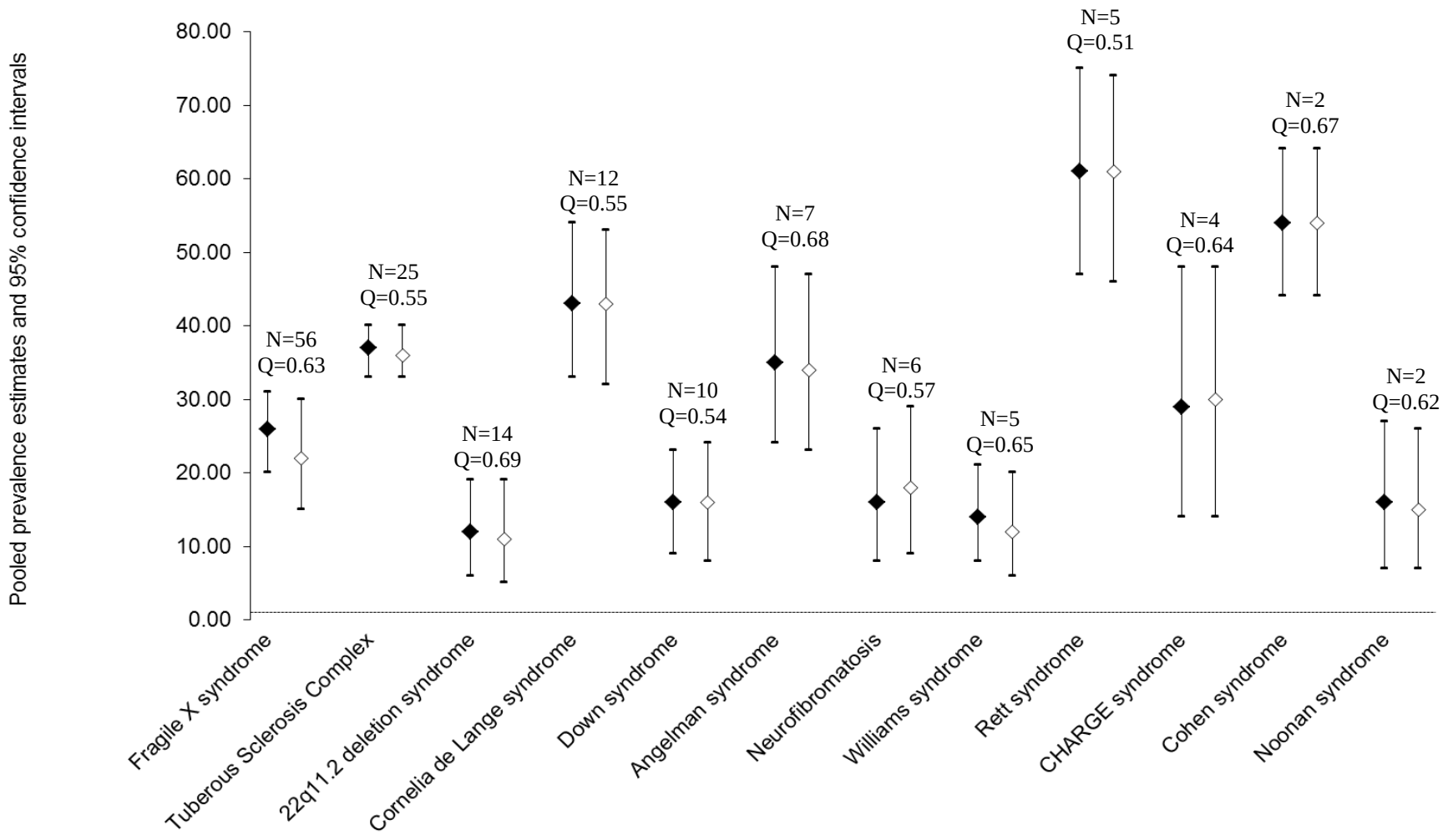

Figure 1.31. Pooled prevalence estimates, with 95% confidence intervals for each group (filled = random-effects; unfilled = quality-effects); N = Number of papers used to generate pooled prevalence estimates; QW = mean quality weighting for syndrome.

Table 1.22. Relative risk statistics, with 99% confidence intervals for the prevalence of ASD phenomenology in each syndrome in comparison to all other syndromes. Significant differences between syndromes are highlighted in bold, + = ASD phenomenology prevalence is significantly more likely than in one other syndrome ; - = ASD phenomenology is significantly less likely than in one other syndrome.

	Test Syndrome											
	FraX - - -	**TSC** +++++ -	**22q11.2** - - - - - -	**CdLS** ++++++	**DS** - - - - -	**AS** ++++ - -	**NF1** - - - -	**WS** - - - - - -	**Rett** +++++ ++++	**CHARGE** ++ - -	**Cohen** +++++ +++	**Noonan** - - - - -
FraX	-	1.64 (0.90-2.97)	0.50 (0.21-1.21)	**1.95 (1.11-3.45)**	0.73 (0.34-1.56)	1.55 (0.84-2.83)	0.82 (0.39-1.71)	0.55 (0.23-1.28)	**2.77 (1.64-4.70)**	1.36 (0.73-2.55)	**2.45 (1.43-4.22)**	0.68 (0.31-1.49)
TSC	0.61 (0.34-1.11)	-	**0.31 (0.14-0.69)**	1.19 (0.76-1.88)	**0.44 (0.22-0.88)**	0.94 (0.57-1.55)	**0.50 (0.26-0.96)**	**0.33 (0.15-0.73)**	**1.69 (1.13-2.53)**	0.83 (0.49-1.41)	1.50 (0.99-2.28)	**0.42 (0.21-0.84)**
22q11.2	2.00 (0.83-4.82)	**3.27 (1.46-7.36)**	-	**3.91 (1.77-8.63)**	1.45 (0.57-3.73)	**3.09 (1.37-7.00)**	1.64 (0.65-4.10)	1.09 (0.40-3.00)	**5.55 (2.59-11.89)**	**2.73 (1.19-6.27)**	**4.91 (2.27-10.62)**	1.36 (0.52-3.55)
CdLS	**0.51 (0.29-0.90)**	0.84 (0.53-1.32)	**0.26 (0.12-0.56)**	-	**0.37 (0.19-0.72)**	0.79 (0.50-1.26)	**0.42 (0.22-0.78)**	**0.28 (0.13-0.60)**	1.42 (0.99-2.04)	0.70 (0.43-1.14)	1.26 (0.86-1.84)	**0.35 (0.18-0.69)**
DS	1.38 (0.64-2.96)	**2.25 (1.14-4.46)**	0.69 (0.27-1.76)	**2.69 (1.39-5.21)**	-	**2.13 (1.06-4.24)**	1.13 (0.50-2.52)	0.75 (0.30-1.87)	**3.81 (2.04-7.13)**	1.88 (0.92-3.82)	**3.38 (1.78-6.38)**	0.94 (0.40-2.20)
AS	0.65 (0.35-1.18)	1.06 (0.64-1.74)	**0.32 (0.14-0.73)**	1.26 (0.79-2.02)	**0.47 (0.24-0.94)**	-	0.53 (0.27-1.02)	**0.35 (0.16-0.77)**	**1.79 (1.19-2.72)**	0.88 (0.52-1.50)	**1.59 (1.03-2.44)**	**0.44 (0.22-0.90)**
NF1	1.22 (0.59-2.55)	**2.00 (1.04-3.83)**	0.61 (0.24-1.53)	**2.39 (1.28-4.47)**	0.89 (0.40-1.99)	1.89 (0.98-3.65)	-	0.67 (0.27-1.62)	**3.39 (1.88-6.10)**	1.67 (0.85-3.28)	**3.00 (1.65-5.47)**	0.83 (0.37-1.90)
WS	1.83 (0.78-4.29)	**3.00 (1.38-6.54)**	0.92 (0.33-2.53)	**3.58 (1.68-7.66)**	1.33 (0.53-3.33)	**2.83 (1.29-6.22)**	1.50 (0.62-3.65)	-	**5.08 (2.45-10.53)**	**2.50 (1.12-5.58)**	**4.50 (2.15-9.41)**	1.25 (0.49-3.17)
Rett	**0.36 (0.21-0.61)**	**0.59 (0.40-0.88)**	**0.18 (0.08-0.39)**	0.70 (0.49-1.01)	**0.26 (0.14-0.49)**	**0.56 (0.37-0.84)**	**0.30 (0.16-0.53)**	**0.20 (0.09-0.41)**	-	**0.49 (0.32-0.77)**	0.89 (0.65-1.21)	**0.25 (0.13-0.47)**
CHARGE	0.73 (0.39-1.37)	1.20 (0.71-2.02)	**0.37 (0.16-0.84)**	1.43 (0.88-2.35)	0.53 (0.26-1.09)	1.13 (0.66-1.93)	0.60 (0.30-1.18)	**0.40 (0.18-0.89)**	**2.03 (1.30-3.17)**	-	**1.80 (1.14-2.85)**	0.50 (0.24-1.04)
Cohen	**0.41 (0.24-0.70)**	0.67 (0.44-1.01)	**0.20 (0.09-0.44)**	0.80 (0.54-1.17)	**0.30 (0.16-0.56)**	**0.63 (0.41-0.97)**	**0.33 (0.18-0.61)**	**0.22 (0.11-0.46)**	1.13 (0.82-1.55)	**0.56 (0.35-0.88)**	-	**0.28 (0.14-0.54)**
Noonan	1.47 (0.67-3.21)	**2.40 (1.19-4.85)**	0.73 (0.28-1.91)	**2.87 (1.45-5.67)**	1.07 (0.45-2.50)	**2.27 (1.11-4.62)**	1.20 (0.53-2.74)	0.80 (0.32-2.03)	**4.07 (2.13-7.77)**	2.00 (0.96-4.15)	**3.60 (1.86-6.96)**	-

1.4.19 Comparisons to General Population Estimates

In order to explore the final aim of the meta-analysis, odds ratios with 95% confidence intervals were generated, comparing each syndrome with the most recent Centre for Disease Control (2014) estimates for ASD diagnoses in the general population. Figure 1.32 presents the results and reveals that ASD phenomenology was significantly more likely in all of the syndromes, compared to the general population. Odds ratios ranged from 8.3 for 22q11.2 deletion syndrome to 104.8 for Rett syndrome. Calculations also revealed that ASD phenomenology was significantly more likely for males with Fragile X syndrome, compared to the general population (OR 28.71, CI 3.81 – 216.54).

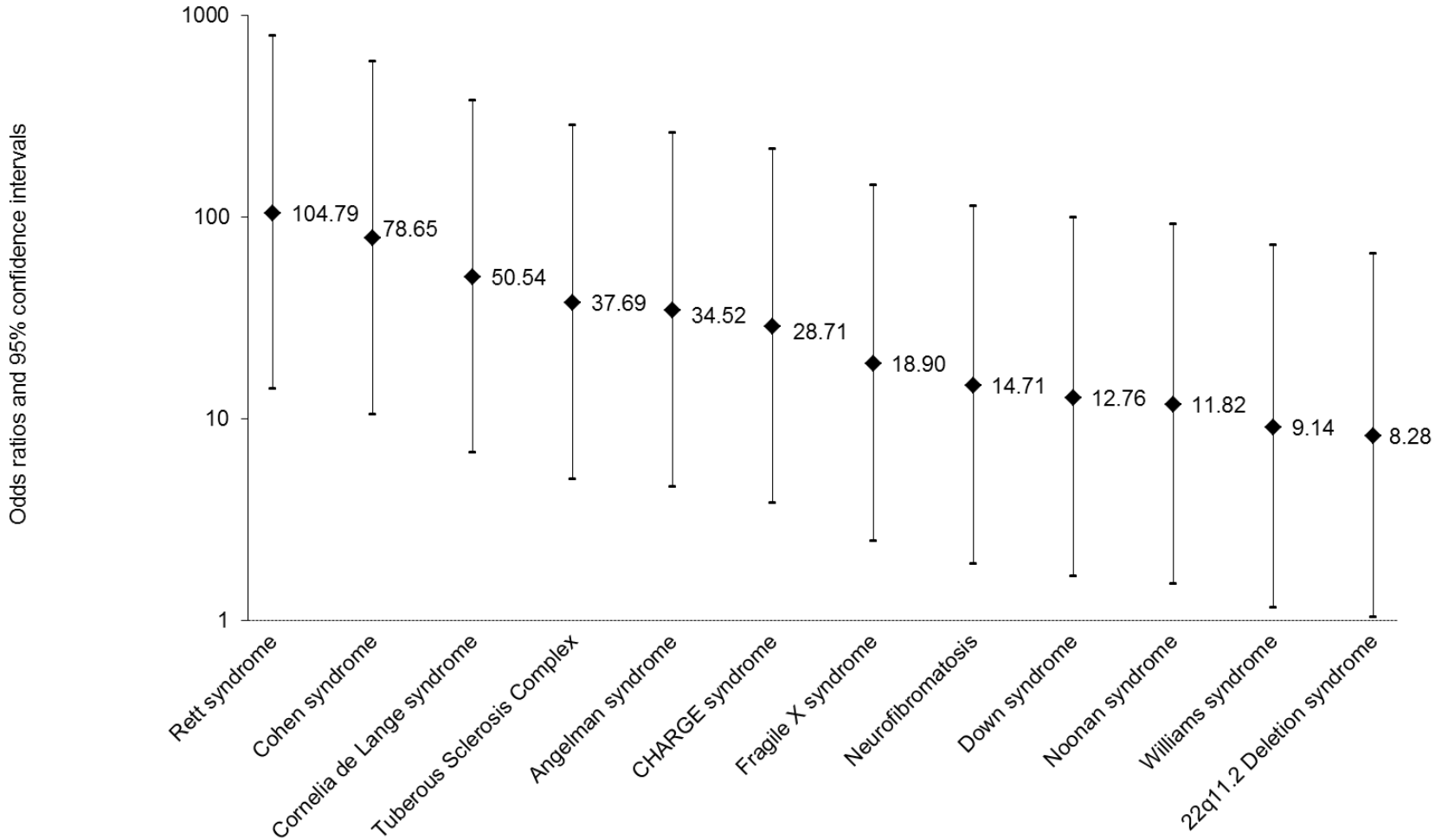

Figure 1.32. Odds ratios and 95% confidence intervals comparing the likelihood of ASD phenomenology in each syndrome to the general population

1.5 Discussion

The prevalence of ASD phenomenology in rare genetic and metabolic syndromes was detailed in this meta-analysis. Pooled prevalence estimates were generated, including estimates weighted by the quality of the identified research. Statistical cross-syndrome comparisons and contrasts to the prevalence of ASD in the general population were also conducted. This was the first meta-analysis of the prevalence of ASD phenomenology in syndromes, and thus extended findings from previous systematic reviews (Moss & Howlin, 2009, Moss *et al.,* 2011, Zafeiriou *et al.,* 2007, Zafeiriou *et al.,* 2013). The study employed wide search criteria, and was strengthened by screening both abstracts and titles during the initial search stages, thus allowing for the identification and inclusion of a greater number of studies than previous systematic reviews. The creation of a unique quality rating scheme to evaluate and weight the prevalence data further strengthened the findings of the meta-analysis. The inclusion of multiple syndromes and the application of novel statistical comparisons between syndromes and the general population provided useful and robust data that could be transferred to an understanding of the gene, brain, cognition, behaviour pathways implicated in idiopathic ASD, and to the development of clinical services for individuals with syndromes. The results demonstrated that ASD phenomenology was highly prevalent in Cohen and Rett syndrome and in Tuberous Sclerosis Complex, Cornelia de Lange, Angelman and CHARGE syndromes. ASD phenomenology was moderately prevalent in Neurofibromatosis Type 1, Fragile X, Noonan, 22q11.2 deletion, Williams and Down syndromes. However, despite cross-syndrome differences, the presence of ASD phenomenology was found to range between eight and one hundred and five times more likely in *all* syndromes compared to general population estimates.

The pooled prevalence estimates revealed that ASD phenomenology ranged in prevalence across 12 syndromes, from 61% in individuals with Rett syndrome to 11% in individuals with 22q11.2 deletion syndrome. Prevalence estimates were also generated for Moebuis syndrome, Phenylketonuria and Joubert syndromes (7%, 9%, 9% respectively) but these data were not deemed to be robust. Overall, the generated prevalence figures were similar to previous prevalence range estimates cited in systematic reviews (Moss & Howlin, 2009, Moss *et al.,* 2011, Zafeiriou *et al.,* 2007, Zafeiriou *et al.,* 2013). However, a number of differing results were identified. First, the prevalence figure of 22% generated for Fragile X syndrome was at

the very low end of the range indicated by Moss and Howlin (2009; 21-50%) and Zafeiriou *et al.* (2013; 22-33%). It is likely that the more conservative prevalence estimate proposed in this meta-analysis was due to the inclusion of samples with both males and females with Fragile X syndrome. The prevalence estimate generated for solely male samples of 30% was in line with previous reviews. However, in order to maintain parity with other syndromes, the generated prevalence estimate including data from mixed gender samples was used to conduct cross syndrome comparisons. Secondly, the generated prevalence estimates for Cornelia de Lange syndrome, Angelman, Down and 22q11.2 deletion syndrome were slightly more conservative than *some* of the ranges reported in previous systematic reviews (Cornelia de Lange syndrome: 50-67%, Moss *et al.,* 2011, 46-67% Zafeiriou *et al.,* 2013; Angelman syndrome: 50-81% Moss *et al.,* 2011, 50-61% Zafeiriou *et al.,* 2013; 22q11.2 deletion syndrome: 20-31% Zafeiriou *et al.,* 2007, 14-50% Zafeiriou *et al.,* 2013). In all cases, the prevalence estimates in the systematic reviews were based upon far fewer studies than the prevalence estimate for this meta-analysis. Additionally, this review aimed to improve the quality of prevalence estimates for each of the syndromes, by including quality review and weighting the estimates more heavily by the most robust papers. Thus, whilst the reported prevalence data may be more conservative in some cases, it is likely to also be more robust.

A key strength of this meta-analysis has been to provide between syndrome comparisons and comparisons to a general population estimate. These statistics revealed that the syndromes appeared to cluster into groups; those where ASD phenomenology was highly likely (Rett and Cohen syndrome), moderately likely (Tuberous Sclerosis Complex, Cornelia de Lange, CHARGE and Angelman syndrome), less likely (Fragile X syndrome and Neurofibramatosis Type 1) and least likely (22q11.2 deletion, Noonan William and Down syndromes). In combination with the data comparing prevalence rates to the general population, these data provide useful evidence for research investigating the gene, brain, cognition, behaviour pathways implicated in idiopathic ASD. The results demonstrate that even within a group of very high risk syndromes, in which prevalence rates for ASD phenomenology are significantly higher than in the general population, there is still significant variation, and cluster of syndromes in which ASD phenomenology is more or less likely. These data can be used to focus further research into underlying pathways of idiopathic ASD. Studies directed towards delineating the profile of ASD behaviour in the syndromes where ASD

phenomenology has been demonstrated to be highly likely would allow for an exploration of the cognitive and genetic explanations for idiopathic ASD. Some researchers have begun to reject unified explanations of ASD phenomenology and instead suggest a fractionation of the social communicative and repetitive impairments present in idiopathic ASD (Happé, Ronald & Plomin, 2006). However, research in idiopathic ASD is limited by circularity in recruitment strategy; individuals are included in studies by virtue of an ASD diagnosis which necessitates impairments in all areas of the triad, and then these same individuals are assessed to investigate the unitary coherence of the triad. Investigation of the convergence or divergence of the triad in these 'high risk' syndromes would progress unitary or fractionated models of the triad of impairments, whilst removing the inclusion bias present in studies of individuals with idiopathic ASD.

The results of this study have important implications for clinical and educational services for individuals with syndromes. Despite between syndrome differences in the likelihood of ASD phenomenology, the results indicate that an individual with *any* of these syndromes is at greater risk of displaying ASD-type behaviours than individuals in the general population. Regardless of empirical questions about whether these behaviours are commensurate with idiopathic ASD, the presence of ASD-like difficulties in communication, social interaction and restrictive and repetitive behaviours should lead to the tailored support for individuals with these syndromes that is proposed for those with idiopathic ASD. Additionally, detailed assessments of ASD impairments should be undertaken in order to ascertain whether an additional diagnosis of ASD would be beneficial. Assessments should also include an exploration of the impact of any identified ASD impairments upon the individual's quality of life, and that of their families and carers. It may be that in some cases, ASD specific educational placements are of benefit, or that ASD specific clinical interventions to support communication and/or social skills development could be useful. Most importantly, these results demonstrate the importance of reducing diagnostic overshadowing and the necessity of assessing and identifying concurrent ASD impairments, rather than attributing any identified difficulties to the syndrome itself (Moss & Howlin, 2009).

