Biopsychosocial risk factors for the development of conduct problems in children with autism spectrum disorder

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Thesis Declaration Form

I confirm that the work presenting in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

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Date: 14/07/2022

Overview

Part I

The first section of this thesis is comprised of a systemic review and meta-analysis of 19 studies that investigate the rates of co-occurring oppositional defiant disorder (ODD) and conduct disorder (CD) in the population of both children and adolescents with autism spectrum disorder (ASD). The meta-analysis explores the association between methodological factors used by studies, and population characteristics on the reported prevalence rates in current research. The findings of the study suggest that children with ASD are at greater risk of developing ODD and CD than non-autistic individuals. The study also found that studies containing more methodological bias tended to report higher prevalence rates of ODD and CD.

Part II

The second section of the thesis is a quantitative empirical paper which used secondary cohort data to explore the relationship between biopsychosocial risk factors and the development of conduct problem trajectories in children with ASD. Three statistically different developmental trajectories were identified: children with conduct problems desisting, persisting, and escalating in severity. The study identified low maternal education, high parent-child conflict, and single parent households as potential risk-factors for children with ASD developing persistent and escalating conduct problems by early adolescence.

Part III

The third section for the thesis provides a clinical appraisal of the empirical research, which discusses my initial interest in pursuing the research, some of the methodological and conceptual challenges that emerged while making decisions as part of the research process.

Impact Statement

Research into ASD is continually informing and shaping our understanding of this complex neurodevelopmental condition. The findings from this empirical research and meta-analysis have the potential to not only assist future research, but also guide service planning to improve servicing the needs of the ASD community.

There is a shortage of clinical services in the United Kingdom dedicated to the treatment of psychiatric difficulties in children and adolescents with ASD. By documenting the high prevalence rates of ODD and CD in the ASD population, the meta-analysis helps raise awareness of the need for additional services to serve this population. The findings from the meta-analysis also suggest the need for future research to include more minoritized ASD samples. It is hoped these research findings may encourage future research to use more representative samples of the ASD population thereby helping to reduce methodological bias.

Children with ASD frequently exhibit of conduct problems. Whilst many children outgrow their conduct problems, others develop more severe conduct problems over time. Most research has focused on the development of conduct problems in ASD children solely during childhood. The empirical paper explored the development of conduct problem into early adolescence. The findings identified several risk factors that make individuals vulnerable to developing more persistent or severe conduct problems over time. These findings might be informative to clinicians as awareness of these risk-factors may assist them in identifying children in need of early interventions and could help with service planning.

Contents

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Part I: Meta-Analysis

Systemic review of co-occurring disruptive behavioural disorders in children and adolescents with autism spectrum disorders

Abstract

Background: The aim of this systemic review and meta-analysis was to estimate the rates at which oppositional defiant disorder (ODD) and conduct disorder (CD) occur in children and adolescents with a diagnosis of autism spectrum disorder (ASD). Furthermore, the study aimed to explore moderating factors which might influence prevalence rates of these co-occurring conditions between studies.

Methods: A systematic search was conducted on August 10, 2020 using the PsycInfo and Medline databases to identify relevant literature using key words and MeSH terms. Only studies of children and adolescents aged between 3-25 were included in the meta-analysis. A modified Hoy's risk of bias tool was used to assess the bias of the included studies. Following the identification and selection of relevant articles, a meta-analysis was conducted using R-studio software. Moderator analysis was performed to explore whether participant characteristics and methodological design of studies were associated with differences in reported ODD and CD prevalence rates. Potential moderators included age, gender, intellectual ability, ethnicity, nationality, sample type, detection bias, and sampling bias.

Results: Nineteen eligible studies were identified including a total sample of 6,085 individuals with a diagnosis of ASD. The diagnostic rates of comorbid ODD and CD within the pooled sample were 14.03% [95% CI 9.0-21.22] and 3.13% [95% CI 1.4-5.4] respectively. There was significant heterogeneity in the rates of diagnosis between studies. Greater study bias was associated with increased rates of co-occurring diagnoses. Recruitment bias moderated the prevalence of CD but not ODD diagnoses. Detection bias moderated the number of ODD but not CD diagnoses. Study demographics, sample type, and intelligence were not associated with the prevalence rate of comorbidity found in the pooled sample.

Discussion: Study bias played a significant role over the rates of co-occurring CD and ODD reported in the ASD population, yet the findings should be interpreted with some caution. The meta-analysis was based on a predominantly Caucasian male sample and studies which used DSM-IV criteria to assign diagnoses. This lack of participant heterogeneity limits the generalizability of the study and underscores the importance of studying both population characteristic and methodology in meta-analyses. Future research should explore the impact that the updated DSM-5 have over co-occurring ODD and CD and focus on including more minoritized populations.

Introduction

Current estimates indicate that approximately 70%-85% of individuals with a diagnosis of autism spectrum disorder (ASD) meet the diagnostic criteria for at least one other psychiatric disorder (Leyfer et al., 2006; Simonoff et al., 2008). Epidemiological research indicates that among the ASD population oppositional defiant disorder (ODD) is the third most common co-occurring psychiatric diagnosis with conduct disorder (CD) occurring less frequently (Lai et al., 2019; Simonoff et al., 2008). Children with ODD or CD, heretofore referred to collectively as disruptive behavioural disorders (DBD), often struggle with anxiety, self-harm, suicidality, and the proclivity for committing criminal acts (Ashworth, 2016; Gjevik et al., 2010; Heeramun et al., 2017; Hofvander et al., 2019; McDonnell et al. 2019). The treatment of these psychiatric disorders is complicated by underlying ASD impairments, and clinicians are often required to modify treatment protocols to provide effective interventions (Zaboski & Storch, 2018; Mannion, Brahm, & Leader, 2014). While publicly funded treatment is available for these children (Xu et al., 2019), there is a shortage of specialist services for treating psychiatric difficulties in the ASD community (Malik-Soni et al., 2021). Given their limited resources services often use epidemiological research to improve service planning (Pearce 1996; Savitz, Poole, & Miller, 1999).

Studies have estimated ODD and CD to occur in 1%-40% and 1%-23% of the ASD population (Amer et al., 2012; Bryson et al. 2008; Lamanna et al.,2017; Mayes et al., 2012). These rates are considerably higher than the rates of ODD and CD diagnosis found in the non-autistic population, which occur in 1%-11% and .5%-9% respectively (Canino, Polanczyk, Bauermeister, Rohde, & Frick, 2010). The wide variance in diagnostic prevalence rates of ODD and CD, in studies of children with ASD, suggests variations to diagnostic criteria, study methodology, and population characteristics may significantly influence DBD rates. Study methodology and population characteristics have long been implicated in influencing diagnostic prevalence rates (Heltzer et al., 1977; Whiting et al., 2011). The accuracy of diagnoses is further complicated by diagnostic nosology and the large degree of overlap between different disorders. For example, a high

proportion of children with ASD diagnoses have learning disabilities, which increases the likelihood of challenging behaviours (Rojahn, Wilkins, Matson, & Boisjoli, 2010; Russell et al., 2019). While challenging behaviours increase the risk of receiving DBD diagnoses (Moss et al., 2000; Rojahn, Matson, Naglieri, & Mayville, 2004), determining what constitutes a DBD diagnosis in children with learning disabilities involves a complex differential diagnosis of understanding the aetiology, function, and symptoms severity of each challenging behaviour (Ageranoiti-Belanger et al., 2012; Bertelli, Rossi, Scuticchio, & Bianco, 2015; Matson & Nebel-Schwalm, 2007). While systemic reviews and meta-analyses have investigated the prevalence of DBD diagnoses within the ASD population (Lai et al., 2019; Lecavalier et al., 2019), none have explored the role that study methodology has in potentially biasing their estimates. Recent nosology changes to the Diagnostic and Statistical Manual of Mental Disorders (DSM) have seen a shift in the prevalence rates of ASD and concomitant disorders (Hollingdale et al., 2020; Mahjouri, & Lord, 2012; Matson, Hatteir, & Williams 2012). The present study aims to estimate the prevalence rate of ODD and CD in children and adolescence with ASD diagnoses, while controlling for varying population characteristics and methodological bias. Providing a more accurate estimate of DBD rates within the ASD population will help services to better allocate their resources, thereby helping to rectify the shortage of specialist's services dedicated the treatment of psychiatric difficulties in the ASD community (Malik-Soni et al., 2021).

Changes in Psychiatric Nosology

Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition affecting millions of individuals worldwide (Chiarotti & Venerosi, 2020). The past several years has seen the estimated prevalence rates of the disorder increase precipitously, from 1 in 110 individuals receiving a diagnosis in 2006 to 1 in 54 individuals in 2016 (CDC, 2007, 2020). Current epidemiological studies estimate that approximately 1% of the population have a diagnosis of ASD (Lyall et al., 2017). The changes in diagnostic rates of ASD is largely attributed to the

broadening of the diagnostic criteria, increased awareness of ASD's diverse presentations, and the proliferation of diagnostic services (Rapin, Roberto, & Tuchman, 2008).

In the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), ASD was categorized by a range of different subtypes including: autism, Asperger's, pervasive developmental disorder not otherwise specified (PDD-NOS), child disintegrative disorder, and Rhett's disorder (APA 1994). There were many nosology problems behind the DSM-IV's categorical definitions of autism (for review see Lord & Bishop 2015). Clinicians were not able to distinguish reliably between autism subtypes (Bennett et al. 2008, Kamp-Becker et al. 2010) and diagnoses were highly influenced by clinician bias (Lord et al. 2011; Sharma, Woolfson, & Hunter, 2011). The different diagnostic subtypes in the DSM-IV proved unreliable, and children could receive one diagnosis of ASD only to be re-diagnosed with a different subtype later in life (Lord et al., 2006).

The shortcomings of the DSM-IV paved the way for a reconceptualization of ASD under the new DSM-5, which consolidated the subtypes of autism, Asperger's, and PDD-NOS, into the single diagnostic category of ASD. Historically, to receive a diagnosis of one of the ASD subtypes individuals needed to display impairments of social interaction, verbal or non-verbal communication and, with the exception of PDD-NOS, repetitive and stereotyped behaviours (APA 1994). The DSM-5 removed verbal communication impairments from its list of ASD criteria, requiring individuals to present solely with socio-communicative impairments and restrictive-repetitive behaviours to receive a diagnosis (APA, 2013).

Disruptive, Impulse Control, and Conduct disorders

The DSM 5 categorizes ODD and CD among the disruptive, impulse control, and conduct disorders. These disorders are characterized by impairments of self-control over emotions and behaviours (APA, 2013). ODD is defined by its recurrent patterns of angry-irritable, argumentative, defiant, and vindictive behaviour. While CD is defined by its patterns of

aggression, destruction of property, deceitfulness, theft, and serious violations of rules (APA, 2013). Since defiant behaviours occur as part of normative development ODD was initially thought to be a benign disorder, and precursor to the more severe behaviours characteristic of CD (Loeber, Burke, & Pardini, 2009; Rowe, Maughan, Costello, & Angold, 2005). The similarity in the symptoms of ODD and CD lead some researchers to question the need for ODD as a distinct diagnostic category under the DSM-IV (Rey et al., 1988). Despite some overlap in presentation, ODD and CD differ consistently in their aetiologies (Cavanagh, Quinn, Duncan, Graham, & Balbuena, 2017). Children and adolescents with a diagnosis of ODD have increased risk of suffering from anxiety, depression, and mood disorders as they enter adulthood (Burke, 2012; Rowe, Costello, Angold, Copeland, & Maughan, 2010). Whereas children with CD have a greater likelihood of developing antisocial personality disorder and perpetrating criminal acts in adulthood (Frick et al., 2005; Loeber, Burke, & Lahey, 2002). The differences in aetiology and developmental trajectory support the diagnostic distinction between ODD and CD in the DSM-5 (Cavanagh et al., 2017; Maughan, Rowe, Messer, Goodman, & Meltzer, 2004). According to a meta-analysis of worldwide psychiatric diagnoses, ODD and CD, occur in 3.6% (95% CI 2.8–4.7) and 2.1% (95% CI 1.6–2.9) of typically developing children between 5-18 years old, respectively (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015).

Impact of DSM nosology

There are many symptoms that are shared between ASD and DBD diagnoses. Children with ASD often struggle with a lack of self-control and emotional dysregulation (Lecavalier, 2006; Maskey, Warnell, Parr, Le Couteur, & McConachie, 2013). Many children with ASD exhibit aggression (Kanne & Mazurek, 2011; Farmer & Aman, 2011), chronic irritability (Green, Gilchrist, & Cox, 2000; Mayes, Calhoun, Murray, Ahuja, & Smith, 2011), and behavioural problems (Matson, Wilkins, & Macken, 2008; Jang; Dixon, Tarbox, & Granpeesheh, 2011). Since no reliable biomarkers exist for diagnosing CD, ODD, or ASD (Loth et al., 2016; Sing & Rose 2009), the

diagnosis of these disorders relies on identifying each by their behavioural phenotypes and symptom clusters established by diagnostic manuals (Borsboom, 2017).

Historically the similarities between disorders made diagnosing children with ASD with DBD challenging. Until recently co-occurring psychiatric difficulties in children with ASD were often simply attributed to the core impairments of ASD (Romero et al., 2013), and while children with ASD could theoretically receive ODD or CD diagnoses under the DSM-IV, ASD symptoms often overshadowed the presence of additional psychiatric disorders (Matson & Williams, 2013; Rosen, Mazefsky, Vasa, & Lerner 2018; Salazar et al., 2015). The DSM-IV children also restricted individuals from receiving joint ODD/CD diagnoses due to what was considered a diagnostic overlap in symptoms (APA 1994; Rey et al., 1988).

The DSM-5 made changes to ASD nosology which reflected the growing awareness of the large degree of diagnostic overlap between ASD and other psychiatric diagnoses (Romero et al., 2016; Grzadzinski, Huerta, & Lord, 2013). Under the DSM-5 additional specifications were attached to ASD diagnoses to indicate the presence of co-occurring intellectual impairments, behavioural disorders, and catatonia (APA 2013). This change to the DSM-5 has led to an increase in the prevalence of psychiatric difficulties including behavioural problems found alongside ASD (Beighley et al., 2013; Romero et al., 2016). The DSM-5 was also amended so that children could receive dual diagnoses of ODD and CD, in recognition of their diagnostically distinct aetiologies (APA 2014; Rowe et al., 2010). These diagnostic changes suggest that rates of co-occurring DBD among the ASD population will increase under the criteria of the DSM-5 compared to the previous DSM-IV.

Impact of Methodological Factors

Detection Bias and Diagnostic Accuracy

Detection bias refers to the ability to accurately detect cases of interest within a sample. The detection bias of psychiatric diagnoses is largely determined by a study's diagnostic accuracy and

consistency. Clinicians typically rely on a battery of tools including parental interviews, teacher reports, and questionnaires to aid them in diagnosing children with ASD and DBD. Alongside their judgement, clinicians use the information extracted from these tools to reach diagnostic conclusions. When the diagnostic measures used have poorer accuracy it increases the chances of false positives and false negative diagnoses, thereby effecting the prevalence rates found in studies (Oliveira, Gomes, & Toscano, 2011; Šimundić 2009; Whiting et al., 2011).

Researchers often do not have the same expertise as seasoned clinicians when it comes to assigning diagnoses. Therefore, the use of sensitive diagnostic measures is of paramount importance to assure the diagnostic validity of studies. The sensitivity of diagnostic tests measures the accuracy and ability to detect true positive diagnoses. Despite their importance, researchers may not have the appropriate time or budgetary resources to use the most accurate diagnostic tools in studies, forcing them to make difficult decisions that impacting study validity (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2006; Simonoff et al., 2008). Diagnostic tools can be expensive, and researchers may opt to use less expensive and thorough diagnostic tools rather than limit the number of participants recruited. Researchers also may also decide to use a mixture of diagnostic methods of varying validity further increasing a study's risk of detection bias (Altzy, Bozatli, Sipka, & Gorker, 2019; Amr et al., 2012). It is important to first determine the diagnostic accuracy and consistency of studies before relying on the reported prevalence rates (Oliveira, Gomes, & Toscano, 2011). Studies using measures with poorer sensitivity tend to report inflated DBD prevalence rates, due to lower cut-off scores or less significant behavioural problems needed for individuals to receive a DBD diagnoses(Gomez, Vance, Watson, & Stavropoulos, 2021) and we expect to find similarly inflated DBD diagnostic rates in studies of ASD individuals using poor diagnostic measures for CD or ODD.

Selection Bias

Selection bias measures the degree to which participants who have been selected for each study accurately represent the population of interest. Different types of selection bias can produce increased or decreased diagnostic prevalence rates which inaccurately reflect the prevalence rates found in the actual population. There are multiple sources of selection bias including, failed random selection, source of recruitment, and participant dropout. Individuals' self-selection to participate in studies can lead to particular groups of people being over or underrepresented in samples (Nilsen et al., 2013). The random selection of participants is particularly important to mitigate against this self-selection bias (Hernan, Hernandez-Diaz, & Robins, 2004). Similarly, the sources researchers choose to recruit participants can heavily influence the degree to which rates of diagnosis, and a study's findings, are representative of a population at large. Clinical samples are recruited through mental health, medical, and diagnostic services. Community samples are recruited from mainstream schools, community centres, online platforms, and as part of epidemiological research. Unsurprisingly, participants recruited from clinical settings tend to have more psychiatric problems than participants being recruited from community settings (Compton, Nelson, & March, 2000; Patten, 1997; Parker et al., 2013; Polier et al., 2012). Even after the initial recruitment for studies, high participant dropout can impact diagnostic prevalence rates. Dropping out from studies often occurs in higher rates when children possess behavioural disorders, which would logically reduce the prevalence rates of children with behavioural disorders (Wolk et al., 2019).

Limited information is available on the impact selection bias has over rates of DBD diagnoses in the ASD population. Searches of the existing literature indicate that no studies have investigated the role of random selection over ASD comorbidity. Two studies reported differences in DBD diagnostic rates between clinical and community samples of ASD children (Mattlia et al. 2010; Stratis & Lecavalier, 2013). However, these studies did not evaluate the moderating effect of recruitment bias, due to some participants falling in both clinical and community categories

(Mattlia et al. 2010), and samples being to too small for comparison (Stratis & Lecavalier, 2013). Still studies of non-autistic samples have found higher rates of psychiatric diagnoses in clinical samples. We expect similar findings from ASD samples regarding rates of DBD. Research has not yet explored the impact of dropout rates on ASD co-occurring diagnoses. Common knowledge would suggest that if children with behavioural disorders are more likely to drop out from studies, increased dropout rates would correlate with lower rates of DBD in studies of ASD comorbidity. Given the divergent impact of different sources of selection bias, with some sources of selection bias associated with higher diagnostic rates and others associated with lower ones, it is unclear how overall selection bias will influence the prevalence of DBD.

Population Characteristics

Demographic Differences

Demographics are associated with differences in the prevalence of psychiatric disorders. In the non-autistic population, boys are more likely to receive a diagnosis of ODD and CD than are girls. The disparity between genders is more pronounced for diagnosis of CD, where boys are nearly three times (OR =2.7, 95% CI 1.9-3.8) more likely to receive a diagnosis than girls (Maughan, et al., 2004). This gender disparity is slightly lower for ODD diagnoses (OR = 1.59, 95% CI 1.36-1.86) (Demmer et al., 2017). Males are also approximately three times as likely (OR = 3.32; 95% CI 2.88–3.84) to receive a diagnosis of ASD than females (Loomes, Hull, & Mandy, 2017). These findings suggest that the co-occurrence of these disorders would be heavily skewed towards male diagnoses. Several studies which investigate gender as a moderator of ASD comorbidity support this notion. Studies show males with ASD to exhibit higher rates of problem behaviours and DBD co-occurrence than females (Araz-Atlay et al., 2019; Mayes et al., 2012; Mattila et al., 2013; Salazar et al., 2015). Despite these findings, several studies found no difference between males and females with ASD, and rates of comorbid ODD (Simonoff et al., 2008; Skewer et al., 2019) or CD (Amr et al., 2012).

Age is another important factor to consider when investigating rates of comorbid diagnosis. A child's age tends to be correlated with receiving certain diagnoses. For example, ASD is typically diagnosed upon entry into primary school, with ASD individuals with typical range intelligence receiving their diagnoses later (Hosozawa et al., 2020). Research behind the moderating effect age has on rates of comorbid ASD diagnoses present inconsistent findings. Some evidence points to age being a factor behind the types of diagnoses children receive alongside autism (Simonoff et al. 2008). Children with ASD who receive co-occurring diagnoses of DBD most often get diagnosed in middle school, as opposed pre-school or secondary school (Mattilia et al., 2010; Vasa et al., 2013). Araz-Altay and his colleagues (2019) found children with ASD to have higher rates of ODD in middle school, with CD occurring more frequently in adolescence. Some studies suggest that DBD diagnoses are more likely to decrease overtime (Flouri et al., 2015; Midouhas et al., 2013). Other studies found tenuous or no connection between age and comorbid diagnoses of DBD. One study found that age explained only .03% of the variance in the rates of problem behaviours (Mayes et al., 2012). While another study found no correlation between age and comorbid diagnosis (Skewer et al., 2019). Given the inconsistent findings, surrounding both age and gender, the analysis surrounding the impact these variables had on comorbid rates of ASD and DBD was purely exploratory.

Intellectual Disability

Intellectual disability (ID) is a commonly identified risk factor for diagnosis of DBD within the non-autistic population, with up to 39% of learning-disabled children receiving a DBD diagnosis (Baker, Neece, Fenning, Crnic, & Blacker, 2010). Between 50%-55% of the ASD population have an ID (Charman et al., 2010; Loomes, Hull, & Mandy, 2017). These findings suggest that children with an ASD diagnosis, and specifically those with lower intellectual functioning, have a greater likelihood of receiving DBD diagnoses (Lamanna et al., 2017). Despite the high rates of ID in the ASD population, there is a paucity of research examining the association between intellectual functioning and comorbidity in those with ASD (Russell et al., 2019). Most available research on

intellectual functioning in children with ASD, found no moderating effect between ID and diagnosis of DBD, (Baker & Blacher, 2015; de Bruin et al., 2007; Hayashida et al., 2010; Mayes et al., 2012; Salazar et al., 2015, Simonoff et al., 2008; Skewer et al., 2019). However, other studies found children with ASD and lower intellectual functioning to have an increased risk of developing ODD (Mayes et al., 2012) and CD (Amr et al., 2011). Another study found ASD children with borderline intellectual functioning to have the highest rates of DBD (Barnevik-Olsson et al., 2016). Given these conflicting findings ID was explored as a potential risk factor for co-occurring diagnoses (Mannion & Leader 2013).

