RISK FACTORS FOR MENTAL HEALTH CONCERNS AND SEIZURES IN PRE-TEENS AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER (ASD)

by

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Abstract

Objectives: The purpose of this thesis was to identify risk factors for the development of mental health concerns in pre-teens and adolescents with Autism Spectrum Disorder (ASD), and in particular the role of early childhood ASD symptomatology in their development. Additionally, this thesis generated prevalence estimates for mental health concerns in Canadian adolescents with ASD.

Methods: The parents of 390 individuals with ASD were invited to participate in a survey, either online or by mail. Sixty-seven parents completed and returned surveys. Kendall tau *b* correlation coefficients were calculated for the association between age at assessment with ADI-R and score in each domain. Prevalence estimates with 95% confidence intervals were generated, and the Kappa statistic was used to determine the strength of agreement between parent-reported diagnoses and clinical CBCL scores. Finally, bivariate analysis was used to determine if childhood ASD symptomatology was associated with mental health in adolescence, followed by logistic regression modeling to evaluate the effect of other possible risk factors.

Results: Scores on two domains of the ADI-R were significantly associated with age at assessment, therefore, it was necessary to control for age at assessment with the ADI-R on these domains in the analysis conducted in Chapter Four. Forty-five percent of the study sample met case criteria for a comorbid psychiatric disorder. Anxiety, mood and attention-deficit disorders were the most common disorders in this sample. Early childhood ASD symptoms were not associated with the development of mental health concerns in adolescence. Family history and female gender were associated with the development of mental health concerns in adolescence. **Conclusions:** Nearly half of the individuals in our sample have been diagnosed with a psychiatric disorder, or are experiencing clinically significant symptoms that may be indicative of such a disorder. Our findings of discrepancies between parent-reported diagnoses and CBCL scores, indicates that many individuals in our sample are experiencing clinically significant mental health

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concerns, but do not have an official diagnosis. Finally, as has been reported previously, family history of mental illness and female gender were found to be associated with the development of a mental health concern in adolescence.

Co-Authorship

This thesis presents research that was conducted by Caitlin McGarry, under the supervision of Drs. Hélène Ouellette-Kuntz and Elizabeth Kelley. Caitlin McGarry developed the study design and methodology with assistance and input from Hélène Ouellette-Kuntz and Elizabeth Kelley, and designed the parent survey entitled "Risk Factors for Mental Health Concerns and Seizures in Pre-teens and Adolescents with an Autism Spectrum Disorder", with feedback from Hélène Ouellette-Kuntz and Elizabeth Kelley. Deborah Gorski and Heidi Penning pilot-tested the survey and provided valuable feedback on content and clarity. Participant recruitment was conducted by Caitlin McGarry, Jamie Hagen (recruitment of participants from the National Epidemiologic Database for the Study of Autism in Canada (NEDSAC)) and Melissa Hudson (Autism Spectrum Disorders Canadian-American Research Consortium (ASD-CARC)). Helen Coo and Deborah Gorski provided valuable assistance with NEDSAC data. All surveys that were returned by mail were manually entered into the online survey form by Caitlin McGarry. Data analyses were performed by Caitlin McGarry, with guidance from Drs. Miu Lam and Michael McIsaac for manuscript three. All manuscripts were written by Caitlin McGarry with feedback from Hélène Ouellette-Kuntz and Elizabeth Kelley.

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Chapter 1

General Introduction

Mental health concerns are a significant contributor to poor quality of life for individuals with autism spectrum disorder (ASD), and may be difficult to recognize and treat in this population for a variety of reasons. This thesis attempts to establish prevalence estimates for mental health concerns in a Canadian population of pre-teens and adolescents with ASD and to identify risk factors for the development of mental health concerns in this specific population, with a particular focus on the role of early childhood ASD symptomatology in the development of mental health concerns. In this thesis, the term "mental health concerns" is used to refer to behaviours, or symptoms that indicate a mental health problem and are impacting quality of life, but may not yet have been evaluated and diagnosed by a clinician (for example, clinical scores on the Child Behaviour Checklist screening tool), in addition to parent-reported psychiatric diagnoses. The phrase "psychiatric disorders" is used exclusively to refer to Diagnostic and Statistical Manual (DSM) disorders diagnosed by a clinician, such as mood disorders or anxiety disorders. "Psychiatric comorbidities" is a phrase that is used in the literature to refer to two or more cooccurring but diagnostically distinct psychiatric disorders in the same individual. "Dual diagnosis" is a term used to refer to both Intellectual Disability and psychiatric disorders occurring in the same individual (National Coalition for Dual Diagnosis, 2011). Finally, Intellectual Disability (ID) is defined by the American Psychiatric Association as an IQ of less than 70, with significant limitations in adaptive functioning (which includes cognitive, social and self-care abilities), with impairments beginning during the developmental period (American Psychiatric Association (APA), 2013).

1.1 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder. In the Diagnostic and Statistical Manual-IV-Text Revision (DSM-IV-TR), ASD falls under the umbrella of "Pervasive Developmental Disorders" (PDD). The label "autism spectrum disorder" encompasses Autism (or Autistic Disorder), Asperger's syndrome and Pervasive Developmental Disorder- Not Otherwise Specified (PDD-NOS). Other disorders falling under the PDD umbrella include Rett's Syndrome and Childhood Disintegrative Disorder (American Psychiatric Association (APA), 2000).