The meta-analysis has also afforded the opportunity to evaluate and compare research methodologies for assessing the prevalence of ASD phenomenology within and between syndromes. A key issue that was present in a number of different syndromes was a propensity

for research groups to publish data which appeared to have been collected in a similar, but not identical sample, in multiple papers. Whilst there may be legitimate reasons for doing this, specifically publishing data regarding different aspects of the same syndrome, it is imperative for authors to fully describe their sample, and whether the whole sample or a proportion of the sample have been reported previously. If authors had specified the proportion of their sample that overlapped with other published data, it would have been possible to perform statistical calculations to control for this, and thus the likelihood of an individual participant being counted more than once within the meta-analysis would have been reduced. This is a key area for methodological improvement in future research.

Significant variability was also noted in the reporting of intellectual disability and the reporting of the professional involved in interpreting the ASD assessments. Where ASD assessments require clinical interpretation (e.g., CARS) or significant pre-assessment training (e.g., ADI-R or ADOS), it is critical that studies report these data clearly in their papers. For the purposes of this review, it was imperative to include as many studies as possible in order to evaluate the current state of the literature. However, future reviews should seek to determine more stringent inclusion criteria, requiring adequate description of the delivery and interpretation of ASD assessment tools, in order to improve the internal validity of any future prevalence estimates. This type of inclusion criteria would have resulted in a significant reduction of papers in the present meta-analysis. The quality of description of intellectual disability within the studies was also variable. Intellectual disability is associated with ASD, and it has been suggested that degree of disability may more fully account for the prevalence of ASD phenomenology within syndromes, rather than the presence of the syndrome itself (Skuse, 2007). Only half of the studies (54%) reported the proportion of their sample that had an intellectual disability, and there was great variability in the depth of assessment used to determine this (ranging from an individual question delivered to parents/carers to a full psychometrically robust cognitive assessment). Future studies to evaluate the prevalence and phenomenology of ASD in syndromes must appropriately assess intellectual disability, and conduct analysis to determine how far intellectual disability can account for the prevalence of ASD phenomenology in the syndrome.

A number of limitations of the present meta-analysis were also identified. Firstly, due to the large number of included papers, it was not possible to provide more detailed analysis or

review of individual papers. Whilst attempts were made to highlight notable studies and patterns across and within syndromes, inevitably, some interesting findings or patterns may not have been discussed. However, this limitation is a direct consequence of the size and scope of the literature identified within the meta-analysis. This study was unique in capturing a large literature and providing robust, quality weighted prevalence estimates for 16 syndromes. Future reviews may seek to provide a more in-depth analysis of the literature in individual syndromes, particularly those with a large combined dataset (e.g., Fragile X syndrome and Tuberous Sclerosis Complex). A second limitation of the meta-analysis is that it was not possible to provide an evaluation of the profile of ASD within and between syndromes. Whilst robust prevalence data were generated, there is emerging evidence to suggest that the profile of ASD impairments within syndromes may be qualitatively different in phenomenology to that of idiopathic ASD (Moss *et al.*, 2011; Moss & Howlin, 2009). Thus, the generated prevalence data may not be indicative of the prevalence of diagnosable ASD. However, this limitation was noted from the outset, and the meta-analysis has afforded some progress, through identifying those syndromes in which the data are accumulating on the profile of ASD (e.g., Fragile X, Cornelia de Lange, Down and Angelman syndrome) and by exclusion, those syndromes in which this is still under-researched. As further robust research evaluating the profile of ASD in syndromes is undertaken, it may soon be possible to conduct a similar meta-analytic review, detailing the profile of ASD within and between syndromes.

The results and limitations identified in this meta-analysis also serve to highlight areas for future research. Firstly, five syndromes were excluded from the meta-analysis on the basis of a paucity of research delineating the prevalence of ASD phenomenology in these groups (Goldernhar, Soto, Ehlers-Danlos, Lujan-Fryns and Leber's Amaurosis syndromes). Hypomelanosis of Ito was later excluded from the statistical meta-analysis, due to the poor quality of the research conducted in this population. In addition, generated pooled prevalence estimates for Phenylketonuria, Joubert, and Moebuis were not deemed sufficiently robust to allow for further interpretation or cross-syndrome comparison. Thus, given the putative associations between each of these syndromes and ASD phenomenology, there is a need for future robust research in each of these groups, to detail the prevalence and profile of ASD phenomenology. Secondly, given the wide variety of ASD assessments and reported

differences in the sensitivity and specificity of these instruments (e.g., Charman & Gotham, 2013), it would be useful to evaluate the psychometric properties of ASD assessments in marginal populations such as those with syndromes and intellectual disability, and to evidence the differing prevalence data that these assessments generate. Johansson, Gillberg and Rastam (2010) present a useful methodology for conducting this type of research, by contrasting the utility of the ADI-R, CARS and ABC to identify ASD phenomenology in Moebuis, CHARGE and Goldenhar syndrome. This method could be usefully applied across all other groups, in order to reach a more unified consensus on the most appropriate ASD assessments for use in syndromes, in both research and clinical practice.

A final and key area for future research is to more robustly detail the profile of ASD phenomenology in each syndrome. Whilst some syndromes within the meta-analysis had a significant body of evidence regarding the profile of ASD impairments, the quality and breadth of this analysis was variable. Genetic or metabolic confirmation of syndromes, where appropriate, should be conducted, in order to make more precise links between aetiology and ASD profile. Gold standard assessments of the profile of ASD phenomenology should necessarily include comparison to other syndrome groups, to afford control of degree of intellectual disability, and comparisons to idiopathic ASD to evaluate the similarities and differences in the profile of behaviour. Subscale or item level analyses of ASD measures between groups would allow for greater specificity in the delineation of the profile. The generation of these data would allow for improved delineation of the psychological constructs associated with ASD in each of these syndromes, specifically the cognitive and social profiles and their developmental trajectories. As detailed assessment of the behavioural phenomenon in each syndrome develops, it is likely that differences in ASD phenomenology may emerge and that these differences may align or disassociate with the hypothesised cognitive underpinnings of idiopathic ASD (e.g., Theory of Mind deficits, Weak Central Coherence, Deficits in Executive Functioning).

In summary, the meta-analysis has generated robust estimates of the prevalence of ASD phenomenology for 16 genetic and metabolic syndromes. Despite between syndrome variations in these prevalence data, ASD phenomenology was significantly more likely in all of the syndromes, compared to the general population.

CHAPTER 2

Autism Spectrum Disorder Phenomenology in Phelan-McDermid Syndrome

2.1 Abstract

Background: The behavioural phenotype of Phelan-McDermid syndrome (PMS) is relatively unknown. Research has indicated atypically high levels of activity, impulsivity and autism spectrum disorder (ASD) behaviours. Divergent profiles of ASD in PMS are reported, with some studies demonstrating similarities to idiopathic ASD and others indicating an uneven profile of the triad of impairments. An evaluation of the behavioural phenotype of PMS and the prevalence and phenomenology of ASD is warranted, particularly given the putative causal involvement of the *SHANK3* gene in the aetiology of PMS.

Methods: Carers of individuals with PMS, (N = 30; mean age = 10.55, SD = 7.08) completed questionnaires relating to impulsivity, overactivity, mood, interest and pleasure, repetitive behaviour and ASD phenomenology. These data were compared to data from matched samples of individuals with Fragile X and Down syndromes, and idiopathic ASD. In order to evaluate the profile of ASD phenomenology in PMS, two comparisons were made; first, including the total sample with PMS and second, including only those who met clinical threshold for autism on the screening measure.

Results: The results revealed lower mood in individuals with PMS, but no difference in impulsivity and overactivity compared to the comparison groups. Compulsive and routine driven repetitive behaviours were less common in the total sample with PMS; however, motor based stereotyped behaviours were more common. ASD phenomenology was highly prevalent, with 87% of the sample meeting criteria for ASD and 57% meeting criteria for autism. The profile of ASD phenomenology in the total sample with PMS was heterogeneous across the triad of impairments. However, the profile of those who met clinical threshold for autism was homogenous, and analogous to those with idiopathic ASD.

Conclusions: ASD phenomenology is common within PMS. Whilst the total sample may display an atypical profile of ASD behaviour, the profile in those who meet clinical thresholds for autism is very similar to those with idiopathic ASD. These results are discussed in relation to the wider behavioural phenotype.

2.2 Introduction

Phelan-McDermid syndrome (PMS) is a micro-deletion syndrome caused by loss or disruption of chromosome 22q13.3 (Phelan, 2008). The incidence of PMS is unknown, with under-diagnosis suspected due to the subtlety of the deletion (Phelan *et al.*, 2001). Approximately 80% of people with PMS have *de novo*, simple terminal deletions and the remaining 20% typically result from unbalanced translocations and ring chromosomes (Phelan, 2008). The 22q13 region contains the *SHANK3* gene; haploinsufficiency of the *SHANK3* gene is proposed to cause the major features of PMS (Durand *et al.*, 2006; Phelan & McDermid, 2011; Wilson *et al.*, 2003). Dysmorphic physical features associated with PMS are subtle and include hypotonia, normal to accelerated growth, long eye lashes, large ears, full brow, dolicocephaly, full cheeks, bulbous nose and pointed chin (Luciani *et al.*, 2003; Phelan, 2008; Phelan & McDermid, 2011). The most characteristic clinical features of PMS are moderate to profound intellectual disability and absent to severely delayed speech (Havens, Visootsak, Phelan & Graham, 2004; Luciani *et al.*, 2003; Phelan, 2008; Phelan *et al.*, 2001). Preliminary research suggests that the physical features and severity of intellectual disability correlate with the size of the genetic deletion; however, expressive speech deficits are not associated with the size or type of deletion (Luciani *et al.*, 2003). Research investigating the behavioural phenotype of PMS has recently developed due to improvements in cytogenetic testing, specifically the introduction of subtelomeric fluorescence *in-situ* hybridization (FISH) analysis (Havens *et al.*, 2004). These advances have allowed for more robust detection of the deletion in PMS and thus, better delineation of the genotype-phenotype association within the syndrome.

A number of behavioural characteristics have been reported in PMS. Hyperactivity, impulsivity and difficulties in sustaining attention have been identified. Shaw, Rahman & Sharma (2011) reported that 34% of their sample of 35 children had existing diagnoses of Attention Deficit Hyperactivity Disorder (ADHD). When assessed using the Parent Form of the Children's Interview for Psychiatric Symptoms (PChIPS; Weller, Weller, Fristad, Rooney & Schecter, 2000), a high proportion of parents endorsed items indicative of impulsivity and inattention; similarly the mean Attention Deficit score of the Reiss Scales for Children's Dual Diagnosis (Reiss & Valenti-Hein, 1990) was above clinical cut off. Jeffries *et al.*, (2005) identified convergent results, with 36% of a sample of 31 children with PMS scoring above

the clinical cut off for ADHD on the Strengths and Difficulties Questionnaire (PSDQ; Goodman, 1997). Taken together, these findings suggest a potential association between PMS and ADHD phenomenology. However, only the Reiss Scale was designed for individuals with intellectual disabilities, and none of the studies compared the results for the PMS group to control groups. Thus, it is unclear whether the presence of ADHD symptoms should be attributed to the behavioural phenotype of PMS, or to the severity of intellectual disability, age of the children assessed or the measures used. Similar threats to validity weaken results associating atypical affect with the behavioural phenotype of PMS. Cohort and case studies have identified behaviours indicative of depression and psychosis/atypical bipolar disorder in PMS (Shaw *et al.,* 2011; Verhoeven, Egger, Willemsen, Leijer, Kleefstra, 2012). However, given deficits in expressive language, it is unclear how internal experiences of positive symptoms of psychosis have been reported and assessed. Nonetheless, given the clinical implications of mood disturbances, these findings warrant further investigation. Finally, there is emerging robust evidence of a heightened prevalence of self-injurious behaviour and destruction of property in PMS (Powis, Richards, Moss & Oliver, In Review). Importantly, these data have been established using measures validated for individuals with intellectual disability, and in comparison to matched contrast groups and can therefore be identified as components of the behavioural phenotype of PMS (Powis *et al.,* In Review). However, further investigation of hyperactivity, impulsivity and affect in PMS is required, utilising robust measures validated for individuals with intellectual disability, and contrasting findings with appropriate comparison groups.

A final characteristic, frequently identified in PMS, is that of autism spectrum disorder[153] (ASD; Jeffries *et al.,* 2005; Phelan *et al.,* 2001; Shaw *et al.,* 2011; Soorya *et al.,* 2013). The putative association between ASD and PMS is of particular interest as the *SHANK3* gene is one of many genes implicated in the aetiology of idiopathic ASD (Bill & Geschwind, 2009; Durand *et al.,* 2006; Uchino & Waga, 2013). Thus, delineation of the prevalence and phenomenology of ASD in PMS may have clinical implications for individuals with PMS *and* individuals with idiopathic ASD. Results from screening instruments have demonstrated convergent results: mean autism/Pervasive Developmental Disorders scale scores for children on the Reiss Scales were above clinical cut off (Shaw *et al.,* 2011); 94% of children with PMS

[153] As in Chapter 1, ASD is used as an umbrella term for the range of neurodevelopmental disorders specified as Pervasive Developmental Disorders in DSM-IV, DSM-V and ICD-10

scored in the mild-moderate range for ASD and 67% in the severe range for ASD using the Childhood Autism Rating Scale (CARS; Phelan *et al.,* 2001); 85% of children with PMS met the ASD criteria on the Social Communication Questionnaire, and 67% met the more stringent cut off for autism (SCQ; Jeffries *et al.,* 2005). More robust evidence is found in studies employing 'gold standard' diagnostic measures of ASD. Soorya *et al.,* (2013) utilised both the Autism Diagnostic Observation Schedule (ADOS; Lord *et al.,* 2000) and Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur & Lord, 2003), and found that 84% of the sample with PMS met criteria for ASD and 75% met criteria for a more stringent classification of autistic disorder. However, whilst there appears to be a strong association between ASD phenomenology and PMS, no studies have employed contrast or comparison groups to evaluate whether ASD phenomenology can be identified as a component of the behavioural phenotype of PMS[154]. This is particularly important given the degree of intellectual disability and expressive speech deficits in PMS, and the potential for over estimating ASD when these comorbities are present (Skuse, 2007).

Whilst there is a purportedly high prevalence of ASD phenomenology in PMS, the profile of the triad of ASD impairments in the syndrome is less well described. This profile is known to vary across genetic syndromes (Moss & Howlin, 2009). For example, ASD phenomenology is common in Cornelia de Lange (Section 1.4.5) and Fragile X syndromes (Section 1.4.2). Detailed item-level analysis of screening (Moss, Oliver, Nelson, Richards & Hall, 2013) and diagnostic measures (Moss, Howlin, Magiati & Oliver, 2012) reveal that both syndromes evidence an atypical profile of ASD. Those with Cornelia de Lange evidence greater impairments in communication domains, whereas those with Fragile X evidence more impairment in repetitive behaviour, and a profile consistent with social anxiety (Hall, deBernardis, & Reiss, 2006). Phillipe *et al.* (2008) reported that whilst children with PMS attained high ADI-R scores, these only reached clinical thresholds in social interaction, play, and communication domains. They argue that the relative lack of repetitive behaviours distinguishes PMS from idiopathic ASD. However, the study was limited by not including an

[154] Behavioural phenotypes can be defined as "…the heightened probability or likelihood that people with a given syndrome exhibit certain behavioural and developmental sequelae relative to those without the syndrome." (Dykens, 1995, p.523) Thus, in order for ASD characteristics to be deemed part of the behavioural phenotype of PMS, ASD phenomenology must be: 1) equally as likely in PMS as in syndromes where ASD phenomenology is a known characteristic of the behavioural phenotype and/or 2) more likely in PMS compared to syndromes where ASD phenomenology is known to *not* be a characteristic of the behavioural phenotype.

idiopathic ASD comparison group and relying upon visual inspection of data. Additionally, a number of sub-threshold items in the repetitive behaviour domains necessitated expressive language, which is often delayed or absent in individuals with PMS (e.g., delayed echolalia, verbal rituals). Interestingly Soorya *et al.,* (2013) also found that interpretation of the ADI-R algorithm alone indicated that many children with PMS presented with sub-threshold levels of repetitive behaviour. However, when they included statistical analysis of all items, including a two factor algorithm of repetitive behaviour identified in research on the ADI-R, they found that repetitive and sensory-motor behaviours were present in the majority of the participants, and were similar in range to those reported in idiopathic ASD.

Finally, authors have suggested that behaviours indicative of psychopathology (psychosis and low mood) may be misinterpreted as ASD phenomenology in PMS (Shaw *et al.,* 2011). Shaw and colleagues (2011) report that some endorsed items could indicate both ASD and mental health problems e.g., "Does not seem to listen when spoken to directly," "Random and inappropriate speech," "Appears confused". Additionally, they suggest that other items such as "Maintains a rigid posture", "Appears to be in a stupor, as if intoxicated" and "Laughs or appears angry for no apparent reason" may be more indicative of psychosis than ASD. However, it could be argued equally that these behaviours are indicative of repetitive behaviour, sensory difficulties or problems with emotional regulation, all of which are commonly reported in idiopathic ASD. Thus, there is a need to evaluate further the profile of ASD in PMS, utilising measures appropriate for individuals with intellectual disability, and with sufficient specificity and psychometric properties to allow for item-level statistical analysis. Additionally, these analyses need to be made in comparison to contrast groups, necessarily including individuals with idiopathic ASD, and ideally including groups with other genetic syndromes with known ASD profiles, in order to determine the relative position of the ASD profile in PMS.

A final point of interest is that the investigation of the profile of ASD impairments in PMS appears to have been largely driven by the hypothesised genetic links between PMS and idiopathic ASD. This has resulted in studies analysing the ASD profile of *all* participants in the PMS samples (Phillipe *et al.,* 2008; Shaw *et al.,* 2011; Soorya *et al.,* 2013) in order to establish whether the profile in the syndrome is similar to individuals with idiopathic ASD.

These data could support or weaken the hypothesised genetic *SHANK3* link. A complementary analysis approach would be to restrict analyses to those who score above thresholds on measures of ASD. These data would answer a second question about whether individuals with PMS meet criteria for ASD *for the same reasons* as individuals with idiopathic ASD. Answers to this question would inform discussion of the specific clinical needs for individuals with PMS who evidence ASD behaviours, thus increasing the specificity of clinical provision and interventions for individuals with PMS.

In summary, there is emerging evidence of attentional differences and differences of affect in individuals with PMS (Jeffries *et al.*, 2005; Shaw *et al.*, 2011), however these findings require further investigation utilising measures appropriate for individuals with intellectual disabilities, allowing for statistical comparisons with contrast groups. Additionally, there is evidence of a heightened prevalence of ASD phenomenology in PMS (Jeffries *et al.*, 2005; Phelan *et al.*, 2001; Shaw *et al.*, 2011; Soorya *et al.*, 2013). The prevalence and profile of these ASD behaviours requires further investigation with particular attention to the profile of repetitive behaviours in the syndrome. There is a need to delineate the profile of ASD phenomenology in PMS in contrast to individuals with idiopathic ASD, and individuals with genetic syndromes with known ASD profiles. Fragile X and Down syndromes may provide a useful comparison as they evidence divergent prevalence of ASD phenomenology (30% in males with Fragile X syndrome, see 1.4.2; 16% in Down syndrome, see 1.4.6) and well known profiles of ASD behaviour. Finally, given tentative hypotheses regarding diagnostic overlap between ASD phenomenology and mental health problems (Shaw *et al.*, 2011), an evaluation of the associations between ASD phenomenology and the broader behavioural phenotype in PMS may prove useful. Therefore, this study has the following aims:

i) To describe the behavioural phenotype of PMS; specifically the profile of overactivity/impulsivity, mood and repetitive behaviour. This will be achieved by comparing a sample with PMS to matched comparison groups with Fragile X syndrome, Down syndrome and idiopathic ASD.

ii) To delineate the prevalence of ASD behaviours, as measured by an ASD screening tool, in PMS in comparison to matched samples with Fragile X syndrome, Down syndrome and idiopathic ASD.

iii) To delineate the profile of ASD phenomenology in PMS, through analysis of

subscales and items on the ASD screening tool, in comparison to matched samples with Fragile X syndrome, Down syndrome and idiopathic ASD.

iv) To investigate whether individuals with PMS reach clinical threshold on the ASD screening measure for the same reasons as matched individuals with idiopathic ASD.

v) To investigate associations between scores on the ASD screening measure and the profile of repetitive behaviour, impulsivity/overactivity and mood in individuals with PMS, compared to the matched samples with Fragile X syndrome, Down syndrome and idiopathic ASD.