Nationality and Ethnic Differences

Children living in economically developing countries and coming from ethnic minority backgrounds often experience environmental stressors, predisposing them to ODD and CD (Burk, Loeber, & Birmaher, 2002). When studies controlled for the moderating effect of environmental stressors, ethnicity and nationality were not associated with rates of CD or ODD diagnoses in the non-autistic population (Canino et al., 2010; Polanczyk et al., 2015). To our knowledge only one study investigated the association that ethnicity or nationality has over rates of ASD and DBD comorbidity. This study found no difference between Caucasians and other minoritized ethnicities vis-a-vis rates of co-occurring ASD and ODD (Mayes et al., 2012). Given this limited information, the investigation into the impact that ethnicity has over rates of CD or ODD in our analysis was also exploratory.

Study Aim

The aim of this study was to estimate through meta-analysis the rates at which ODD and CD diagnoses occur within the ASD population of children and adolescents. A secondary aim was to determine whether the version of DSM used, population characteristics, or methodology used in studies moderate the prevalence rate of DBD co-occurrence. Accounting for the studies' research methodology will help underscore the moderating role bias plays over the report prevalence rates

of DBD diagnoses. Investigating the moderating role of population characteristics will help determine whether specific groups have a greater prevalence of DBD diagnoses.

Method

Search Strategy

The following study was reported in line with the updated PRISMA guidelines (Page et al., 2021). A systematic search was conducted on August 10, 2020, using the PsycINFO and Web of Science databases. The search included both published and unpublished studies in order to reduce the risk of publication bias. The search terms in PsycINFO included key words and MeSH terms for ASD: "autism spectrum disorder" and "autis*". Since there were no MeSH terms for ASD on Web of Science the subtypes "PDD-NOS", "autis*", and "asperg*" were used to capture the different ASD presentations. The terms "Oppositional defiant disorder", and "Conduct disorder" were used on both platforms to search for articles reporting CD or ODD diagnoses. These terms were combined to yield the search results for the meta-analysis (Appendix A).

Article Screening

The articles that were identified in the systemic search were screened against the predetermined criteria listed below. Only the articles that met all criteria were selected for inclusion into the meta-analysis. First titles and abstracts of the identified articles were screened. If it was clear from an articles title or abstract that it was not suitable for the study, it was omitted from further analysis. The remaining articles were read in full and screened against the inclusion and exclusion criteria to determine their suitability. Reference lists of included studies were also read to identify further studies, which were screened for inclusion.

Inclusion Criteria

1. Studies needed to have either reported rates of ODD or CD.
2. Studies had to include a sample size of at least 20 individuals with an ASD diagnosis. Smaller sample sizes can bias meta-analytic findings including estimated prevalence rates.

Ensuring sample sizes of at least 20 helped to ensure the statistical validity of the study's findings (Lin, 2018).

3. All diagnoses were based on either DSM-5, DSM-IV-TR, DSM-IV, ICD 10, or ICD 11 criteria.
4. Only study samples of children and adolescents were included. Samples with adults older than twenty-five were excluded because of the limited research and understanding surrounding ASD and DBD diagnoses in adults (Harpold et al., 2007; Howlin et al., 2015). While there is no absolute consensus regarding the end of adolescence research typically uses twenty-five as a standard cut off point (Sawyer, Azzopardi, Wickremarathne, & Patton, 2018). Studies recruiting children younger than 3 were excluded as children this young cannot receive reliable ASD or DBD diagnoses (Moore & Goodson, 2003; Volkmar, 2002).
5. All studies had to have been written in English.

Exclusion Criteria

1. Studies which included data available in other selected studies (For studies using the same underlying data the study with the largest sample size were selected).
2. Studies reporting rates of DBD in specific subgroups of autistic young people as defined by another characteristic such as a co-occurring condition. For example, a study reporting rates of DBD among individuals with co-occurring ASD and epilepsy (McLellan et al., 2005).
3. Studies focused on reporting the rates of DBD in individuals with subclinical behavioural problems. Studies recruiting participants from a subpopulation rather than the general population violate a specific type of selection bias known in research as Berkson's bias (Westreich, 2012). For example, studies which explored the rates of DBD among ASD samples experiencing bullying was excluded (Zablonsky, Bradshaw, Anderson, & Law,

2013) as were studies looking at DBD rates among ASD samples with pre-existing behavioural problems (Baker and Blacher, 2015; Heeramun et al., 2017).

The identification and screening of the articles selected for the meta-analysis was undertaken by a single researcher. The selected articles were then reviewed and approved by the supervising researcher on the project (WM).

Study risk of bias

The establishment of a strict set of criteria for inclusion into the meta-analysis was crucial for determining the generalizability and significance, of the study's current findings. Despite the strict selection process, studies used in meta-analyses still often exhibit varying degrees of detection and selection bias (Eggers, Smith, & Stern, 2001). Including studies without a comprehensive understanding of their bias increases the likelihood of misinterpreting results. The studies underwent a comprehensive quality appraisal to ensure the quality of the studies that were to be included in the meta-analysis, and to determine the impact methodological bias had over the meta-analytic results.

Hoy's risk of bias tool assesses the bias found in studies investigating diagnostic prevalence rates (2012) and has been used in the meta-analyses of psychiatric problems (Lai, Cleary, Sitharthan, & Hunt, 2015; Thomas et al., 2015). Hoy's risk of bias tool is comprised of two separate sections, which quantify selection bias and detection bias. The tool consists of 10 questions that receive values of 0 or 1, with higher scores indicating a greater risk of bias. The tool was not developed to measure bias of co-occurring diagnoses, and alterations were made to more accurately capture the bias found in our samples.

Modified Hoy's Risk of Bias Tool

The first section of Hoys risk of bias tool measures selection bias in studies and is composed of four questions. The only alteration made to this section of the tool was an additional question accounting for the recruitment bias of each study. This question scores studies between 0 and 2

depending on whether participants came from community, mixed, or clinical settings. The second section of Hoy's risk of bias tool is made up of six questions which address studies' detection bias. Four of these questions were deemed superfluous or irrelevant for the current metanalysis. Some of these questions pertained to the numerator and denominators found in sensitivity analyses, as well as questions pertaining to the data collection period, and whether acceptable case definitions were used. Therefore, only two questions were used to capture the detection bias of studies' psychiatric diagnoses. The first of these questions focused on diagnostic constancy within each study, and the second focused on diagnostic accuracy of the test's studies used. To capture the impact of measuring for co-occurring diagnosis studies received scores between zero and three depending on the diagnostic accuracy of both diagnoses. The overall scores on the modified risk of bias tool ranged from 0-10. Studies were subdivided evenly by their scores and classified as having low (0-3), moderate (4-6), or high (7-10) risk of bias (Lai et al., 2019). Studies with a high bias were excluded from the meta-analysis to ensure the reliability of the study findings (see Appendix B). Study bias of the identified studies was conducted by a single researcher.

Meta-Analysis

Statistical analyses were performed with R version 4.02 using the "Meta" and "Metafor" packages (Schwarzer 2007; Viechtbauer & Viechtbauer, 2015). Before running meta-analysis, Funnel-plots were computed to investigate the presence of publication bias, and a linear regression of effect sizes was run to check for outliers. Afterwards a random effects model was used for calculating the effect sizes and confidence intervals of the pooled samples (Schroll, Moustgaard, & Gøtzsche, 2011). The Restricted Maximum Likelihood (REML) estimator was chosen against its alternatives for its improved statistical reporting for larger sample sizes (Viechtbauer, 2005) and its ability to account for high between study variability (Langan, Higgins, & Simmonds, 2017). The proportions of ODD and CD comorbid diagnoses were extracted from each ASD sample. These proportions were then logarithmically transformed to account for their skewed distributions. The

logit transformation was applied for ODD diagnoses, while the double arcsine transformation was used to transform the proportion of CD diagnoses. The double arcsine transformation was selected to account for diagnostic rates of CD in all studies being uniformly below 20% (Barendregt, et al., 2013). The between-study heterogeneity was then computed using the I^2 statistic while the Q statistic was used to determine statistical significance. Afterwards the pooled proportions were transformed back from their logarithmic transformations for ease of understanding is standard for meta-analysis of proportion (Wang, 2017).

Moderator Analysis

Subgroup analyses were performed to determine what degree of heterogeneity in the rates of DBD could be accounted for by participant characteristics or methodological features. Categorical variables were analysed using a mixed effects model to account for assumed differences in variances across subgroups (Cuijpers et al., 2016). A random effects model was used to determine the variance and $\tau 2$ within each subgroup. The variances were then imputed into a fixed effects model to determine whether there was a significant difference between subgroups and rates of DBD diagnoses. The following categorical variables were included in the moderator analysis: risk of bias and sample type. Continuous variables, which included the proportions of dichotomous variables found in studies, were analysed using meta-regression. The continuous variables included in the moderator analysis were diagnostic accuracy, selection bias, ethnicity, intelligence, age, and gender. To ensure content validity of the data, information on each variable needed to be recorded in at least ten studies to be included in the moderator analysis (Littell, Corcoran, & Pillai 2008).

Results

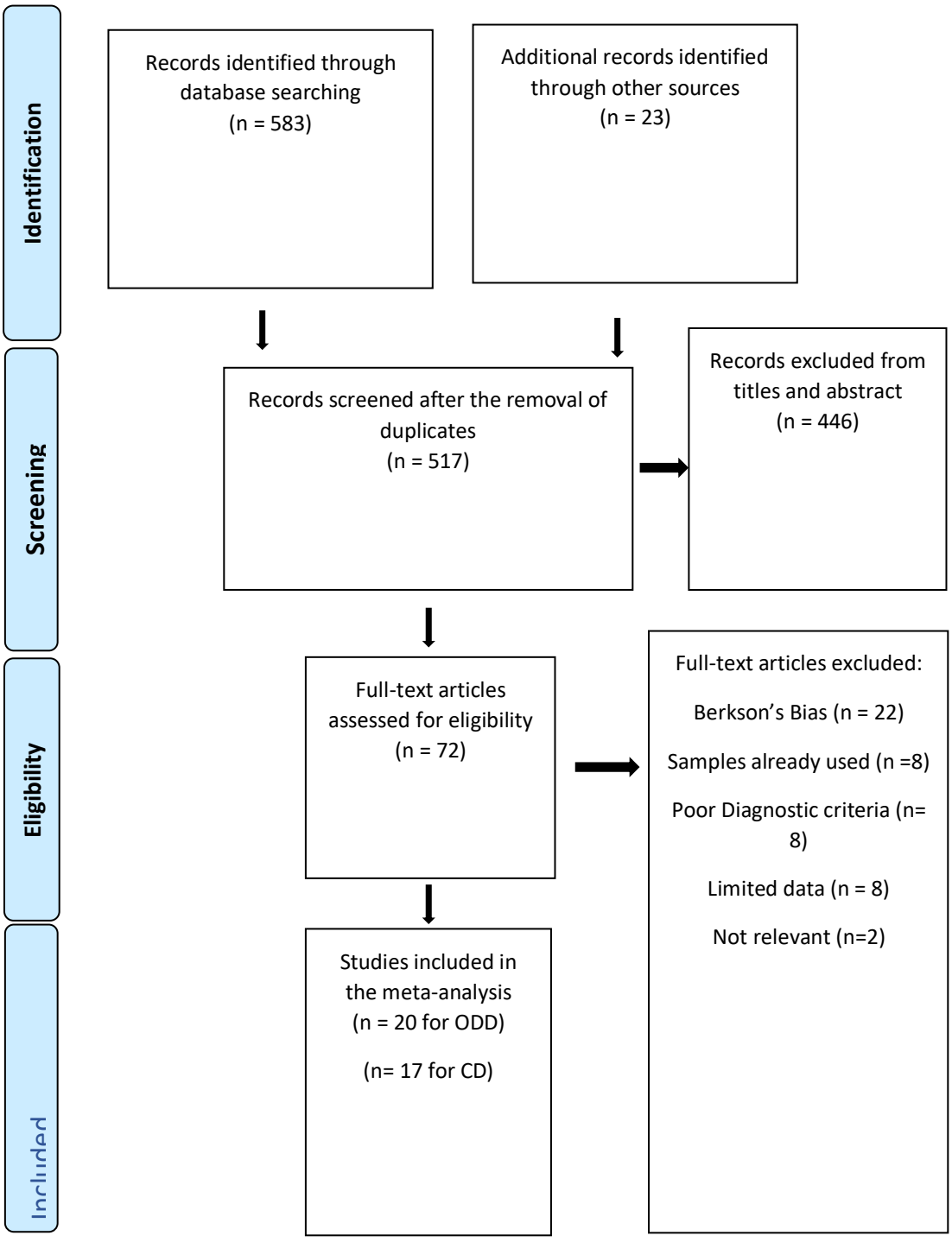
Article Screening

The systemic search on Web of Science and PsycINFO yielded a combined 583 articles (see the PRISMA diagram plot below). An additional 23 articles were also identified from the reference screening of the sourced articles. After the removal of duplicates, and screening of 517 titles and

abstracts, 72 articles remained. These remaining articles were read in full and underwent a more comprehensive screening against the stipulated criteria.

Article screening revealed seven studies which met most criteria but were missing key information concerning diagnostic rates (Araz Altay, Bozatli, Demirci Sipka, & Gorke, 2019; Barnevik-Olsson et al., 2016; Emerson & Hatton, 2007; Gyllenberg et al., 2014; Logan et al., 2015; Rosenberg, Kaufmann, Law, & Law, 2011; Stratis & Lecavalier, 2013;). To reduce the risk of publication bias, the first authors of these studies were emailed for the missing information. Four of the authors were unreachable or declined response (Emerson & Hatton, 2007; Gyllenberg et al., 2014; Logan et al, 2015; Rosenberg, Kaufmann, Law, & Law, 2011). The remaining authors provided the requested information (Araz Altay, Bozatli, Demirci Sipka, & Gorke, 2019; Barnevik Olsson et al., 2016; Stratis & Lecavalier, 2013). Therefore, a total of 22 articles were available for inclusion into the meta-analysis, 20 of which included data on ODD prevalence and 17 for CD prevalence.

Figure 1: PRISMA Diagram



Quality Appraisal

Hoy's quality appraisal identified two articles as possessing a high risk of bias (Barnevik-Olsson et al., 2016; Green, Gilchrist, Burton & Cox, 2000). The high degree of bias in the articles is perhaps best underscored in the use of diagnostic measures with poor accuracy. Green and colleagues (2000) used the Isle of Wight, a semi structured psychiatric measure, based on DSM-III criteria (Rutter 1976). This psychiatric measure was modified to conform to DSM-IV definitions. However, no information was available on the updated measures diagnostic validity or reliability. Therefore, the diagnoses identified by Green, and colleagues were not considered substantive. Barnevik-Olsson and colleagues (2016) used the Autism - Tics, ADHD and other Comorbidities inventory (A-TAC) to detect cases of DBD. The accuracy of the A-TAC has only been tested on small samples and possesses poor diagnostic sensitivity (Larson et al., 2014; Marland et al., 2017). These articles were excluded to prevent further biasing the meta-analysis.

Outliers

A linear regression of effect sizes was run for both CD and ODD groups to check for the presence of any outliers. Outliers are data points that deviate from the normative data (Aggarwal, 2015). The presence of outliers has the potential to influence the validity of a meta-analytic conclusions (Viechtbauer & Cheung, 2010). Most of the identified studies used the DSM-IV criteria to assign diagnoses. Therefore, outlier analysis was included to account for potential diagnostic bias between ODD and CD diagnoses. Effect sizes with studentized residuals above 2 in both diagnostic groups were considered outliers (Viechtbauer & Cheung, 2010). Only one study had high studentized residual for both ODD and CD diagnostic groups (Amer et al., 2012). This study contained the greatest proportion of CD diagnoses and smallest proportion of ODD diagnoses, suggesting a diagnostic bias towards CD, and was excluded from the meta-analysis. Summarily 19 studies of ODD and 16 studies featuring CD diagnoses were used (see Table 1).

TABLE 1. Details of studies included in the meta-analysis

Author	Date	ASD # of Diagnoses	ODD %	CD %	Diagnostic Manual	Male	Female	Sample type	Nationality	Age Avg	SD	FSIQ Avg	SD	Caucasian Sample %	Drop-out Rate
Bryson et al.	2008	586	13.99%	1.54%	DSM-IV-TR	84%	16%	Clinical	USA	9	N/A	N/A	N/A	85%	N/A
Leyfer et al.	2006	86	6.98%	0.00%	DSM-IV-TR	95%	6%	Community	USA	9.2	2.7	81.51	24.5	N/A	N/A
Kaat, Gadow, & Lecavelier	2013	77	33.77%	9.09%	DSM-IV	86%	14%	Clinical	USA	8.5	1.8	85	23	91%	
Mattila et al	2010	50	16.00%	2.00%	DSM-IV-TR	76%	24%	Mixed	Finland	12.7	1.5	N/A	N/A	N/A	26%
Gjevik et al.	2011	71	4.23%	2.82%	DSM-IV	82%	18%	Community	Norway	11.8	3.3	65.2	29.6	N/A	24%
Salazar et al.	2015	101	28.71%	1.98%	DSM-IV	56%	44%	Clinical	UK	6.7	1.1	66.4	28	51%	23%
Levy et al.	2010	2568	4.01%	0.19%	DSM-IV-TR	81%	19%	Community	USA	8	0	N/A	N/A	63%	N/A
Simonoff et al.	2008	112	27.68%	3.57%	DSM-IV	88%	13%	Community	UK	11.5	N/A	72.7	26.8	95%	N/A
**Mayes et al.*	2012	435	41.61%	N/A	DSM-IV	87%	13%	Clinical	USA	8.4	N/A	89.9	N/A	93%	N/A

Vasa et al.	2013	150	10.00%	5.33%	DSM-IV	85%	15%	Clinical	USA, Canada	13.9	1.6	76.8	23.7	83%	N/A
§Vasa et al.	2013	450	19.11%	15.11 %	DSM-IV	85%	15%	Clinical	USA, Canada	7.8	1.7	80.8	23.4	83%	N/A
**§Vasa et al.*	2013	716	18.99%	N/A	DSM-IV	83%	17%	Clinical	USA, Canada	3.5	1.2	73.6	23.4	77%	N/A
de Bruin et al.	2007	94	37.23%	9.57%	DSM-IV	88%	12%	Clinical	Netherlands	8.5	1.9	91.22	17.4	N/A	13%
Skwerer et al,	2019	33	3.03%	3.03%	DSM-5	82%	18%	Community	USA	7.59	1.9	70.53	14.7	61%	N/A
§Skwerer et al.	2019	32	6.25%	3.13%	DSM-5	69%	31%	Community	USA	14.79	1.9	48.97	13	69%	N/A
Hayashida et al.	2010	175	8.57%	8.57%	DSM-IV	78%	22%	Clinical	USA	4.4	1.3	72.4	26.8	73%	3.4%
Amr et al.	2012	60	0.00%	23.3%	DSM-IV-TR	62%	38%	Clinical	Egypt, Saudi Arabia, Jordan	8.63	1.8	60.93	20.9	N/A	N/A
**Pugliese et al.*	2013	20	10.00%	N/A	DSM-IV	90%	10%	Clinical	USA	11.75	2.9	93.75	12.9	92%	N/A
Mukaddes,	2010	60	31.67%	1.67%	DSM-IV	100 %	0%	Clinical	Turkey	10.65	N/A	90.5	N/A	N/A	N/A

Hergüner & Tanidir														
Mukaddes & Fateh	2010	37	5.41%	5.41%	DSM-IV	86%	14%	Clinical	Turkey	10.9	4.5	116	14	N/A	N/A
**Stratis & Lecavalier*	2013	71	29.58%	N/A	DSM-IV-TR	89%	11%	Mixed	USA	11	3.3	64.8	14.9	73%	5.6%
Araz Altay, et al.	2019	94	0.00%	2.13%	DSM-5	80%	20%	Clinical	Turkey	8.7	4.5	N/A	N/A	N/A	N/A
**Lamanna et al.*	2017	67	1.49%	N/A	DSM-IV	85%	15%	Clinical	Italy	7.66	4.4	66.9	N/A	N/A	20%

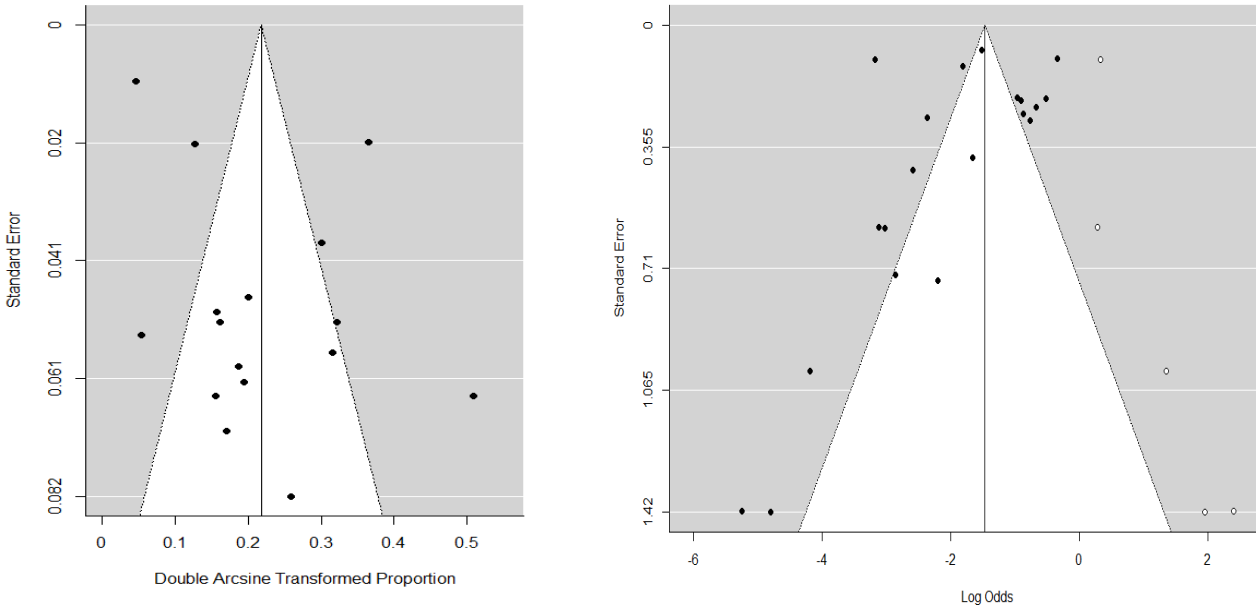
Notes: § Study used samples with from different age groups * Study samples only investigating the rates of ODD

Publication Bias

Funnel plots were run for each of the two diagnostic groups to investigate the presence of publication bias (Stern & Eggers, 2001). Publication bias refers to the likelihood that studies with significant findings will be published or reported, over studies with weak or insignificant results. Obvious asymmetry between the right and left sides of the funnel plot is indicative of a publication bias. The funnel plot for the CD group is relatively symmetrical, while the funnel plot for the ODD diagnostic group shows some asymmetry, suggesting that studies reporting high rates of ODD, may be missing from the literature (figure 2). The trim and fill method (Duval & Tweedie, 2000a/b) suggests that an additional five studies would need to be represented on the right of the ODD graph to correct this bias. These studies are represented by white data points, in the ODD funnel plot below. Eggers's test confirmed the asymmetry in the ODD group funnel plot ($z=-4.04$ $p < .0001$), but not the CD group funnel plot ($Z=.631$, $p=.528$).