Autism spectrum disorders are characterized in the DSM-IV-TR by impairments in three domains: reciprocal social interaction (including behaviours such as social smiling, interest in other children, and showing attention), communication (including pointing to express interest, imaginative play, and idiosyncratic speech) and restricted, repetitive and stereotyped behaviours (including unusual preoccupations or compulsions and rituals). To be diagnosed with Autistic Disorder, an individual must meet a minimum of six behaviour criteria, at least two from the reciprocal social interaction domain and one from each of the other domains, and these behaviours must be present before age 3 (APA, 2000; McPartland, Reichow, & Volkmar, 2012).

The DSM 5 was released in May 2013. In this updated version, considerable changes have been made to the diagnostic criteria for ASD. The changes as they were initially proposed were met with protest from parents, individuals with ASD, and many experts (Frazier et al., 2012; Ghaziuddin, Ghaziuddin, & Greden, 2002; Matson & Nebel-Schwalm, 2007; Wing, Gould, & Gillberg, 2010). Preliminary assessment of the new criteria indicates that as many as 12% of individuals with ASD would be missed by the DSM 5 criteria, and that females and those with Asperger's would be disproportionately affected (Frazier et al., 2012; Matson, Hattier, & Williams, 2012; Wing et al., 2010). Changes in the DSM 5 include the elimination of separate

diagnoses within the autism spectrum, so that each person meeting criteria will be diagnosed as having an Autism Spectrum Disorder. The term "Pervasive Developmental Disorder" was eliminated from the DSM 5. Further, instead of three domains of impairment, the new criteria include only two domains: a stereotyped interests domain revised to include sensory abnormalities, and deficits in social communication and interaction (Matson et al., 2012). Since this research was conducted prior to the release of the DSM 5, the individuals in this study were diagnosed according to DSM-IV-TR guidelines.

1.2 Study Rationale and Objectives

The purpose of this study initially was to examine mental health and seizures in individuals with ASD, with a specific focus on pre-teens and adolescents. After data collection had finished, it was apparent that the prevalence of adolescent seizures in our sample was too low to conduct the planned analysis for this outcome, and so the outcome of seizures was excluded from the thesis. There were three objectives to this project, presented here in three manuscripts. The first objective was to assess if the Autism Diagnostic Interview-Revised (ADI-R) (Rutter, Le Couteur, & Lord, 2008) could be used in retrospective studies to establish ASD symptomatology at a standard age across the study sample (presented in Chapter Three). The second objective was to estimate the prevalence of mental health concerns in Canadian pre-teens and adolescents with ASD (presented in Chapter Four, manuscript two). Finally, Chapter Five (manuscript three) presents the results of an analysis of risk factors in early childhood for the development of mental health concerns and seizures in adolescence.

1.3 General Methods

1.3.1 Study Setting and Participant Recruitment

Participants for this study were recruited through two ASD research databases housed at Queen's University. The National Epidemiologic Database for the Study of Autism in Canada (NEDSAC) was established in 2001. NEDSAC's research goals include monitoring the prevalence of ASD in Canadian children, understanding regional variations in diagnostic practice, assessing differences in age at diagnosis across study regions, and understanding how factors such as maternal and paternal age and inter-pregnancy interval are related to ASD. NEDSAC data were collected from British Columbia, Calgary, Manitoba, Southeastern Ontario, Prince Edward Island and Newfoundland and Labrador (NEDSAC, 2012). Between 2003 and 2010 (2008 in Newfoundland and Labrador), data collection focused on Southeastern Ontario, Prince Edward Island and Newfoundland and Labrador, identifying 2377 children ages 2 to14 with ASD (NEDSAC, 2012). The NEDSAC database was developed using a surveillance approach to identifying cases. In each region of surveillance, partnerships were formed with regional service providers to identify cases in a manner similar to using administrative data. A noted weakness of this method of case identification is that it may under-detect cases due to the methods agencies use to identify individuals who qualify for services (Ouellette-Kuntz et al., 2013).

The second source from which participants were recruited is the Autism Spectrum Disorders Canadian-American Research Consortium (ASD-CARC) research registry. Research interests of the ASD-CARC team include genetic and environmental factors that contribute to the development of ASD, ASD neurophysiology, the epidemiology of ASD (in collaboration with NEDSAC), and developing methods for early identification of ASD and better treatment. The ASD-CARC research registry currently consists of 2991 families in North America. ASD-CARC collects data through participant surveys hosted on their website with the Laboratory Information Management System (LIMS) software Progeny, as well as by mail and in-person. Recruitment for the ASD-CARC database is less systematic than that for NEDSAC, as any interested individuals are able to enroll in the database.

This study was conceptualized as a retrospective cohort study, with the study cohort consisting of individuals meeting the following participation criteria:

- 1. An ASD diagnosis, confirmed by parent,
- 2. Age 10-19 in 2012,
- 3. Completed Autism Diagnostic Interview-Revised (ADI-R) in either database,
- 4. Lived in Canada in 2012

Identifying potential participants was a multi-stage process. First, a query for the inclusion criteria was performed for both databases separately. To screen for duplicates between databases (i.e. participants registered to both databases), we first used birthdates. First and last initials were extracted for individuals with duplicate birthdates, with full names being used in rare cases where there was confusion about initials. Following the removal of duplicates, the number of potential participants was 425. The next stage of the process involved double-checking consent status for NEDSAC participants. The original consent forms were collected between 2003 and 2010 (or 2008) and were valid for a period of 5 years, therefore it was necessary to ensure that potential participants still had valid consent forms. After checking these forms, 15 participants were removed due to expired consent forms. After mailing questionnaires to potential participants to 390. The questionnaire was made available online, through the ASD-CARC website, as well as by mail for participants who did not have available email addresses.