2.3 Methods

2.3.1 Recruitment

Participants with PMS were contacted via UNIQUE, the UK syndrome support group for rare genetic disorders, and were invited to participate in the study. 85 parents and carers were contacted and 36 completed and returned the questionnaires (return rate 42%).

Participants for the comparison groups with idiopathic ASD, Fragile X syndrome and Down syndrome were recruited via the National Autistic Society, Fragile X Society and the Down's Syndrome Association respectively. 288 carers of individuals with ASD (return rate 19.63%), 144 carers of individuals with Down syndrome (return rate 28.80%) and 212 carers of individuals with Fragile X syndrome (return rate 44%) completed the questionnaire pack. Data from a subsection of these comparison groups have been reported previously (Richards, Oliver, Nelson & Moss, 2012)[155].

2.3.2 Procedure

All carers received an information sheet, cover letter, consent form, demographic questionnaire and questionnaire pack (see Appendix C). To avoid priming, the study was described as 'Understanding behaviour in people with neurodevelopmental disorders'. Carers returned completed questionnaires and consent forms in a prepaid envelope. Ethical approval for this study was obtained from the University of Birmingham's Science, Technology, Engineering and Mathematics Ethical Review Committee (see Appendix D).

2.3.3 Participants

Participants from all groups were excluded from the study if:

1) They were under the age of four, as some measures were not appropriate for young children
2) A large proportion of the data was missing or incomplete (25% or more across the questionnaire pack)
3) They did not have a confirmed diagnosis of the respective syndrome from an appropriate professional. For individuals with PMS, Fragile X syndrome and Down syndrome, the diagnosis professionals included General Practitioners, Clinical

[155] 93.3% (N=28) of the Fragile X sample, 100% (N=30) of the ASD sample and 90% (N=27) of the Down syndrome sample were previously reported on by Richards *et al.,* (2012).

Geneticist, Paediatricians and Neurologists[156]. For individuals with ASD, the professionals additionally included Psychiatrists, Clinical Psychologists and Educational Psychologists.

These exclusions resulted in a total of 30 participants with PMS. Matched groups with ASD, Fragile X syndrome and Down syndrome were then selected from the comparison samples. These groups were matched on chronological age (+/- 3 years) and self-help score (+/- 3) derived from the Wessex Scale (Kushlick, Blunden & Cox, 1973). Self-help scores were utilised as a proxy measures of degree of disability. Table 2.1 presents the demographic characteristics of the groups. The mean age of the total sample was 10.80 years (SD=7.06; Range= 4-39 years), 83 (69.2%) were male and 60 (50.0%) were able/partly able (score above six on the self-help subscale of the Wessex Scale). 91 (75.8%) were mobile, 89 (74.2%) verbal, 100 (83.3%) had normal hearing and 94 (78.3%) had normal vision. After matching, significant differences were still found between the groups for gender[157], self-help score, hearing and speech.

[156] 21 (70%) of the PMS diagnoses were given by Clinical Geneticists; 8 (27%) by Paediatricians. The remaining diagnosis (3%) was confirmed by FISH test; however the parent did not stipulate which professional group had given the diagnosis.

[157] The difference for gender was expected as only males were recruited in the Fragile X syndrome comparison group.

Table 2.1 Mean age (standard deviation) and range, percentage of males, mean self-help score (standard deviation), percentage of participants who were mobile, verbal, had normal hearing and normal vision for all groups.

		Syndrome group				Chi –square			Post Hoc <.01
		PMS	**ASD**	**FraX**	**DS**	**df**	X^2	**P value**	
N		30	30	30	30				
Age[a]	Mean (SD)	10.55 (7.08)	10.60 (7.46)	11.37 (7.02)	10.67 (7.00)	3	1.29*	.732	-
	Range	4.00 – 37.00	4.00 – 39.00	6.00 – 39.00	4.00 – 36.00				
Gender	Male	13	26	30	14	3	34.19	<.01	ASD, FraX>PMS,DS
	(%)	(43.33)	(86.67)	(100.00)	(46.67)				
Self help[b]	Mean (SD)	4.77 (1.14)	5.33 (1.24)	5.33 (1.09)	6.20 (1.06)	3	20.47*	<.001	DS>PMS,ASD,FraX
Mobility[b]	Fully mobile	22	23	20	26	3	34.10	.33	-
	(%)	(73.33)	(76.67)	(66.67)	(86.67)				
Vision[b]	Normal	24	27	24	19	3	6.89	.08	-
	(%)	(80.00)	(90.0)	(80.0)	(63.33)				
Hearing[b]	Normal	26	27	29	18	3	15.23**	.001	PMS,ASD,FraX>DS
	(%)	(86.67)	(90.00)	(96.67)	(60.00)				
Speech[c]	Verbal	5	20	24	24	3	33.96	<.001	ASD,DS,FraX>PMS
	(%)	(16.77)	(66.77)	(80.00)	(80.00)				

Groups: PMS = Phelan McDermid syndrome; ASD = Autism Spectrum Disorder; FraX = Fragile X syndrome; DS = Down syndrome
[a] In years (decimal); [b] data derived from the Wessex Scale (Kushlick et al. 1973) [c] According to Item 1 on the SCQ "Is he/she now able to talk using short phrases or sentences"
* Kruskal Wallis Test for continuous non-normally distributed data
** Fishers exact T calculated

2.3.3.1 Idiopathic ASD Comparison Group

To confirm the validity of the idiopathic ASD comparison sample as a reference group, Social Communication Questionnaire (SCQ; Berument, Rutter, Lord, Pickles & Bailey 1999) data were compared to that of the normative sample reported in the SCQ manual (Rutter, Bailey, Lord, & Berument, 2003). This method for validating an ASD reference group has been utilised previously in a study investigating the profile of autism phenomenology in genetic syndromes (Moss *et al.*, 2013a). The manual reports the percentage of individuals in the SCQ normative sample who displayed "impairments" for each item. Data were extracted based on calculations from these percentages and the total sample size. These data were then used to calculate odds ratios at item level, using 99% confidence intervals. Odds ratio analyses revealed no significant differences between the idiopathic ASD comparison sample in the present study and the normative SCQ sample on 34 of 39 items. The idiopathic ASD comparison group in the present study was more likely to score as ''impaired'' on four SCQ items including three algorithm items: social chat, neologisms and unusual sensory interests, and one non-algorithm item: unusual attachments to objects. The idiopathic ASD comparison sample in the present study was less likely to score as ''impaired'' on seeking to share enjoyment. Overall, these findings validate the matched sample selected in this study, demonstrating that they are very similar to the normative sample reported in the SCQ. See Appendix E for odds ratio data.

2.3.4 Measures

The questionnaire pack included the following informant based questionnaire measures which are all appropriate for children and adults with intellectual disabilities. The order of the measures in the questionnaire pack was counterbalanced across the group to reduce order effects.

A demographic questionnaire that required information on date of birth, gender, mobility, verbal ability and diagnosis was included. The Wessex (Kushlick *et al.*, 1973) was used to assess ability. It comprises five subscales including: continence, mobility, self help skills, speech and literacy. For this study, the self help subscale was used to estimate degree of ability, and responses to items on mobility, vision and hearing were used to further describe the groups. The Wessex Scale has modest inter-rater reliability at subscale level for both

children and adults (mean Kappa value of .62 and .54 for overall classification and item level reliability respectively; Kushlick *et al.,* 1973; Palmer & Jenkins, 1982). The Wessex has been argued to be an effective tool for large-scale questionnaire studies (Palmer & Jenkins, 1982).

The Mood Interest and Pleasure Questionnaire – Short form (MIPQ-S; Ross & Oliver, 2003) was used to assess affect and comprises twelve items, forming two subscales: Mood, and Interest and Pleasure. The measure has good internal consistency (Cronbach's alpha coefficients: total = .88, Mood = .79, Interest and Pleasure = .87), test-retest (.97) and inter-rater reliability (.85). Internal consistency for subscales is good (alpha coefficient range for subscales .84 - .94). Concurrent validity between the MIPQ and the Aberrant Behavior Checklists (ABC) ranged from medium to strong (0.36 – 0.73; $p<.001$).

The Activity Questionnaire (TAQ; Burbidge *et al.,* 2010) was included to assess behaviours indicative of overactivity and impulsivity. The measure has eighteen items which form three subscales of Overactivity, Impulsivity and Impulsive Speech. Item level inter-rater reliability ranges from .31 to .75 (mean .56) and test-retest reliability ranges from .60 to .90 (mean .75). Inter-rater and test-retest reliability indices for subscales and total score exceed .70. Internal consistency for the subscales is good (alpha coefficient range for subscales .67 - .94).

The Repetitive Behaviour Questionnaire (RBQ; Moss, Oliver, Arron, Burbidge & Berg, 2009) was used to assess repetitive behaviours and comprises five subscales: Stereotyped behaviour, Compulsive behaviour, Insistence on Sameness, Restricted Preferences and Repetitive Speech. Previous examination of the psychometric properties of the RBQ (Moss *et al.,* 2009) reveals good inter-rater reliability coefficients (range .46 - .80), test-retest reliability (range .61 - .93; Moss *et al.,* 2009) and internal consistency (alpha coefficient range for subscales .50 - .78). Concurrent validity and content validity between the RBQ and the repetitive behaviour subscale of the ASQ is good (0.6; $p<.001$).

The Social Communication Questionnaire – Lifetime version (SCQ; Berument *et al.,* 1999) was included to assess ASD behaviours. The SCQ was developed as a tool for screening for ASD in children and adults and is based on the Autism Diagnostic Interview (Rutter *et al.,*

2003). The measure consists of 40 items which are scored to indicate the presence (a score of 1) or absence (a score of 0) of autistic impairments. These items are grouped into three subscales which correspond to the triad of impairments: Communication; Social Interaction and Repetitive and Stereotyped patterns of behaviours. The authors identify a cut off score of 15 as indicative of Autistic Spectrum Disorder and a higher cut off of 22 to differentiate between individuals with autism and those with other Pervasive Developmental Disorders. The SCQ shows good concurrent validity with the Autism Diagnostic Interview and the Autism Diagnostic Observation Schedule (Howlin & Karpf, 2004). Importantly, the SCQ demonstrates higher precision in samples with low IQ than other screening tools, including the Children's Communication Checklist and the Social Responsiveness Scale (Charman *et al.,* 2007). Internal consistency is also good (α = .90 for the total scale). The SCQ has good item level validity, with 33 out of 39 items differentiating between those with ASD and those without ASD (Rutter *et al.,* 2003). The Fragile X and Down syndrome groups completed an earlier version of the SCQ (Autism Screening Questionnaire; ASQ). One item differed between the ASQ and SCQ for non-verbal individuals for subscale scoring (Item 20: Social chat). Following the approach taken by Moss *et al.,* (2013a), to ensure consistency across the groups, this item was treated as missing and pro-rated for all non-verbal participants.[158] Item 20 was not included in item-level analysis.

Internal consistency for the PMS group on the self-help scale of the Wessex (0.68) was moderate. Internal consistency was good for the Interest and Pleasure (0.88) subscale of the MIPQ, and the Total Score of the MIPQ (0.81). However, internal consistency of the Mood subscale of the MIPQ was poor (0.23). Internal consistency was good for the Overactivity (0.86) and Impulsivity (0.83) subscales of the TAQ, and the Total Score of the TAQ (0.90). Internal consistency was moderate for the Stereotyped Behaviour (0.54) subscale of the RBQ, and good for the Compulsive behaviour (0.84) and Insistence on Sameness (0.76) subscales of the RBQ, and the Total Score of the RBQ (0.84). Finally, internal consistency of the Communication (0.88) and Social Interaction (0.81) subscales of the SCQ and the SCQ Total Score (0.86) were all good. The internal consistency of the Repetitive and Restricted Behaviour (0.55) subscale of the SCQ was moderate.

[158] The prorated score was calculated as the mean item score, based on other completed items within the communication domain.

2.3.5 Data analysis

Data were tested for normality using Kolmogorov–Smirnov tests. Where data were not normally distributed ($p<.05$), non-parametric techniques were employed. To control for multiple comparisons, alpha levels were set at a conservative value of $p <.01$.

In order to describe the behavioural phenotype of PMS relative to the comparison groups, subscale scores were derived to describe mood (taken from the MIPQ), activity levels (taken from the TAQ) and repetitive behaviour (taken from the RBQ). A series of Kruskal Wallis tests were performed to test for differences in the subscales between the groups.

To investigate the prevalence of ASD phenomenology in each group, the percentage of each group scoring above the cut off for ASD (score $\geq$ 15) and autism (score $\geq$ 22) were derived from the SCQ. Differences between the proportions of each group scoring above these thresholds were compared using Chi-Square tests.

The profile of ASD phenomenology in PMS was explored by comparing subscale scores from the SCQ between the groups, and testing for differences using Kruskal Wallis tests. In order to allow for the high proportion of individuals with PMS who were non-verbal, subscale scores excluding verbal items were also generated, and differences between the groups were evaluated using Kruskal Wallis tests. In order to further explore the profile of ASD phenomenology in PMS relative to the other groups, the proportion of individuals in each group who scored as 'impaired' on all non-verbal items of the SCQ was generated. Chi-square tests were used to test for item level differences between all groups.

In order to explore whether individuals with PMS reach threshold on the SCQ for similar reasons as individuals with idiopathic ASD, item level comparisons were conducted, comparing those with PMS who scored over the threshold for autism ($\geq$ 22) to the idiopathic ASD group. The number of individuals in the PMS group scoring as 'impaired' on each item was compared to the number of individuals in the idiopathic ASD comparison group scoring as impaired on each item, using odds ratio analyses.

Finally, to investigate the association between ASD phenomenology and behavioural phenotype, a series of Spearman's Rank Correlations were performed between SCQ total score and: chronological age; self-help score; subscale scores on the MIPQ, RBQ and TAQ.

2.4 Results

2.4.1 Behavioural Phenotype of PMS

In order to investigate the first aim of the study, delineating the behavioural phenotype of PMS, subscale and total scores on the MIPQ, TAQ and RBQ were generated for each group. Table 2.2 displays the subscale, total scores and Kruskal Wallis statistics.

The results in Table 2.2 reveal that individuals with PMS had significantly higher total mood scores than individuals with idiopathic ASD[159], although they also demonstrated significantly lower total mood scores than individuals with Down syndrome. The PMS group evidenced significantly higher levels of stereotyped behaviour than individuals with Down syndrome. However, they also had significantly lower scores for compulsive behaviour than the idiopathic ASD group. Additionally, individuals with PMS obtained significantly lower scores for insistence on sameness and total repetitive behaviour than both the Fragile X and idiopathic ASD groups. Individuals with PMS did not differ from individuals with idiopathic ASD, Fragile X or Down syndrome on measures of activity level.

In summary, individuals with PMS evidenced higher mood, but lower levels of repetitive behaviour than those with idiopathic ASD. The PMS group had lower mood scores than those with Down syndrome. The activity levels in individuals with PMS did not differ to those identified in any of the contrast groups.

[159] For brevity and to prevent duplication of results from previously published data, this paper will only describe the differences between the PMS group and other comparison groups, rather than also describing inter-comparison group differences.

Table 2.2 MIPQ, RBQ and TAQ subscale and total score medians and interquartile ranges for each group. Kruskal Wallis statistics to evaluate differences between the groups. Significant differences (p<.01) are indicated in bold.

Measure	**Median scores** *(interquartile range)*				***Kruskal Wallis Test***			**Post Hoc <.01**
	PMS	**FraX**	**DS**	**Idiopathic ASD**	**df**	**k**	***P* value**	
MIPQ-S								
Mood	20.00 *(17.75 – 21.25)*	21.00 *(19.75 – 21.18)*	22.00 *(19.75 – 22.25)*	17.00 *(16.00 – 21.00)*	3	22.26	**<.001**	FraX,DS>ASD
Interest and Pleasure	16.00 *(12.88 – 20.00)*	18.00 *(13.00 – 19.25)*	20.00 *(17.75 – 22.00)*	12.00 *(8.75 – 15.25)*	3	27.53	**<.001**	DS>ASD
Total Score	36.00 *(31.75 – 41.00)*	39.00 *(31.75 – 42.00)*	41.00 *(38.75 – 44.00)*	29.50 *(25.00 – 35.25)*	3	30.34	**<.001**	PMS,DS,FraX>ASD DS>PMS
RBQ[160]								
Stereotyped behaviour	7.50 *(5.75 – 12.00)*	9.00 *(7.37 – 12.00)*	0.50 *(0.00 – 6.50)*	9.50 *(6.00 – 12.00)*	3	24.84	**<.001**	PMS,ASD,FraX>DS
Compulsive behaviour	0.00 *(0.00 – 4.50)*	6.00 *(0.00 – 9.00)*	0.00 *(0.00 – 3.25)*	6.00 *(3.50 – 15.25)*	3	21.81	**<.001**	ASD>DS,PMS
Insistence on sameness	0.00 *(0.00 – 2.50)*	4.00 *(3.00 – 7.25)*	0.00 *(0.00 – 2.25)*	4.00 *(2.00 – 6.00)*	3	30.45	**<.001**	ASD,FRaX>DS,PMS
Total Score	12.00 *(7.75 – 19.75)*	29.50 *(22.50 – 36.25)*	10.50 *(4.00 – 15.25)*	25.00 *(16.00 – 32.50)*	3	39.44	**<.001**	ASD,FRaX>DS,PMS

[160] The RBQ contains two subscales scored only for verbal individuals (Restricted Preferences and Repetitive Language). The TAQ also contains a subscale scored only for verbal individuals (Impulsive Speech). As only 5 of the PMS sample were classified as verbal, these subscales were not analysed in the present study.

Measure	**Median scores** ***(interquartile range)***				***Kruskal Wallis Test***			**Post Hoc <.01**
	PMS	**FraX**	**DS**	**Idiopathic ASD**	**df**	**k**	***P* value**	
TAQ								
Impulsivity	16.50 *(12.00 – 20.25)*	20.72 *(15.75 – 23.25)*	12.00 *(7.75 – 18.25)*	20.00 *(16.50 – 23.00)*	3	18.22	**<.001**	ASD,FraX>DS
Overactivity	19.00 *(12.75 – 25.25)*	24.00 *(12.75 – 32)*	9.50 *(6.00 – 23.25)*	20.50 *(15.75 – 30.00)*	3	14.54	**.002**	ASD,FraX>DS
Total Score	37.00 *(26.50 – 45.25)*	48.50 *(32.00 – 59.25)*	23.00 *(17.00 – 41.75)*	50.00 *(33.25 – 53.75)*	3	17.45	**.001**	ASD,FraX>DS

2.4.2 Prevalence of ASD phenomenology in PMS

In order to investigate the second aim of the study, prevalence data were calculated to compare the proportion of each group scoring above the ASD and autism thresholds on the SCQ. Table 2.3 displays the results.

Table 2.3 Percentage of individuals scoring above the ASD cut off and autism cut off on the SCQ in each group

Group	% scoring above ASD cut off *(N)*	% scoring above autism cut off *(N)*
PMS	86.7 *(26)*	56.7 *(17)*
FraX	80.0 *(24)*	51.9 *(14)*
DS	23.3 *(7)*	22.2 *(6)*
Idiopathic ASD	100.0 *(30)*	76.7 *(23)*

The results revealed that 86.7% of individuals with PMS scored above the threshold for ASD and 56.7% scored above the threshold for autism. There was a significant difference between the proportion of individuals in each group scoring above the cut off for ASD (χ^2 (3) = 51.38, p <.001; ASD, FraX, PMS> DS). There was also a significant difference between the proportion of individuals in each group scoring above the cut off for autism (χ^2(3) = 17.17, p = .001; ASD, FraX, PMS>DS).