Despite the asymmetry, in the ODD group's funnel plot, it is unlikely caused by publication bias. Studies reporting lower rates of ODD are represented in the meta-analysis, and the studies with higher diagnostic rates were often excluded, due to the presence of Berkson's bias. These studies contained samples of participant already predisposed to higher rates of ODD diagnoses (Baker & Blacker, 2015; Mayes et al., 2017; Murray et al., 2014; Van Lieshout et al., 2016). For example, Baker and Blacher (2015) recruited individuals with pre-existing behavioural problems and reported 54% of ASD children in their study to have a diagnosis of ODD. The visible asymmetry in the ODD funnel plot likely reflects efforts to reduce inflated rates of ODD found in specific subgroups of ASD prone to behavioural problems.

Figure 2: Funnel Plots



CD Funnel Plot *ODD Funnel Plot*

Note: The empty data points in the ODD funnel plot calculated from the trim and fill method are visual representations of studies needed to correct for asymmetry.

Study Characteristics

The studies included in the meta-analysis consisted of a total sample of 6085 individuals diagnosed with ASD (males= 5091). The proportion of males found in the sample reflects a higher rate than found in the overall ASD population (Loomes, Hull, & Mandy, 2017). The selected studies captured diverse age groups (3-25 years) with a wide range of intellectual functioning captured by a full-scale intellectual quotient (FSIQ = 16-152). The weighted average of age and FSIQ for the pooled samples was 8 and 78.4 respectively. The type of diagnostic criterion used were excluded from the moderator analysis, since most of the studies (N=17, 89.4%) used a version of the DSM-IV.

The included studies recruited participants from a variety of sources, ranging from mental health clinics to online social media, and represented nationalities from across Europe (N=6), North America (N=10) and the Middle East (N=3). None of the studies recruited participants from South America or Asia. Nationality was excluded as a variable from moderator analysis as the national subgroups contained less than 10 data points limiting the power of results. Similarly, the rate of

dropout from studies was only reported in a minority of studies (N=7) and therefore also excluded. Approximately 91% of the pooled sample recorded information on participant ethnicity. Of this sample 72% of the participants came from a Caucasian background. Limited information was available on other ethnic groups (Hayashida et al., 2010; Levy et al., 2010; Pugliese et al., 2013; Skwerer et al, 2019) or socio-economic status (Amr et al., 2019; Bryson, 2008; Pugliese et al., 2013; Simonoff et al., 2008; Skwerer, 2019). Given the predominantly Caucasian sample, other (non-Caucasian) ethnicities were grouped together in a single category.

Meta-Analysis

The meta-analysis of ASD comorbidity was run independently for both the ODD and CD groups. Studies that reported rates of comorbidity separately for multiple age groups were combined so that each study was represented by a single sample (Skwerer et al. 2019; Vasa et al., 2013). The pooled proportion of ODD and CD diagnoses among the ASD samples was 14.03% (95% CI: 9.0-21.22) and 3.13% (95% CI 1.4-5.4), respectively. The I^2 statistic indicated a significant between study heterogeneity for both the ODD ($P < .0001$, $Q=535.14$, $I^2=96.73\%$) and CD samples ($P < .0001$, $Q=260.78$, $I^2=94.2\%$). The summary of the studies' pooled proportions for each of the comorbid diagnoses, and their effect sizes are captured in the forest plots below.

Figure 3 Forest Plot: Prevalence Rates of ODD

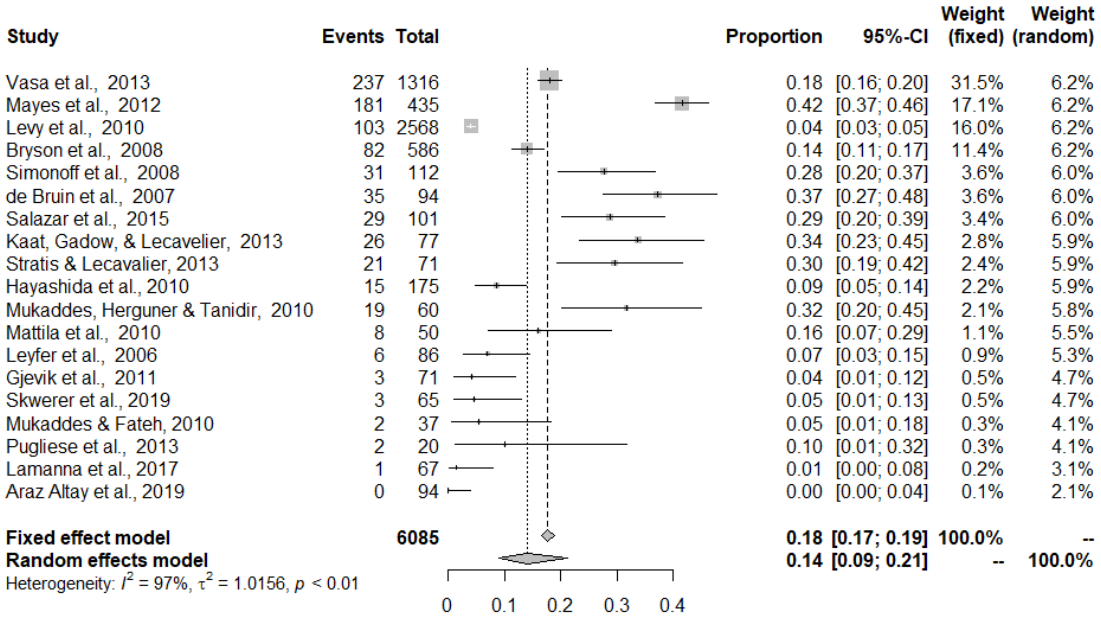
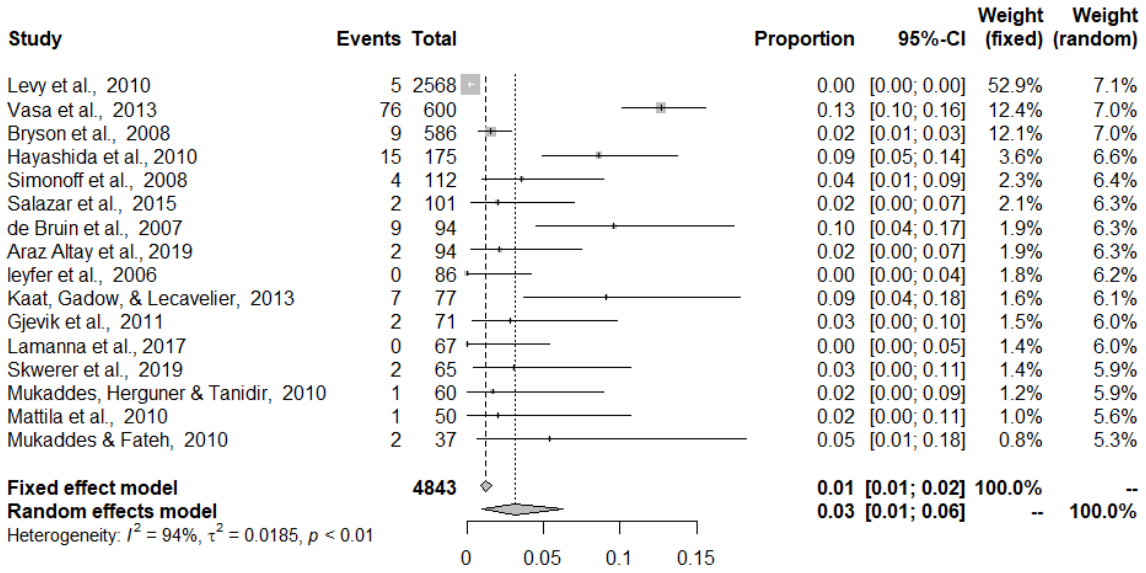


Figure 4 Forest Plot: Prevalence Rates of CD



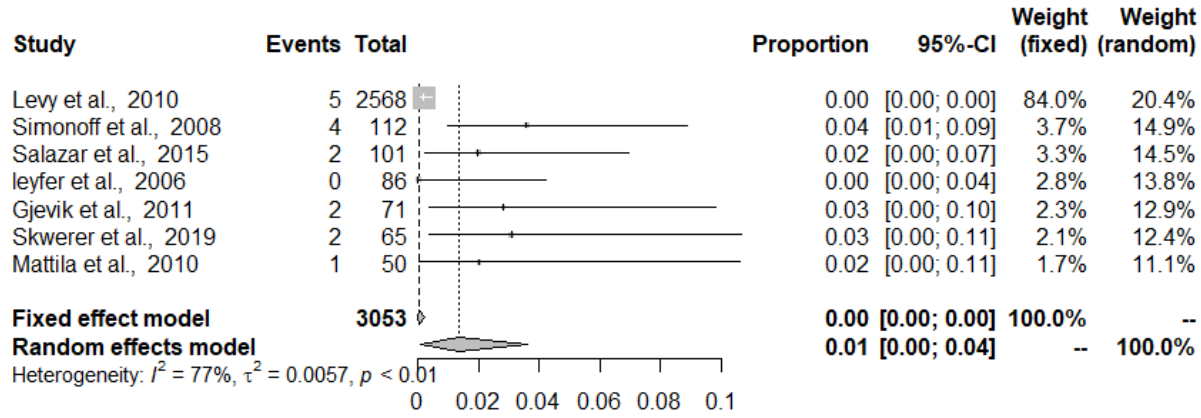
Analysis of Methodological factors

Subgroup analysis was performed using the overall scores on Hoy's risk of bias tool to determine the influence that study bias had over rates of DBD diagnoses. The rates of CD diagnoses were significantly higher in studies classified as having moderate bias (4.82%, 95% CI 2.06-8.51, p=.0349) than in the studies classified as having low bias (1.26%, 95% CI .14-3.1). Meta-

regression revealed that 39.88% (p=.006) of the heterogeneity in the rates of CD between studies could be explained by the scores on the modified Hoys risk of bias tool. Risk of bias was also found to account for 29.89% of the heterogeneity in the rates of ODD (p=.0249). However, rates of ODD with low risk of bias (10.45%, 95% CI 5.08-20.2) were not significantly different from the studies of ODD with moderate bias (14.36% 95% CI 9.0 -21.2; p=.27).

Figure 4 Forest Plot: Risk of Bias and CD Diagnoses

Low bias studies



Moderate bias studies

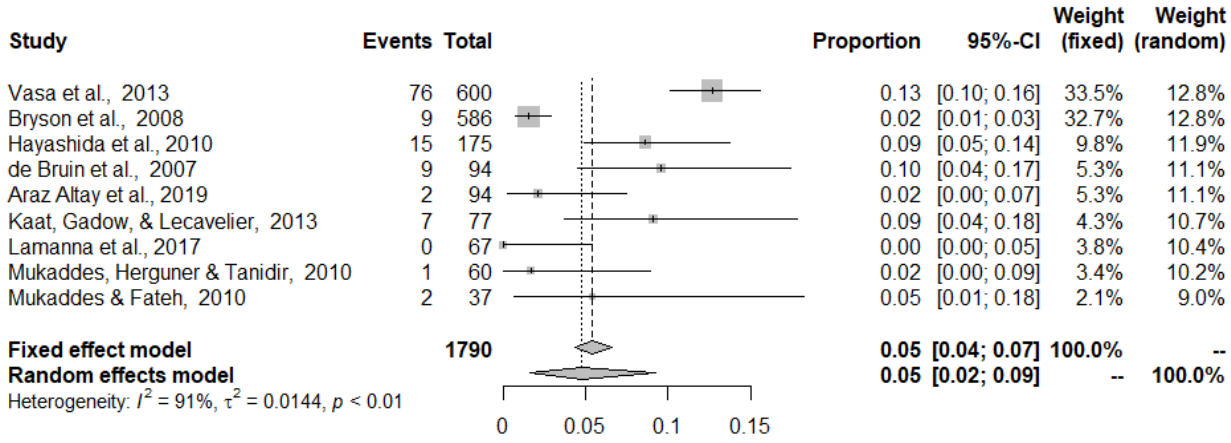
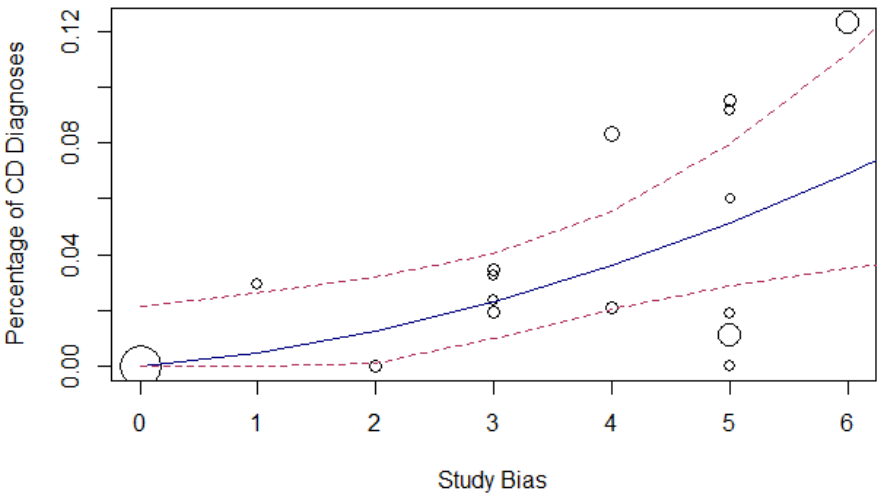


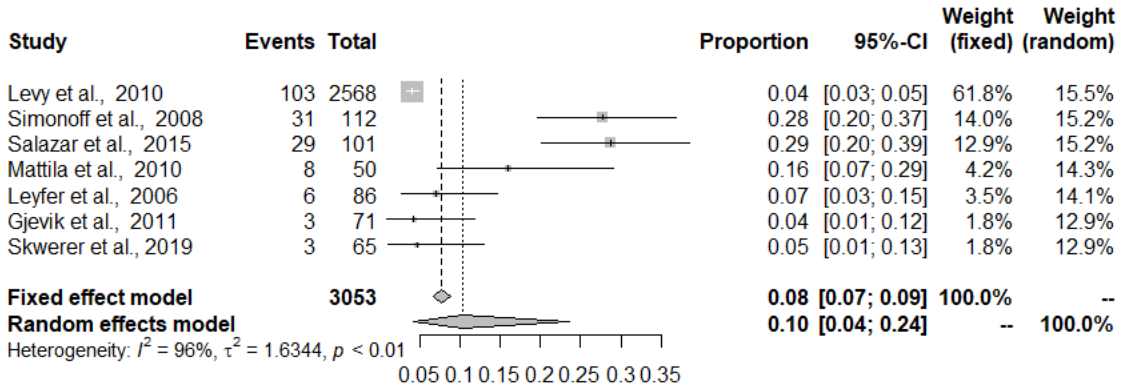
Figure 5 Meta Regression: Study Bias and Rates of CD Diagnosis



Note: *red lines indicate confidence interval limits*

Figure 6 Forest Plot: Risk of Bias and ODD Diagnosis

Low Bias Studies



Moderate Bias Studies

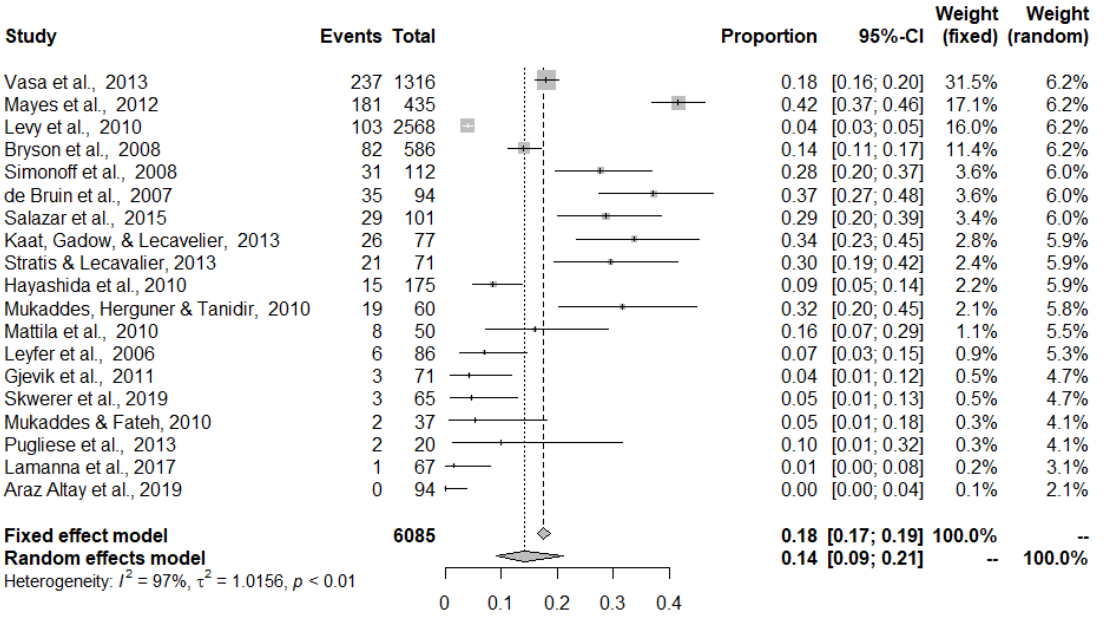
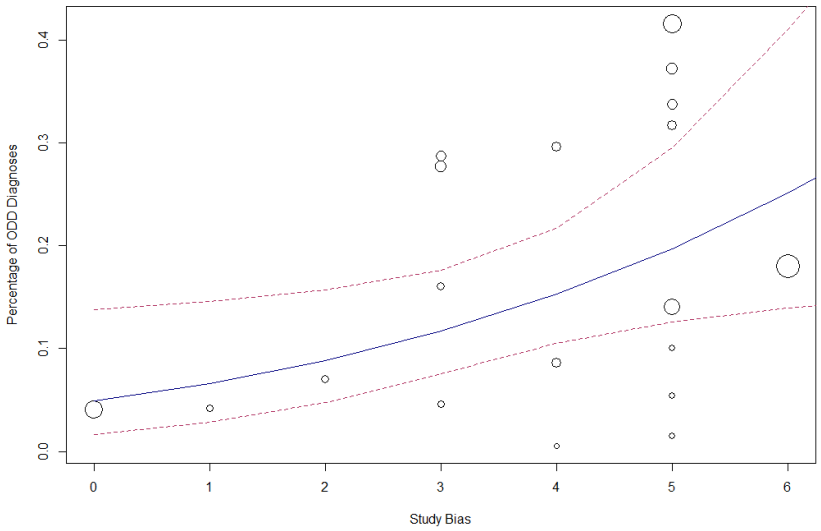


Figure 7 Meta Regression: Study Bias and Rates of ODD Diagnosis



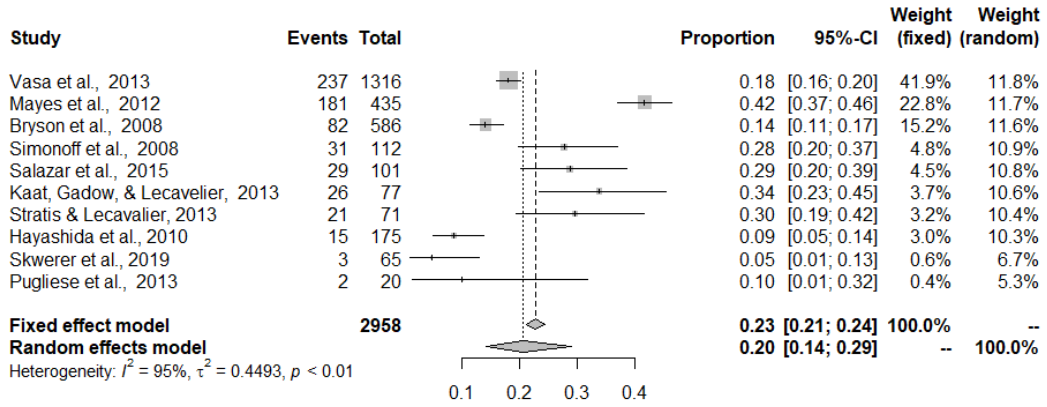
Note: red lines indicate confidence interval limits

Detection and Selection Bias

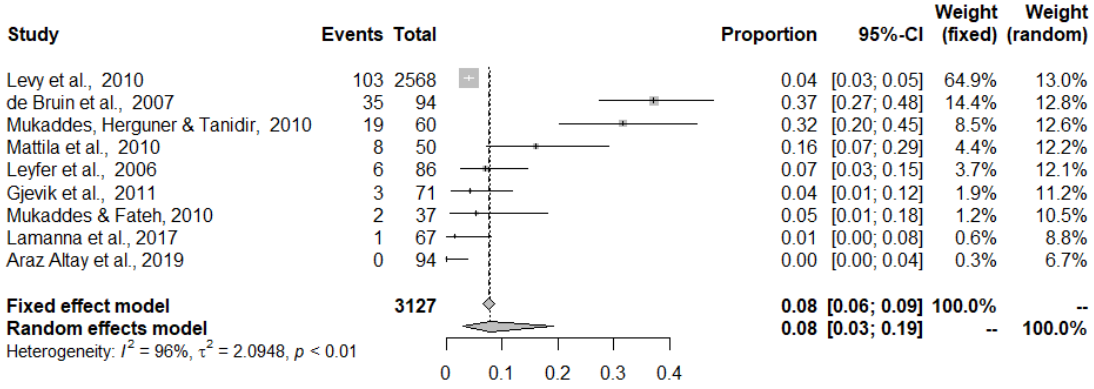
The impact of studies' selection and detection bias on the rates of DBD diagnoses was investigated separately. Detection bias impacted the rates of ODD diagnosis found in studies as hypothesized. Meta regression revealed Detection bias of tools to account for 31.01% of the between study heterogeneity in rates of ODD (p=.018). Studies scoring 0 on their overall detection bias were considered to possess high diagnostic accuracy while studies scoring 1 or more on their detection bias were considered to possess moderate diagnostic accuracy (Appendix H). Studies using moderately accurate diagnostic tools, reported higher rates of ODD (20.31, 95% CI: 13.54%-23.6%, p=.044) than studies using tools with greater diagnostic accuracy (8.2 95% CI 3.5-18). However, the degree of diagnostic accuracy did not account for the between study heterogeneity in reports of CD (R^2=.17, p=.076). Studies using moderately accurate diagnostic tools (5.2, 95% CI: 2.4%-9%) did not have significantly different rates of CD diagnoses than studies using diagnostic tools with greater accuracy (1.6, 95% CI: .18%-4%, p=.15).