1.3.2 Questionnaire Development

Collection of outcome data for manuscript two and three in this study took the form of a parent questionnaire. The questionnaire went through several stages of development. Wherever possible, we used previously developed questions and prompts from the Canadian Community Health Survey (CCHS) (Statistics Canada, 2012), the National Longitudinal Survey of Children and Youth (NLSCY) (Statistics Canada, 2008) and the Interactive Autism Network's (IAN) family history questionnaire (Kennedy Krieger Institute, 2012). The questionnaire was piloted by two NEDSAC staff members and the parent of a potential study participant who had expressed interest in being involved in the development process. The final version of the questionnaire consisted of two parts. The first part included 26 questions about the individual's IO, living arrangements, school arrangements, classroom setting, psychiatric history, medical history, medication and service use, and family psychiatric history. The second part consisted of the Child Behaviour Checklist (CBCL 6-18) Parent Report Form (Achenbach & Rescorla, 2001), a 113-item screening tool for emotional and behavioural problems. Information and consent forms are presented in Appendix A. Manuscript one was designed as an exploratory study, requiring a Health Sciences Research Ethics Board (HSREB) short form, while manuscripts two and three required a complete HSREB approval application. Both approval forms are presented in Appendix B. The complete questionnaire is presented in Appendix C. To use the CBCL, a licensing agreement was obtained from ASEBA (Achenbach System of Empirical Behavioural Assessments), the organization that produces the tool. The CBCL was reproduced in accordance with the guidelines in the licensing agreement.

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Chapter 2

Literature Review

2.1 Mental Health

Mental health is defined by the World Health Organization as a state of well-being, in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community (World Health Organization, 2013). Mental health concerns and challenges are increasingly being recognized as important contributors to poor quality of life. The Mental Health Commission of Canada reports that more than 20% of Canadians will experience a mental health problem at some point in their lifetime, and that mental health concerns cost the economy in excess of 50 million dollars annually (Mental Health Commission of Canada, 2012; Public Health Agency of Canada, 2002). Mood and anxiety disorders are the most common mental health concerns in the general population (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Kessler et. al, 2005; Public Health Agency of Canada, 2002). While the field of mental health research in individuals with Autism Spectrum Disorder (ASD) is still quite young, there is a great deal of research on the epidemiology and risk factors for mental health concerns in typical individuals.

2.1.1 Epidemiology of Psychiatric Disorders in the General Population

Epidemiological research provides an idea of the scope of mental health concerns faced by the general population. The National Comorbidity Survey replication, a nationally-representative survey of more than nine thousand Americans 18 years and older, found that the lifetime prevalence of all psychiatric disorders in the United States was 46.5% (Kessler et al., 2005), using

DSM-IV criteria and the World Mental Health Survey Initiative version of the World Health Organization Composite International Diagnostic Interview.

The Great Smokey Mountains Study is a longitudinal study of the development of psychiatric disorders (Costello et al., 2003). In this population-based study, three waves of participants were recruited at ages nine, eleven and thirteen and followed until sixteen years of age, evaluated annually with the Child and Adolescent Psychiatric Assessment (CAPA). In a sample of 1420 individuals aged nine to thirteen from the Great Smokey Mountains Study, Costello et al. (2003) reported a mean three-month prevalence of 13.3% for any psychiatric disorder and an estimated cumulative prevalence of 36.7% by age 16 (Costello et al., 2003).

In Canada, approximately one in five individuals (or 20% of Canadians) will experience a mental health concern at one point in their lives, and poor mental health represents a substantial burden on the health care system (Public Health Agency of Canada, 2002). The Public Health Agency of Canada reports that eight percent of Canadians will experience Major Depression, and 12% of Canadians will experience an anxiety disorder throughout their lifetimes (Public Health Agency of Canada, 2002). Schizophrenia and Bipolar Disorder affect approximately 1% of the population each (Public Health Agency of Canada, 2002).

2.1.2 Risk Factors for Mental Health Concerns in the General Population

Many potential risk factors for psychiatric disorders have been identified in typically developing individuals. Genetics play a role, although the degree of influence depends on the disorder (Gadow et al., 2008; Green et al., 2010). Environmental factors are also extremely important, and in many cases, different constellations of risk factors are associated with different disorders- for example, poor family functioning, male gender, and socioeconomic status have been associated with Conduct Disorder, while anxiety and depression have been linked to age, adverse life events,

and overall poor health (Ford, Goodman, & Meltzer, 2004). Other risk factors that have been associated with the development of psychiatric disorders include family history of psychiatric disorders (Green et al., 2010; Herpertz-Dahlmann et al., 2013), parental loss (Green et al., 2010), parental substance abuse (Green et al., 2010), physical or sexual abuse, family violence, and neglect (Green et al., 2010), coming from an immigrant family (Herpertz-Dahlmann et al., 2013), and poverty or economic adversity (Herpertz-Dahlmann et al., 2013). Age and sex are also risk factors; older individuals are more likely to have experienced a psychiatric disorder at some point in their lives (Gadow et al., 2008), and sex-specific risk factors exist at both the biological and social levels (Herpertz-Dahlmann et al., 2013). Girls are more likely to experience internalizing mental health problems such as eating disorders, mood disorders and anxiety disorders. Boys are more likely to experience externalizing or disruptive mental health problems such as Conduct Disorder and Oppositional-Defiant Disorder (Herpertz-Dahlmann et al., 2013). Adolescence has also been identified as a critical period for the development of mental health concerns (Herpertz-Dahlmann et al., 2013).