In summary, the proportion of individuals with PMS who scored above the SCQ thresholds for ASD and autism was higher than the Down syndrome group, but did not differ from those with idiopathic ASD or Fragile X syndrome.

2.4.3 Profile of ASD phenomenology in PMS

In order to investigate the third aim of the study, subscale scores for Communication, Repetitive Behaviour and Reciprocal Social Interaction domains were derived from the SCQ for each group. In addition to calculating the subscales and total score according to the SCQ manual, subscales and totals scores were also derived excluding all verbal items for each group. These subscale and total scores are presented in Table 2.4 with Kruskal Wallis test results to evaluate differences between the groups.

Table 2.4 SCQ subscale and total score medians and interquartile ranges for each group, calculated according to the SCQ manual *and* calculated with all verbal items removed. Kruskal Wallis statistics to evaluate differences between the groups. Significant differences (p<.01) are indicated in bold.

Domain	**Median scores all items *(interquartile range)***				***Kruskal Wallis Test***			**Post Hoc <.01**
	PMS	**FraX**	**DS**	**Idiopathic ASD**	**df**	**k**	***P* value**	
Communication (SCQ Manual Scoring)	8.00 *(6.86 – 8.00)*	7.40 *(5.00 – 9.00)*	4.00 *(3.00 – 7.69)*	8.00 *(6.97 – 10.25)*	**3**	**20.10**	**<.001**	**ASD>DS**
Communication (Verbal Items Removed)	7.00 *(4.00 – 7.00)*	4.00 *(3.00 – 5.80)*	1.00 *(0.00 – 4.00)*	6.00 *(4.00 – 7.00)*	**3**	**29.97**	**<.001**	**ASD,PMS>DS**
Repetitive Behaviour (SCQ Manual Scoring)	4.00 *(2.82 – 5.00)*	5.85 *(4.00 – 7.00)*	2.00 *(1.00 – 4.00)*	6.00 *(4.75 – 7.00)*	**3**	**33.83**	**<.001**	**ASD, FraX>DS ASD>PMS**
Repetitive Behaviour (Verbal Items Removed)	4.00 *(2.75 – 5.00)*	5.00 *(3.00 – 6.00)*	1.00 *(0.00 – 4.00)*	5.50 *(4.00 – 7.00)*	**3**	**32.72**	**<.001**	**ASD,FraX>DS**
Reciprocal Social Interaction	10.00 *(7.75 – 13.00)*	9.00 *(6.00- 11.00)*	3.00 *(1.00 – 8.00)*	11.25 *(9.00 – 13.00)*	**3**	**28.04**	**<.001**	**ASD,PMS>DS**
Total Score (SCQ Manual Scoring)	22.57 *(19.82 – 26.00)*	23.00 *(18.28 – 28.00)*	9.29 *(7.00 – 24.69)*	27.50 *(23.39 – 32.00)*	**3**	**22.63**	**<.001**	**ASD>DS**
Total Score (Verbal Items Removed)	21.50 *(18.75 – 25.00)*	18.50 *(12.00 – 23.25)*	5.00 *(2.00 – 12.50)*	23.40 *(19.00 – 27.00)*	**3**	**35.66**	**<.001**	**ASD,PMS>DS**

The results in Table 2.4 reveal that the PMS group did not significantly differ from the comparison groups on communication impairments when calculated according to the SCQ manual. However, when verbal items were removed, the PMS group showed significantly more 'ASD-like' communication impairments than the Down syndrome group. When calculated according to the SCQ manual, the PMS group showed significantly fewer 'ASD like' repetitive behaviours than the idiopathic ASD comparison group. However this difference was no longer significant when verbal items were removed. The PMS group evidenced significantly more 'ASD like' reciprocal social interaction impairments than individuals with Down syndrome. When calculated according to the SCQ manual, the PMS group did not differ from any of the comparison groups in total scores for 'ASD like' impairments. However, when verbal items were removed, the PMS group were significantly more impaired than those with Down syndrome.

In order to further evaluate the profile of ASD phenomenology in PMS, the percentage of individuals in each group scoring as 'impaired' (score of 1) for each non-verbal item of the SCQ was calculated. Differences between the groups for each item were evaluated using Chi-Square tests. Table 2.5 presents the results.

The results revealed that significantly more of the PMS group than the Down syndrome group scored as impaired on five of the seven items in the Communication subscale. Additionally, for the item describing 'nodding to say *no*', significantly more individuals with PMS were identified as impaired than individuals with Fragile X syndrome and Down syndrome. Significantly more of the PMS group than the Down syndrome group scored as impaired on four of the seven items in the Repetitive Behaviour subscale. However, significantly fewer individuals with PMS were identified as showing ritualistic repetitive behaviours, relative to individuals with idiopathic ASD and Fragile X syndrome. Significantly more of the PMS group than the Down syndrome group scored as impaired on eight of the fifteen items in the Reciprocal Social Interaction subscale. Importantly, significantly more individuals with PMS showed impairments in 'showing and directing attention' than individuals with idiopathic ASD or Down syndrome. Conversely, significantly fewer individuals with PMS showed impairments in items regarding interest in other children, and responding to other children's approaches, than individuals with idiopathic ASD.

Table 2.5 Percentage of individuals in each group that scored as 'impaired' on each non-verbal algorithm item of the SCQ. Chi-square statistics to test for differences between the groups, significant differences are highlighted in bold (p<.01). '+' indicates that significantly more individuals in the PMS group scored as impaired than individuals in one of the comparison groups; '-' indicates that significantly fewer individuals in the PMS group scored as impaired than individuals in one of the comparison groups; N/A indicates no differences between any of the groups.

		% Impairment				Chi Square				
Domain	**Item**	**PMS**	**FraX**	**DS**	**ASD**	**df**	**X^2**	**P value**	**Post Hoc <.01**	
Communication	Imitation	76.7	46.7	33.3	83.3	3	**15.53**	**.001**	**ASD>FraX,DS; PMS>DS**	+
	Pointing	86.7	56.7	33.3	70.0	3	**15.87**	**.001**	**PMS>DS**	+
	Gestures	70.0	46.7	36.7	60.0	3	5.53	.137	N/A	N/A
	Nodding to mean *yes*	86.7	46.7	23.3	83.3	3	**31.50**	**<.001**	**ASD,PMS>FraX,DS**	+ +
	Head shaking to mean *no*	73.3	36.7	23.3	76.7	3	**21.22**	**<.001**	**ASD>FraX,DS; PMS>DS**	+
	Imitative social play	80.0	60.0	16.7	76.7	3	**28.22**	**<.001**	**ASD,PMS,FraX>DS**	+
	Imaginative play	83.3	80.0	36.7	80.0	3	**21.05**	**<.001**	**ASD,PMS,FraX>DS**	+
Repetitive Behaviour	Rituals	40.0	73.3	46.7	83.3	3	**17.18**	**.001**	**ASD>PMS,DS; FraX>PMS**	**- -**
	Unusual preoccupations	60.0	63.3	20.0	70.0	3	**19.44**	**<.001**	**ASD,PMS,FraX>DS**	**+**
	Stereotyped play	66.7	60.0	30.0	76.7	3	**13.97**	**.003**	**ASD,PMS>DS**	**+**
	Circumscribed interests	30.0	56.7	36.7	60.0	3	7.40	.060	N/A	N/A
	Sensory interests	53.3	43.3	13.3	83.3	3	**29.15**	**<.001**	**ASD>FRaX,DS; PMS>DS**	**+**
	Hand stereotypies	70.0	86.7	33.3	90.0	3	**27.40**	**<.001**	**ASD,PMS,FRaX>DS**	**+**
	Body stereotypies	56.7	60.0	23.3	66.7	3	**12.64**	**.005**	**ASD,FraX>DS**	N/A
Reciprocal Social Interaction	Inappropriate facial expressions	40.0	23.3	6.7	40.0	3	**11.49**	**.009**	**ASD,PMS>DS**	**+**
	Use of other's body to communicate	83.3	56.7	40.0	86.7	3	**20.10**	**<.001**	**ASD,PMS>DS**	**+**
	Friends	70.0	80.0	30.0	76.7	3	**19.72**	**<.001**	**ASD,PMS,FRaX>DS**	+
	Eye contact	56.7	53.3	23.3	56.7	3	8.57	.036	N/A	N/A
	Social smiling	40.0	36.7	16.7	66.7	3	**13.66**	**.003**	**ASD>DS**	N/A
	Showing and directing attention	70.0	46.7	16.7	36.7	3	**15.69**	**.001**	**PMS>ASD,DS**	++
	Offering to share	80.0	63.3	33.3	76.7	3	**15.41**	**.001**	**ASD, PMS>DS**	+
	Seeking to share enjoyment	43.3	26.7	23.3	36.7	3	2.27	.519	N/A	N/A
	Offering comfort	83.3	56.7	20.0	86.7	3	**32.27**	**<.001**	**ASD,PMS,FraX>DS**	+
	Quality of social overtures	56.7	26.7	13.3	46.7	3	**12.67**	**.005**	**ASD,PMS>DS**	+

Domain	Item	% Impairment				Chi Square			
		PMS	**FraX**	**DS**	**ASD**	**df**	X^2	**P value**	**Post Hoc <.01**	
	Range of facial expression	63.3	56.7	23.3	80.0	3	**17.82**	**<.001**	**ASD,PMS,FRaX>DS**	+
	Interest in children	60.0	56.7	26.7	90.0	3	**21.91**	**<.001**	**ASD>PMS,DS**	-
	Response to other children's approaches	53.3	63.3	23.3	86.7	3	**23.64**	**<.001**	**ASD>PMS,DS; FraX>DS**	-
	Imaginative play with peers	90.0	86.7	60.0	100.0	3	**14.12***	**.001**	**ASD>DS**	N/A
	Group play	86.7	73.3	46.7	86.7	3	**12.64**	**.005**	**ASD,PMS>DS**	+

* Fishers exact T calculated as multiple cells had expected count < 5.

In summary, the PMS group did not differ from the idiopathic ASD or Fragile X syndrome groups in levels of 'ASD like' communication impairments. When verbal items were removed, they evidenced significantly more communication impairments than those with Down syndrome. At item level, individuals with PMS evidenced specific impairments in using nodding to communicate with others. The PMS group did not differ from the Fragile X or Down syndrome groups in levels of 'ASD like' repetitive behaviour, but did evidence significantly less impairment than the idiopathic ASD group when verbal items were included in analysis. At item level, the PMS group demonstrated significantly less ritualistic behaviour. The PMS group evidenced significantly more impairment in social interaction than the Down syndrome group, and did not differ from the idiopathic ASD or Fragile X syndrome groups. At item level, those with PMS evidenced significant impairment in showing and directing attention, but relative preservation of interest in, and responses to, other children compared to those with idiopathic ASD.

2.4.4 Analysis of items associated with meeting threshold for autism in PMS

In order to meet the fourth aim of the study, odds ratios were generated with 99% confidence intervals, to compare the likelihood of individuals with PMS who scored above the autism threshold on the SCQ displaying impairments on individual SCQ items, compared to those with idiopathic ASD. The results in Figure 2.1 reveal that individuals with PMS who met criteria for autism on the SCQ were no more or less likely to evidence impairments in the Communication or Repetitive Behaviour items than individuals with idiopathic ASD. However, they were significantly more likely to score as impaired on the 'Showing and directing attention' item in the Reciprocal Social Interaction domain.

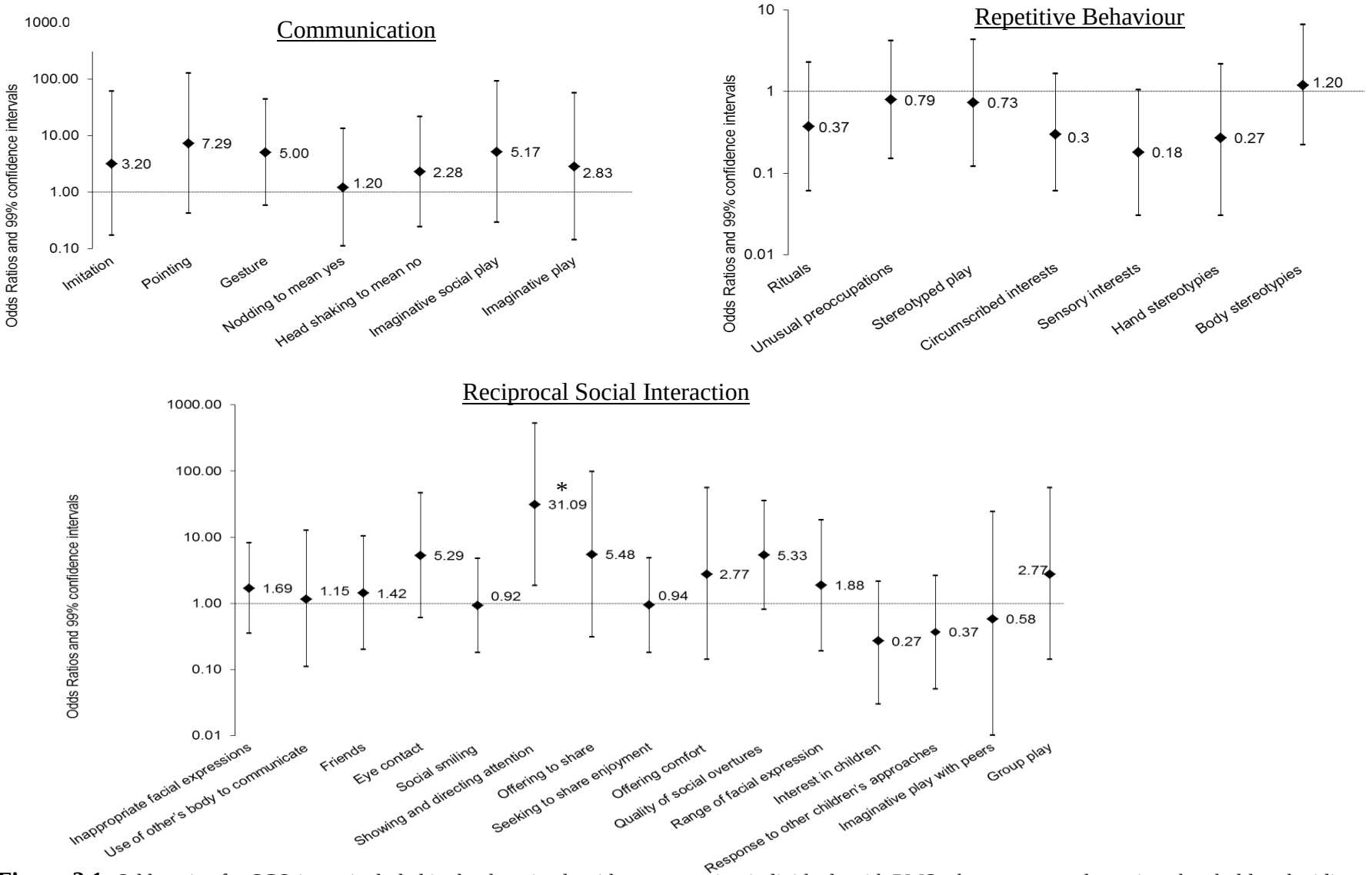

Figure 2.1. Odds ratios for SCQ items included in the domain algorithms comparing individuals with PMS who score over the autism threshold to the idiopathic ASD group. Error bars indicate 99% confidence intervals, significant differences are indicated with '*'. Y axis scales differ between subscales.

2.4.5 Association between behavioural phenotype and ASD phenomenology in PMS

In order to investigate the final aim of the study, a series of correlations were conducted for each group, evaluating associations between total SCQ score and demographic characteristics (self-help score and chronological age) and behavioural characteristics (affect, activity and repetitive behaviour). Table 2.6 reveals that higher scores on the SCQ were significantly correlated with lower scores for interest and pleasure for individuals with PMS. The correlation between SCQ score and mood score approached significance ($r_s(28) = -.37$, P = .043).

Table 2.6 Correlation coefficients for Spearman's Rank Correlations between total SCQ score and: Self-help score; Chronological age; MIPQ subscales (mood, interest and pleasure); RBQ subscales (stereotyped behaviour, compulsive behaviour, insistence on sameness); TAQ subscales (impulsivity, overactivity). Significant correlations ($p<.01$) and highlighted in bold.

Demographic/ Behavioural Characteristic	PMS	FraX	DS	Idiopathic ASD
Self-help	-0.20	-0.07	-0.21	-0.02
Age	0.35	0.28	0.24	-0.11
Mood	-0.28	-0.06	0.07	-0.40
Interest and pleasure	**-0.50**	-0.20	-0.38	-0.14
Stereotyped behaviour	0.36	0.34	**0.63**	0.12
Compulsive behaviour	-0.08	-0.21	0.22	0.39
Insistence on sameness	-0.04	-0.32	0.13	0.04
Impulsivity	0.21	0.22	0.32	0.25
Overactivity	0.32	0.25	0.19	0.23

2.5 Discussion

The behavioural characteristics, prevalence and profile of ASD phenomenology in PMS were delineated in this study. The relationship between ASD phenomenology and broader behavioural and demographic characteristics was also evaluated. Importantly, the recruitment of comparison groups with Fragile X and Down syndrome, in which the profile of ASD phenomenology is well described, strengthens the validity of the study. The inclusion of a matched idiopathic ASD comparison group allows for robust delineation of the profile of ASD phenomenology in PMS. The utilisation of validated measures, with appropriate psychometric properties established in populations with intellectual disabilities further improves the validity and reliability. The majority of these measures exhibited good internal consistency in the PMS group. The results revealed that the PMS group evidenced lower levels of affect than the Down syndrome group, but higher affect than the idiopathic ASD group. The PMS group also evidenced higher levels of stereotyped repetitive behaviours, but lower levels of other topographies of repetitive behaviour. No evidence was found for heightened overactivity or impulsivity in PMS. The results identified a high prevalence of ASD phenomenology in PMS. The profile of ASD behaviours was similar to those with Fragile X syndrome and idiopathic ASD, and when compensation was made for verbal ability, those with PMS evidenced significantly more impairments in communication and social interaction than those with Down syndrome. Item level analyses revealed lower levels of some ASD repetitive behaviours in the total sample with PMS. Interestingly, analyses also revealed significant impairments in behaviours indicative of social skill, but relative preservation in behaviours indicative of social motivation. Analysis of those with PMS who met clinical threshold for autism revealed a very similar profile of ASD phenomenology compared to those with idiopathic ASD, including a similar profile of repetitive behaviours. This suggests that individuals with PMS meet criteria for ASD for similar reasons to those with idiopathic ASD. Finally, higher total levels of ASD phenomenology in PMS were found to be associated with lower levels of mood in the group, which is of clinical significance.

The results of the behavioural phenotype analyses revealed that individuals with PMS evidenced higher total mood scores than those with idiopathic ASD, but lower total mood scores than those with Down syndrome. Importantly, this finding was established using a measure designed specifically for individuals with intellectual disability, and good internal

consistency was established for the total mood score for the PMS group. Despite the differences at the total score level, there were no identified differences on the Mood or Interest and Pleasure subscales between the PMS and comparison groups, although it should be noted that internal consistency was poor for the Mood subscale. These findings support previous research identifying low mood in individuals with PMS (Shaw *et al.,* 2011), but also demonstrate the utility of including multiple comparison groups in order to position the behavioural phenotype in PMS relative to other syndromes. The PMS group achieved higher total mood scores than those with idiopathic ASD and comparable total mood scores to those with Fragile X syndrome, suggesting that whilst lower mood is present in PMS it may not be significantly atypical, given the degree of intellectual disability in the group. The use of a carefully designed and detailed assessment of repetitive behaviour (Moss *et al.,* 2009) revealed a mixed profile in individuals with PMS. The group evidenced similar levels of stereotyped behaviour, but lower levels of compulsive behaviour, insistence on sameness and total repetitive behaviour than both the Fragile X syndrome and idiopathic ASD groups. This finding supports and synthesises divergent results demonstrating low levels of repetitive behaviour in PMS (Phillippe *et al.,* 2008) and the presence of repetitive and sensory-motor behaviours in the group (Soorya *et al.,* 2013). Individuals with PMS appear to evidence a dissociation between motor driven repetitive behaviours, which are common in the sample, and more compulsive and routine driven behaviours, which are less evident in the group. It is important to note that this finding is at the level of the total sample, including those who meet threshold for autism and those who do not. Finally, the results revealed no significant differences in levels of overactivity or impulsivity between the PMS and comparison groups. This finding differs from those previously reported, where high levels of ADHD type behaviours were identified (Jeffries *et al.,* 2005; Shaw *et al.,* 2011). However, previous research did not compare individuals with PMS to matched comparison groups, and thus the high levels of activity and impulsivity may be more appropriately associated with the degree of intellectual disability in PMS rather than the behavioural phenotype of PMS per se.