Figure 8 Forest Plot: Detection Bias and Rates of ODD Diagnosis

Moderate diagnostic Accuracy



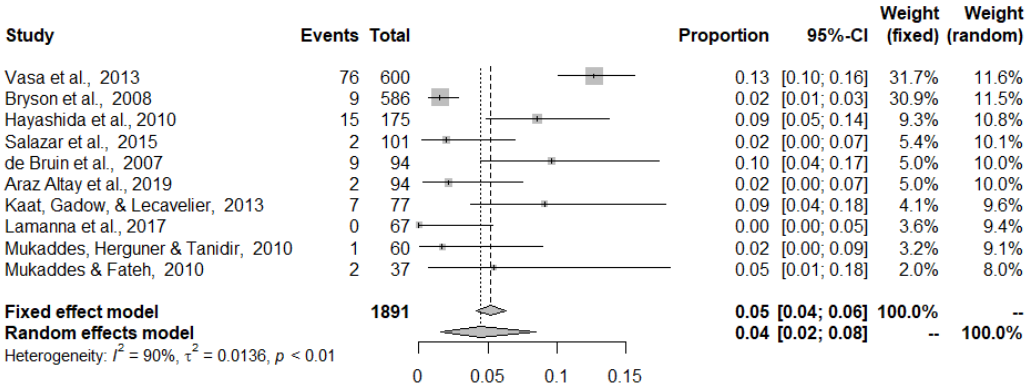
High Diagnostic Accuracy



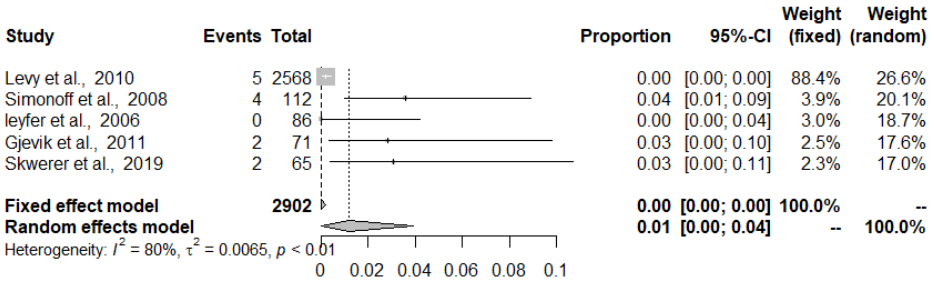
Meta-regression revealed that selection bias in studies did not explain the study heterogeneity in rates of CD diagnoses (R^2=13.19%, p=.3381) or rates ODD (R^2 = 0, p=.57). Recruitment had a significant moderating effect on the number of CD diagnosis (p=.025). Studies recruiting from clinical sources (4.49% 95% CI: 2.0-7.9) had higher rates of CD diagnoses than samples recruiting from community sources (1.14% 95% CI:.2-3.5). Study samples that recruitment participants from clinical sources (18.6%, 95% CI: 12.5-26.75) did not have significantly greater rates of ODD diagnoses than samples recruiting from community sources (7.3%, 95% CI: 2.4-20.1, p=.096). The studies that used mixed sources of recruitment (n=2) were removed from the analysis due to low numbers.

Figure 9 Recruitment Bias CD

Clinical Sample



Community Sample



Sample Characteristics

The average age and gender ratios were recorded in all but one study in the meta-analysis. Average age did not moderate rates of ODD (R^2 = 0, p=.757) or CD diagnoses (R^2 = 0, p =.820). Gender ratios also did not predict rates of ODD (R^2 = 0, p=.544) or CD diagnoses (R^2 = 0, p=.976) among the ASD samples. A post-hoc meta-regression was run to account for any interaction between age and gender on the rate of DBD co-occurrence (Maughan et al., 2004). However, no interaction was found for either CD (R^2 = 0, p=.646) or ODD groups (R^2 = 0, p=.986). Eleven of the studies included in the meta-analysis reported participant ethnicity. Samples with higher proportions of individuals from Caucasian backgrounds were no more likely to receive a diagnosis of CD (R^2 = 22.11%, p=.736) or ODD (R^2 = 10.16%, p=.116) than non-Caucasian ethnicities. The Intelligence of children and adolescents with ASD was measured in 14 studies (See table 1.4 below). Intelligence was measured using a variety of validated tools used to capture participants' full-scale intelligence quotient (FSIQ). Two studies measured the intelligence of ASD children across separate age groups (Vasa et al., 2013; Skewer et al., 2019). The age groups in these studies were kept as separate samples for the purpose of the moderator analysis. The average FSIQ did not significantly explain the differences in the diagnostic rates of ODD (R^2 = 0%, p= .48) or CD (R^2 = 0%, p= .43).

Discussion

The primary objective of this meta-analysis was to investigate the rates of CD and ODD within the population of children and adolescents with an ASD diagnosis. The pooled proportion of co-

occurring ODD in children and adolescents within our sample of studies was 14.03%. The prevalence rate of ODD is significantly higher than the 3.2% found in the non-autistic population (Canino et al., 2010), indicating that ASD children and adolescents appear approximately four times as likely to meet an ODD diagnosis than their non-autistic counterparts. The proportion of ASD children and adolescents with CD diagnoses was 3.13%. Recent estimates suggest that ~2.5% of children have a diagnosis of CD with the proportion of diagnoses increasing to ~3-4% for boys (Canino et al., 2010). Given the predominantly male sample within the meta-analysis, rates of CD in children with ASD seem commensurate to those found in non-autistic population (Fairchild et al., 2019). This may simply be given the male gender bias found in the pooled sample (Loomes, Hull, & Mandy, 2017). These meta-analytic findings found corroboration in another recent meta-analysis, which estimated rates of disruptive impulse control and conduct disorders to occur in 12% (95% CI 10-15) of the ASD population (Lai et al. 2019). Despite the contribution of Lai et al.'s research, they did not investigate the rates of ODD and CD independently or explore the research methodology as potentially moderating factor behind DBD prevalence rates.

The secondary objective of the current meta-analysis was to determine the association between methodological and population characteristics on DBD prevalence. The pooled sample possessed a high variability in prevalence rates, captured by the I^2 statistic (Higgins, Thompson, Deeks, & Altman, 2003), which calculated heterogeneity in CD and ODD diagnostic rates to be 94% and 97% across samples. A substantial amount of this heterogeneity was accounted for by methodological bias. The scores from the modified hoy's risk of bias tool accounted for 40% of the variability in the prevalence rates of CD and 30% of the variability in the prevalence rates of ODD, with higher bias correlated with increased rates of co-occurring DBD diagnoses within the ASD samples.

The studies' overall selection bias did not account for heterogeneity in DBD diagnoses. This finding was unsurprising as some sources of selection bias are more likely to inflate diagnostic

rates among studies while other sources of selection bias are likely to deflate them. For example, increased bias from high participant dropout generally leads to reduced rates of DBD, while increased bias stemming from recruitment from clinical sources generally leads to increase rates of psychiatric diagnoses. While some sources of selection bias, such as dropout rate, were not investigated due to limited data (Littell, Corcoran, & Pillai, 2008), recruitment sources were found to be positively correlated with CD diagnoses. As hypothesized, studies recruiting participants from clinical samples showed significantly higher numbers of CD diagnoses (4.49%) than community samples (1.15%, p=.025). However, counter to our expectation, recruitment was not associated with rates of ODD diagnoses. One explanation behind this finding, may be the high prevalence of behavioural problems found in the ASD community. Most children with ASD exhibit at least one behavioural problem (Matson, Wilkins & Macken, 2008; Jang et al., 2011). Clinical settings are likely to use more comprehensive tools while assigning diagnoses. However, children recruited from community sources may be assigned diagnoses based on the use poorer diagnostic tools leading to false positives and inflating the number of ODD diagnoses found in community settings.

Detection bias accounted for 31% of the heterogeneity in the prevalence rates of ODD, with increased bias correlating with higher diagnoses. The rates of ODD in studies was more strongly correlated with the level of detection bias than overall study bias, providing further credence to the deflationary effects different sources of selection bias have over diagnostic rates. Contrary to expectation detection bias could not explain the variation in rates of CD between studies. However, CD is more easily identifiable even with less sensitive diagnostic measures while more discerning measures may be required to accurately diagnose ODD (Lindhiem, Bennett, Hipwell, & Pardini, 2015). The symptoms associated with CD diagnoses, such as theft and arson, are rather conspicuous making it easy to differentiate between children with CD and children undergoing normative development even with less sensitive tools. Whereas behaviours characterizing ODD

diagnoses, such as loss of temper, arguing, and deliberately annoying people are commonly displayed by children undergoing normative development, albeit at a lesser extent.

Population characteristics did not account for this diagnostic heterogeneity in rates of DBD. No significant differences were found in the number of DBD diagnoses across average age, gender, average intelligence, or ethnicity. However, these findings should be interpreted with some hesitation, as the population characteristics of the pooled sample may not accurately represent the ASD population at large. The pooled sample of ASD participants had a 5:1 male to female ratio, considerably higher than the 3:1 male to female ratio found in the overall ASD population (Loomes, Hull, & Mandy 2017). Since females are underrepresented within the pooled sample, we cannot definitively say that gender does not impact DBD rates within the ASD population. Rather since males are more likely to receive DBD diagnoses, our estimates might have slightly inflated DBD rates. Similarly, the pooled sample of ASD individuals came predominantly from western countries and were of Caucasian background, which does not account for the majority of the world's population (Henrich, Heine, & Norenzayan, 2010). It is also unclear whether the intellectual abilities of the pooled sample accurately reflect the ASD population (Russel et al., 2019). Given the homogeneity of population characteristic, these findings are ultimately limited in their ability to inform service planning decisions.

Limitations

The selection of the studies ultimately included in the analysis were approved by the supervising researcher. However, the screening and risk bias assessments were conducted by a single researcher, increasing the risk of bias. Ideally both screening and risk of bias assessments would have been conducted by at least two independent researchers. This procedure would have helped ensure that relevant articles were not excluded from the meta-analysis, and that bias was appropriately assessed. Unfortunately recruiting independent researchers to screen and assess bias could not be met given the time and resource constraints of the current project.

The exclusion of studies due to their focus on subpopulations of ASD may have increased the focus of the meta-analysis at the expense of a more general ASD population. Increasingly, research has reflected that the vast majority of children in the ASD population struggle with additional psychiatric difficulties (Matson & Goldin, 2013) with nearly a third of the population struggling with multiple psychiatric diagnoses (Simonoff et al., 2008). Therefore, the exclusion of some of the studies with a more specific focus on subpopulations may have failed to capture a significant minority of the ASD population and impacted the external validity of the study.

Another significant limitation of the present study was that diagnoses of the pooled sample were primarily based on DSM-IV, and not the updated DSM-5 criteria. Since under the DSM-IV criteria, ODD and CD are considered mutually exclusive disorders, this may have contributed to inflated or deflated rates of ODD or CD in the included studies. For example, Amr et al., (2012) reported CD rates four times higher than other studies included in the meta-analysis. This may represent the clinicians' bias to diagnose children with CD instead of ODD under the DSM-IV nosology. While this study was excluded as an outlier, the impact of DSM IV criteria on the prevalence rates in the other included studies is still unclear.

The DSM 5 introduced disruptive mood dysregulation disorder (DMDD), as a newly defined diagnosis, under depressive disorders. DMDD has a similar presentation to ODD, and is characterized by frequent temper outbursts, and persistently irritable or angry mood (APA, 2013). Given their similarities, most children meeting a DMDD diagnosis would also qualify to receive a diagnosis of ODD (Freeman, Youngstrom, Youngstrom, & Findling, 2016; Mayes, Waxmonsky, Calhoun, & Bixler, 2016). Under the DSM-5 children can only receive a diagnosis of ODD if they do not already meet criteria for DMDD (APA 2013). It is still unclear how the introduction of DMDD in the DSM 5 will impact the comorbid rates of ODD in the ASD population. Given these limitations future meta-analytic research should seek to investigate ASD comorbidity based solely on DSM 5 nosology.

Clinical Implications and Conclusions

The following meta-analysis was the first of its kind to explore the co-occurring rates of ODD and CD within the ASD population while investigating the influence of multiple sources of methodological bias. As expected, methodological bias impacted the diagnostic rates of DBD between studies and generally inflated diagnostic rates. However, the results of the study need to be interpreted with some caution given the use of the DSM-IV criteria to ascertain diagnoses, the data from the study coming predominantly from Caucasian males. These factors limit the studies generalizability and its potential to inform service-wide planning. Therefore, while meta-analysis and epidemiological studies are often used to help guide services and shape public policy, the findings of the present study highlight some of the challenges to using meta-analytic data. Researchers should continue to investigate minoritized ASD populations to get a more comprehensive picture of the difficulties facing the entire ASD population.

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Part II: Empirical Paper

Biopsychosocial risk factors of conduct problem development in children with autism spectrum disorder

Abstract

Background: Children with autism spectrum disorder (ASD) often exhibit conduct problems which can progressively evolve into more serious conduct disorders later in life. Early Intervention has been shown to have a positive effect on the long-term behaviour of ASD children. The time sensitive nature surrounding effective treatment of conduct problems in ASD makes early identification of children at-risk for developing enduring conduct problems a significant public health concern. The objective of the current study was to identify the trajectories of conduct problem severity in children with ASD and explore which potential risk-factors were associated with persistent or escalating conduct problems by adolescence.

Methods: A total of 508 children recruited in the Millennium Cohort Study with a parent-reported diagnosis of ASD were included. Data relating to conduct problem severity was collected from parents when children were between the age of 3 to 14 years old along with information concerning potential biopsychosocial risk-factors. Growth mixture modelling (GMM) was used to identify the developmental trajectories of conduct problem severity. Multinomial logistic regression was used to explore the association between potential biopsychosocial risk-factors and these trajectories.

Results: GMM analysis identified three different trajectories of conduct problem severity characterized as ‘desisting’, ‘persistent’, and ‘escalating’. Children falling into the desisting group displayed low to moderate conduct problems that diminished over time. Children in the persistent group displayed moderate conduct problems that persisted over time. Children falling into the escalating conduct problem group initially displayed moderate to high conduct problems which progressively worsened. Low levels of maternal education, and early parent-child conflict placed children at-risk for developing persistent and escalating conduct problems in adolescence. Among children exhibiting chronic conduct problems, living in single parent households increased the risk of developing escalating conduct problems over persistent ones by adolescence.

Conclusions: The current study contributes to the growing body of research exploring the risk factors associated with the development trajectory of conduct problem severity in children with ASD. There may be value in the early screening of certain biopsychosocial factors to help identify children at risk for chronic conduct problems, so that appropriate support can be offered to them and their families. More research is needed to understand the aetiology behind chronic conduct problems in the ASD population.

Introduction

Approximately a quarter of all referrals to Child and Adolescent Mental Health Services in the United Kingdom today have a diagnosis of oppositional defiant disorder (ODD) or conduct disorder (CD; Gibbons, Harrison, & Stallard, 2021). The costs of treating these disorders places a heavy financial burden on mental health services and society at large (Beecham, 2014; Frey et al., 2019; Rivenbark et al., 2018). This is especially true for children with co-occurring ASD and conduct disorders (Knapp, Romeo, & Beecham, 2009). Consequentially, there has been a recent push towards studying the developmental trajectories of conduct problems as a means of identifying the risk-factors which place children with autism spectrum disorder at risk for developing more enduring psychiatric disorders (Flouri, Midouhas, Charman, & Sarmadi, 2015; Midouhas, Yogaratnam, Flouri, & Charman, 2013; Shattuck et al., 2007; Stringer et al., 2020; Taylor & Seltzer, 2010).

Conduct problems encompass the diagnostic entities of ODD and CD, and are characterized as hostile, defiant, angry, and irritable behaviours as well as social norm violations. (American Psychological Association, APA 2013; McMahon, Wells, & Kotler, 2006). For some children conduct problems are the antecedents for future psychiatric conditions. However, for most conduct problems reflect normative patterns of development, which do not reach the clinical thresholds necessary to receive psychiatric diagnoses (Ezinga et al., 2007; Hong, Tillman, & Luby, 2015). For example, toddlers commonly display irritability in the form of tantrums (Osterman & Bjorkqvist, 2010), and children often display hostility and even physical aggression in fights with siblings (Hoffman, Kiecolt, & Edwards, 2005). As children mature into adolescence these normative forms of conduct problems almost invariably dissipate (Barker & Maughan, 2009; Lemerise & Dodge, 2008; Raphael-Leff, 2012; Tremblay et al., 1999). Children become at-risk of developing future ODD and CD diagnoses when their conduct problems persist in frequency and

severity, outside what is considered developmentally appropriate behaviour (APA, 2013; Baker, 2013; Barker & Maughan, 2009; Scott, 2015).

Conduct Problems in children with ASD

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in the social and communicative domains of life, as well as restrictive and repetitive behavioural interests (American Psychological Association, APA 2013). Children and adolescents with ASD are at high risk of receiving co-occurring CD and ODD diagnoses (see Part 1 of this thesis). Approximately 90% of children and adolescents with ASD display at least one conduct problem (Matson, Wilkins & Macken, 2008; Jang et al., 2011). These conduct problems range widely in presentation from yelling, tantrums, and leaving parental supervision, to severe forms of antisocial behaviours such as aggression, destruction of property, and inappropriate sexual behaviours (Ambler, Eidels, & Gregory, 2015; Kanne & Mazurek, 2011; Jang et al., 2011; Lidstone et al., 2014; Matson, Wilkins, & Macken, 2008; McClintock, Hall, & Oliver, 2003). Although they did not explore causality, Mahan and Matson found that conduct problems exhibited by children with ASD are more severe than those displayed by their non-autistic counterparts (2011). These severe conduct problems place children with ASD at increased risk for future psychopathology including the conduct disorders ODD and CD (Kaat, Gadow, & Lecavalier, 2013; Robins & Price, 1991).

Conduct disorders in children with ASD cause significant distress to parents and deleteriously impacts family wellbeing (Estes et al.,2009; Lanyi et al., 2021; Lecavalier, Leone, Wiltz, 2006; Matson & Jang, 2014; Tint & Weiss, 2016). Therapeutic interventions can help children with ASD replace their conduct problems with more adaptive behaviours (Fitzpatrick 2016; LaVigna & Willis, 2012; McClean & Grey, 2012; Oono, Honey, & McConachie, 2013) and prevent further deterioration (Frick et al., 2014; Hawes & Dadds, 2005). However, the effectiveness of these interventions for children with ASD is time sensitive, with earlier interventions leading to

more positive prognoses (Bargiela, Steward & Mandy, 2016; Frazier et al., 2021; Harris & Handleman, 2000; Lai & Baron-Cohen, 2015; Rogers, 1996). While early interventions are effective, they are also prohibitively expensive to implement on a large scale (Beecham, 2014; Frey et al., 2019). Given the psychological cost to parents, the financial cost of services, and the time sensitive nature of treatment, it is important for children with ASD to receive these interventions before developing more entrenched and enduring psychiatric difficulties.

Trajectories of conduct problems in children with ASD

There has been a recent push towards studying the different developmental pathways of conduct problem severity as a means of identifying children with ASD who are at risk for future conduct disorders (Flouri, Midouhas, Charman, & Sarmadi, 2015; Midouhas, Yogaratnam, Flouri, & Charman, 2013; Shattuck et al., 2007; Stringer et al., 2020; Taylor & Seltzer, 2010). These studies found, like their non-autistic counterparts, that most children with ASD overcome their conduct problems with time. One of the most comprehensive longitudinal studies to date, explored conduct problem severity in individuals with ASD over a period of 18 years (Gray et al. 2012). This study measured the severity of conduct problems using the developmental behaviour checklist, a well-established psychometric measure (Hastings, Brown, Mount, & Cormack, 2001). The data from the developmental behaviour checklist was collected approximately every 4.5 years from a sample of 119 individuals with ASD. The study found that conduct problem severity for individuals with ASD followed one of three distinct trajectories over the 18 year period: 61.8% of individual's conduct problems diminished, 22.5% of individuals displayed persistent problems, and 15.7% exhibited conduct problems which escalated in severity overtime (Gray et al. 2012). While the study mapped out trajectories across a significant period, there was a large variance in the ages of participants, with some displaying as much as a 20 years of age difference at each time point. The large variance in the ages fails to capture age-specific changes in conduct problems across time (Vugteveen, de Bildt, & Timmerman, 2022). Exploring conduct problem trajectories enable

researchers to successfully identify risk factors which increase the likelihood of children with ASD developing enduring conduct problems (Flouri, Midouhas, Charman, & Sarmadi, 2015; Gray et al. 2012; Midouhas, Yogaratnam, Flouri, & Charman, 2013; Shattuck et al., 2007; Stringer et al., 2020; Taylor & Seltzer, 2010).