2.1.3 Adolescence and Mental Health in the General Population

A 2012 report from the Mental Health Commission of Canada highlights adolescence as a critical period in the development of mental health challenges. It reports that up to 70% of young adults with mental health problems began experiencing symptoms in childhood (Mental Health Commission of Canada, 2012). Furthermore, only about one in four children with mental health problems receive treatment (Mental Health Commission of Canada, 2012), emphasizing the need for correct recognition and treatment of symptoms of mental health problems in children and youth. Given that mental health problems that begin in childhood are likely to persist into adolescence and adulthood (Mental Health Commission of Canada, 2012), recognizing and

treating mental health problems early in life can reduce burden on the healthcare system and improve individual wellbeing.

Mental health concerns can be particularly challenging for individuals with Autism Spectrum Disorder (ASD), because they can worsen ASD symptoms and exacerbate social difficulties (Josh et al., 2010; Leyfer et al., 2006). It can be difficult for someone with ASD and potentially limited verbal ability to communicate distress, which may make obtaining assessment or treatment difficult (Witwer & Lecavalier, 2010), and untreated mental health concerns can lead to poor outcomes in adulthood (Billstedt, Gillberg, & Gillberg, 2005). Individuals with ASD may be at greater risk than individuals without ASD for the development of mental health concerns throughout their lives. Understanding the epidemiology of mental health concerns and specific risk factors for their development in individuals with ASD is necessary to improve diagnostic and treatment methods, and to facilitate a better understanding of how ASD progresses with age and ASD comorbidities across the life course.

2.2 Etiology of Autism Spectrum Disorder

While the exact causes of ASD remain unknown, in the last decade, several dozen genes have been implicated in ASD susceptibility (Geschwind, 2011). Twin and family studies have estimated the heritability of ASD is as high as 70%-80% (Rosenberg et al., 2009), indicating that genetics play an important role in ASD development. However, ASD is a complex disorder, and there are other environmental factors that may lead to the development of ASD (Duchan & Patel, 2012; Geschwind, 2011). Other factors that have been implicated include advanced maternal and paternal age (Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2011; Lauritsen, Pedersen, & Mortensen, 2005), low birth weight or small for gestational age (Hultman et al., 2011; Kolevzon, Gross, & Reichenberg, 2007; Williams, Helmer, Duncan, Peat, & Mellis, 2008) and a shorter interval between pregnancies (Cheslack-Postava, Liu, & Bearman, 2011). Prenatal exposures that have been implicated in the development of ASD include exposure to valproic acid, thalidomide, misoprostol (Dufour-Rainfray et al., 2011), and smoking (Hultman et al., 2011). Consumption of prenatal vitamins has been shown to decrease the risk of ASD in offspring when taken by genetically-susceptible mothers (Schmidt et al., 2011).

Two additional areas of research on the causes ASD are neuroanatomy and functional brain imaging. Results of functional imaging studies indicate that there may be structural abnormalities in the brains of individuals with ASD (Longo, Fauci, Kasper, Stephen, Jameson & Loscalzo, 2012), including abnormalities in total brain volume, parieto-temporal lobe volume, cerebellar volume and abnormalities in the amygdala, hippocampus and corpus callosum (Brambilla, 2003). It is hypothesized that abnormalities in brain structure are linked to neural network abnormalities, although whether these abnormalities are a cause or consequence of ASD is still unknown (Brambilla, 2003).

Seizures are a common feature of ASD that are also neurodevelopmental in origin (Matson & Neal, 2009; Volkmar & Pauls, 2003) with a lifetime prevalence estimated to be between 10% and 40% (Giovanardi, Posar, & Parmeggiani, 2000; Volkmar & Pauls, 2003). The prevalence of seizures varies by ASD diagnosis, with one review indicating a prevalence of approximately 25% in individuals with Autistic Disorder (Volkmar & Pauls, 2003) and 10% in those with Asperger's or PDD-NOS. Seizures have been linked to underlying brain abnormalities, providing further evidence for the role of brain structural abnormalities in ASD (Deonna & Roulet, 2006; Levisohn, 2007). Like with neural network abnormalities, whether seizures are a result of or a precipitating factor in ASD is not yet clear (Deonna & Roulet, 2006; Matson & Neal, 2009).