The results demonstrated a high prevalence of ASD phenomenology in PMS, with 87% meeting threshold for ASD and 57% meeting the more stringent criteria for autism. These findings support the prevalence figures identified in previous studies using screening measures (94% mild-moderate ASD, 67% severe ASD, Phelen *et al.,* 2011; 85% ASD, 67%

autism, Jeffries *et al.,* 2005) and diagnostic tools (84% ASD, 75% autistic disorder, Soorya *et al.,* 2013). The results of this study extend findings by demonstrating that a similar proportion of individuals with PMS meet threshold for ASD and autism as males with Fragile X syndrome, in whom ASD phenomenology is characteristically common. Importantly, the proportion of individuals in the PMS group meeting clinical thresholds on the SCQ was significantly higher than the Down syndrome group, suggesting that a high prevalence of ASD phenomenology can be associated with the behavioural phenotype of PMS. It is important to note that whilst this study has demonstrated a high prevalence of ASD phenomenology in PMS, this does not directly equate to a high prevalence of ASD diagnoses in PMS, given the necessity of thorough, multimodal assessment in the clinical diagnoses of ASD.

Analyses to evaluate the profile of ASD phenomenology in the total PMS sample provided heterogeneous results across the triad of impairments. Firstly, at subscale level the group did not differ from the idiopathic ASD or Fragile X syndrome groups in 'ASD-like' communication impairments. When verbal items were removed from the analysis, the PMS group evidenced more impairments than those with Down syndrome. This finding supports previous results highlighting 'ASD-like' impairments in communication in PMS (Phillipe *et al.,* 2008; Soorya *et al.,* 2013). Item-level analyses extended these findings to reveal that the PMS group evidenced specific impairments in 'nodding to communicate *yes*', with a higher proportion of the PMS sample scoring as impaired on this item than all three comparison groups, although this did not reach statistical significance when compared to the idiopathic ASD group. The PMS group did not significantly differ from the idiopathic ASD group on any item in the communication domain, suggesting that the profile of 'ASD-like' communication impairments is similar in the total PMS and idiopathic ASD groups.

Secondly, the PMS group did not differ from the Fragile X or Down syndrome groups in 'ASD-like' repetitive behaviours. However, when verbal items were included in the subscale analysis, the PMS group evidenced significantly lower repetitive behaviour scores than the idiopathic ASD group. This finding mirrors those previously reported (Phillipe *et al.,* 2008) and highlights the need to evaluate the specificity of measures when assessing ASD phenomenology in groups with intellectual disabilities and communication impairments.

When verbal items were excluded from the subscale analysis, the PMS group did not differ from the idiopathic ASD group. This suggests the perceived profile of reduced ASD repetitive behaviour in PMS is, in part, due to the group being unable to score on some verbal items of measures. However, item-level analysis also revealed that the PMS group was significantly less likely to engage in non-verbal ritualistic behaviours than those with Fragile X syndrome or idiopathic ASD. Thus, the profile of repetitive behaviour is still somewhat unclear in PMS. Fine-grained observational analysis of repetitive behaviours would be beneficial, in order to detail topography, frequency and any potential management difficulties of repetitive behaviour in the syndrome.

Finally, at subscale level, the PMS group evidenced significantly more impairments in social interaction than the Down syndrome group and showed comparable levels of impairment to the idiopathic ASD and Fragile X syndrome groups. This finding supports data demonstrating 'ASD-like' social interaction impairments in PMS (Phillipe *et al.*, 2008; Soorya *et al.*, 2013). An interesting dissociation in social interaction was revealed at item level; the PMS group showed significantly more impairments in 'Showing and directing attention' than both the Down syndrome and idiopathic ASD groups, but significantly less impairment in items assessing interest in, and responses to, other children. One interpretation of this finding is that there is a divergence in social skills and social motivation in PMS, with relatively preserved social motivation in contrast to deficits in social competence, potentially due to low levels of expressive speech. Alternatively, the result may represent a specific impairment in initiating interaction, with relatively preserved abilities to respond to interactions initiated by others. This finding warrants further investigation, including attempts to replicate the results in larger samples with PMS, using both indirect and direct assessments of social competence and motivation.

Whilst the profile of ASD impairments across the triad was varied within the total PMS sample, the results within the subgroup that scored above the autism threshold were homogenous. The results in this subgroup revealed that individuals with PMS were no more or less likely to score on items in any area of the triad, including the repetitive behaviour domain, than those with idiopathic ASD. This was true for all items except for 'Showing and directing attention', where the PMS group were approximately 30 times *more* likely to score

as impaired than the idiopathic ASD group. This finding extends previous research, affording a more refined understanding of the nature ASD impairments in affected individuals with PMS. The result suggests that when individuals with PMS meet criteria for autism, they do so for similar reasons to those with idiopathic ASD. Clinically, this may indicate that interventions to support individuals with idiopathic ASD could be usefully applied to individuals with PMS who meet diagnostic criteria, for example, Reciprocal Imitation Training (RIT; e.g., Ingersoll & Schreibman, 2006). The result also replicates the specific deficit noted in the total sample in showing and directing attention. Interventions to extend the behavioural repertoires of individuals with PMS, focused on behaviour to recruit and maintain others' attention may be warranted in this population, particularly given the high levels of functional challenging behaviour identified in the group (Powis *et al.,* In Review).

The final results of this study demonstrated that across all demographic and behavioural scores, only 'Interest and pleasure' was (negatively) correlated with SCQ score in the PMS group. The correlation between 'Mood' and total SCQ score approached significance; however this result should be interpreted with caution due to the poor internal consistency of the Mood subscale in the PMS group. These findings lend tangential support to previous research indicating an association between the presentation of mood disorders and ASD phenomenology in the syndrome (Shaw *et al.,* 2011). However, given the strength of evidence of behaviours indicative of ASD in PMS, the correlation between interest and pleasure and SCQ score is not interpreted as substantiation of mood disorders being wholly explanatory for ASD phenomenology in PMS. Instead, it is possible that behaviours indicative of low mood are associated with ASD impairments in PMS, similarly to the association reported in idiopathic ASD (Stewart, Barnard, Pearson, Hasan, O'Brien, 2006). Alternatively, it may be that mood disorders and ASD impairments co-exist within PMS due to similar genetic underpinnings, perhaps with greater severity of mood disorder being associated with more significant genetic deletion, as ASD phenomenology is hypothesised to (Luciani *et al.,* 2003). These hypotheses are tentative and further research is required to delineate the association between mood and ASD phenomenology in PMS, including any causal links between the two phenomena.

A number of caveats must be considered when interpreting the findings in this study. Firstly, the assessment of ASD phenomenology is somewhat limited, due to the utilisation of a screening measure rather than a diagnostic measure; the 'gold standard' for assessment of ASD in individuals with intellectual disability is a combination of ADOS (Lord *et al.,* 2000) and ADI-R (Rutter *et al.,* 2003). However, utilising a brief parent screening measure reduced time and assessment demands, and conferred the advantage of assessing multiple comparison groups in order to position the profile of ASD phenomenology in PMS relative to other syndromes (Oliver, Berg, Moss, Arron & Burbidge, 2011). Additionally, the SCQ is recognised as more appropriate for assessing ASD phenomenology in samples with intellectual disabilities than other ASD screening tools (Charman *et al.,* 2007). Similarly, the Wessex adaptive behaviour scores were utilised as a proxy measure for intellectual disability. Whilst it would have been beneficial to conduct full cognitive assessments of all of the participants, it would not have been possible within the scope of this study. Thus, a brief assessment of adaptive behaviour was chosen in order to balance the need to assess intellectual disability, and the need to maximise participants in all four groups. Secondly, despite careful matching of the groups, it was not possible to reduce all differences in adaptive behaviour. Therefore, the Down syndrome group were significantly more able than the PMS, Fragile X syndrome and idiopathic ASD samples. Previous researchers have argued that delineating the behavioural phenotype of a given genetic syndrome in relation to multiple other syndromes reduces the need for chronological or mental age matched comparison groups (Oliver *et al.,* 2011). Additionally, the PMS, Fragile X syndrome and idiopathic ASD groups were well matched for chronological age and adaptive ability. Nonetheless, the results should be interpreted with this caveat in mind. Finally, due to the relatively small PMS sample, there was insufficient statistical power to test causal associations between expressive speech, adaptive behaviour and ASD scores. Previous research has highlighted that it is important to explore these associations in samples with genetic syndromes (Moss & Howlin, 2009). Correlational evidence from this study indicates that adaptive behaviour was not associated with SCQ score; however this still warrants further exploration in larger sample sizes, where causal statistical modelling is possible.

The results of this study have a number of important clinical implications. Firstly, the similarity in ASD profile between those with PMS who reach the autism threshold and those

with idiopathic ASD suggests that interventions utilised in those with idiopathic ASD could be usefully applied to individuals with PMS. Secondly, the results indicate that assessment of behaviours indicative of low mood should be routine in individuals with PMS. Research in individuals with severe intellectual disabilities has revealed that low mood scores may indicate pain and undiagnosed health conditions (Breau, Camfield, McGrath & Finley, 2003; Carr & Owen-Deschryver, 2007; Luzzani, Macchini, Valade, Milani & Selicorni, 2003). There are reports of gastro-oesophageal reflux and other painful conditions in PMS (Phelan, 2008). Therefore, thorough health assessments should routinely be conducted for individuals with PMS. Finally, the results of this study have implications for research investigating the genetic underpinnings of idiopathic ASD. The results demonstrate that those with high levels of ASD impairment evidence a profile of ASD impairments similar to that of idiopathic ASD. However, the wider PMS sample presents a more heterogeneous pattern with fewer impairments in repetitive behaviours. This may suggest that social and communicative impairments would be a useful autism endophenytpe to be investigated in relation to 22q13.3 deletions (Bill & Geschwind, 2009).

In summary, this study has demonstrated that differences in affect and repetitive behaviour are common in PMS. Additionally, autism spectrum disorder phenomenology is prevalent within the syndrome. The profile of ASD impairments in the total sample with PMS is heterogeneous; the profile within those who meet clinical threshold for autism is more homogenous and analogous to those with idiopathic ASD. The presence of ASD phenomenology is associated with lower mood in those with PMS.

CHAPTER 3

Executive Summary

3.1. Literature Review

3.1.1. Background

Autism spectrum disorder (ASD) is a term used to describe a neurodevelopmental disorder in which three key areas of impairment are seen; difficulties in communication, difficulties in social interaction, and difficulties in flexibility of thought and imagination, with accompanying restricted and repetitive behaviours. ASD is very common, with recent estimates suggesting that 1 in 68 individuals has a diagnosis of ASD. ASD is also known to be hereditable, although the precise genetic pathway for this is still unclear.

There is emerging evidence that ASD behaviours are more common in individuals with rare genetic or metabolic syndromes, compared to other syndromes and/or compared to the general population. This is important for two key reasons. First, it is possible that knowing the specific genetic cause of a rare syndrome *and* knowing that ASD behaviours are very common in that syndrome could help researchers to understand the pathway from genetics, to brain development, to cognition (or the style and type of thinking processes) that leads to ASD behaviour. The development of this understanding would be important for individuals and families with these rare syndromes, and to individuals and families with ASD that is not associated with a syndrome. Second, having robust estimates of how common ASD behaviour is in each rare syndrome would help to improve the provision of clinical and educational services for individuals with those syndromes.

There has been a lot of published scientific research in individual rare syndromes, detailing how common ASD behaviours are in these syndromes (for an accessible overview of this research see Moss & Oliver, 2012). However, there has not yet been a systematic review of all of these studies, which brings together the estimates of how common ASD behaviour is in each syndrome, summarises these estimates, compares them between syndromes and compares them to the general population.

3.1.2. What did the review do?

A large literature search was conducted to find all of the research papers that detailed how common ASD behaviours were in 21 rare genetic and metabolic syndromes. A system for reviewing the quality of each individual research paper was devised, and overall estimates were generated for how common ASD behaviour was in each syndrome. These overall estimates were influenced more heavily by the highest quality research papers, and least heavily by the poorest quality papers.

3.1.3 What did the review find?

After poor quality papers had been removed, it was possible to generate robust estimates of how common ASD behaviours were for 12 syndromes. Figure 3.1 presents the results of this, showing that ASD behaviour was most common in Rett syndrome (with estimates suggesting that 61 in 100 individuals with Rett syndrome may show ASD behaviour) and least common in 22q11.2 deletion syndrome (with estimates suggesting that only 11 in 100 individuals with 22q.11.2 deletion syndrome may show ASD behaviour).

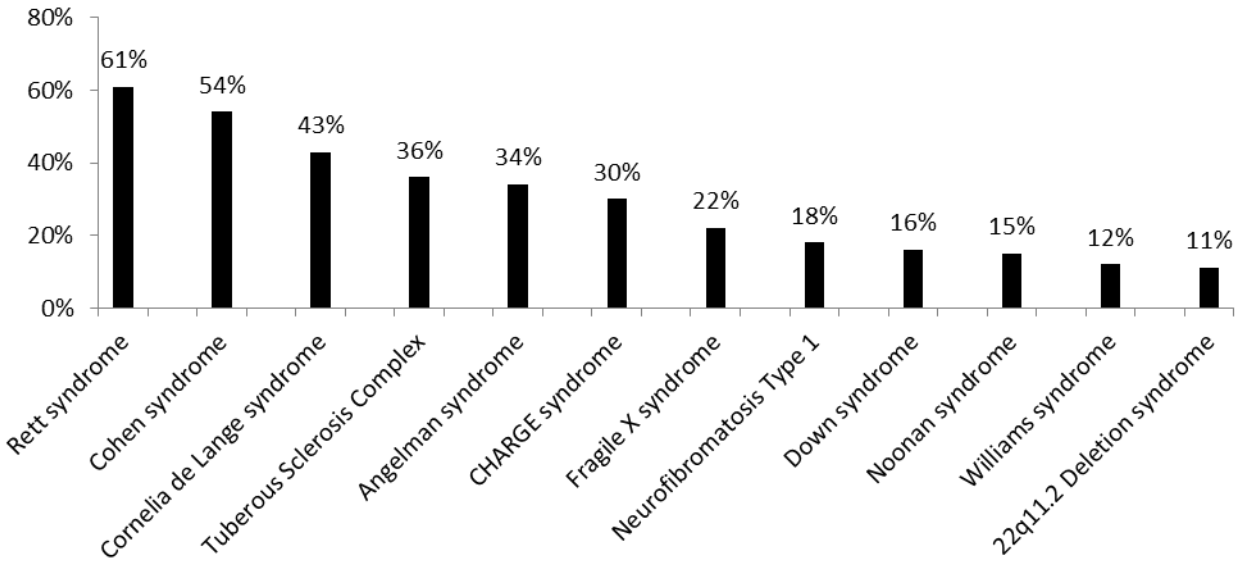

Figure 3.1 Generated estimates of how common ASD behaviour is in syndromes.

For each syndrome, it was also possible to estimate how many times more likely ASD behaviour was, compared to the general population. Figure 3.2 presents the results of this. The results revealed that ASD behaviour was significantly more common in each of the

syndromes, compared to the general population. In Rett syndrome, the odds of showing ASD behaviour were almost 105 times greater than in the general population. In 22q11.2 deletion syndrome, the odds of showing ASD behaviour were 8 times greater than in the general population.

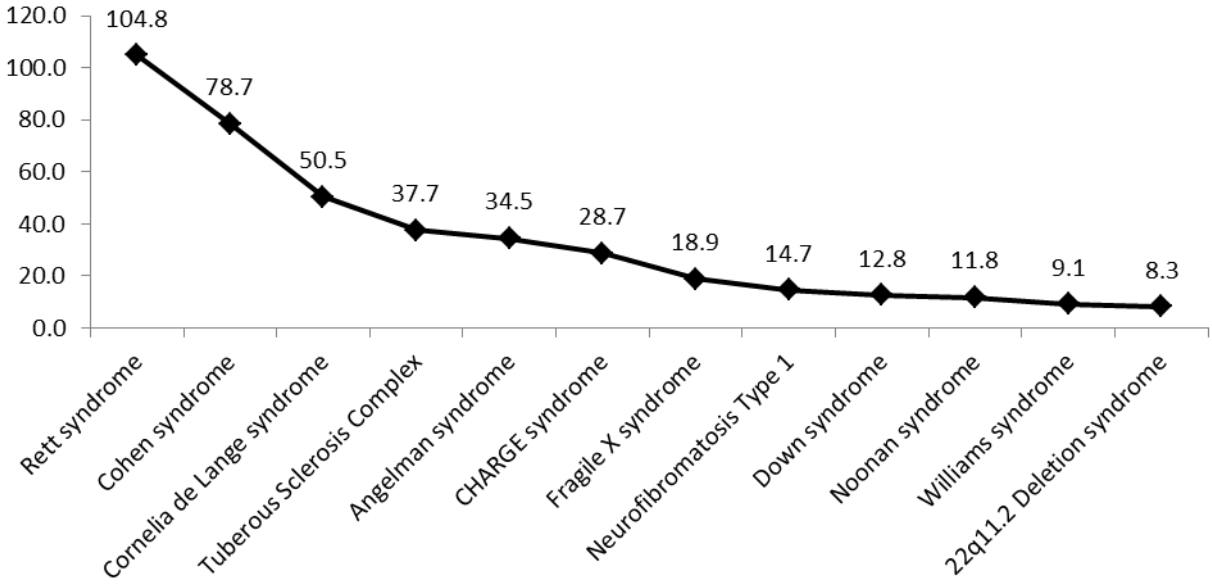

Figure 3.2 Generated estimates of how likely ASD behaviour is in each syndrome compared to the general population.

3.1.4 What do these findings really mean?

These findings give us important robust estimates of how common ASD behaviour is in lots of rare syndromes. This can help us to plan clinical and educational services more appropriately for individuals with these syndromes. These estimates can also be used to focus future research into the underpinnings of ASD and the precise nature of ASD type difficulties in people with rare syndromes.

3.2. Empirical Paper

3.2.1. Background

Phelan McDermid syndrome (PMS) is a rare genetic syndrome, caused by a deletion on chromosome 22q13.3. This deletion is very small and recent developments in genetic testing have made it easier to detect. There has been some research to suggest that certain behavioural characteristics are more common in individuals with PMS compared to other

individuals. These characteristics include higher levels of activity and impulsivity, lower mood and higher levels of ASD behaviours. There is also some limited research suggesting that although ASD behaviours are more common in PMS, that individuals with PMS do not demonstrate all three areas of ASD impairment equally. Some researchers have argued that although difficulties with social interaction and communication are common in PMS, difficulties with repetitive and restricted behaviours are less common.

The published research to date in PMS has been limited by the use of assessment measures that do not take into account the degree of intellectual disability present in PMS. Additionally, there has been little research using appropriate comparison groups for individuals with PMS. Comparison groups are useful as they allow us work out whether behavioural characteristics are simply due to intellectual disability or due to the specific genetic syndrome. Comparison groups with ASD not associated with a genetic syndrome also allow us to find out whether the profile of the three areas of impairment in PMS is similar to people with ASD, or atypical, as the previous research had suggested.

3.2.2. What did the study do?

Parents of 30 individuals with PMS took part in a questionnaire study. The parents completed questionnaires that had been specifically designed for people with intellectual disabilities. These questionnaires measured activity levels, mood, repetitive behaviour and ASD type impairments. Additionally, parents of three comparison groups also completed the questionnaires. These comparison groups were Fragile X syndrome, Down syndrome and ASD not associated with a genetic syndrome.

3.2.3. What did the study find?

The study showed that the levels of activity and impulsivity in PMS did not differ from those with Fragile X syndrome, Down syndrome or ASD not associated with a genetic syndrome. Individuals with PMS were found to have lower mood than the ASD group, but higher mood than the Down syndrome group. Repetitive behaviours involving repetitive physical actions were common in the group, but compulsive repetitive behaviours were less common.