Identifying risk in early adolescent children with ASD

Most research has focused on identifying the risk-factors which place children with ASD at risk of developing more severe conduct problems during childhood (Flouri, Midouhas, Charman, & Sarmadi, 2015; Midouhas, Yogaratnam, Flouri, & Charman, 2013) or have focused on conduct problem development from adolescence into adulthood (Shattuck et al., 2007). Notably absent from this body of research is the development of conduct problem severity as children transition into adolescence. The transition from childhood into adolescence is often a period of relative upheaval (Graber & Brooks-Gunn, 1996). Adolescents experience major biological, cognitive, and socio-emotional changes (for review see Orr & Ingersoll 1988). These biopsychosocial changes markedly impact an adolescent's behaviour and, operating in concert with environmental factors, can lead to the emergence of severe conduct problems (Dandreaux, & Frick, 2009; Dodge & Pettit, 2009; Graber & Brooks-Gunn, 1996; Olson & Sameroff, 2009). The impact of psychiatric difficulty during adolescence can have long term implications on their adult mental health (Colman et al., 2009; Copeland et al., 2013). Despite the periods influence on future mental health, the transition from childhood to adolescence has rarely been explored in the context of ASD development of conduct problems (McGovern & Sigman, 2005).

Current research has typically focused on a limited range of biopsychosocial domains. The exclusion of additional biopsychosocial factors often limits the significance of the research findings (Frick et al., 2012). For example, Gray and colleagues' (2012) study explored some of the risk factors behind conduct problems development but failed to account for relationships between parents, peers, or genetically influenced components such as temperament. The current

study contributes to the growing field by using Dodge and Pettit's comprehensive biopsychosocial model to explore the development of conduct problems from childhood until early adolescence. Dodge and Pettit's model (2009) has emerged as a dominant model for explaining the aetiology of conduct disorders. This model highlights the impact of different mental processes, parental and peer relationships, biological dispositions, and socio-cultural contexts on the development of conduct disorder as children enter adolescence. The model considers the complex interactive effects of different risk factors in their association with the development of conduct disorders (Burke, Loeber, & Birmaher, 2002; Dodge & Pettit, 2009).

Application of Biopsychosocial model

Socio-Cultural Context

Researchers have known for a long time the deleterious impact that socioeconomic disadvantage (SED) has on the development of children's mental health problems (Piotrowska et al., 2015; Reiss, 2013). SED is typically measured using family income and parental education status (Bradley & Corwyn, 2002; Currie et al., 2012). Studies have shown low household income and limited parental education to negatively influence early development of conduct problems in typically developing children (Gutman et al., 2018; Gutman, Joshi, & Schoon, 2019) and children with ASD (Colvert et al., 2021; Midouhas et al., 2013). The impact of SED as a predictor of conduct problems was found to be strongest for younger children and gradually declines through childhood (Piotrowska, Stride, Croft, and Rowe's 2015). Research has established a link between SED and conduct problem pathways; however, whether a causal relationship exists between conduct problems and SED remains unclear (Midouhas et al., 2013; Miech, Caspi, Moffitt, Enter-Wright, & Silva, 1999). The impact of SED is moderated by multiple other factors including children's temperament (Jansen et al., 2009; Kim-cohen, Moffit, Caspi, & Taylor, 2004) intellectual abilities (Flouri, Midouhas, & Joshi, 2015) and parental practices (Flouri & Midouhas, 2017; Haapasalo & Tremblay, 1994; McCoy et al., 1999). While significant amounts of research have investigated the association between SED and the development of conduct problems, most

research has focused on the non-autistic population. It is still unclear what role SED has over the conduct problem trajectories in children with ASD given the amount of potentially confounding variables.

Temperament

Temperament is the physiological and behavioural pattern of relating to the world (Fox et al., 2008). Many researchers have grouped temperament into three dimensions: negative mood, effortful control, and surgency, categories first delineated by Rothbart and Bates (2006). Negative mood is defined as the tendency to experience negative valanced emotions. Effortful control is defined as the ability to sustain attention, control behaviour, and regulate emotion. Surgency is defined as the tendency to approach people in a positive way (De Pauw et al., 2011). A recent meta-analysis found temperament to be associated with conduct problems in children with ASD (Chetcuti et al., 2021). Negative mood, low surgency, and low effortful control were all independently correlated with greater conduct problems in children with ASD (Adamek et al., 2011; Korbut, Hedley, Chetcuti, Sahin, & Nuske, 2020), with negative mood being the most robust predictor of future conduct problems (Adamek et al., 2011; De Pauw et al., 2011). However, research exploring the association between temperament and conduct problems in children with ASD never controlled for additional biopsychosocial variables, which potentially confounded the findings (Adamek et al., 2011; Chetcuti et al., 2021; De Pauw et al., 2011; Korbut et al., 2020). Children's temperament is influenced by socioeconomic status (Jansen et al., 2009) and parenting relationships (Van Den Akker et al., 2010). The quality of early parent-child relationships also plays a profound impact on a child's temperament. For example, the severity and frequency of parent-child conflictual interactions is associated with greater negative mood in children at 3 years old (Laible, Panfile, & Makariev, 2008). High levels of SED is also related to increased negative mood and lower surgency (Jansen et al., 2009). It is unclear whether temperament will be

associated with the development of conduct problems when controlling for other variables from the biopsychosocial model.

Peer Relationships

It has been found that peer relationships have a significant moderating role in the development of children's conduct problems (Glaser et al., 2010). Despite their social and communicative impairments, rejection by their peers causes children and adolescents with ASD to struggle with anxiety, lower self-esteem, and lower sense of belonging, similar to their non-autistic counterparts (Fisher & Taylor 2016; Sebastian, Blakemore, Charman, 2009). The experience of peer rejection is linked with increased conduct problems for non-autistic children and children with ASD alike (Arsland 2021; Boer & Pijl, 2016). Conversely, closeness between peers significantly mitigates the development of conduct problems in non-autistic children (Glaser, Shelton, & van den Bree, 2010; Rogers et al., 2018). Children with ASD typically struggle to initiate and sustain relationships with peers which may predispose them to more conduct problems than non-autistic children (Chevallier et al., 2012). Nevertheless, we do not expect that peer relationships will have predict the development of conduct problem in early childhood. Peer relationships only become more influential in the development of conduct problems during adolescence, with parent-child relationships playing a more salient role in younger children (Moffit 1993).

Parent Relationships

Parenting practices in early childhood are one of the strongest predictors of later conduct problems (Frick, Christian, Wooton, 1999). Parent disciplinary action, such as using corporal punishment and failure to use positive reinforcement has been consistently associated with severe conduct problems in non-autistic children (Bevilacqua et al., 2018). Snyder and Patterson (1995) found that negative reinforcement for 4-year-old children predicted later aggressive behaviour in adolescence. The predictive power of harsh disciplinary practices and the development of later chronic conduct problems was also found for children with ASD (Flouri et al., 2015).

The degree of parental closeness and parental conflict with children is also linked to the development of future conduct problems. Conflict between young children and their parents predict the severity of conduct problems in adolescents (Klahr et al., 2011). The same patterns were found for children with ASD, with high conflict at age 3 associated with greater problems behaviours at 7 (Flouri et al., 2015). Conversely, parental warmth is a protective factor against the development of severe conduct problems for typically developing children (Patrick et al., 2005; Weaver & Schofield, 2015) and children with ASD (Midouhas et al., 2013). Parent-child relationships and discipline is influenced by other biopsychosocial variables including temperament (Larkin & Otis, 2019) and SED (Midouhas et al., 2013). Lower effortful control and greater negative mood was associated with increased maternal negativity, (Klein et al., 2018) poor discipline, and greater severity of conduct problems (Langua & Kovacs, 2005). Poverty was associated with conflictual parent-child relationships and conduct problem development in children with ASD (Midouhas et al., 2013).

Language Ability

Conduct problems often arise in children with ASD as by-products of frustrated attempts to communicate (Brewer et al., 2014; Larson 2006; Tick et al., 2016). Without the words to express themselves children with ASD might throw a tantrum, display physical aggression, or destroy property in attempt to communicate their needs (Girard et al., 2014; Moffitt, 1993; Roths et al., 2018). One longitudinal study found verbal ability to have a small predictive impact on the rate conduct problems diminish in children with ASD (Shattuck et al., 2007). Children's verbal ability is highly correlated with maternal education and SED (Olson et al., 2021). When controlling for SED and maternal distress, verbal ability was not associated with the conduct problems trajectories in children with ASD (Flouri et al., 2015). Ultimately verbal ability seems to play only a moderating role over conduct problem trajectory, and one which continues to diminish overtime

(Hopkins, Yuill, & Branigan, 2021). Therefore, we do not expect to verbal ability to be associated with conduct problem trajectories when controlling for other potential risk-factors.

Aims

This study uses Dodge and Pettitt's model as a framework to explore the multivariate impact of different biopsychosocial variables and their association with conduct problem trajectories. The research has two aims. First, the study seeks to identify the different developmental trajectories of conduct problems in individuals with ASD. Second, the research explores the associations between early biopsychosocial factors and the identified trajectories.

Methods

Participants

Participant data came from a pooled sample of 11,726 children and families recruited as part of the Millennium Cohort Study (MCS), an ongoing population-based study of children born in the United Kingdom between September 2000 and January 2002 (IOE, 2022). Data was collected across 5 time periods, when children were 9 months, 3, 5, 7, and 14 years old (Mostafa & Ploubidis, 2017). During these time periods parents, children, and teachers were interviewed and approached with a battery of cognitive tests and questionnaires. The MCS used stratified sampling to adequately represent disadvantaged groups and ethnic minorities across the United Kingdom (Plewis, Calderwood, Hawkes, Hughes, & Joshi, 2007). Approval for the study was granted by the UK Data Service and the UK National Health Service Research Committee.

In the MCS, 639 children were identified as having received a diagnosis of ASD through parental self-reports. Parents were asked "Has a doctor or health professional ever told you that [Child name] had autism or Asperger's syndrome" at each time period, when children were between 5 and 14 years old. Children were only excluded from further study if they were identified as belonging to a pair of twins (N=36), to avoid clustering effects (Midouhas et al., 2013), or if they were missing reports of conduct problem severity from a single time period (N=95) (Jakobsen et

al., 2017). The exclusion of these children left an overall sample of 508 children with ASD diagnoses.

Measures

SDQ

The conduct problem subscale of the strengths and difficulties questionnaire (SDQ) was used to calculate the conduct problem trajectories as the dependent variable. The SDQ is a well-established measure used to screen for different types of psychopathologies in children and adolescents (Goodman, 2001; Mathai, Anderson, & Bourne, 2002) and has been used to screen for psychopathology in children with ASD (Findon et al., 2016; Salayev & Sanne, 2017). The questionnaire is comprised of five subscales, with five questions each, to assess levels of emotional symptoms, hyperactivity/inattention, peer relationships, prosocial behaviour, and conduct problems. For each question individuals can receive scores between 0-2, with higher scores indicating greater difficulties, with the exception of the prosocial subscale where higher scores indicate less difficulty. On the conduct problems subscale 80% of children from the UK score between 0-2 which falls within a normative range of challenging behaviour (Bourdon, Goodman, Rae, Simpson, & Koretz, 2005). However, by adolescence what is considered a normative score on the SDQ increases slightly. For 14 years old adolescents scores of up to 3 are considered normative, with individuals scoring 4 or more falling within the upper 10% of the adolescent population, placing them at risk of future psychopathology (Vugteveen, de Bildt, & Timmerman, 2022).

The SDQ for children was completed by parents from the ages of 3 until 14 years old. Conduct problem trajectories were calculated based on changes on the conduct problem subscale across multiple time periods (see statistic procedure below). The peer relationships subscale on the SDQ was included as an independent variable to measure the quality of the peer relationships in children at 3 years old. The SDQ's conduct problem (α=.89) and peer relationship subscales (α=.85) have

demonstrated excellent internal consistency (Björnsdotter, Enebrink, & Ghaderi, 2013), and both the conduct problem (*r*=.70) and peer relationship (*r*=.58) subscales have displayed good test-retest reliability within the ASD population (Findon et al., 2016)

Sociocultural Context

SED was measured using data from the self-reported annual family income, and maternal education level. Data on family income was banded by the MCS into six income brackets and collected when children were 9 months old. Data on maternal education was also gathered when children were 9 months old and divided into five separate groups depending on their level of qualification, ranging from individuals without any educational qualifications to individuals with higher education diplomas (Flouri et al., 2015).

The Child – Parent Relationship Scale

The relationship between parents and children was measured using the short form of the Child Parent Relationship Scale (CPRS; Driscoll & Pianta, 2011) and the Conflict Tactics Scale (CTS; Straus & Hamley, 1997). The CPRS assesses the level of conflict and closeness that exists between caregivers and children. Data from the conflict subscale was collected from primary caregivers when children were three years old. The CPRS short form has demonstrated a high internal consistency (α=.84) and reliability (α= .83; Driscoll & Pianta, 2011). The CTS is a seven-item questionnaire which measured the frequency of parents' harsh disciplinary action for child's misbehaviour at 3 years old (Straus, Hamby, Boney-McCoy, & Sugarman, 1996). The CTS has a good internal consistency with a Cronbach's alpha of .61 (Flouri et al., 2015).

British Ability Scale – Verbal Intelligence

Verbal intelligence was measured based on children's' verbal percentile score on the naming subsection of the British Ability Scale II (BAS II). The BAS II resembles the Wechsler Intelligence Scale for children and was designed to measure the general conceptual abilities of British children, including those with learning disabilities (Hill, 2005). The verbal subsection of the BAS II was administered to children when they were three years old. On the naming subsection of the BAS II

children were showed different pictures and asked to describe what each picture showed. Children were graded on whether their answer was correct, incorrect, or partially correct. Scores were categorized based on whether children fell above or below the 69-percentile range of verbal ability.

Carey's Infant Temperament Scale

Data on temperament was collected in the MCS when children were 9 months old using Carey's Infant Temperament Scale (ITS; McDevitt & Carey, 1978). The Carey's Infant Temperament Scale assesses temperament by measuring mood, approach, adaptability, and rhythmicity subscales. The mood subscale measures the amount of friendly or pleasant behaviour in contrast to unfriend and unpleasant behaviour. The approach subscale measures the degree of approach and withdrawal behaviour in response to new objects or people. The adaptability subscale measures the ease infants adapt to changes to their environment. Finally, the rhythmicity subscale measures the consistency in infants' daily schedule. These subscales each consisted of five questions each and possess high levels of internal consistency (α= .66, .72, .80) and excellent test-retest properties (α=.87, .85, .94), Only the rhythmicity subscale was not included in the study given its low internal consistency (α= .48; McDevitt & Carey, 1978).

Covariates

Several additional covariates were included to account for factors known to influence conduct problem trajectories. Prenatal alcohol consumption is a risk factor for the development of conduct problems (Disney et al., 2008; Gaysina et al., 2013; Larkby et al., 2011; Wakschlag et al., 2006), and was coded as a dichotomous variable, for mothers who consumed alcohol during their pregnancy and those who abstained. Non-autistic children from single parent households are also at greater risk of developing externalization disorders such as conduct problems (Daryanani, Hamilton, Abramson, & Alloy, 2016; Matijasevich et al., 2014). Research has not yet explored the impact of single parent households in the development of conduct problems in children with ASD. Information on single parent families was collected when children were 9 months old. Ethnic minorities have an increased chance of developing severe conduct problems (Frick et al., 2003).

Since, most participants (87%) came from a Caucasian background, ethnicity was recoded as a dichotomous variable for Caucasian background and other ethnic groups. The age which the child received an ASD diagnosis was also included as a covariate. Children who receive earlier ASD diagnosis may have access to pivotal interventions when undiagnosed children are ineligible, which may potentially influence clinical outcomes (Malik-Soni et al., 2021). Gender is associated with conduct problem development in non-autistic individuals. Males tend to display conduct problems more than females, and display conduct problems earlier (Gutman et al., 2018). Research suggests that gender does not mediate conduct problem pathways for ASD individuals (Shattuck et al., 2007). Nevertheless, given the limited evidence and possible mediating effect of gender it was included as a covariate in the subsequent analysis.

Statistical Procedure

Growth Mixture Modelling

Growth Mixture Modelling (GMM) is a longitudinal form of mixture modelling used in the present study to identify different subgroups of participants based on their conduct problem trajectories (Muthén et al., 2002). Multiple methods exist for identifying the trajectories of latent classes among longitudinal data, but GMM produces optimal outcomes for continuous variables (Nguefack et al., 2020). GMM uses iterative processes to determine growth parameters using increasing numbers of subgroups. These growth parameters are used to calculate the trajectory curves (Myung, 2003). The number of latent classes used in the GMM analysis were increased until the optimal model of trajectories was found using the procedure described below. GMM typically operates using normally distributed data as skewed data distributions can bias results (Lore et al., 2021; Son, Lee, Jang, Yang, & Hong, 2019). Shapiro-Wilk's test was run to check for normality and determine whether additional data transformation was needed. Data with skewness and kurtosis scores within the ±2.00 range are treated as normally distributed, as scores within this range do not influence subgroup membership (George & Mallery, 2010; Nam & Hong, 2021). Missing data from the SDQ conduct score subscale was managed through the Full Information

Maximum-Likelihood estimation using an Expectation Maximisation algorithm (Dempster, Laird, & Rubin, 1977).

The number of conduct problem trajectories were determined using established Information Criterion (IC) and likelihood ratio tests as recommended through simulations (Nylund et al 2008), and extrapolated from the GMM analysis (Tein, Coxe, & Cham 2013). The IC statistics indicate how well a specified number of trajectories classes fit, with lower values specifying better model fit (Feldman et al., 2009). The IC included in the study were the Akaike Information Criterion (AIC; Akaike, 1998), Baysian Information Criterion (BIC; (Schwartz, 1978), and the sample-size adjusted BIC (SSABIC; Sclove, 1987). The AIC and SABIC statistics are more liberal than the BIC statistic and slightly biased towards additional subgroups being included in models (Bauer & Corran, 2003; Tofighi & Enders, 2007). Likelihood ratio tests (LRT) are used to differentiate between the fit of the current model (K) and the model with one fewer class (K-1 model). These tests use p-values to determine whether there is a statistically significant improvement ($p<0.05$) in including an additional subgroup into the model. The likelihood ratio tests included were the Lo-Mendell-Rubin Likelihood ratio Test (LMR-LRT; Lo, Mendells & Rubin, 2001) and the bootstrapped LRT (BLRT; McLachlan & Peel, 2000). The BLRT typically outperforms the LMR-LRT in confirming the optimal number of classes (Nylund, Asparouhov, & Muthen, 2007; Tein et al., 2013). Entropy values range from 0 to 1 and signify the degree of classification accuracy. Higher entropy values signify more accurate trajectory classification (Feldman et al., 2009; Nagin, 2005). For selecting optimal models, trajectory classes containing less than 5% membership were not considered (Saunders et al., 2019). Given the iteration process, subgroups containing less than 5% of sample membership are considered unstable and less meaningful clinically (Gueorguieva, Mallinckrodt, & Krystal, 2011; Spinhoven et al., 2016, Smyth et al., 2022).

Multinomial Logistical Regression

Multiple logistical regressions were run to explore the associations between the conduct problem trajectories identified in the GMM analysis and the selected biopsychosocial factors. As a first stage, the biopsychosocial factors that were initially selected were investigated further for their suitability. Descriptive statistics were run for all variables to determine the percentage of missing data values from each biopsychosocial factor. Only variables with less than 40% of their values missing would be included in the study (Jakobsen et al., 2017). Given the large number of excluded participants, the biopsychosocial factors were investigated for differences between the excluded (N=508) and included groups (N=131). If the values of a specific biopsychosocial factor differed significantly between these groups, then that factor were excluded from further analysis. Multicollinearity between variables was also checked using logistic regressions to determine their variance inflation factor (VIF) and tolerance. VIF values above 5 and tolerance values below .2 indicate multicollinearity between factors. The presence of multicollinearity would impact the study's internal validity therefore factors exhibiting multicollinearity were to be excluded (Daoud, 2017). The exclusions of any biopsychosocial factors failing to meet these criteria, helped avoid exclusion bias and ensure the robustness of the study's findings.

After the final selection of potential risk-factors, an analysis of missing data patterns was performed to get a visual representation of the biopsychosocial factors' missing data. This visual representation of missing data was used to determine whether the potential risk-factor data was systematically missing or missing at random (Garcia-Laencina, Sancho-Gomez, & Figueiras-Vidal, 2009; Schafer & Graham 2002). Since the pattern of missing data was considered missing at random, Multiple Imputation (MI) was selected as the most suitable statistical approach for handling the missing data. Compared to other available imputation methods the MI approach reduces the normalized RMSE for data thereby reducing bias (Cheema, 2014). Predictive Mean Matching (PMM) was used to calculate the missing values to account for the non-parametric data

and wide range in distribution values (Horton & Lipsitz 2001; Lee & Carlin, 2017; See Appendix E). Thereafter, multinomial logistical regressions were run to explore the associations between the developmental pathways of conduct problems identified in GMM and imputed data sets of selected biopsychosocial factors. Post-hoc correlations were performed to help establish the level of association between the potential risk-factors. All Statistical analyses were conducted using, the Statistical Package for Social Sciences (SPSS, version 28) and MPLUS software (MPLUS, version 8).

Results

Descriptive Statistics

Participants in the included sample were predominantly male (69%) and struggling with significant language impairments, captured by the BAS mean percentile score of 37.4. Despite the high language impairment of the sample 66% of ASD diagnoses were reported between 7 and 11 years old. Most participants came from a Caucasian background (86%) and were living in two parent households (74.7%). The Maternal education of the sample revealed that few received higher education (20.9%). Data from the study shows that most families earned an income of less than £20,800 per annum, with a significant portion of these families falling below the OECD's defined poverty level, earning 60% less than the median UK income.

Table 1

Descriptive Statistics.