2.3 Epidemiology of Autism Spectrum Disorders

A recent study of ASD prevalence in children ages 2-14 in three regions of Canada revealed that the 2010 prevalence of ASD was 129.2 per 10 000 in Southern Ontario and 90.6 per 10 000 in PEI. The 2008 (the most recent available) prevalence estimate in Newfoundland and Labrador was 83.0 per 10 000 (Ouellette-Kuntz, et al., 2013). It is accepted that the prevalence of ASD has increased drastically over the last two decades (Duchan & Patel, 2012; Fombonne, 2003; Gurney et al., 2003), however the reasons for this increase remain under debate: it may reflect changes in diagnostic practices or changes in the true number of individuals developing ASD (Coo et al., 2008; Wing & Potter, 2002).

ASD affects more boys than girls, however the ratios differ by diagnosis. Autistic Disorder is twice as prevalent in males as females, while Asperger's syndrome is four times as common in males (Levy, Mandell, & Schultz, 2009; Volkmar & Pauls, 2003). The commonly reported overall gender ratio is 4:1 for males to females (Kogan et al., 2009; Manning et al., 2011).

Intellectual Disability (ID) is a common feature of ASD, although again the prevalence is different by diagnosis. Intellectual Disability is defined in the DSM 5 as an IQ of less than 70, with significant impairment in adaptive functioning (cognitive, social and self-care skills) (American Psychiatric Association, 2013). More than 60% of individuals with Autistic Disorder are estimated to have an ID, while the prevalence is considerably less in those with PDD-NOS. Individuals with Asperger's display no Intellectual Disability (Volkmar & Pauls, 2003). Epidemiological estimates of the prevalence of ID across the autism spectrum range from 40% to 80% (Newschaffer & Curran, 2003).

2.4 Comorbid Psychiatric Disorders

Comorbid disorders can be described as two or more co-occurring but diagnostically distinct disorders in the same individual (Matson & Nebel-Schwalm, 2007). In this thesis, the term comorbid disorder is used to refer to a psychiatric disorder that occurs in addition to an ASD diagnosis. The recognition of psychiatric comorbidities in individuals with ASD has been the subject of debate in the literature. The debate centers on whether emotional and behavioural problems should be attributed to distinct psychiatric disorders, or whether they are simply part of the ASD symptom cluster (AACAP, 1999; Georgiades, 2011; Lecavalier, 2006; Leyfer et al., 2006; Matson & Nebel-Schwam, 2007; Witwer & Lecavalier, 2010). The process by which true emotional or behavioural problems are attributed to ASD is known as diagnostic overshadowing (Pandolfi, Magyar, & Dill, 2012).

Matson & Nebel-Schwalm (2007) provide a comprehensive overview of the literature on comorbid psychiatric disorders in individuals with ASD, with particular attention to mood disorders, anxiety disorders, and psychosis. Matson and Nebel-Schwalm (2007) also address the difficulty of separating ASD symptoms from symptoms of mental health concerns and point out that some disorders may be more easily distinguished from ASD than others. Obsessive-Compulsive Disorder (OCD) is a good illustration of the difficulty in diagnosing psychiatric disorders in individuals with ASD. Features of ASD include adherence to nonfunctional routines and rituals and restricted, repetitive behaviours, while features of OCD include persistent impulses and repetitive behaviours aimed at reducing stress (American Psychiatric Association, 2000). Although not identical, the similarity is clear (Matson & Nebel-Schwalm, 2007). In 2007, Matson and Nebel-Schwalm concluded that at that point in time, existing data suggested that comorbid psychiatric disorders do occur in children and adolescents with ASD, and that further research to determine how to best differentiate ASD symptoms from symptoms of psychiatric disorders was necessary.

Gadow, DeVincent, and Schneider (2008) assessed risk factors for the development of mental health concerns in a population of 238 eight- to-twelve-year-olds with an ASD diagnosis referred to a developmental disabilities clinic. Risk and protective factors that were assessed included: living with a single parent; living with at least one biological parent; level of parental education; socioeconomic status; current school placement (special education vs. regular education); early intervention; pregnancy and birth complications; other medical conditions; hospitalizations; psychotropic medication use; family psychiatric history; and family history of ASD (Gadow et al., 2008). An important finding of this study was that while family history of psychiatric disorders was associated with the development of psychiatric disorders in this study population, family history of ASD was not (Gadow et al., 2008). This lends support to psychiatric disorders being distinct entities from ASD (Gadow et al., 2008). This study excluded individuals with an IQ of less than 70 (i.e. none of the individuals in the study had an Intellectual Disability). Intellectual Disability (ID) is known to complicate the assessment and even manifestation of psychiatric disorders (Lecavalier, 2006; Witwer & Lecavalier, 2010); therefore the findings from this study may not be generalizable to individuals with ASD and ID.

There are several reasons for the continued difficulty in differentiating symptoms of psychiatric disorders from symptoms of ASD. A major reason is the prevalence of ID and limited verbal ability in this population; individuals with ASD may have limited verbal ability, no verbal ability, or difficulty with the abstract thoughts necessary to describe their fears or worries (Leyfer et al., 2006; Witwer & Lecavalier, 2010). Since many diagnostic tools require individuals to articulate their distress, clinicians may have difficulty making diagnoses and interpreting behaviours in the absence of the ability to describe one's mental state.