ASD behaviour was very common in individuals with PMS. Figure 3.3 shows that 86.7% of the group met criteria for ASD on the questionnaire measure. 56.7% of the group met criteria for a more stringent category of autism. However, it should be noted that although these individuals met criteria on the questionnaire measure, this does not necessarily mean they would fulfil criteria for a clinical diagnosis of ASD.

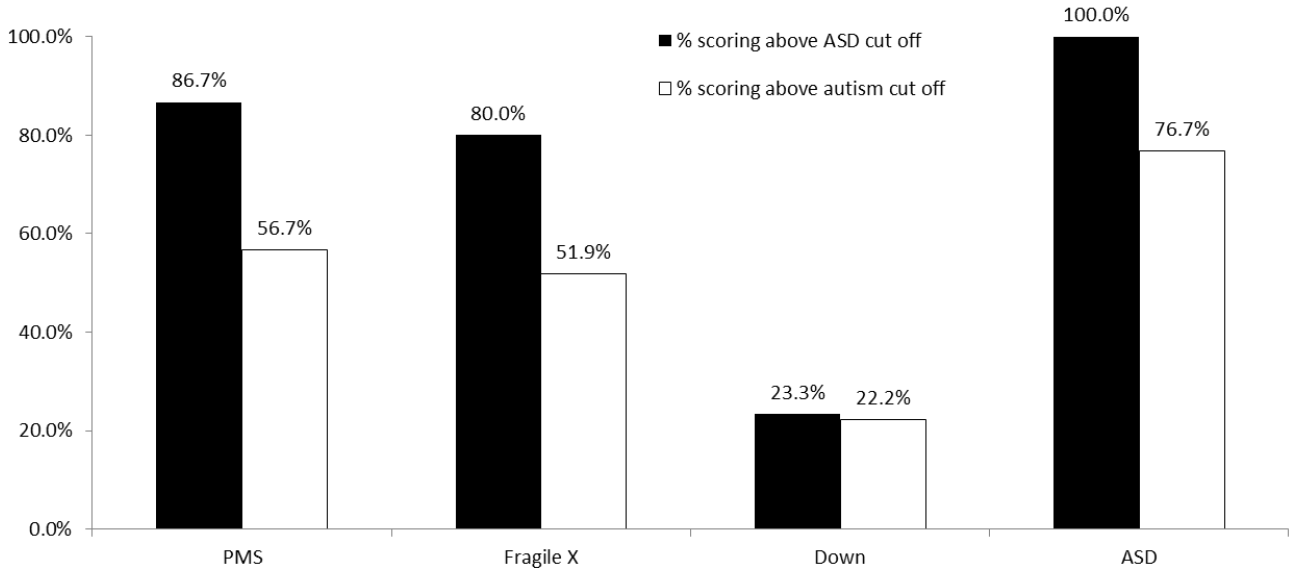

Figure 3.3. Percentage of each group meeting criteria for ASD and autism

A very fine-grained analysis of each of the three areas of ASD impairments in PMS revealed that individuals with PMS who meet criteria for autism, have a very similar profile of social, communication and repetitive behaviour impairments as individuals with ASD not associated with a genetic syndrome. Interestingly, for individuals with PMS, higher levels of ASD behaviour were associated with lower mood scores.

3.2.4. What do these findings really mean?

These findings mean that individuals with PMS are no more or less likely to have problems with attention and activity levels than other individuals with a similar level of intellectual disability. They may however have lower levels of mood than other individuals. ASD behaviour is very common in the group, and therefore clinical assessments should always include an evaluation of ASD. As the profile of ASD impairments in PMS is very similar to individuals with ASD not associated with a genetic syndrome, it is possible that the vast wealth of interventions designed for individuals with ASD could be usefully used with individuals with PMS.

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VOLUME ONE - APPENDICES

Appendix A – Development of Quality Criteria

Well validated quality criteria for evaluating case-control and intervention studies are published (e.g., Downs & Black, 1998) which provide numerical outcome data. However, these criteria are not suitable for evaluating the quality of prevalence studies due to significant differences in the design and methods of intervention and prevalence studies. There is wide variation in the application of quality criteria in health science meta-analyses of prevalence. Some studies take an inclusive approach and do not specify an evaluation of quality (e.g., an evaluation of the prevalence of community acquired MRSA; Salgado, Farr & Calfee, 2013). Others have delineated areas of potential bias, such as the type of measure used to assess depression, and then conducted post-hoc statistical analyses to evaluate the effect of these differing measurement techniques upon the identified prevalence rates (Anderson, Clouse, Freedland & Lustman, 2001). Whilst both of these approaches have utility, they do not allow for a-priori evaluation of the overall quality of the literature. For the present review, the ability to assess within and between syndrome variations in evidence quality will be paramount. Therefore, an alternative approach of pre-analysis assessment of quality was selected.

Shamliyan and colleagues (2011) developed a preliminary checklist for assessing the quality of prevalence studies included in meta-analyses. The checklist includes an assessment of external validity (primarily sampling method, assessment of sampling bias and estimate of return rate) and internal validity (assessment measurement utilised to assess prevalence). Whilst this checklist does not generate numerical ratings for the quality of studies, it does provide a broad framework for assessing quality, which the present study has drawn upon. The authors emphasise the need for each meta-analysis to tailor the quality criteria to their study, in order to produce the most robust assessment of quality. A useful example of individually tailored quality criteria is presented by Reijnders *et al.*, (2008) who conducted a meta-analysis of the prevalence of depression in Parkinson's Disease. Similarly to the present study, Reijnders *et al.* (2008) investigated the prevalence of a behaviourally defined disorder (depression) within a clinically selected sample (individuals with Parkinson's Disease). They

applied a simple rating scale to evaluate how each study identified cases, confirmed diagnosis of Parkinson's Disease and confirmed diagnoses of depression. This system allowed for an evaluation of both internal and external validity and produced a numerical rating of quality which could be used to weight the overall prevalence data. The present study applied a similar model to evaluate: 1) the selection of the samples with syndromes 2) the confirmation of syndrome, 3) the assessment of ASD.

In order to develop idiosyncratic quality ratings for each of these three areas, literature reviews were conducted and active research experts in the field of autism and rare syndromes were consulted for advice on areas of methodological concern.

Quality Criterion for Sample Identification

The primary focus of this quality criterion was whether the recruited sample could be considered to be representative of the total population. Downs and Black (1998) state that "Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample". Similarly, Shamliyan and colleagues (2011) identify sampling restricted to a specific geographic area and convenience sampling as minor flaws, and sampling through medical records, insurance claims, work places and health care service (i.e., clinics and hospitals) as major flaws.

Utilising similar principles, the sampling strategies employed by studies in the present meta-analysis were ranked on a 0 – 3 scale, with a score of 0 assigned to studies where no sampling strategy was reported, and a score of 3 assigned for random or total population sampling. A score of 1 was assigned for studies sampling from a single restricted source, for example a specialist clinic or regional support service. A score of 2 was assigned for studies recruiting from multi-site restricted sources, for example national parent support groups or multi-region specialist clinics.

Quality Criterion for Confirmation of Syndrome

The primary focus of this quality criterion was confidence in the accuracy of the diagnosis of the specified syndromes. Diagnosis of syndromes can be made on the basis of the presence of clinical features and/or on the basis of molecular, cytogenetic or metabolic tests. The

diagnostic strategies employed by studies in the present meta-analysis were ranked on a 0 – 3 scale, with a score of 0 assigned to studies where diagnosis of syndrome was not reported or confirmed, or where a diagnosis based on clinical features was only suspected. A score of 1 was assigned for studies where a clinical diagnosis had been made by a 'generalist', whereas a score of 2 was assigned for studies where a clinical diagnosis was made by an 'expert' or 'specialist'. Finally, a score of 3 was assigned only if a diagnosis of syndrome was confirmed by molecular, cytogenetic or metabolic testing. To ensure a conservative estimate of quality, in studies in which only a proportion of the sample were administered a more stringent test (e.g., some participants had cytogenetic testing, others clinical diagnosis by a geneticist), the dataset as a whole were assigned the more conservative quality rating.

Quality Criterion for ASD Assessment

The primary focus of this quality criterion was confidence in the accuracy of the identification of ASD phenomenology in the sample. As discussed above (see Section 1.2), ASD diagnoses in clinical practice are made on the basis of multi-modal comprehensive assessments, the breadth and depth of which are rarely conducted in a research context. However, there is a wide variety of tools used in research to assess ASD, which can be helpfully separated into categories of screening and diagnostic instruments. Screening instruments can be used as tools to identify an increased likelihood of ASD. However, in a detailed scope of these tools for the Autism NICE guidelines (2011), the Guideline Development Group (GDG) stated that the accuracy of these tools was very low, and whilst they 'may be useful in gathering information about signs and symptoms of autism' they 'should not be used to make or rule out a diagnosis of autism'. Conversely, the accuracy of diagnostic tools was better. However, as discussed above (see Section 1.2) whilst many of these instruments evidence good reliability and validity, no diagnostic or screening instruments are validated for marginal populations, such as those with syndromes. Thus, whilst diagnostic tools can be seen to be more broadly accurate than screening tools in the assessment of ASD, none of these tools, used in isolation, can definitively diagnose ASD in individuals with genetic and chromosomal disorders.

Therefore, a broad quality criterion of ASD assessments was constructed. The ASD assessments employed by studies in the present meta-analysis were ranked on a 0 – 3 scale, with a score of 0 assigned to studies where no information was specified or reported on the

type of ASD assessment conducted. A score of 0 was also assigned to studies where clinician judgement alone was used to assess ASD, without reference to any specified tools or diagnostic criteria. A score of 1 was assigned when a robust screening instrument was employed, for example SCQ or M-CHAT. A score of 1 was also assigned when clinician judgement against specified diagnostic criteria such as ICD-10 or DSM-V was used. A score of 2 was assigned for studies that employed robust diagnostic instruments, such as the ADI-R or ADOS. Finally, a score of 3 was assigned if studies used consensus from multiple assessments, and that *at least one* of these assessments would have obtained a score of 2 in isolation. This rating was assigned as the closest research approximation to multi-model diagnostic clinical assessments. Where studies have employed multiple ASD assessments of varying quality, the most robust assessment (as defined by this quality criterion) was used. Where studies have employed multiple ASD assessments of the same quality, for example multiple screening measures, the measure which yielded the most conservative estimate of prevalence was used.

Appendix B – Forest Plots for Pooled Prevalence Estimates for Males Only with Fragile X syndrome

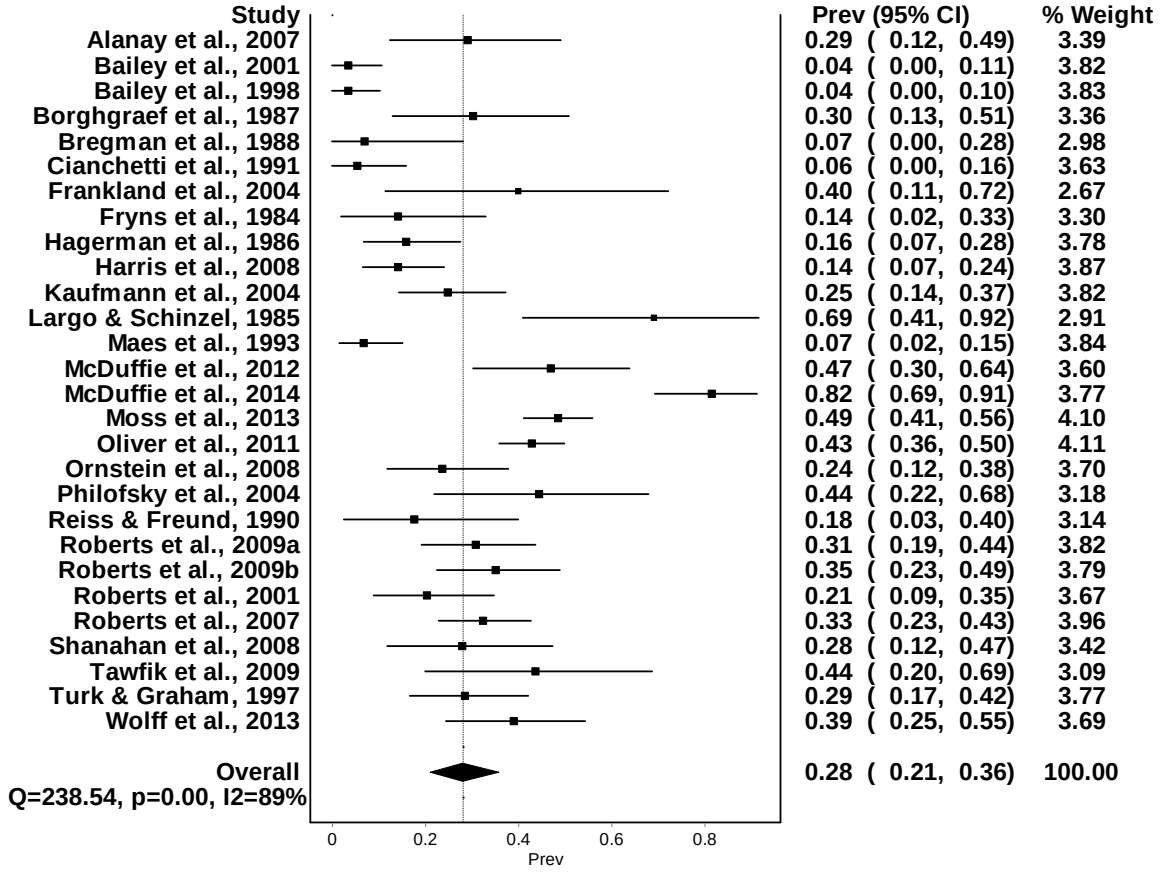

Figure 1. Pooled prevalence estimates for ASD phenomenology in males with Fragile X syndrome using a random-effects model.

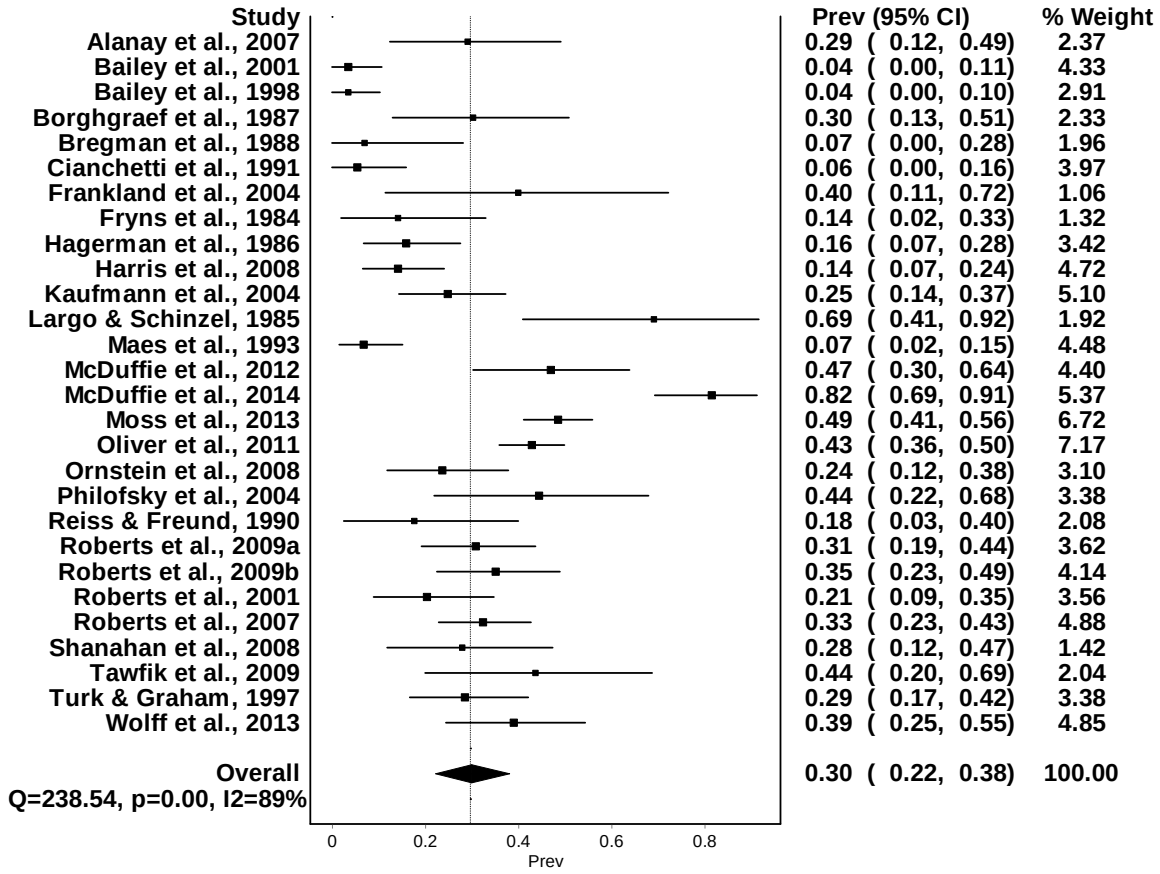

Figure 2. Pooled prevalence estimates for ASD phenomenology in males with Fragile X syndrome using a quality-effects model.

Appendix C – Questionnaire pack

UNIVERSITY OF BIRMINGHAM

27th June 2011

Dear Parent,

We are writing to inform you of a new research project that is being carried out at the Cerebra Centre for Neurodevelopmental Disorders at the University of Birmingham. We would like to invite you and the person you care for to take part in this new research project. Briefly, the research is a questionnaire study looking at different behaviours in children and adults with Phelan-Mcdermid syndrome that have received minimal attention within the literature.

We have contacted you through Unique. Your personal details will not be known to us unless you decide to take part in the study. There is an information sheet enclosed that gives you more details about why the research is being carried out and what participation will involve. If you feel it is appropriate you may wish to discuss the research with the person you care for before a decision is made about taking part.

There is an information sheet enclosed that gives you more details about why the research is being carried out and what it will involve. If you and your child/person you care for would like to take part in the study then please complete the enclosed consent form and questionnaire pack and return them in the pre-paid envelope provided.

Please read the information sheets before completing the questionnaires and if you are unclear about any aspect of the study or have any questions then

Thank you for your time and we look forward to hearing from you.

Yours sincerely

Consent Form A : For individuals who are able to provide consent to participate in the study

Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders

Study Director: Professor Chris Oliver

SECTION 1: Please complete this section if you are a person with Phelan-McDermid syndrome:

1. Has somebody else explained the project to you? YES/NO
2. Do you understand what the project is about? YES/NO
3. Have you asked all of the questions you want? YES/NO
4. Have you had your questions answered in a way you understand? YES/NO
5. Do you understand it is OK to stop taking part at any time? YES/NO
6. Are you happy to take part? YES/NO

If any answers are 'no' or you don't want to take part, don't sign your name!

If you do want to take part, you can write your name below

You can also choose if you want to say 'yes' to these questions:

7. If your Dr asks to see your results from this project is that OK? YES/NO
8. Are you happy for us to contact you again in the future? YES/NO

Your name:_____

Date:_____

The person who explained this project to you needs to sign too. If you are under the age of 16, this should be your parent/guardian.

Print name:_____ Sign:_____
Date:_____

<u>SECTION 2:</u> Please complete this section if you are a parent/carer/guardian of a person with PMS

who has provided their consent to participate in the study. **Please initial box…**

1. I confirm that I have read and understood the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation and that of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reason, without my or that of my child's/person I care for's medical care or legal rights being affected. ☐

3. I understand that relevant sections of my child's/person I care for's GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the Cerebra Centre for Neurodevelopmental Disorders research team at the University of Birmingham, where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐

4. I agree to my child's/person I care for's GP being informed of my participation and that of my child/person I care for's in the study, where access to my child's/person I care for's medical records is required. ☐

5. I agree to take part in the above study. ☐

Optional clause: The statement below is <u>optional</u>:

1. I agree to the University of Birmingham research team sharing my research data with any professionals or clinicians working with me and the person I care for should they request to see them. ☐

Print Name: _____
Telephone number: _____

Address: _____
Email: _____

Relationship to participant: _____
Signature: _____
Date: _____

<u>SECTION 3:</u> This is <u>optional</u> and allows you to provide consent for us to keep your personal details on the Regular Participant Database. See section titled 'Regular Participant Database' in the information sheet.