Characteristic	Category	N	%	Cumulative%
Gender	Male	349	68.7	68.7
	Female	100	19.7	88.4
	Missing	59	11.6	100
Ethnicity	White	438	86.2	86.2
	Other	43	8.5	94.7
	Missing	27	5.3	100
Parents at home	Two Parent household	374	73.6	73.6
	One Parent household	107	21.1	94.7
	Missing	27	5.3	100

Family income	£0 – £3,100	7	1.4	1.4
	£3,100 – less than £10,400	129	25.4	26.8
	£10,400 – less than £20,800	144	28.3	55.1
	£20,800- less than £31,200	83	16.3	71.4
	£31,200- less than £52,000	65	12.8	84.2
	£52,000 and above	15	3.0	87.2
	Missing	65	12.8	100
OECD Poverty level	Income above poverty line	293	56.8	56.8
	Income below poverty line	200	38.8	94.8
	Missing	23	5.2	100
Maternal Education	No Qualifications	79	15.6	15.6
	GCSE grades D-G	69	13.6	29.2
	GCSE grades A-C	170	33.5	62.7
	A/AS/S levels	53	10.4	73.1
	Higher Education Diplomas	106	20.9	94
	System Missing	31	6.1	100
Age of ASD diagnosis	Age 5	37	7.2	7.2
	Age 7	162	32	39.2
	Age 11	172	33.9	73.1
	Age 14	137	26.9	100
British Ability Scale: Verbal IQ score	69 and below	313	61.6	61.6
	70-79	47	9.1	70.7
	80-89	7	1.2	71.9
	90-109	36	7.1	79.0
	System Missing	107	21.1	100
Alcohol consumption during pregnancy	Yes	147	28.9	28.9
	No	318	68.4	100

Screening for risk factor suitability

None of the risk factors were missing more than 40% of their data. Significant differences were found between the included and excluded participants in the distributions of five biopsychosocial factors. Ethnic minorities were found in significantly higher proportions amongst excluded participants X^2 (1, n = 610) = 11.51, p =.002. Significant differences were also found in the age children received an ASD diagnosis X^2 (3, n = 639) = 76.6, p < .001. Despite the median age being the same (Median=11), ASD diagnoses were reported slightly earlier in the excluded group of

participants than the included group U=25814.5, z=-3.105, p=.002. CTS scores were lower (mean =17.8) for the excluded group than individuals in the included group of participants (mean =21) U=3259, z=2.139, p=.032. Scores on the approach subscale of the ITS were lower (mean =6.6) for individuals in included than the excluded group (7.6) U=25848, z=2.365, p=.018. The distribution of family income was significantly higher U=13764, Z=2.796, p=.005 for the excluded group (Median=3) than the included group (Median=3). These biopsychosocial factors were subsequently removed from further analysis. The VIF and tolerance values suggests no collinearity violations between gender, alcohol consumption, maternal education, peer problems, parent-child conflict, parent-child closeness, mood, adaptability, verbal ability, and single parent households, which were all included in the multivariate logistic regression (Appendix H).

Identified Trajectories

Missing data analysis revealed 8.3% of the longitudinal conduct problem scores were missing, with 30% of the sample missing at least one data point. Shapiro-Wilk's test revealed that conditions of normality were met, and no additional transformations were needed (Appendix D). The results of the GMM analysis suggested that the best model for conduct problems consisted of 3 distinct trajectories. Since the BIC typically produces more accurate indices than other IC statistics it was used to help determine the optimal model fit (Peugh & Fan, 2012). In the present analysis the BLRT statistic was unhelpful in choosing between models as all models displayed significant BLRT values. The findings suggests that the presence of additional subgroups continued to improve the models fit. While the BIC value was lowest in the model using four trajectories, subgroup membership fell below 5% for one of the classes. Therefore, the three trajectories model was selected for the present study, as it contained the lowest BIC statistic with sufficient subgroup membership.

Figure 1 Conduct Problem Pathways

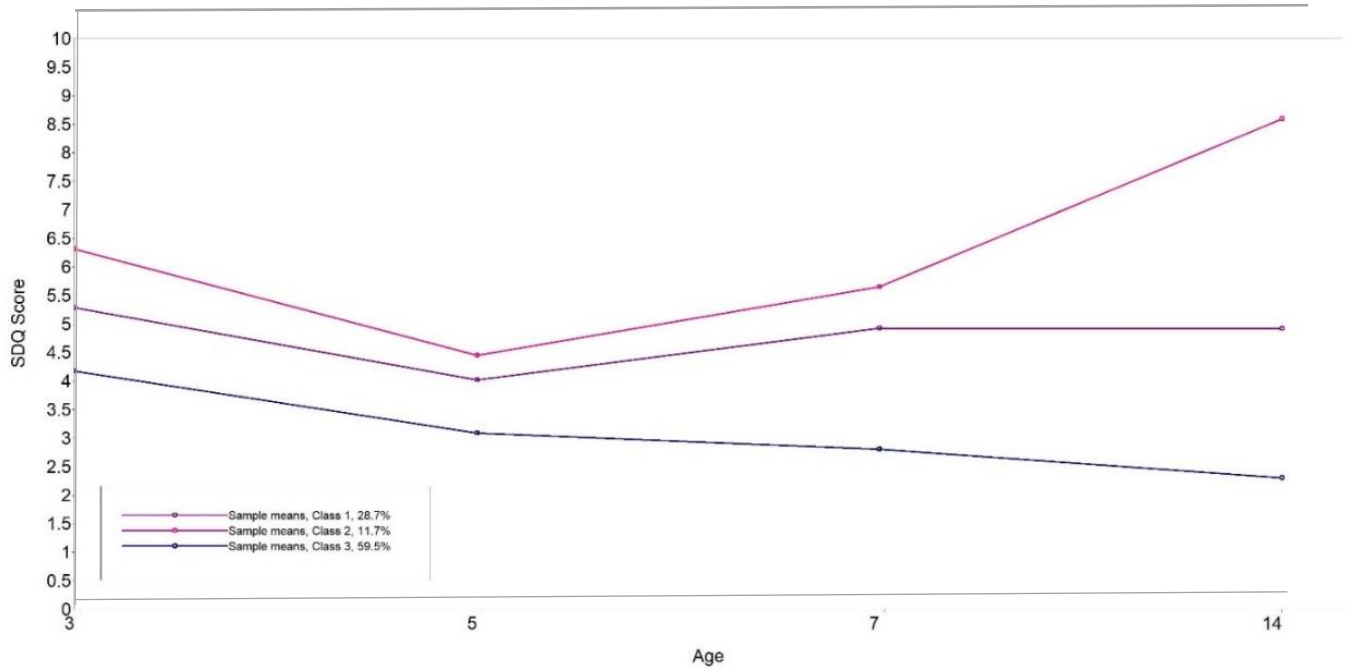

Table 2: Classes membership

		Subgroup1	*Subgroup2*	*Subgroup3*	*Subgroup4*	*Subgroup5*
Class 2	N	432	76	-	-	-
	%	85	15	-	-	-
Class 3	**N**	**146**	**51**	**302**	-	-
	%	**28.7**	**11.7**	**59.5**	-	-
Class 4	N	37	24	135	312	-
	%	7.3	4.7	26.6	61.4	-
Class 5	N	136	24	302	34	12
	%	26.8	4.7	59.4	6.7	2.4

Note: bold indicates the number of trajectory classes creating the best fit using GMM analysis.

The Class numbers indicate the number of trajectories found in each model

The Subgroups capture the number of individuals in each distinct trajectory

Table 3: Model Fit Indices

	AIC	*BIC*	*SABIC*	*LMR-LRT*	*BLRT*	*Entropy*
Class 2	7622.099	7719.4	7646.395	0.2398	0.002	0.79
Class 3	7598.805	7717.259	7628.383	0.1611	0.001	0.728
Class 4	7568.223	7707.829	7603.083	0.2398	0.001	0.794
Class 5	7555.482	7716.24	7595.624	0.2398	0.001	0.804

AIC: Akaike information criteria; BIC: Bayesian information criteria; SABIC: Sample size adjusted BIC; LMR-LTR: Lo-Mendell-Rubin likelihood ratio test; Bootstrap-LRT: Bootstrapped likelihood ratio test. Bold values indicate best model fit indices.

Multinomial Logistic Regressions

Missing data imputation

Missing data from the biopsychosocial variable ranged from 5.3% to 24.8%. Of the included participants 247 were missing at least some data with an overall, of 11.8% of the data values missing. Visual representation of missing data was non-monotonic, suggesting data values were missing at random (Appendix F). Von Hippels (2020) quadratic equation suggests that 4 imputed datasets would be sufficient for the current sample. However, lower imputations can cause problems of replicability. Therefore Rubin's rule was used for determining the number of imputations which was increased to 25 to ensure the reliability of our results (Bodner, 2008; White, Royston, & Wood, 2011).

Associations between risk-factors and conduct problem development

Multinomial logistical regressions identified several associations between risk-factors and conduct problem trajectories. Children scoring higher on the CPRS conflict scale at three years old were more likely to develop conduct problems of persistent (OR = 1.075; CI: 1.036, 1.115, p <.001) and escalating severity (OR = 1.087; CI: 1.026, 1.152, p = .005), compared to children falling into the desisting severity group. Lower levels of maternal education were also related to an increase likelihood of persistent (OR =.703; CI: 0.589, 0.839 p <.001) or escalating conduct problems (OR =0.665; CI: .512, .864 p = .002), compared to those children falling into the desisting conduct problems group. Among children displaying chronic conduct problems, living in two-parent

households served as a protective factor against the escalating conduct problems (OR = 0.475; CI: .23, .982, p = .044). No significant associations were found for gender, alcohol consumption, verbal disability, mood, adaptability, peer problems, and parent-child closeness. A post-hoc Pearson's correlation coefficient revealed most of the potential risk-factors to be significantly correlated with one another. However, these correlations were generally weak (table 3).

Table 4

Multivariate Analysis of Conduct Problem Trajectories

	Persistent CP (vs Desisting)			Escalating CP (vs Desisting)			Escalating CP (vs Persistent)		
	OR	95% Cis	p-value	OR	95% Cis	p-value	OR	95% Cis	p-value
Peer Problems	0.901	0.803;1.01	0.075	0.976	.828;1.151	0.772	1.060	.904;1.242	0.474
ITS Mood	0.983	0.927;1.04	0.569	0.950	.871;1.037	0.252	0.879	.674;1.147	0.342
Maternal Education	**0.703**	**0.589;0.839**	**<0.001**	**0.665**	**.512;.864**	**0.002**	1.012	.962;1.065	0.641
CPRS Conflict	**1.075**	**1.036;1.115**	**<0.001**	**1.087**	**1.026;1.152**	**0.005**	0.994	.911;1.086	0.902
CPRS Closeness	1.023	0.949;1.101	0.555	1.014	.912;1.127	0.800	0.978	.905;1.057	0.572
ITS Adaptability	1.001	0.910;1.102	0.977	1.006	.877;1.153	0.934	1.088	.507;2.332	0.829
Gender (Male)	0.951	0.557;1.624	0.855	0.996	.449;2.206	0.992	0.791	0.362;1.729	0.556
Parents at home (Two Parents)	1.439	0.827;2.507	0.198	1.002	.466;2.154	0.996	**0.475**	**.23;.982**	**0.044**
Verbal Disability (Below 70 VIQ)	1.572	0.915;2.70	0.102	1.178	.514;2.699	0.699	0.925	.466;1.837	0.824
Alcohol Consumption	0.653	0.406;1.05	0.079	0.639	3.09;1.322	0.227	1.060	.904;1.242	0.474

CPRS: Child parent relationships scale, CP: conduct problems, ITS : Infant Temperament Scale

Table 5

Pearson's Correlation Matrix

	Peer Problems	Maternal Education	CPRS Conflict	CPRS Closeness	Verbal IQ	ITS Mood	ITS Adaptibilty	Parents living in Household	Gender	Alcohol consumption
Peer Problems	1	-.083**	.256**	-.347**	0.011	-.110**	.037**	.095**	.045**	.028**
Maternal Education	-.083**	1	-.086**	.143**	.113**	-.026**	-.049**	-.264**	0.004	.139**
CPRS Conflict	.256**	-.086**	1	-.172**	-.020*	-.050**	-.040**	.110**	.059**	.038**
CPRS Closeness	-.347**	.143**	-.172**	1	.047**	.073**	-0.014	0.003	-.046**	.047**
Verbal IQ	0.011	.113**	-.020*	.047**	1	.094**	-.038**	-0.001	-0.010	.096**
ITS Mood	-.110**	.026**	-.050**	.073**	.094**	1	-.240**	0.007	-.053**	-.035**
ITS Adaptability	.037**	-.049**	-.040**	-0.014	-.038**	-.240**	1	-.040**	-0.010	-.075**
Parents living in Household	.095**	-.264**	.110**	0.003	-0.001	0.007	-.040**	1	.031**	-.104**
Gender	.045**	0.004	.059**	-.046**	-0.010	-.053**	-0.010	.031**	1	-.077**
Alcohol consumption	.028**	.139**	.038**	.047**	.096**	-.035**	-.075**	-.104**	-.077**	1

Notes **. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

Discussion

Identification of trajectories

GMM analysis identified three distinct patterns of conduct problem development in individuals with ASD from early childhood to adolescence. Most children (59.5%) displayed diminishing conduct problems severity over time. Another group (28.7%) of children developed persistent conduct problems, and the smallest group of children (11.7%) developed escalating conduct problems which progressively worsened by early adolescence. The conduct problems of these children with ASD started off in a non-normative range however by early adolescence the large majority of these children's problems diminished and ended up falling within a normative range of conduct problems severity (Vugteveen, de Bildt, & Timmerman, 2022). There was an initial improvement in conduct problems across all group trajectories, from ages 3 to 5. This trend mirrors normative development, whereby tantrums and other conduct problems decline as toddlers mature into early childhood (Barker & Maughan, 2009). Between the ages of 5 and 7, children who exhibited higher levels of conduct problems trended towards displaying similar or increased levels of problematic behaviour. Meanwhile, children with ASD and lower initial SDQ conduct problem scores were likely to reduce their problematic behaviour overtime (Stringer et al., 2020). For children with higher scores on the SDQ conduct problem subscale, ages 7 to 14 years seems to be a critical period which determines whether conduct problems persisted at a moderate level or whether they escalated in severity. The trajectories identified in the current study closely resembles the findings of Gray and his colleagues (2012) who investigated conduct problem trajectories in individuals with ASD. Their study identified three trajectories of conduct problems within their sample, the majority of individuals' displayed conduct problems which diminished overtime (61.8%). The remaining individuals displayed conduct problems whose severity remained persistent (22.5%) or escalated in severity (15.7%). The similarity between Gray's (2012) finding and the trajectories identified in the present study provide further support for the current model.

Multinomial Logistical regression of Biopsychosocial Model

The results from the multinomial logistical regression found lower maternal education levels, early parent-child conflict, and number of parents living at home, to be associated with conduct problem severity in adolescents. Increased parent-child conflict slightly increases the likelihood of children developing persistent and escalating conduct problems in adolescence, compared to children whose conduct problems desist. Lower maternal education was also associated with persistent and escalating conduct problem developing in early adolescence. Low maternal education was 4 times more strongly associated with the development of future conduct problems than conflictual parent-child relationships. The influence of parent-child conflict and of high SED on conduct problems in ASD children has already received substantial support in the scientific literature (Bevilacqua et al., 2018; Flouri et al., 2015; Frick, Christian, Wooton, 1999).

Two-parent households were strongly associated with an increased likelihood of children developing persistent as opposed to escalating conduct problems in adolescence. To our knowledge previous research has not explored the influence single parent households have on conduct problem development in children with ASD. Studies of non-autistic children found parents are better able to manage their children's conduct problems with the help of a spouse (Webster-Stratton & Hammond, 1990). In cases where there is a lack of spousal support, such as in single parent households, parents tend to be less resilient against stressors stemming from SED and may be less equipped to meet the psychosocial needs of their children, which also often leads to increased parent-child conflict (Orthner, Jones-Sanpei, & Williamson, 2004). The stress of raising children with extra needs, such as individuals with ASD, only exacerbates the difficulties experienced by parents (Baker-Ericzén, Brookman-Frazee, & Stahmer, 2005). When it comes to dealing with managing children's difficult behaviour this extra support is significant. Therefore, it comes as no surprise that children with ASD growing up in two-parent

households are at reduced risk for their moderate conduct problems escalating into more severe behavioural infractions.

The results from the correlation matrix suggest that some biopsychosocial variables, while not directly associated with the conduct problem development, may influence the existing associations between other risk-factors. There is a near significant association between early peer-problems and the likelihood of children with ASD developing persistent conduct problems, compared to diminishing ones. Early peer relationships have limited predictive ability over peer relationships in adolescence (Becker, Rothenberger, & Sohn, 2015), at which stage they are more likely to influence adolescent behaviour (Hopkins, Yuill, & Branigan, 2021). The near significant association may be due in part due to the correlation between peer problems and parent-child relationships (Elicker, England, & Sroufe, 2016). Previous studies found temperament to be associated with increased conduct problems in ASD (Chetcuti et al., 2021). However, these studies did not control for potentially confounding variables. In the present study, when controlling for other potential risk-factors, no association was found. Consistent with research of non-autistic children, there was a significant correlation between temperament, maternal education, parent-child conflict, in addition to many of the other biopsychosocial factors (Jansen et al., 2009; Kim-cohen et al., 2004). Similarly, maternal closeness was also not associated with conduct problem as expected but was significantly correlated with several other biopsychosocial factors. Given the interaction between these factors, future research should investigate them for the potential moderation effects.

Strengths and Limitations

The following study contributes to the growing body of research on the influence of biopsychosocial risk factors on conduct problem trajectories in children confirming, clarifying, and extending previous research to the ASD population. The study confirms the findings of other relevant studies concerning SED and parental relationships as a significant risk-factors

for chronic conduct problems in ASD children. The study clarifies that in the presence of a more comprehensive model temperament does not increase the conduct problem severity for children with ASD, contrary to previous meta-analytic findings. The study also extends the finding from non-autistic population concerning the importance of two-parent households as a mitigating factor against increased conduct problem severity in children with ASD. While most studies explored the risk factors associated with the development of conduct problem in early childhood (Flouri et al., 2015; Midouhas et al., 2013) and adulthood (Gray et al., 2012; Shattuck et al., 2007; Stringer et al., 2020; Taylor & Seltzer 2010), our study expands on the limited conduct problems research of ASD children in emerging adolescence (Colvert et al., 2021).

Despite the current study's strict research methodology, it suffers from some limitations of external validity. The children recruited as part of MCS come disproportionately from low-income families (Plewis 2017). More than 70% of individuals from our sample came from families that earned below the average UK salary (Clark, 2021). The ages of ASD diagnoses found in the MCS were also found to be significantly different from the diagnostic ages found in the ASD population. The median age of reported ASD diagnosis within the MCS was 11 years old, while the median age of diagnosis within the UK is 55 months (Brett, Warnel, McConachie, & Parr, 2016). There are several explanations behind the late diagnoses found in the MCS sample including cognitive delays, low parental concern, and high SED (Hosozawa et al., 2020). Furthermore, the study sample consisted of 86% Caucasians, with minoritized ethnicities appearing in higher proportion in the excluded group of participants. Since the study findings apply to a specific subsection of the ASD population they should be interpreted with some caution.

The absence of important risk factors from the multivariate logistical analysis may also impact the internal validity of the present study. The impact of early intervention is pivotal to improve conduct problems. Children who receive early help from children's mental health services are

less likely to develop chronic conduct problems. However, information on early therapeutic or behavioural interventions was not available given the limitations of the MCS data (Fitzpatrick 2016; LaVigna & Willis, 2012). Also, notably absent from the multinomial logistic analysis is a measure considering the severity of ASD impairment. Shattuck and his colleagues (2007) found conduct problem severity to be positively correlated with the degree of ASD impairment. Conversely, Stringer and his colleagues (2020) could not find any significant association between ASD severity and conduct problem development. Future research should incorporate ASD severity and early interventions alongside the identified risk factors to provide a more comprehensive understanding of conduct problem development.

While the current study identified associations between maternal education and child-parent conflict on conduct problem development, the exclusion of important biopsychosocial factors throws the reliability of these associations into question (Yu & Li, 2020). ASD severity moderates the link between conduct problems and parenting style (Dieleman et al., 2018). The greater the severity of ASD impairments the more reactive children are towards parenting style. There is also a strong correlation between disciplinary action and parent-child conflict (Wang, Wang, Wang, & Wang, 2021). Given the omission of parental discipline and ASD severity from the model, it is unclear whether the weak association of parent-child conflict is a confounding risk factor. Family income and maternal education define different aspects of SED, which are highly correlated with one another (Pepper & Nettle, 2017). The absence of family income from the multivariate analysis may have also inflated the association between maternal education and conduct problem development.

Future Directions

The current study focused on the risk factors associated with conduct problem trajectory without considering their many different presentations. Frick and colleagues (1993) subdivided different conduct problems into categories: proactive/reactive, overt/covert, and

internalizing/externalising based on their presentation. These categories are distinguishable from one another, not only in their aetiology but also their potentially risk factors for children with ASD (De Pauw et al., 2011). For example, boys are said to exhibit more overt conduct problems than girls (Storvoll, & Wichstrøm, 2002). While no gender differences were found in the present study, this may have been due to exploring conduct problems as a single undifferentiated group. Differentiating between types of conduct problems and mapping their developmental trajectories could lead to improved methods of pre-emptive identification and treatment of at-risk children with ASD.

Exploring the time sensitive influence of different risk factors over conduct problem development would enhance the understanding of conduct problem development at different stages of maturity. The influence of peer relationships and language ability over conduct problem development is different from childhood to adolescence (Driscoll & Pianta, 2011; Hopkins, Yuill, & Branigan, 2021). The relationships of SED over mental health outcomes also changes as individuals mature (Williams, Cunich, & Byles, 2013). The present research focused on exploring the association of early risk factors on later conduct development. Most of the included biopsychosocial factors were not measured across multiple time periods in the MCS. Future research might use generalization estimation equations to explore the associations between time sensitive risk factors and conduct problem development, across multiple time periods (Ye & Pan, 2006).