Witwer and Lecavalier (2010) examined symptoms of disruptive behaviour, mood disorders, and anxiety in 61 children with ASD, including 14 children with no conversational language abilities. The study also assessed the effects of IQ and language skills on the manifestation of mental health symptoms. In this study sample, children with an IQ less than 70 (Intellectual Disability) had fewer reported mental health symptoms than those with an IQ greater than or equal to 70. Individuals in this study sample with ID were significantly less likely to meet diagnostic criteria for Generalized Anxiety Disorder. The diagnostic criteria for anxiety disorders require individuals to verbalize their distress, which is difficult for those with an ID. Individuals in this study with conversational language abilities were significantly more likely than individuals with limited or no verbal ability to meet diagnostic criteria for Oppositional Defiant Disorder (ODD), with diagnostic criteria including "argues with parents and teachers", and Generalized Anxiety Disorder (Witwer & Lecavalier, 2010). Witwer and Lecavalier's findings provide evidence for differential symptom manifestation in those with ID and ASD than in those with ASD who do not have ID, and support the need for further research on the manifestation of psychiatric disorders in those with ID and ASD (Witwer & Lecavalier, 2010).

Additionally, there is insufficient research on the way symptoms of psychiatric disorders manifest in individuals with ASD (Joshi et al., 2010; Witwer & Lecavalier, 2010), with some experts believing that symptoms manifest differently in individuals with ASD than typical individuals (Lecavalier, 2006; Leyfer et al., 2006). As discussed previously, ID can also complicate the manifestation of psychiatric disorders even further in individuals with ASD (Lecavalier, 2006; Witwer & Lecavalier, 2010). These factors make it difficult to generate a model of definitive symptom presentation and create guidelines for the assessment and diagnosis of psychiatric disorders in individuals with ASD. A further contributor to the lack of recognition of psychiatric disorders in individuals with ASD is the DSM-IV-TR, which prohibits the diagnosis of more than one Axis 1 disorder (American Psychiatric Association, 2000).¹ This limitation was eliminated in the DSM 5, which may lead to an increase in the prevalence of psychiatric disorders in individuals with ASD. However, without a clear understanding of how to differentiate between ASD symptoms and symptoms of psychiatric disorders, at this time there are few diagnostic tools and limited assessment and diagnostic guidelines designed specifically for this population (Leyfer et al., 2006).

A potential alternate method for identifying psychiatric disorders in individuals with ASD is the use of behaviour equivalents (Witwer & Lecavalier, 2010). Behaviour equivalents are observable behaviours that can be equated with DSM criteria and that are compatible with cognitive and verbal communication delays (Witwer & Lecavalier, 2010). Proposed behaviour equivalents for depression include property destruction, aggression or self-injury (Witwer & Lecavalier, 2010), for example. The Royal College of Psychiatrists in the United Kingdom has released guidelines for incorporating behavioural equivalents into diagnostic practices (Royal College of Psychiatrists, 2001). However, some experts believe that caution must be exercised with behaviour equivalents as they are non-specific and while they may indicate underlying mental health problems, cannot be used to diagnose any specific disorders (Tsiouris, Mann, Patti, & Sturmey, 2003).

¹ The Axis I disorders of the DSM-IV-TR are "clinical disorders or other disorders that may be the focus of clinical attention" with sub-categories including "disorders usually first diagnosed in infancy, childhood, or adolescence", "mental disorders due to a general medical condition", "substance-related disorders", schizophrenia and other psychotic disorders, mood disorders, anxiety disorders, somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, eating disorders, sleep disorders, "impulse control disorders- not otherwise classified", and "adjustment disorders". The first sub-category includes pervasive developmental disorders, as well as attention deficit disorders, conduct disorder and oppositional defiant disorder (American Psychiatric Association, 2000).

The accurate recognition of emotional and behavioural problems as symptoms of psychiatric disorders, distinct from an ASD, has important clinical implications. Recognition and diagnosis of psychiatric comorbidities is essential for effective treatment. Effectively addressing mental health concerns can improve long-term outcomes, including social and educational attainment and can even reduce problematic ASD symptoms as untreated psychiatric disorders can exacerbate ASD symptoms (Leyfer et al., 2006). Furthermore, as in the general population, some psychiatric disorders (such as depression and anxiety) frequently occur together, meaning that some individuals with ASD may have more than one psychiatric disorder (Joshi et al., 2010; Leyfer et al., 2006) at the same time, and may be in need of specialized treatment programs or services to address their complex needs (Leyfer et al., 2006).

2.5 Screening and Diagnostic tools for Mental Health Concerns in Adolescents with ASD

One of the challenges in correctly detecting and diagnosing mental health concerns in adolescents with ASD is that there were, until fairly recently, no screening tools specifically developed for individuals with ASD. More recently, there have been attempts to create mental health screening tools that are designed to separate mental health symptoms from ASD symptoms. One such tool is the Nisonger Child Behaviour Rating Form (NCBRF) (Aman, Tasse, Rojahn, & Hammer, 1996). The NCBRF was specifically constructed for assessing mental health concerns in individuals with intellectual and developmental disabilities with the goal of accurately differentiating symptoms of mental health concerns from symptoms that are a consequence of ASD (Aman, Tasse, Rojahn, & Hammer, 1995). The NCBRF was also designed to be brief (it can be completed in 7 or 8 minutes), and can be completed by parents or teachers (Aman et al.,

1995). Confirmatory factor analysis of the NCBRF in a sample of youth with ASD supports the use of the NCBRF in this population (Lecavalier, Aman, Hammer, Stoica, & Mathews, 2004).