Please initial box…

1. I have read and understood the section titled 'Regular Participant Database' and I would like my personal details to be added to the database. ☐

2. I understand that my name and contact details will be kept by the research team at the University of Birmingham in accordance with the provisions of the Data Protection Act 1998 and I will be contacted by an approved member of the team with information about future research that I and the person I care for may like to participate in. ☐

3. I understand that if my details are held on the database it will be possible for the research team to trace the results of the assessments that I complete in this project back to me and my child/person I care for so that they can look at changes over time if I take part in future projects. ☐

4. I understand that even after I have agreed for my details to be added to the database, I can request that they be removed by contacting Chris Oliver on 0121 414 7206 or at <u>cndd-enquiries@contacts.bham.ac.uk</u> or by post at the School of Psychology, University of Birmingham, Edgbaston, B15 2TT. ☐

5. I understand the Professor Chris Oliver holds ultimate responsibility for the database. ☐

Print Name: _____Signature: _____Date: _____

<u>Consent Form B:</u> For Children under the age of 16 who are <u>not</u> able to provide consent.

<u>Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders</u>

Study Director: Professor Chris Oliver

SECTION 1: Please complete this section if you are a parent/ guardian of a child (under 16 years) with Phelan-McDermid syndrome who is not able to provide consent.

Please initial box…

1. I confirm that I have read and understood the information sheet dated 01.02.2010 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation and that of my child/person I care for is voluntary and that I am free to withdraw at any time without giving any reason, without my or that of my child's/person I care for's medical care or legal rights being affected. ☐
3. I understand that relevant sections of my child's/person I care for's GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the Cerebra Centre for Neurodevelopmental Disorders research team at the University of Birmingham, where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐
4. I agree to my child's/person I care for's GP being informed of my participation and that of my child/person I care for's in the study, where access to my child's/person I care for's medical records is required. ☐
5. I agree to take part in the above study. ☐

Optional clause: The statement below is <u>optional</u>:

6. I agree to the University of Birmingham research team sharing my research data with any professionals or clinicians working with me and the person I care for should they request to see them. ☐

Print Name: _____Name of person you care for_____

Address:_____Email: _____

Telephone number:_____Relationship to participant: _____

Signature: _____Date: _____

<u>SECTION 2:</u> This is <u>optional</u> and allows you to provide consent for us to keep your personal details on the Regular Participant Database. See section titled 'Regular Participant Database' in the information sheet.

Please initial box…

6. I have read and understood the section titled 'Regular Participant Database' and I would like my personal details to be added to the database. ☐

7. I understand that my name and contact details will be kept by the research team at the University of Birmingham in accordance with the provisions of the Data Protection Act 1998 and I will be contacted by an approved member of the team with information about future research that I and the person I care for may like to participate in. ☐

8. I understand that if my details are held on the database it will be possible for the research team to trace the results of the assessments that I complete in this project back to me and my child/person I care for so that they can look at changes over time if I take part in future projects. ☐

9. I understand that even after I have agreed for my details to be added to the database, I can request that they be removed by contacting ☐

10. I understand the Professor Chris Oliver holds ultimate responsibility for the database. ☐

Print Name: _____Signature: _____Date: _____

Consent Form C: For individuals over the age of 16 who are not able to provide consent.

Understanding behaviour and family adjustment in individuals with neurodevelopmental disorders

Study Director: Professor Chris Oliver

SECTION 1: Please read the following statements:

Please initial box…

1. I (your name)_____have been consulted about (name of participant)_____'s participation in the above research project. I have had the opportunity to ask questions about the study and understand what is involved. ☐
2. In my opinion he/she would have no objection to taking part in the above study. ☐
3. I understand that I can request he/she is withdrawn from the study at any time without giving any reason and without his/her care or legal rights being affected. ☐
4. I understand that relevant sections of his/her GP medical notes or records confirming genetic diagnosis and health status may be looked at by members of the Cerebra Centre for Neurodevelopmental Disorders research team at the University of Birmingham, where it is relevant to this research project. I give permission for these individuals to have access to these records. ☐
5. I agree to his/her GP being informed of their participation in the study, where access to medical records is required. ☐
6. I agree to take part in the above study. ☐

Optional clause: The statement below is optional:

7. I agree to the University of Birmingham research team sharing his/her research data with any professionals or clinicians working with them should they request to see them. ☐

Print Name: _____ Telephone number:_____

Address:_____
Email: _____

Relationship to participant_____
Signature: _____Date: _____

<u>SECTION 3:</u> This is <u>optional</u> and allows you to provide consent for us to keep your personal details on the Regular Participant Database. See section titled 'Regular Participant Database' in the information sheet.

Please initial box…

11. I have read and understood the section titled 'Regular Participant Database' and I would like my and the person I care for's personal details to be added to the database. ☐

12. I understand that my name and contact details will be kept by the research team at the University of Birmingham in accordance with the provisions of the Data Protection Act 1998 and I will be contacted by an approved member of the team with information about future research that I and the person I care for may like to participate in. ☐

13. I understand that if my details are held on the database it will be possible for the research team to trace the results of the assessments that I complete in this project back to me and the person I care for so that they can look at changes over time if we take part in future projects. ☐

14. I understand that even after I have agreed for my details to be added to the database, I can request that they be removed by contacting ☐

15. I understand the Professor Chris Oliver holds ultimate responsibility for the database. ☐

Print Name: _____Signature: _____
Date: _____

The Cerebra Centre for Neurodevelopmental Disorders
UNIVERSITY OF BIRMINGHAM

Understanding behaviour in Neurodevelopmental Disorders: Information Sheet

Please read this information carefully before deciding whether you wish to take part in the study. If you have any further questions please contact

If you have any medical/ other problems which make it difficult for you to read this information, please contact Professor Chris Oliver for a verbal explanation of the research.

When you are happy that you have all of the information you need to be able to decide whether or not you and the person you care for would like to take part in the study, please complete the enclosed consent form and questionnaire pack return them to us in the prepaid envelope provided

Background

We would like to invite you to take part in a questionnaire study being conducted at the Centre for Neurodevelopmental Disorders, University of Birmingham. This research work, which is led by Professor Chris Oliver, looks at a range of behaviours, skills and impairments in individuals with Phelan-McDermid syndrome including: Repetitive behaviour, Hyperactivity, Mood, Challenging behaviour, Social functioning and Health. We will also ask some questions that are related to family well-being and the impact that having a child with a disability has on the family.

We hope that this information will enable us to further understand the behaviours, skills and impairments associated with Phelan-McDermid syndrome including challenging behaviour, social functioning, mood, hyperactivity and health and the impact that these behaviours have on the family. The more people that take part in this research, the more meaningful the results will be. A good response will provide new and valuable information about Phelan-McDermid syndrome. In the future we hope to follow up the progress of the people who take part in this study. However, participation in this stage of the project will **not** mean that you are obliged to participate in further surveys in the future.

Aims of the study

1. To further our understanding of challenging behaviour, repetitive behaviour, hyperactivity, mood and social functioning in individuals with Phelan-McDermid syndrome.
2. To understand what happens with regard to these behaviours as children and adults develop.
3. To understand what, if any, changes may occur with regard to these behaviours when the individuals reach a certain age.
4. To understand the impact of having a child with a disability has on the family.

What will happen if you and your child/the person you care for decide(s) to participate?

Where will the research take place?
The research will involve completing the enclosed questionnaire pack. This can be completed by you in your own time.

Who will be involved in collecting the data?
Members of the research team at the Cerebra Centre for Neurodevelopmental disorders including Professor Chris Oliver and Dr. Joanna Moss.

How long will participation in the study take?
The questionnaire pack will take approximately 45 minutes to complete.

In the future you may be asked if you would like to complete the questionnaire again so that we can start to understand what happens to people with Phelan-McDermid syndrome across their lifetime. We will only contact you with this invitation if you have previously agreed to be contacted by the research team at the University of Birmingham with information about research studies conducted by the team.

Sometimes after you have completed the questionnaire, we may need to contact you again in order to clarify any information that you have provided or to ask you for further information regarding the diagnosis of the person you care for. This helps us to ensure that our data is as useful and as accurate as possible. If this happens then we would contact you again within 6 months of receiving your questionnaire pack to ask whether or not you would be willing to provide us with the extra information.

What will participants be required to do during the study?
We will ask parents and caregivers to complete the enclosed questionnaire pack and return it to us alongside the consent form in the pre-paid envelope provided.

Are there any risks that individuals taking part in the study might face?
There will not be any risks associated with participation in this study.

What are the potential benefits for participants from taking part?
You will receive a personalised feedback regarding your child/ the person you care for. This study will help us to find out more about the lives of people with Phelan-McDermid syndrome and the difficulties that these people face. The results might help us to improve things for people with Phelan-McDermid syndrome in the future.

Where will data be stored?
The data collected will be kept in locked or password protected storage at the University of Birmingham. Only members of the research team at the University of Birmingham will have access to information that we collect about you. Information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

If you/ the person you care for decide(s) to participate, what will happen after that participation?
You and your child/ person you care for will receive an individual feedback report describing the results of all of the assessments that were carried out during the study. If requested, this feedback report will be circulated to other interested individuals. Descriptions of research findings will be published in newsletters of the relevant family support groups and

educational institutions involved. Any request for advice concerning the person you care for will be referred to Professor Chris Oliver, Clinical Psychologist.

The researchers will publish the findings from the study in scientific journals and will present the results at relevant conferences.

What will happen to the data afterwards?
The information that you provide will be locked in a filing cabinet at the University of Birmingham or held on a password protected database. Participants will be identified by a unique number so that the information you provide us with cannot be traced to your personal details. You will be able to decide whether or not you want to make your research data available to any professionals or clinicians working with you and the person you care for should they wish to see it. This is optional and will not affect your participation in the current study. If you agree to this, then your research data will only be made available to relevant clinicians or professionals should they contact us directly and request to see it. If you do not agree to this then research data will not be made available to anyone other than the research team at the University of Birmingham.

After 6 months of receiving your questionnaire pack, your personal details will be ***destroyed unless you tell us otherwise.*** This means that we would no longer be able to trace the results of your assessments back to you. ***The section below on 'The Regular Participant Database Information'*** gives information about a database that we use to store the personal details of some participants. Please read this section in order to decide if you would like to join that database.

Regular Participant Database Information:

What is the regular participant database?
We have a database that we keep in the Cerebra Centre where we store the names and contact details of some previous participants. If you would like us to, we can add your details to this database. We would use this information for two things:

1) We will contact you with information about future research work to find out whether or not you would like to participate.
2) It is often important to find out how things change over time. By keeping your details we would be able to trace the results of the previous assessments that you have done with us back to you. This means that if you take part in other studies with us we would be able to look at how things have changed over time.

Who would have access to my details?
Only approved members of out research team would have access to your details. We would not share your details with anyone outside the research team.

When would I be contacted?
You would only be contacted by an approved member of the research team when we are starting another study or phase of a study that we think you might like to participate in or when we need to clarify some information that you have provided us with from participation in a research study.

What happens if I decide that I want my details to be added to the database but then I change my mind?
All you would need to do is contact Chris Oliver on 0121 414 7206 or at cndd-enquiries@contacts.bham.ac.uk or at the School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT. Your details would be removed from the database immediately.

Consent
After having read all of the information and having received appropriate responses to any questions that you may have about the study you and the person you care for will be asked to give your and your child's/ person you care for's consent to participate in the study if you decide that you do wish to participate. The section below on ***'Giving consent'*** will explain this process. We need to receive consent from/ on behalf of potential participants in order for them to participate.

Withdrawal
Even after consent has been granted, participants can request to be withdrawn from the study at any time, without giving a reason. Even after participation has taken place, consent can be withdrawn and any data collected will be destroyed. This will not restrict the access of you/ the person you care for to other services and will not affect their right to treatment.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact

Confidentiality

The confidentiality of participants will be ensured. If published, information on the participant will be presented without reference to their name or any other identifying information. All personal details will be kept separately from the information collected so that it will only be possible to connect results to individuals via a special code. This will ensure that results are kept anonymous. In the unlikely event of any evidence of abuse being identified, this information will be disclosed by the research workers.

Review
The study has been approved by Coventry NHS Research Ethics Committee. For any queries or concerns regarding the ethical approval of this study please contact

Further information
If you would like any more information about the study please contact

Giving consent

Now it is up to you whether you decide that you and your child/the person you care for would like to participate. The decision about whether or not to take part in the study must be 'informed'. This means that anyone making the decision must understand exactly what is involved in the study, what will be required from participants and why.

IMPORTANT:

You need to decide whether your child/the person you care for is able to understand enough about the study to make an 'informed' decision independently about whether or not they would like to participate and to communicate this decision to you. If you are unsure whether or not your child/person you care for is able to understand enough to make a decision independently then we can provide you with some guidelines to help you to assess this A symbol information sheet can also be made available to you if this would be of help. Please contact to request a copy of this.

Please choose from one of the following options:

1. My child/ the person I care for is able to understand what is involved in the study and what will be required from them if they participate and has communicated their decision to me:

If you think that the person ***is* able** to understand enough about the study in order to make an 'informed'
decision and they decide that they would like to participate then please ensure that they complete **Section 1 of Consent Form A coloured YELLOW** enclosed, or that you complete it with them, on their behalf. A parent/carer will need to complete **Section 2 of Consent From A coloured YELLOW** in order to indicate that they also agree to participate in the study. *A symbol information sheet can be made available in order to support your child/person you care for in making this decision if it would be of help.* Please contact the research team if you would like a copy of the symbol consent form or if you need us to adapt this information further, in order to suit your child's needs. Please return the consent form along with the questionnaire pack to us in the prepaid envelope provided.

2. My child/ the person I care for is unable to understand what is involved in the study and what will be required from them if they participate (either because they are too young to understand or because they are unable to understand) and cannot communicate their decision to me:

If you are reading this information on behalf of someone you care for who is under the age of 16 years and you decide that the person ***is not*** able to make an 'informed' and independent decision about whether or not they would like to participate, then we would like to ask you to decide whether or not you think that it is in your child's best interests for them to participate in the study and whether you would like to provide your consent to participation on their behalf. If you would like your child/person you care for to participate in this study, please complete **Consent Form B coloured PURPLE** enclosed. Please return the consent form along with the questionnaire pack to us in the prepaid envelope provided.

UNIVERSITY OF BIRMINGHAM

The Cerebra Centre for Neurodevelopmental Disorders

Understanding behaviour in Neurodevelopmental Disorders: Information Sheet

Please read this information carefully before deciding whether you wish to take part in the study. If you have any further questions please contact

If you have any medical/ other problems which make it difficult for you to read this information, please contact Professor Chris Oliver for a verbal explanation of the research.

When you are happy that you have all of the information you need to be able to decide whether or not you and the person you care for would like to take part in the study, please complete the enclosed consent form and questionnaire pack return them to us in the prepaid envelope provided

Background

We would like to invite you to take part in a questionnaire study being conducted at the Centre for Neurodevelopmental Disorders, University of Birmingham. This research work, which is led by Professor Chris Oliver, looks at a range of behaviours, skills and impairments in individuals with Phelan-McDermid syndrome including: Repetitive behaviour, Hyperactivity, Mood, Challenging behaviour, Social functioning and Health. We will also ask some questions that are related to family well-being and the impact that having a child with a disability has on the family.

We hope that this information will enable us to further understand the behaviours, skills and impairments associated with Phelan-McDermid syndrome including challenging behaviour, social functioning, mood, hyperactivity and health and the impact that these behaviours have on the family. The more people that take part in this research, the more meaningful the results will be. A good response will provide new and valuable information about Phelan-McDermid syndrome. In the future we hope to follow up the progress of the people who take part in this study. However, participation in this stage of the project will **not** mean that you are obliged to participate in further surveys in the future.

Aims of the study

5. To further our understanding of challenging behaviour, repetitive behaviour, hyperactivity, mood and social functioning in individuals with Phelan-McDermid syndrome.
6. To understand what happens with regard to these behaviours as children and adults develop.
7. To understand what, if any, changes may occur with regard to these behaviours when the individuals reach a certain age.
8. To understand the impact of having a child with a disability has on the family.

What will happen if you and your child/the person you care for decide(s) to participate?

Where will the research take place?

The research will involve completing the enclosed questionnaire pack. This can be completed by you in your own time.

Who will be involved in collecting the data?
Members of the research team at the Cerebra Centre for Neurodevelopmental disorders including Professor Chris Oliver and Dr. Joanna Moss.

How long will participation in the study take?
The questionnaire pack will take approximately 45 minutes to complete.

In the future you may be asked if you would like to complete the questionnaire again so that we can start to understand what happens to people with Phelan-McDermid syndrome across their lifetime. We will only contact you with this invitation if you have previously agreed to be contacted by the research team at the University of Birmingham with information about research studies conducted by the team.

Sometimes after you have completed the questionnaire, we may need to contact you again in order to clarify any information that you have provided or to ask you for further information regarding the diagnosis of the person you care for. This helps us to ensure that our data is as useful and as accurate as possible. If this happens then we would contact you again within 6 months of receiving your questionnaire pack to ask whether or not you would be willing to provide us with the extra information.

What will participants be required to do during the study?
We will ask parents and caregivers to complete the enclosed questionnaire pack and return it to us alongside the consent form in the pre-paid envelope provided.

Are there any risks that individuals taking part in the study might face?
There will not be any risks associated with participation in this study.

What are the potential benefits for participants from taking part?
You will receive a personalised feedback regarding your child/ the person you care for. This study will help us to find out more about the lives of people with Phelan-McDermid syndrome and the difficulties that these people face. The results might help us to improve things for people with Phelan-McDermid syndrome in the future.

Where will data be stored?
The data collected will be kept in locked or password protected storage at the University of Birmingham. Only members of the research team at the University of Birmingham will have access to information that we collect about you. Information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.

If you/ the person you care for decide(s) to participate, what will happen after that participation?
You and your child/ person you care for will receive an individual feedback report describing the results of all of the assessments that were carried out during the study. If requested, this feedback report will be circulated to other interested individuals. Descriptions of research findings will be published in newsletters of the relevant family support groups and educational institutions involved. Any request for advice concerning the person you care for will be referred to , Clinical Psychologist.

The researchers will publish the findings from the study in scientific journals and will present the results at relevant conferences.

What will happen to the data afterwards?
The information that you provide will be locked in a filing cabinet at the University of Birmingham or held on a password protected database. Participants will be identified by a unique number so that the information you provide us with cannot be traced to your personal details. You will be able to decide whether or not you want to make your research data available to any professionals or clinicians working with you and the person you care for should they wish to see it. This is optional and will not affect your participation in the current study. If you agree to this, then your research data will only be made available to relevant clinicians or professionals should they contact us directly and request to see it. If you do not agree to this then research data will not be made available to anyone other than the research team at the University of Birmingham.

After 6 months of receiving your questionnaire pack, your personal details will be ***destroyed unless you tell us otherwise.*** This means that we would no longer be able to trace the results of your assessments back to you. ***The section below on 'The Regular Participant Database Information'*** gives information about a database that we use to store the personal details of some participants. Please read this section in order to decide if you would like to join that database.

Regular Participant Database Information:

What is the regular participant database?
We have a database that we keep in the Centre where we store the names and contact details of some previous participants. If you would like then we can add your details to this database. We would use this information for two things:

3) We will contact you with information about future research work to find out whether or not you would like to participate.
4) It is often important to find out how things change over time. By keeping your details we would be able to trace the results of the previous assessments that you have done with us back to you. This means that if you take part in other studies with us we would be able to look at how things have changed over time.

Who would have access to my details?
Only approved members of out research team would have access to your details. We would not share your details with anyone outside the research team.

When would I be contacted?
You would only be contacted by an approved member of the research team when we are starting another study or phase of a study that we think you might like to participate in or when we need to clarify some information that you have provided us with from participation in a research study.

What happens if I decide that I want my details to be added to the database but then I change my mind?
All you would need to do is contact

Your details would be removed from the database immediately.

Consent
After having read all of the information and having received appropriate responses to any questions that you may have about the study you and the person you care for will be asked

to give your and your child's/ person you care for's consent to participate in the study if you decide that you do wish to participate. The section below on ***'Giving consent'*** will explain this process. We need to receive consent from/ on behalf of potential participants in order for them to participate.