Conclusions and Clinical Recommendations

Research has long underscored the importance of early treatment for children with ASD. Determining which children have the greatest risk of future conduct disorders would allow for pre-emptive treatment and improved prognoses. Children with ASD often struggle with conduct problems in early life yet only a small proportion become chronic overtime. The present study identified maternal education and early parent-child conflict as associated risk

factors for persistent and escalating conduct problem severity. The study also identified single parent households as an associated risk factor for children developing escalating conduct problems during adolescence over children whose conduct remain persistently moderate. Clinicians' awareness of these risk factors during early assessments of ASD, can help them flag children at-risk for future psychopathology and fast track them towards receiving early interventions, potentially easing the burdens of services having to treat more entrenched conduct disorders. Children with ASD and severe conduct problems could be placed on different clinical pathways depending on whether they are suspected of persistent or escalating risk. Some questions remain as to the causal relationships between these associated risk-factors and future research should continue to explore the influence of biopsychosocial variable over conduct problems development.

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Part III: Critical Appraisal

Introduction

The following section of the thesis offers a critical appraisal of the empirical research in section two. It starts by describing my initial interest in pursuing this research topic. I address some of the advantages of using secondary data. Later on, the challenges encountered and implications of some of the decisions made during the research are addressed. Finally, I reflect on some lessons I learned from the research process.

Choosing a research topic

The initial appeal, in studying developmental trajectories of conduct problem severity, stemmed from an interest in understanding and improving treatment outcomes. Over the last decade, group-based trajectory modelling was increasingly used by clinical researchers as a means of understanding the aetiology and development of psychiatric disorders (Nagin & Odger, 2010). Group-based trajectory modelling is also used to identify subgroups of vulnerable populations, (Neiman & McGorry, 2015), assist clinicians in determining the effectiveness of interventions (Frankfurt, Frazier, Syed, & Rae Jung, 2016), and understand the heterogeneity of outcomes in randomized clinical trials (Brown et al. 2008; Odger et al., 2008a; Peer & Spaulding 2007). Clinicians may understand the aetiology of psychiatric difficulties, but their responsibility to appropriately treat an individual's psychiatric difficulties based on the unique circumstances and needs of clients can be more challenging. Modelling techniques provide clinicians an opportunity to understand psychiatric problems, explore the impact of different treatments, and determine what interventions work and with whom.

Studying the developmental trajectories of conduct problem severity in children with ASD also held significance given my personal experience of growing up with a younger brother diagnosed with autism and my work at different ASD organizations. A year prior to starting the clinical psychology doctorate, I volunteered at NAS working with adolescents with ASD. Working with children with ASD afforded me the opportunity to connect with many parents who spoke candidly about the challenges involved in raising children with ASD, as well as

some of the behavioural challenges their sons or daughters experienced. Most of these children received early interventions and overcame their behaviour challenges. The following year, I began working at a learning disability service as a trainee clinical psychologist. While there, I was assigned to work with several families with a child diagnosed with ASD. Some of these parents struggled to manage their children's disruptive behaviours. One family struggled to receive a diagnosis for their child's ASD and were unable to initially obtain services. Another family did not approach services for help until their child's behavioural problems became unmanageable. The experiences of their children's behavioural challenges differed profoundly between the two services and between families. Many of their challenges resonated with my own experience, growing up with my younger brother. While my brother has consistently grown in his abilities and independence, I wondered what differentiated his experiences growing up with ASD from that of other similarly diagnosed children. What separated the children whose challenging behaviours improved from those whose challenging behaviours persisted?

As a clinical psychology trainee, I have had the opportunity to work on multiple services and have administered psychometric questionnaires to dozens of clients. Similar to the SDQ, the psychometric measures of the GAD7, PHQ 9, and RCADS were helpful in providing a clinical snapshot of a client's difficulties at a specific point in time. However, these measurements did not provide me with more holistic information as to why interventions worked well for some clients while other clients continued to struggle. One of the significant advantages of trajectory modelling is its potential in guiding treatment and influencing service planning. During a business meeting on my final placement, my clinical supervisor was discussing the possibility of hiring researchers to track the therapeutic progress of the services clients to support the service's development. This brief but frank discussion helped underscore how important it was for service planning to measure the developmental trajectory of their patients' growth and

validated my research choice. I hope to bring the lessons I learned as part of the empirical research, specifically the data modelling skills I have developed, to my next clinical position.

Starting out: advantages and disadvantages of using secondary cohort data

Advantages

The empirical research is based on retrospective data from the Millennium Cohort Study (MCS; IOE, 2022). Working with the MCS data had some practical and methodological advantages. From a practical perspective cohort data allowed me to bypass some bureaucratic difficulties typically involved in the recruitment and data collection process (Rule & LeGouill, 2019). The MCS already received ethical approval for its data collection. Consequently, receiving approval for using MCS secondary data was a relatively simple process, involving an online application. Ethical approval was received within the same week the application was filed. Trying to recruit children from vulnerable populations is often challenging. Many of my colleagues struggled both obtaining the ethical approval necessary and during recruitment process. Having participants' data readily available proved to be especially important during the COVID-19 pandemic when contact with people outside one's immediate household was limited.

The MCS data contained some significant methodological strengths as a cohort study. The MCS collected data across 20,017 variables from hundreds of children with ASD across 6 time periods. The large sample size provided strong statistical power to support the study's findings (Cohen 1992). The longitudinal nature of cohort studies provided researchers, the unique ability to explore and compare developments across multiple time periods (Andy Boyd et al., 2019). Given these methodological strengths cohort data is often used to make significant contributions to shaping healthcare policy and is frequently involved in important epidemiological discoveries (Joshi & Fitzsimons, 2016).

Disadvantages

Since I did not recruit participants or collect data, I needed to work within the limitations of the MCS study. To support such an audacious study there needs to be a substantial amount of financial backing. Therefore, its unsurprising that the MCS received financial backing from the Economic and Social Research Council (ESRC) and was co-funded by multiple governmental departments (Joshi & Fitzsimons, 2016). The interests of funding bodies shape cohort studies' objectives and concomitantly influence both the recruitment and data collection. These objectives unfortunately led to several significant study limitations in the empirical study. The MCS, aimed to investigate "the role initial conditions of social, economic, and health advantage and disadvantages" play in children's development (CLS, 2022). Risk factors such as autism severity were not collected as part of the MCS, since they bore little relevance on the initial MCS objectives (Joshi & Fitzsimons, 2016). Furthermore, since the study of autism was not an area of central relevance, participants' ASD diagnoses were based on parental self-report. Using parental reported diagnoses ASD is not ideal given the potential for parental bias (Daniels et al., 2011; Moricke, Buitellar, & Rommelse, 2016) it was the only information available. The MCS also used stratified sampling to disproportionately represent the children from socioeconomic disadvantaged backgrounds. Given the significant impact of socioeconomic disadvantage over other potential risk factors involved in the empirical study, the stratified recruitment sampling ultimately limited the generalizability of the research results.

Model parsimony and choosing which variables to include

I was initially encouraged by the number of variables I could choose from to perform a multivariate analysis. However, the ability to choose from so many variables proved less useful than I initially anticipated. Many of the MCS variables were missing large amounts of data and few provided the degree of resolution necessary to include them into this research. Even still the MCS contained far too many variables than could be included in a multivariate logistic

regression. Including too many independent variables can lead to saturated regression models and false associations (Lewis, 2007; Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996; van Domburg, Hoeks, Kardys, Lenzen, & Boersma, 2014).

Dodge and Pettit's biopsychosocial model provided a strategic framework for selecting potential risk factors to include in the analysis (2009). Using this comprehensive model, I was able to limit the variables used in the analysis to those which belonged to peer relationships, parenting relationships, cognitive, biogenetic, and sociocultural categories. Nevertheless, even limiting categories left too many variables to select from. For example, the MCS contained multiple variables which captured different aspects of parenting relationships. The child-parent relationships scale measured parent's closeness and conflict with children (Driscoll & Pianta, 2011). The Conflict Tactic Scale measured the frequency of disciplinary tactics used in parenting (Straus & Hamley, 1997). The Rutter Malaise inventory measures the wellbeing of parents (Rutter, Tizard, Whitmore, 1970). The Maternal Attachment Questionnaire explores maternal attachment towards their infants (Condon & Corkindale, 1997). The Parenting Beliefs Questionnaire explored different beliefs around parenting (Niarchou, Zammit, & Lewis, 2015). Each one of these variables might have been associated with the development of conduct problems. Adhering to the principle of parsimony I tried to select the variable that best captured the influence of parenting on conduct problems (Epstein 1984). This process involved determining which concepts were worth investigating by exploring their use in previous studies and examining the psychometrics of each measure. For the current study I selected the child-parent conflict scale to use in the multivariate analysis, the result of which showed that the child-parent conflict was only weakly associated with the likelihood of children developing chronic conduct problems. It would be interesting to see how different measure of parental style might have influenced the study's results. For example, the maternal attachment or the

parenting beliefs questionnaires might have interacted with the other biopsychosocial factors in the current study in a manner that would impact the results.

Choosing a statistical method for trajectories mapping

There are multiple statistical methods available for latent class trajectory modelling. The choice between these statistical methods is ultimately determined by the nature of the underlying data including the type of statistical distribution, variables, and study design (Lore et al. 2020). Given the parameters of my data, growth mixture modelling (GMM) and group-based trajectory modelling (GBTM) were the viable options for mapping out the conduct problem trajectories. GBTM and GMM have been used for mapping out behavioural scores and more specifically conduct problem severity (Connell & Frye, 2006; Wojciechowski, 2020). I initially considered using GBTM as it required a simpler statistical calculation (Nguefack et al., 2020). However, I wanted to account for the natural heterogeneity that occurs within groups. Therefore, I decided to calculate the latent trajectories using GMM analysis.

The software packages commercially available for performing GMM analysis are MPLUS and R (Nguefack et al., 2020). R software and MPLUS are comparable in their statistical accuracy and computational abilities (Wardenaar, 2020). I recently completed a meta-analysis with R but otherwise had no previous experience. My limited experience made me apprehensive of calculating trajectories with R given the level of coding required. Nevertheless, R is known to be more versatile and less costly than MPLUS which appealed to me.

I started to learn lcmm, the package in R dedicated to GMM analysis (Nguefack et al., 2020). I found multiple online guides for lcmm and was optimistic I would be able to perform the necessary code without much difficulty. I soon became aware that to perform my intended analysis in R, I needed to learn multiple additional packages for potentially transforming skewed data and graphing the trajectories. The coding proved more complicated than I anticipated and I spent nearly two months trying to learn R packages before I decided to

abandon my efforts and use MPLUS. While MPLUS requires coding, it was significantly less complex, and I was able to complete my desired analysis without much difficulty.

Working with missing data

One of the unforeseen challenges in working with cohort data was learning how to manage missing data. The variables selected for the empirical paper contained a large amount of missing data. In past, research projects, participants who failed to complete even a single question from the study were excluded using listwise deletion. Using listwise deletion in the current study, would have left a significantly smaller study sample. The challenge was to manage the missing data and preserve the statistical power of the MCS while minimizing the introduction of bias.

Thus began the search for the best practices for imputation missing data (Jackobson et al., 2017). Multiple imputation (MI) outperforms Maximum Likelihood computations of missing data when working with larger sample (von Hipple, 2016). I calculated the multiple imputation needed to perform a multivariate logistic regression using a regression model. Only after further research, it became clear that a regression model of imputation would produce greater bias estimations given the non-normality of my underlying data. Subsequently, I moved towards MI calculations using Predictive Mean Matching (PMM) which produces less bias when using non-parametric data (Horton & Lipsitz 2001; Lee & Carlin, 2017).

In the present study, a considerable amount of data was missing from the SDQ on the conduct problems subscale. Children from the MCS were administered the SDQ conduct problem scale across 5 time periods from age 3 until 14. For the majority of the time periods, the SDQ was completed by parents. However, at age 11 the SDQ scale was completed by children's teachers. More than 40% of the sample's teacher reported conduct scores were missing. A separate study found substantial disagreement in the SDQ scores given by the parents and teachers in the

assessment of children (Cheng et al., 2018). While MI methods for missing data are available for GMM, they rely on pre-existing data to compute the missing values. Due to the disagreement between parent and teacher scoring, imputing missing data using parental reports was unsuitable. The decision to continue with GMM analysis, without including the teacher SDQ scores as a variable, helped mitigate against biased trajectories (Jakobsen et al., 2017; Prokhorov, & Schmidt, 2009; Muthén, Asparouhov, Hunter, & Leuchter, 2011).

The decision to remove the teacher SDQ data reduced the current sample size of the study from 5 to 4 time periods. Since GMM analysis requires a minimum of 3 time periods, participants missing SDQ scores from more than one of these remaining time periods were excluded (Wickrama., Lee., O'Neal, & Lorenz, 2021). Given the missing number of conduct scores, only 79% of the 639 children that were originally identified as having ASD were included in the final analysis. While the need to remove additional participants from the analysis was statistically disappointing it assisted in insuring the validity and accuracy of the research (Nagin & Odgers, 2010).

Given the large number of participants that were excluded from the analysis, it was important to investigate for distribution differences between excluded and included participants to help ensure the external validity of study's findings. Given the non-parametric nature of the biopsychosocial factors, the Chi Square Test and the Mann-Whitney Tests was used for this purpose. The results of these tests bore out 5 biopsychosocial factors that significantly differed between the included and excluded groups. These factors: ethnicity, age at time of ASD diagnosis, the approach scale, the conflict tactic scale, and family income, were all subsequently excluded from the multivariate logistical analysis. Including these variables into the analysis would have made it difficult to generalize the results. The challenges of how to manage missing data in GMM analysis is familiar problem to researchers. The researchers often need to make decisions between biasing findings and the relative efficiency of conducting

research (Abrevaya & Donald 2017). In the current study I chose to address the issues of potential bias over preserving the efficiency of the study.

Final Thoughts

Before starting the current project, my research experience with GMM was non-existent and I never worked with cohort data before. Nevertheless, I naively believed that my prior research would prove a strong foundation for this study. That was not the case. Many of the pivotal decisions in my prior research were made by my project supervisor. With the current empirical research, I had more independence in the research process. I use my judgement to make decisions based on my own investigation, and sometimes learned by trial and error. Each step in the methodological and statistical decision-making process appeared to have a cascading effect on the next step in the research process. Consequently, the importance of making the best-right decision was impressed upon me. These experiences emphasized the critical importance of research planning and bore witness to how much more I needed to learn and understand than I originally anticipated. Despite these challenges, I am pleased to have chosen to engage in the empirical research and learn growth mixture modelling. The fact that the study revealed several novel findings concerning the risk factors underlying conduct problem development, was rewarding. I feel satisfied that this study has contributed a small step in advancing our understanding the conduct problems in ASD children. It is my hope that some children with ASD, like my brother, will benefit from this analysis.

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Appendices

Appendix A.

PsycInfo Search

1	Autis*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]
2	exp Autism Spectrum Disorders/
3	exp Oppositional Defiant Disorder/
4	Oppositional defiant disorder.mp.
5	exp Conduct Disorder/
6	Conduct disorder.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]
7	(Conduct adj3 disorder).af.
8	(Oppositional Defiant adj3 disorder).af.
9	3 or 4 or 5 or 6 or 7 or 8
10	1 or 2
11	9 and 10

Medline Search

# 8	# 7 AND # 8
# 7	#5 OR #4 OR #3
# 6	#2 OR #1
# 5	(TS=PDD-NOS or TI= PDD-NOS)
# 4	(TS= Asperge* or TI= Asperge*)
# 3	(TS=Autis* or TI=Autis*)
# 2	(TS=("Conduct disorder"))
# 1	(TS=("oppositional defiant disorder"))
	Parameters: LANGUAGE: (English) AND DOCUMENT TYPES: (Article) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Appendix B.

Quality Appraisal Tool: adapted from Hoy et al. (2012)

Items	Notes	Scores
ITEM 1: Was the studies population a close representation of the national population in relation to relevant variables	This question aimed at the exclusion of subtypes in the population that would fall under the DSM 5 definition of autism. Rhett's disorder and Childhood disintragrative disorder would not be applicable.	0 - Yes 1 - No
ITEM 2: Was the sampling frame a true or close representation of the target population? AKA -Were any additional diagnostic restrictions made on the sample?	These applied to demographic differences including gender, intelligence. **Additional notes:** Certain ASD subtypes have specific phenotypes. For example, Asperger's is associated with higher IQ.	0 - No 1 - Yes
ITEM 3: Where was the study sample recruited from.		0 – Epidemiological or community sample 1 - Mixed sample 2 - Clinical sample
ITEM 4: Was some form of random selection undertaken		0 - Yes 1 - No
ITEM 5: Was the likelihood of non-response bias minimal	This question is focused on the rate of dropouts from the number of participants initially included in the study	0 - 75%+ response rate 1 - Less than 75% respor
ITEM 6: Was the same mode of data collection undertaken for all subjects?		0 - Yes 1 - No
ITEM 7: What was the accuracy of diagnosis within the sample?	Accuracy was determined by the lowest accuracy rating of diagnostic tools	0 - Accuracy of both diagnoses are excellent 1- Accuracy of one diagr was excellent and one moderate 2 - Both diagnoses had moderate accuracy 3 - Accuracy is poor for or both of the relevant diagnoses

*The accuracy of each study's diagnostic tools was appraised separately using statistical margins delineated by Landis and Kock (1977). Several methods were used to appraise a tools diagnostic accuracy. A tools sensitivity, specificity, area under the ROC curve, and diagnostic odds ratio are all used to measure the statistical accuracy of diagnostic tools (Šimundić 2009). When these values were unavailable, interrater reliability was used to assign a statistical value to the diagnostic tools. If multiple diagnostic measures were used, the diagnostic accuracy was appraised based on the tool with the highest accuracy. Several studies did not make use of diagnostic measures, but instead relied on participants' clinical records. Clinical records were assigned the highest categorical value given their strong validity and reliability (Hagberg and Jick, 2017).

Appendix C.

Table 1.2 – The following table displays the scores the studies earmarked for inclusion into the meta-analysis and their score on the modified quality appraisal tool seen in Appendix B.

Questions	***Q1***	***Q2***	***Q3***	***Q4***	***Q5***	***Q6***	***Q7***	***Sample Bias Q1-Q5***	***Total Bias Score***	***Bias Level***
Bryson et al.	0	1	2	1	0	0	1	4	5	Moderate
Leyfer et al.	0	1	0	1	0	0	0	2	2	Low
Kaat, Gadow, & Lecavelier	0	0	2	1	1	0	1	4	5	Moderate
Mattila et al.	1	0	1	1	0	0	0	3	3	Low
Gjevik et al.	0	0	0	1	0	0	0	1	1	Low
Salazar et al.	0	0	0	1	1	0	1	2	3	Low
Levy et al.	0	0	0	0	0	0	0	0	0	Low
Simonoff et al.	0	0	0	0	1	1	1	1	3	Low
Mayes et al.,	1	0	2	1	0	0	1	4	5	Moderate
Vasa et al.	0	1	2	1	1	0	1	5	6	Moderate
de Bruin et al.	1	0	2	1	0	1	0	4	5	Moderate

Skwerer et al.	0	1	0	1	0	0	1	2	3	Low
Hayashida et al.	0	0	2	1	0	0	1	3	4	Moderate
Amr et al.	1	0	2	1	0	1	0	4	5	Moderate
Pugliese et al.	1	1	2	1	0	0	0	5	5	Moderate
Mukaddes, Herguner & Tanidir	0	1	2	1	1	0	0	4	5	Moderate
Mukaddes & Fateh,	1	0	2	1	0	0	1	4	5	Moderate
Stratis & Lecavalier,	0	0	1	1	0	0	2	2	4	Moderate
Araz Altay et al.	0	0	2	1	0	1	0	3	4	Moderate
Barnevik et al.	0	0	2	1	1	0	3	4	7	High
Green et al.	1	0	2	1	0	1	3	4	8	High
Lamanna et al.	0	1	2	1	0	1	0	4	5	Moderate

Article Authors	*Diagnosis Tools for ASD*	*Accuracy*	*Diagnostic Tools for Co-occurrence*	*Accuracy*
Bryson et al.	Clinical Records	Excellent	CBCL medical records / GAF	Moderate
Leyfer et al.	ADOS + ADI-R	Excellent	ACI-PL	Excellent
Kaat, Gadow, & Lecavelier	ADOS/Medical records	Excellent	CASI-4R	Moderate
Mattila et al.	ASSQ (Autsim screening Questionnaire)	Excellent	K-SADS-PL + CGAS	Excellent
Gjevik et al.	ADI-R+Previous Diagnosis	Excellent	K-SADS-PL	Excellent
Salazar et al.	Clinical Records (Full assessment) + SCQ	Excellent	PAPA	Moderate
Levy et al.	Clinical Records / Educational Records	Excellent	Clinical Records	Excellent
Simonoff et al.	Clinical Records (autism project) +SCQ	Excellent	CAPA	Moderate
Mayes et al.,	Clinical Assessment	Excellent	PBS	Moderate

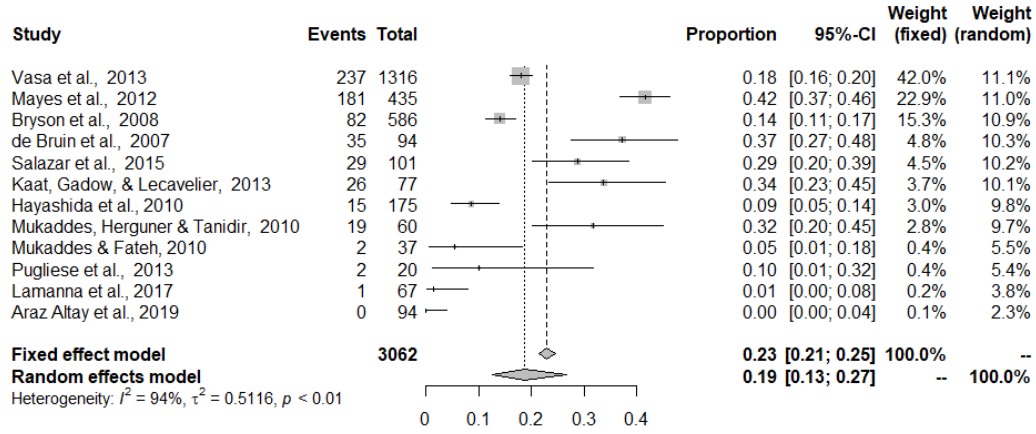
	(interview) +CASD			
Vasa et al.	ADOS	Excellent	CBCL	Moderate
de Bruin et al.	ADOS-G + CSBQ	Excellent	DISC-IV-P	Excellent
Skwerer et al,	ADOS+ADI-R	Excellent	CASI-5	Moderate
Hayashida et al.	Clinical Record	Excellent	CBCL+ECI-4	Moderate
Amr et al.	Clinical Record + Indian Scale for Assessment of Autism	Excellent	Psychiatric DSM-IV interview +SCICA	Excellent
Pugliese et al.	School, Psychiatric, Psychological testing records	Excellent	ADIS+ school, psychiatric, psychological testing records	Moderate
Mukaddes, Herguner & Tanidir	Clinical Record	Excellent	K-SADS-PL-T	Excellent
Mukaddes & Fateh,	Clinical Record - Psychiatric interview	Excellent	K-SADS-PL	Excellent
Stratis & Lecavalier,	Parent Reported ASD + SCQ	Moderate	CBCL	Moderate
Araz Altay et al.	Medical Records + Autism Behaviour	Excellent	Medical Records	Excellent