Although the NCBRF was specifically designed with ASD in mind, its primary use in the literature appears to be in clinical trials evaluating the effectiveness of antipsychotics in treating disruptive behaviour (Loy, Merry, Hetrick, & Stasiak, 2012). Therefore, some experts suggest that its utility in research is limited at this point (Matson, Belva, Hattier, & Matson, 2012). Furthermore, the NCBRF scales do not align with DSM diagnoses; this is an additional reason why this tool was not used in the current study.

Another recent tool specifically developed for evaluating individuals with ASD is the Autism Comorbidity Interview- Present and Lifetime Version (ACI-PL) (Leyfer et al., 2006). This tool, which is adapted from the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Chambers, Puig-Antich, Hirsch, Ambrosini, & Tabrizi, 1985), is a one-on-one interview with parents and caregivers. The tool specifically takes into account the difficulties individuals with ASD have describing their mental experiences and emotions; for example, before asking if the child has indicated feelings of guilt or worthlessness (symptoms of depression), respondents are asked if the child is able to conceptualize this emotion (Leyfer et al., 2006). Furthermore, the ACI-PL scores items in a way that is sensitive to behaviours that are typical of ASD; for example, the scoring for attention deficit hyperactivity disorder distinguishes between attention to special interests and attention in general (Leyfer et al., 2006). This tool is not widely used (a Pubmed search reveals only two published papers using this tool), and does not appear to have undergone psychometric testing. Before it is accepted as a reliable tool, additional testing will be needed to determine the psychometric properties of the ACI-PL. Moreover, as an interview that can take up to three hours, it was deemed inappropriate for the collection of data for the present study.

The first tool that was developed to evaluate psychopathology in individuals with intellectual disabilities was the Psychopathology Instrument for Adults with Mental Retardation (PIMRA), created in 1983 (Kadzin, Matson, & Senatore, 1983). The PIMRA remains in widespread use today and has been used as a comparison scale to evaluate more recently created tools (Matson et al., 2012). At the time of its publication, the PIMRA not only became the first tool for evaluating mental health in individuals with Intellectual Disability, but a statement that the scientific community was beginning to accept that individuals with Intellectual Disabilities could also experience mental health problems (Matson et al., 2012). Between 2003 and 2008, nearly 100 papers were published that detailed measures of psychopathology for this population (Matson et al., 2012). While this is a dramatic increase from earlier decades (between 1983 and 2002, 72 papers were published), it represents only a small fraction of the published research on ASD as a whole, and these tools were again not specifically developed for individuals with ASD (Matson et al., 2012). Since the PIMRA was designed for use in adults, with pre-teens as young as ten in our study sample, it was not an appropriate tool for this study.

Other tools that have been created or adapted for this population include the Developmental Behaviour Checklist (DBC) (Einfeld & Tonge, 1996), and the Diagnostic Assessment for the Severely Handicapped II (DASH-II) (Matson, 1995). The DBC measures psychopathology in children ages six to eighteen, and shares the structure of the Child Behaviour Checklist (CBCL), in that it asks about the previous 6 months of the individual's life and items are evaluated on a three-point scale, with zero being "not true", one being "somewhat or sometimes true" and two being "very true or often true" (Einfeld & Tonge, 1996). The DBC has a total problems score and five additional subscales: disruptive/antisocial, self-absorbed, communication disturbance, anxiety and social relating (Einfeld & Tonge, 1996). A weakness of these scales is that they do not align with DSM diagnoses, making it difficult to compare scores on this tool with parent-reported diagnoses. The DASH-II was developed specifically to assess individuals with severe or profound ID, on the premise that the diagnostic needs of individuals with profound ID are different than the needs of those with moderate ID or no ID (Matson et al., 2012). The DASH-II was not used in this study as we were not sure of the prevalence of ID in our study sample when choosing a screening tool, and required a tool that could accommodate a range of ID, as well as individuals who did not have an ID.

The Child Behaviour Checklist (CBCL) is considered by some experts to be the most widely used and respected scale to assess mental health in children (Matson et al., 2012), and as such, is also used in evaluating children and youth with Intellectual Disability and more recently, ASD (Coury et al., 2012; de Ruiter, Dekker, Verhulst, & Koot, 2007; Mazefsky, Anderson, Conner & Minshew, 2011; Skokauskus & Gallagher, 2012). The CBCL was chosen for this study because of its reputation in the literature (Matson et al., 2012), previous use in individuals with ASD (Coury et al., 2012; de Ruiter, et al., 2007; Mazefsky et al., 2011; Skokauskus & Gallagher, 2012), and perhaps most importantly, the DSM-oriented scales of the CBCL align with clinician diagnoses and allowed us to compare CBCL scores with parent-reported diagnoses.