Withdrawal

Even after consent has been granted, participants can request to be withdrawn from the study at any time, without giving a reason. Even after participation has taken place, consent can be withdrawn and any data collected will be destroyed. This will not restrict the access of you/ the person you care for to other services and will not affect their right to treatment.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact

Confidentiality

The confidentiality of participants will be ensured. If published, information on the participant will be presented without reference to their name or any other identifying information. All personal details will be kept separately from the information collected so that it will only be possible to connect results to individuals via a special code. This will ensure that results are kept anonymous. In the unlikely event of any evidence of abuse being identified, this information will be disclosed by the research workers.

Review

The study has been approved by Coventry NHS Research Ethics Committee. Ref: 10/H1210/01. 8

Further information

If you would like any more information about the study please contact

Giving consent

Now it is up to you whether you decide that you and your child/the person you care for would like to participate. The decision about whether or not to take part in the study must be 'informed'. This means that anyone making the decision must understand exactly what is involved in the study, what will be required from participants and why.

IMPORTANT:

You need to decide whether your child/the person you care for is able to understand enough about the study to make an 'informed' decision independently about whether or not they would like to participate and to communicate this decision to you. If you are unsure whether or not your child/person you care for is able to understand enough to make a decision independently then we can provide you with some guidelines to help you to assess this A symbol information sheet can also be made available to you if this would be of help.

Please contact to request a copy of this.

Please choose from one of the following options:

3. My child/ the person I care for is <u>able to understand</u> what is involved in the study and what will be required from them if they participate and has communicated their decision to me:

If you think that the person ***is* able** to understand enough about the study in order to make an 'informed' decision and they decide that they would like to participate then please ensure that they complete **Section 1 of Consent Form A coloured YELLOW** enclosed, or that you complete it with them, on their behalf. A parent/carer will need to complete **Section 2 of Consent From A coloured YELLOW** in order to indicate that they also agree to participate in the study. A symbol information sheet can be made available in order to support your child/person you care for in making this decision if it would be of help. Please contact the research team if you would like a copy of the symbol consent form or if you need us to adapt this information further, in order to suit your child's needs. Please return the consent form along with the questionnaire pack to us in the prepaid envelope provided.

4. My child/ the person I care for is <u>over the age of 16</u> and <u>cannot understand</u> what is involved in the study or cannot communicate their decision to me:

If you are reading this information on behalf of someone you care for who is **over the age of 16** and you decide that the person ***is not*** able to make an 'informed' decision about whether or not they would like to participate, then we would like to invite you to act as a 'personal consultee' (or 'nominated consultee' where an unpaid carer e.g. parent, legal guardian etc is not able to act as a 'personal consultee') for that person. Please read the enclosed 'Personal and Nominated Consultee Information Sheet' coloured **PINK**. Once you have finished reading the 'Personal and Nominated Consultee Information Sheet' please decide whether or not you feel able to act as a personal or nominated consultee for the person you care for.

If you feel able to act as a personal or nominated consultee for the person you care for please think about whether the person would decide to participate if they were able to make an 'informed' decision themselves about whether or not to participate. If you decide that the person would decide to participate, please complete **Consent Form *C* coloured BLUE** enclosed and return it to us alongside the questionnaire pack in the prepaid envelope provided.

ID_____

BACKGROUND INFORMATION

Please tick or write your response to these questions concerning background details:
Please answer the following about the <u>person you care</u> for:

1. **Today's date:** _____

2. **Gender:** Male ☐ Female ☐

3. **Date of Birth**: ___/___/____ **Age:_____**

4. **Is the person you care for verbal?** (i.e. more than 30 signs/words in their vocabulary)

   Yes/No (delete as appropriate)

5. **Is the person you care for able to walk unaided?**

   Yes/No (delete as appropriate)

6. **Has the person you care for been diagnosed with a syndrome?** Yes/No (delete as appropriate)

If yes, please indicate which syndrome in 5a. and answer questions 6 to 8. If no, please move on to question 9

6.a

Cornelia de Lange syndrome	☐	Cri du Chat syndrome	☐
Prader-Willi syndrome	☐	Rubinstein Taybi syndrome	☐
Fragile X syndrome	☐	Down syndrome	☐
Lowe syndrome	☐	Soto Syndrome	☐
Rubinstein-Taybi syndrome	☐	9q34 deletion	☐
8p23deletion	☐	Tuberous Sclerosis	☐
Other _____	☐		

7. **What is the genetic mechanism causing the syndrome in the person you care for?**

Uni-parental disomy	☐	Sequence repetition	☐
Deletion	☐	Translocation	☐
Unknown	☐		

Other _____

8. **When was the person you care for diagnosed?** _____

9. **Who diagnosed the person you care for?**

Paediatrician	☐	Clinical Geneticist	☐
GP	☐		

Other _____

10. **Has the person you care for had any medical/health difficulties in the last six months? If yes, please give details:**

_____

_____

In the information sheet and consent form we informed you that we may need to contact your child's/person you care for's GP in order to clarify any information regarding your child's health and diagnostic status (see consent form and information sheet for more information). If you have already indicated on the consent form that you are happy for us to do this, please complete the relevant details below:

11. Name of your child's/person you care for's

GP_____

GPAddress_____

_____

GP Telephone number_____

The following questions ask for background information about you and your family. Please tick the appropriate boxes or write in the spaces provided.

1. Are you male or female? Male ☐ Female ☐

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

3. Please tick the highest level of your educational qualifications.

No formal educational qualifications..... ☐
Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC First Diploma… ☐
5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent…….…….. ☐
3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent..... ☐
Polytechnic/University degree, NVQ 4, or equivalent..... ☐
Masters/Doctoral degree, NVQ 5, or equivalent……..... ☐

4. What is your relationship to your child with a genetic syndrome (e.g. mother, father, stepmother, grandmother, adoptive parent)? _____

5. In total how many people currently live in your home? _____ Adults _____ Children

6. Does your child with a genetic syndrome normally live with you? Yes ☐ No ☐

If no, then where do they live?_____

7. What is your current marital status?

Married, and living with spouse..... ☐

Living with partner..... ☐

Divorced/Separated/Widowed/Single and NOT living with a partner..... ☐

If living with partner/spouse, please answer the following questions, if not, please go to question 12.

8. Is your partner male or female? Male ☐ Female ☐

9. What was their age in years on their last birthday? _____ years

10. Please tick the highest level of your partner/spouse's educational qualifications.

No formal educational qualifications..... ☐

Fewer than 5 GCSE or O Level (grades A-C), NVQ 1, or BTEC First Diploma..... ☐

5 or more GCSE or O Level (grades A-C), NVQ 2, or equivalent…… ☐

3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent..... ☐

Polytechnic/University degree, NVQ 4, or equivalent..... ☐

Masters/Doctoral degree, NVQ 5, or equivalent……..... ☐

11. What is your partner/spouse's relationship to your child with a genetic syndrome (e.g., mother, father, stepmother, adoptive parent)?_____

12. 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.

What is your current total annual family income? Please include a rough estimate of total salaries and other income (including benefits) before tax and national insurance/pensions. Please tick one box only:

Less than £15,000…….……..… ☐

£15,001 to £25,000……...……. ☐

£25,001 to £35,000……...……..……. ☐

£35,001 to £45,000……...…… ☐

£45,001 to £55,000……...……..…… ☐

£55,001 to £65,000……..…….….. ☐

£65,001 or more……..……..… ☐

Please check your answers and go on to the next questionnaire.

WESSEX Questionnaire

These items refer to the person you care for. For each question (A, B, C, D etc …), please enter the appropriate code in each box.

(Frequently = more than once a week)

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 up stairs **3** = up stairs and elsewhere ☐

(note: if this person walks *by himself* upstairs and elsewhere, please also code '3' for 'walk with help')

F) Walk by himself **1** = not at all **2** = not up stairs **3** = up stairs and 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 and 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 ☐

Please check your answers and go on to the next questionnaire.

THE MOOD, INTEREST AND PLEASURE QUESTIONNAIRE –

SHORT FORM (MIPQ-S)

Instructions for completing the MIPQ-S

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 2 weeks. For every question you should circle the most appropriate response e.g.

6) 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*

The Mood, Interest and Pleasure Questionnaire - Short Form

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 the time	about half of the time	some of the time	never

*****positive vocalizations: e.g. laughing, giggling, "excited sounds" etc.
*****engaged in activities: i.e. 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 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 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 seem 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: i.e. when someone is actively involved in any activity such as a mealtime, social interaction, 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 that 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 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 meal time, 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 the time	about half of the time	some of the time	never

*****vocalizations: any words, noises or utterances.

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, wigging 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**
8. Attachment to particular people: Continually asking to see, speak or contact a particular 'favourite' person. *E.g. continually asks to see or speak to particular friend, carer, babysitter or schoolteacher.*	**0**	**1**	**2**	**3**	**4**

	Never	Once a month	Once a week	Once a day	More than once a day
9. 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**
10. 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**
11. 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**
12. 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**
13. 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**
14. 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**
15. Preference for routine: Insist on having the same household, school or work schedule everyday. *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 everyday.*	**0**	**1**	**2**	**3**	**4**
16. 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**
17. 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**
18. 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**
19. 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**

THE ACTIVITY QUESTIONNAIRE

Instructions:

- 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**	**Always/ almost all the time**
1. **Does the person wriggle or squirm about when seated or lying down?**	**0**	**1**	**2**	**3**	**4**
2. Does the person fidget or play with their hands and/or feet when seated or lying down?	**0**	**1**	**2**	**3**	**4**
3. **Does the person find it difficult holding still?**	**0**	**1**	**2**	**3**	**4**
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**	**4**
5. **Does the person prefer to be moving around or becomes**	**0**	**1**	**2**	**3**	**4**
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**	**4**
7. **When the person is involved in an activity, are they boisterous and/or rough?**	**0**	**1**	**2**	**3**	**4**
8. **Does the person act as if they are "driven by a motor" (i.e. often very active)?**	**0**	**1**	**2**	**3**	**4**
9. **Does the person seem like they need very little rest to recharge their battery?**	**0**	**1**	**2**	**3**	**4**
10. **Does the person often talk excessively?**	**0**	**1**	**2**	**3**	**4**
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**	**4**
12. **Do you feel that you need to "keep an eye" on the person at all times?**	**0**	**1**	**2**	**3**	**4**
13. **Does the person you care for seem to act/do things without stopping to think first?**	**0**	**1**	**2**	**3**	**4**
14. **Does the person blurt out answers before questions have been completed?**	**0**	**1**	**2**	**3**	**4**
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**	**4**
16. **Does the person want things immediately?**	**0**	**1**	**2**	**3**	**4**
17. **Does the person find it difficult to wait?**	**0**	**1**	**2**	**3**	**4**
18. **Does the person disturb others because they have difficulty waiting for things or waiting their turn?**	**0**	**1**	**2**	**3**	**4**

SOCIAL COMMUNICATION QUESTIONNAIRE © Rutter et al 2003

Please circle 'yes' if <u>any</u> one of the following behaviours is present. Although you may be uncertain about whether some behaviours are present or not, please do answer 'yes' or 'no' to every question on the basis of what you think.

1. Is she/he now able to talk using short phrases or sentences? If no, skip to question 8.	**Yes**	**No**
2. Can you have a to and fro "conversation" with her/him that involves taking turns or building on what you have said?	**Yes**	**No**
3. Has she/he ever used odd phrases or said the same thing over and over in almost exactly the same way (either phrases that she/he has heard other people use or ones that she/he has made up?	**Yes**	**No**
4. Has she/he ever used socially inappropriate questions or statements? For example, has she/he ever regularly asked personal questions or made personal comments at awkward times?	**Yes**	**No**
5. Has she/he ever got her/his pronouns mixed up (e.g., saying you or she/he for I)?	**Yes**	**No**
6. Has she/he ever used words that she/he seemed to have invented or made up her/himself; put things in odd, indirect ways; or used metaphorical ways of saying things (e.g., saying hot rain for steam)?	**Yes**	**No**
7. Has she/he ever said the same thing over and over in exactly the same way or insisted that you say the same thing over and over again?	**Yes**	**No**
8. Has she/he ever had things that she/he seemed to have to do in a very particular way or order or rituals that she/he insisted that you go through?	**Yes**	**No**
9. Has her/his facial expression usually seemed appropriate to the particular situation, as far as you could tell?	**Yes**	**No**
10. Has she/he ever used your hand like a tool or as if it were part of her/his own body (e.g., pointing with your finger, putting your hand on a doorknob to get you to open the door)?	**Yes**	**No**
11. Has she/he ever had any interests that preoccupy her/him and might seem odd to other people (e.g., traffic lights, drainpipes, or timetables)?	**Yes**	**No**
12. Has she/he ever seemed to be more interested in parts of a toy or an object (e.g., spinning the wheels of a car), rather than using the object as it was intended?	**Yes**	**No**
13. Has she/he ever had any special interests that were unusual in their intensity but otherwise appropriate for her/his age and peer group (e.g., trains, dinosaurs)?	**Yes**	**No**
14. Has she/he ever seemed to be unusually interested in the sight, feel, sound, taste, or smell of things or people?	**Yes**	**No**
15. Has she/he ever had any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes?	**Yes**	**No**
16. Has she/he ever had any complicated movements of her/his whole body, such as spinning	**Yes**	**No**

or repeatedly bouncing up and down?		
17. Has she/he ever injured her/himself deliberately, such as by biting her/his arm or banging her/his head?	**Yes**	**No**
18. Has she/he ever had any objects (other than a soft toy or comfort blanket) that she/he had to carry around?	**Yes**	**No**
19. Does she/he have any particular friends or a best friend?	**Yes**	**No**
20. When she/he was 4 to 5, did she/he ever talk with you just to be friendly (rather than to get something)?	**Yes**	**No**
21. When she/he was 4 to 5, did she/he ever spontaneously copy you (or other people) or what you were doing (such as vacuuming, gardening, or mending things)?	**Yes**	**No**
22. When she/he was 4 to 5, did she/he ever spontaneously point at things around her/him just to show you things (not because she/he wanted them)?	**Yes**	**No**
23. When she/he was 4 to 5, did she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wanted	**Yes**	**No**
24. When she/he was 4 to 5, did she/he nod her/his head to mean yes?	**Yes**	**No**
25. When she/he was 4 to 5, did she/he shake her/his head to mean no?	**Yes**	**No**
26. When she/he was 4 to 5, did she/he usually look at you directly in the face when doing things with you or talking with you?	**Yes**	**No**
27. When she/he was 4 to 5, did she/he smile back if someone smiled at her/him?	**Yes**	**No**
28. When she/he was 4 to 5, did she/he ever show you things that interested her/him to engage your attention?	**Yes**	**No**
29. When she/he was 4 to 5, did she/he ever offer to share things other than food with you?	**Yes**	**No**
30. When she/he was 4 to 5, did she/he ever seem to want you to join in her/his enjoyment of something?	**Yes**	**No**
31. When she/he was 4 to 5, did she/he ever try to comfort you if you were sad or hurt?	**Yes**	**No**
32. When she/he was 4 to 5, when she/he wanted something or wanted help, did she/he look at you and use gestures with sounds or words to get your attention?	**Yes**	**No**
33. When she/he was 4 to 5, did she/he show a normal range of facial expressions?	**Yes**	**No**
34. When she/he was 4 to 5, did she/he ever spontaneously join in and try to copy the actions in social games, such as The Mulberry Bush or London Bridge Is Falling Down?	**Yes**	**No**
35. When she/he was 4 to 5, did she/he play any pretend or make-believe games?	**Yes**	**No**
36. When she/he was 4 to 5, did she/he seem interested in other children of approximately the same age whom she/he did not know?	**Yes**	**No**
37. When she/he was 4 to 5, did she/he respond positively when another child approached her/him?	**Yes**	**No**
38. When she/he was 4 to 5, if you came into a room and started talking to her/him without calling her/his name, did she/he usually look up and pay attention to you?	**Yes**	**No**
39. When she/he was 4 to 5, did she/he ever play imaginative games with another child in	**Yes**	**No**

such a way that you could tell that they each understood what the other was pretending?

40.	When she/he was 4 to 5, did she/he play cooperatively in games that required joining in with a group of other children, such as hide-and-seek or ball games?	**Yes**	**No**

Please check your answers and go on to the next questionnaire.

Appendix E – Validation of ASD reference group to the SCQ normative sample.

Table 1. Odds ratios with 99% confidence for each item of the SCQ, comparing the ASD reference group to the ASD normative sample published in the SCQ manual.

Item Number	Item	ASD Normative Sample (SCQ Manual)		ASD Reference Group		Odds Ratio	99% CI for Odds Ratio	
		With Abnormality (N)	Without Abnormality (N)	With Abnormality (N)	Without Abnormality (N)		Lower	Upper
29	Offering to share	122	38	23	7	1.02	0.30	3.44
36	Interest in children	127	33	26	4	1.69	0.39	7.38
40	Group play	129	31	26	4	1.56	0.36	6.85
37	Response to other children's approaches	126	34	26	4	1.75	0.40	7.65
34	Imitative social play	112	48	23	7	1.41	0.42	4.67
31	Offering comfort	116	44	26	4	2.47	0.57	10.61
28	Showing and directing attention	99	61	11	19	0.36	0.12	1.03
30	**Seeking to share enjoyment**	**101**	**59**	**11**	**19**	**0.34**	**0.12**	**0.98**
21	Imitation	113	47	25	5	2.08	0.54	7.95
39	Imaginative play with peers	138	22	30	0	-[a]	-	-
22	Pointing to express interest	108	52	21	9	1.12	0.37	3.43
27	Social smiling	83	77	20	10	1.86	0.63	5.46
26	Eye gaze	104	56	17[b]	12	0.76	0.26	2.21
35	Imaginative play	117	43	24[c]	4	2.21	0.51	9.57
33	Range of facial expressions	87	73	24	6	3.36	0.96	11.68
38	Attention to voice	100	60	20	10	1.20	0.41	3.55
23	Gestures	107	53	18	12	0.74	0.26	2.13
32	Quality of social overtures	65	95	14	16	1.28	0.46	3.59
19	Friends	114	46	23	7	1.33	0.40	4.41
17	Self-injury	64	96	18	12	2.25	0.79	6.42
25	Head shaking to mean *no*	106	54	23	7	1.67	0.51	5.53
2	Conversation	34	70	11	9	2.52	0.70	9.04

Item Number	Item	ASD Normative Sample (SCQ Manual)		ASD Reference Group		Odds Ratio	99% CI for Odds Ratio	
		With Abnormality (N)	Without Abnormality (N)	With Abnormality (N)	Without Abnormality (N)		Lower	Upper
24	Nodding to mean *yes*	110	50	25[b]	4	2.84	0.66	12.20
20	**Social chat**	**28**	**132**	**27**	**3**	**42.43**	**8.07**	**223.00**
9	Inappropriate facial expressions	44	116	12	18	1.76	0.61	5.10
15	Hand and finger mannerisms	122	38	27	3	2.80	0.54	14.48
3[d]	Stereotyped utterances	85	19	18	2	2.01	0.26	15.34
7[d]	Verbal rituals	72	32	15	5	1.33	0.32	5.63
4[d]	Inappropriate questions	59	45	13	7	1.42	0.38	5.26
6[d]	**Neologisms**	**49**	**55**	**16[b]**	**3**	**5.99**	**10.9**	**32.79**
5[d]	Pronoun reversal	55	49	17	3	5.05	0.93	27.45
12	Repetitive use of objects	106	54	23	7	1.67	0.51	5.53
14	**Unusual sensory interests**	**86**	**74**	**25**	**5**	**4.30**	**1.14**	**16.24**
8	Compulsions and ritual	111	49	25	5	2.21	0.58	8.42
11	Unusual preoccupations	108	52	21	9	1.12	0.37	3.43
10	Use of other's body to communicate	98	62	26	4	4.11	0.97	17.49
16	Complex body mannerisms	98	62	20	10	1.27	0.43	3.74
18	**Unusual attachment to objects**	**36**	**124**	**15**	**15**	**3.44**	**1.19**	**9.95**
13	Circumscribed interests	87	73	18	12	1.26	0.44	3.58

a. Due to N=0 participants in the ASD group without the abnormality, it was not possible to calculate odds ratio for this item. Chi square analysis revealed no significant differences between the two groups $\chi^2(1, N = 190) = 3.41, p = .06$
b. One participant in the ASD reference group had missing data for this item.
c. Two participants in the ASD reference group had missing data for this item.
d. This item was only calculated for verbal individuals. In the ASD normative sample (SCQ manual), 104 individuals were verbal. For the ASD reference sample, 20 individuals were verbal.