	Checklist + M-CHAT			
Barnevik et al.	Clinical Records	Excellent	A-TAC	Poor
Green et al.	Clinical Records	Excellent	Isle of Wright	Poor
Lamanna et al.	ADOS-G + ADI-R + SCQ	Excellent	CPRS-R	Excellent

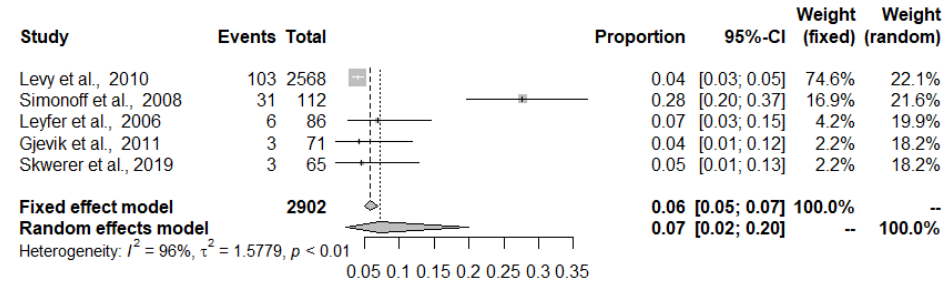
Appendix C. Forest Plots and Meta-Regressions

Recruitment Bias ODD

Clinical Sample

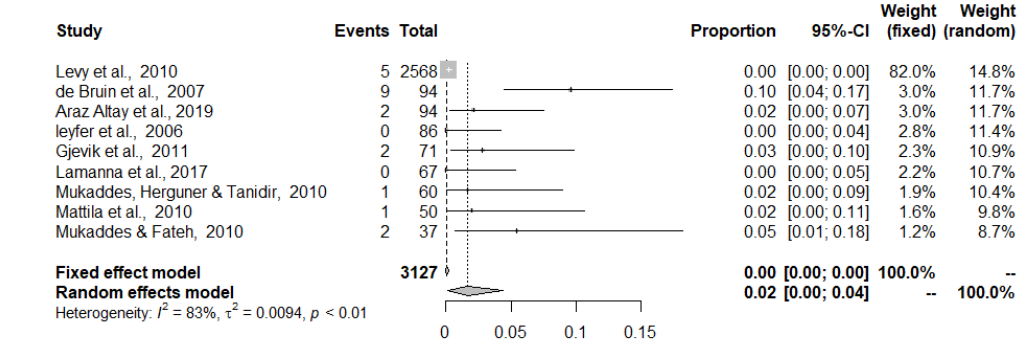


Community Sample

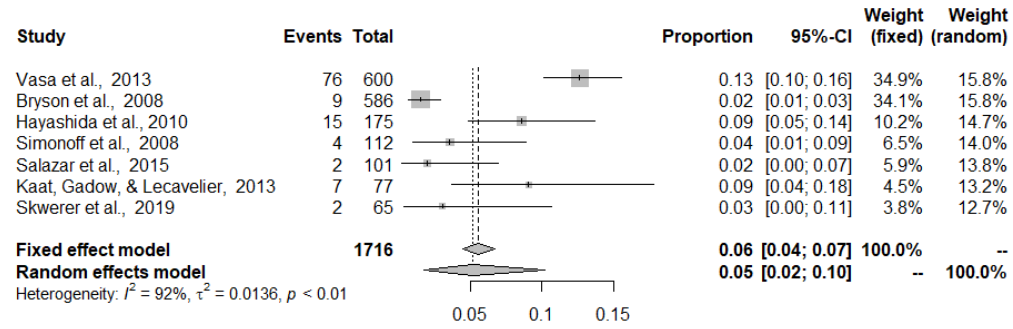


Detection Bias

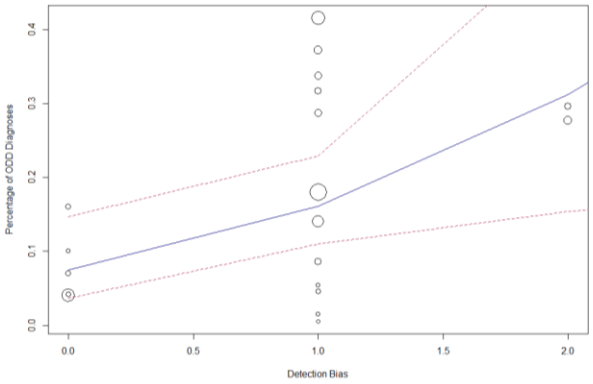
High Diagnostic Accuracy



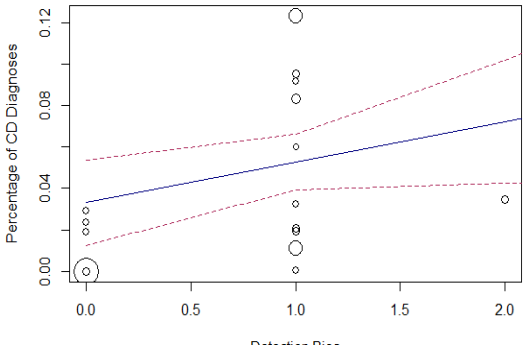
Moderate Diagnostic Accuracy



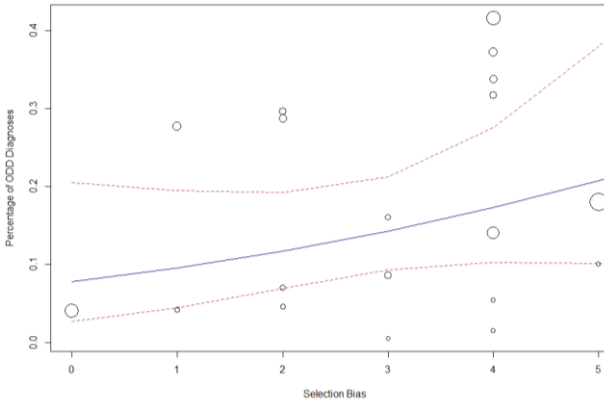
Detection Bias and Rates of ODD Diagnosis



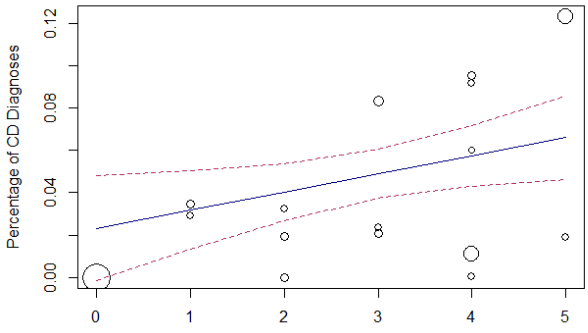
Detection Bias and Rates of CD Diagnosis



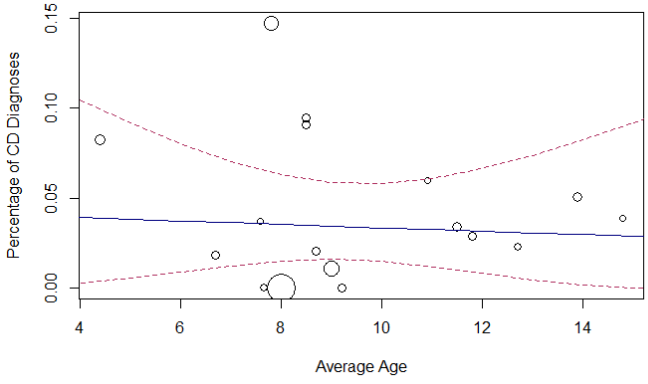
Selection Bias and Rates of ODD Diagnosis



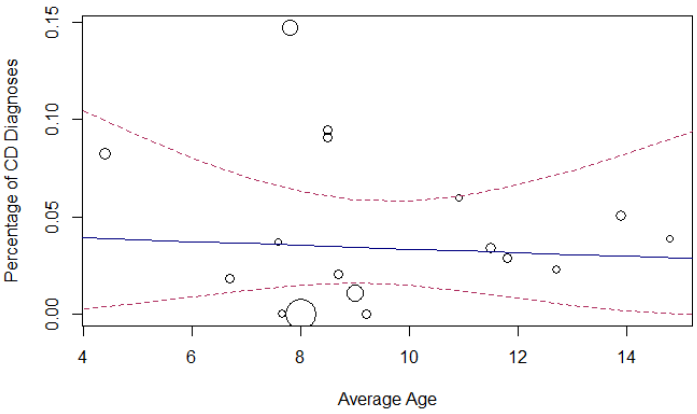
Detection Bias and Rates of CD Diagnosis



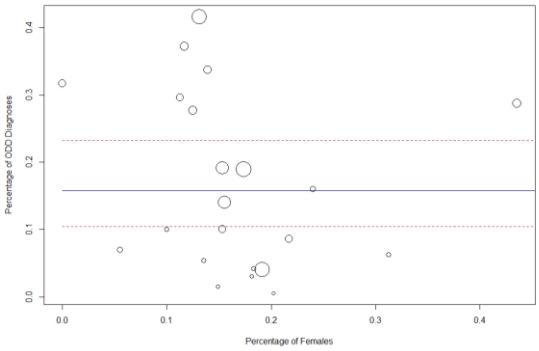
Average Age and Rates of ODD Diagnosis



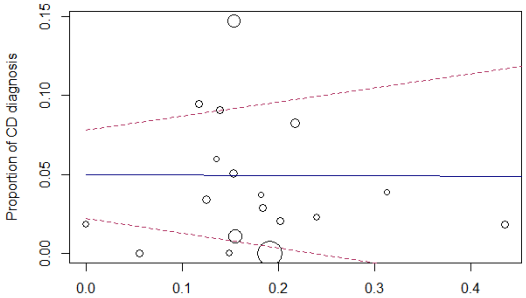
Average Age and Rates of ODD Diagnosis



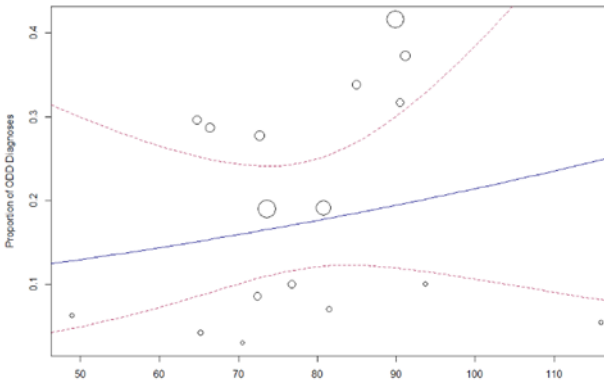
Gender and Rates of ODD Diagnosis



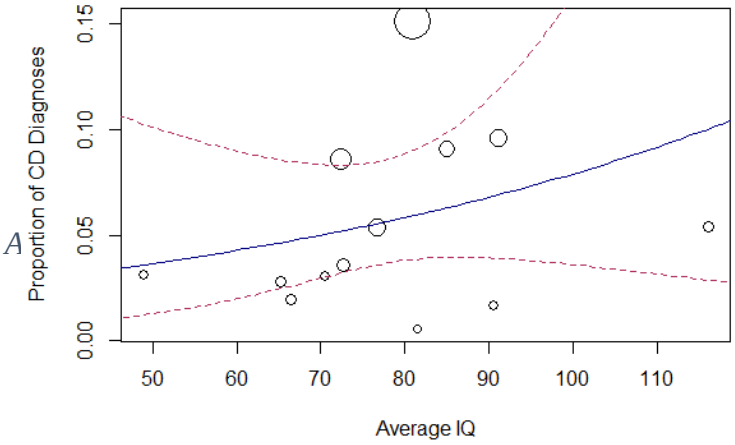
Gender and Rates of CD Diagnosis



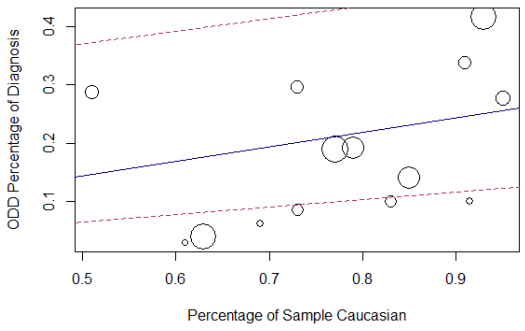
IQ and Rates of ODD Diagnosis



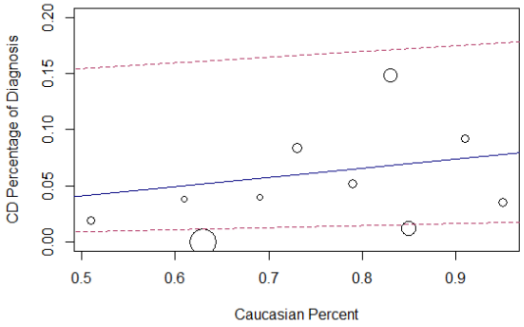
IQ and Rates of CD Diagnosis



Ethnicity and Rates of ODD Diagnosis



Ethnicity and Rates of CD Diagnosis



Appendix D.

Shapiro-Wilk Tests of Normality

	Included Participants		Excluded Participants	
	Statistic	Sig.	Statistic	Sig.
Age Diagnosed	0.855	0.000	0.736	0.006
Mood	0.923	0.000	0.900	0.291
Approach	0.892	0.000	0.883	0.201
Adapt	0.910	0.000	0.919	0.425
Income Bracket	0.875	0.000	0.882	0.197
Adaptability	0.931	0.000	0.871	0.153
Vocabulary ability	0.544	0.000	0.418	0.000
Peer Problems (SDQ)	0.894	0.000	0.891	0.241
Maternal Education	0.879	0.000	0.803	0.031
CPRS Conflict	0.984	0.007	0.972	0.915
CPRS Closeness	0.624	0.000	0.899	0.282
Conflict Tactic Scale	0.988	0.037	0.826	0.054

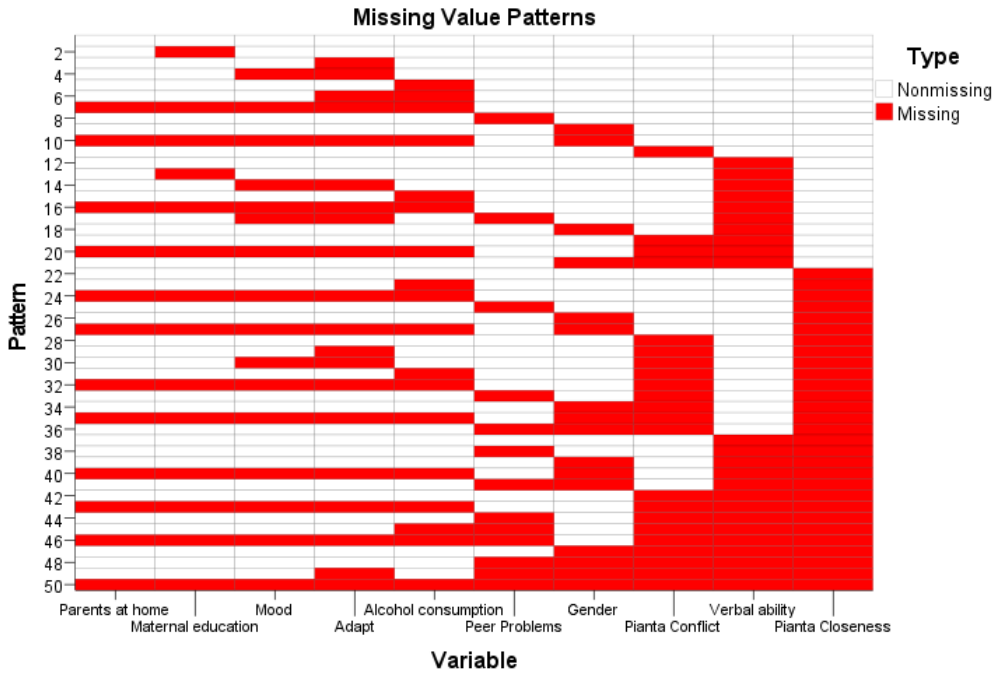
Appendix E.

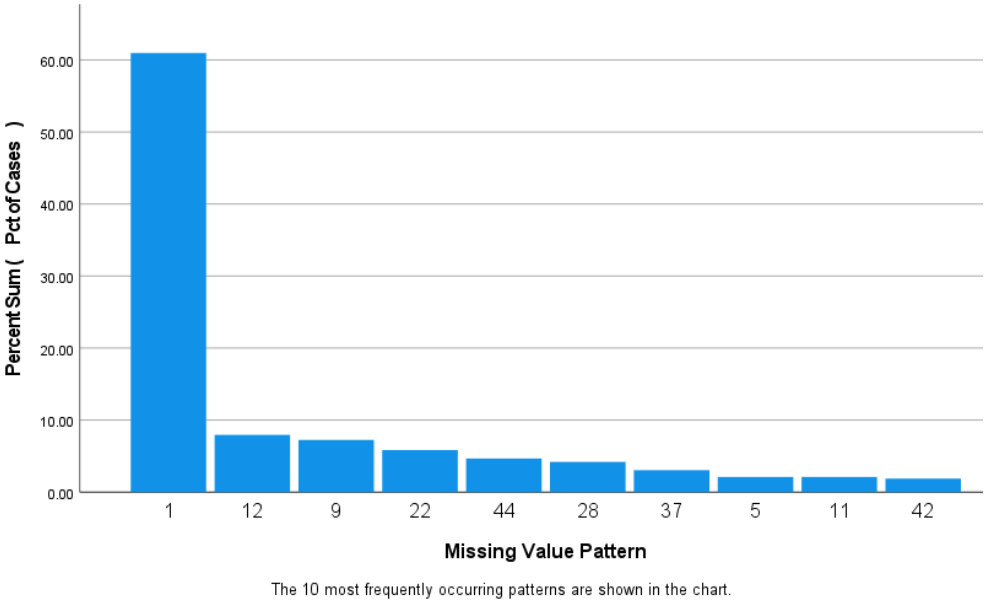
Included vs Excluded Group

Variable	Independent Median Test	Mann-Whitney Test
Age Diagnosis	0.033	>.001
Mood	0.963	0.254
Approach	0.023	0.018
Adapt	0.799	0.799
Verbal Ability	0.243	0.198
Maternal Education	0.236	0.06
Peer Problems (SDQ)	0.136	0.681
CPRS Conflict	0.962	0.975
CPRS Closeness	0.408	0.309
Conflict Tactic Scale	0.836	0.032
Family Income	0.025	0.005

Appendix F.

Missing Data Patterns





The 10 most frequently occurring patterns are shown in the chart.

Appendix G.

Missing Variables

Dependent Variable	Missing N	Percent	Valid N
Age 3 Conduct scores	73	14.4%	435
Age 5 Conduct scores	33	6.5%	475
Age 7 Conduct scores	22	4.3%	486
Age 14 Conduct scores	12	2.4%	496

Independent Variables	Missing N	Percent	Valid N
CPRS Closeness	126	24.80%	382
CTS Parenting	110	21.70%	398
BAS Verbal IQ	107	21.10%	401
Pianta Conflict	89	17.50%	419
Family Income (banded)	65	12.80%	443
Gender	54	10.60%	454
SDQ Peer Problems	49	9.60%	459
Alcohol Consumption	43	8.50%	465
Temperment Adapt	40	7.90%	468
Temperment Mood	34	6.70%	474
Maternal Education	31	6.10%	477
OECD poverty indicator	27	5.30%	481
Parents/Carers in Household	27	5.30%	481
Ethnicity	27	5.30%	481

Appendix H.

Collinearity Statistics

Variables	Tolerance	VIF
Gender	0.985	1.015
Parents/Carers in Household	0.912	1.097
CPRS Conflict	0.896	1.116
CPRS Closeness	0.866	1.155
BAS Verbal IQ	0.910	1.099
Mood - Temperament	0.886	1.129
Adapt – Temperament	0.905	1.105
Maternal Education	0.864	1.157
SDQ Peer Problems	0.871	1.148
Alcohol Consumption	0.932	1.073

Appendix I.

Descriptive Statistics of each class

		Class 1	Class 3	Class 3
Gender	Male	76.2%	75.9%	76.3%
	Female	23.4%	23.7%	22.6%
BAS verbal IQ	From 70-99	21.2%	25.9%	30.4%
	From 1-69	78.2%	73.5%	68.1%
Maternal Education	No Qualifications	21.9%	14.6%	13.9%
	GCSE grades D-G	15.5%	33.0%	11.4%
	GCSE grades A-C	39.1%	36.6%	31.9%
	A/AS/S levels	8.7%	7.8%	14.0%
	Higher Education Diplomas	14.5%	7.8%	27.9%
Alcohol during pregnancy	Consumption	35.9%	35.7%	29.6%
	Abstained	63.8%	63.6%	69.5%
Parents at home	Single Parent household	79%	70.5%	77.8%
	Two Parent household	20.8%	29.2%	29.6%
CPRS conflict	Mean	21	22.1	18.59
	SD	6.1	6.3	6.44
CPRS closeness	Mean	32	31.7	32.13
	SD	3.6	3.6	3.877
Adapt- Temperament	Mean	4.92	5	4.88
	SD	2.4	2.8	2.4
Mood -Temperament	Mean	18.47	17.86	18.81
	SD	4.0	4.2	3.8