2.6 Epidemiology of Psychiatric Disorders in ASD

Due to the difficulty in recognizing and diagnosing psychiatric comorbidities in individuals with ASD, it is difficult to obtain accurate prevalence and incidence estimates. A 2006 cross-sectional study of 381 youth aged four to eighteen years with Autistic Disorder indicated that as many as 75% of the study sample met clinical cutoffs for a psychiatric disorder on a psychological screening tool, the Developmental Behaviour Checklist (Brereton, Tonge, & Einfeld, 2006). In what has been perhaps the most comprehensive study of this topic to date, a

2012 cross-sectional study of 2853 children aged two to seventeen years with ASD revealed that 15.5% of the study sample had a parent-reported psychiatric disorder, and 36% met clinical criteria on the CBCL (Coury et al., 2012). This study sample skewed heavily to ages six and younger, and as the authors reported an association between age and psychiatric disorders, it is likely that the prevalence is even higher in adolescents and adults (Coury et al., 2012). However, the authors did not specify if they used the preschool version of the CBCL for individuals under six in their study sample (Coury et al., 2012). The CBCL for school-aged children was designed for use with individuals between the ages of six and eighteen years of age (Achenbach & Rescorla, 2001). The preschool CBCL is designed for children aged one-and-a-half to five years, and contains questions that are developmentally appropriate for this age period; as such, using the incorrect version of the CBCL is problematic and may have led to error in assessment of children who were not at an appropriate age for that particular version of the CBCL.

The differences in reported prevalence estimates of psychiatric disorders may be partly accounted for by differences in study populations. Brereton et al (2006) evaluated only individuals with Autistic Disorder, and included those with Intellectual Disability in their sample population. Conversely, Coury et al. (2012) included all ASD diagnoses in their sample. A significant limitation of the Coury study is that it does not provide any information on the IQ or ID status of individuals in the study sample, however given that all ASD diagnoses were included, it is likely that some study participants had an ID. Furthermore, the populations that study participants are recruited from may change prevalence estimates of psychiatric disorders; with a higher prevalence likely in a population of individuals recruited from a psychiatrically referred population, for example. Brereton et al. (2006) recruited study participants from individuals attending regional ASD assessment services, while Coury et al. (2012) recruited participants from the Autism Speaks Autism Treatment Network Research Registry.

Another factor that may account for differences in prevalence estimates of psychiatric disorders in individuals with ASD is the lack of consistency in tools used among studies to detect the disorders. While some tools are aligned with the DSM, others are not, making meaningful comparisons between studies that use different tools and inferring associations with DSM disorders difficult.

2.7 Risk Factors for Mental Health Concerns and Psychiatric Disorders

There is very little published information on risk factors for the development of mental health concerns specific to the ASD population. Gadow et al. (2008) evaluated) risk factors for the development of mental health concerns in a population of 238 eight to twelve- year-olds with an ASD diagnosis referred to a developmental disabilities clinic. Using bivariate correlations and regression analysis, they assessed the outcomes of aggression, mood disorders, anxiety disorders and attention-deficit disorder separately, similar to the methodology used in Chapter Five. Risk and protective factors that were assessed included: living with a single parent; living with at least one biological parent; level of parental education; socioeconomic status; current school placement (special education vs. regular education); early intervention; pregnancy and birth complications; other medical conditions; hospitalizations; psychotropic medication use; family psychiatric history; and family history of ASD (Gadow, De Vincent & Schneider, 2008).

Each outcome was found to have different risk factors in this study, although the magnitude of correlations were low, indicating that additional research and the inclusion of a wider range of risk factors is necessary for future studies (Gadow, et al., 2008). In this study population, family history of psychiatric disorders uniquely predicted most outcomes (aggression, mood disorders, and anxiety disorders). Some factors, such as living in a single-parent family,
were correlated with disruptive disorders such as aggression, while pregnancy complications and individual hospitalization for a medical problem were associated with mood and anxiety disorders (Gadow et al., 2008).

2.8 Adolescence and Mental Health

Adolescence has been identified as a critical period for the development of psychiatric disorders in individuals with and without ASD, with over half of all lifetime disorders first emerging during adolescence (Belfer, 2008; Billstedt et al., 2005; Kessler et al., 2012). Social and biological changes that occur during this time may lead to alterations in the ASD phenotype, changes in the severity of existing comorbidities, or the development of new ones (Simonoff et al., 2008). The additional stress of coping with a mental health challenge can negatively impact social functioning and educational attainment, causing adolescents with ASD to fall further behind their peers (Joshi et al., 2010). This may be particularly apparent in the area of social functioning, as typically developing peers begin to establish their independence and social hierarchies become more complex in the adolescent years. Social, emotional and educational difficulties may in turn further exacerbate mental health challenges. Since adolescence is such a critical period for the development of mental health concerns, (Belfer, 2008) and poor mental health in adolescence can compromise adult outcomes (Billstedt et al., 2005), we chose to focus on adolescence in this thesis.

2.9 Predicting the Developmental Trajectory of ASD

As an increasing number of children with ASD reach adolescence and adulthood, caregivers and service providers are struggling to map the developmental trajectory of ASD. Predicting adult or

adolescent outcomes from childhood characteristics has proved difficult due to the heterogeneity of ASD symptoms, associated medical conditions, a lack of standard outcome measures (Howlin, Goode, Hutton, & Rutter, 2004) and a lack of longitudinal research on this subject.

The literature on long-term outcomes for individuals with ASD that does exist is sobering. While one 4.5 year longitudinal study of 241 individuals with ASD aged 10 to 52 found that ASD symptoms and maladaptive behaviour improved throughout adolescence and into adulthood (Shattuck, Seltzer, Greenberg, Orsmond, Bolt, Kring, Lounds, & Lord, 2007), overall, individuals with ASD typically fare poorly in adulthood with respect to measures of independence, educational attainment, employment, communication and social abilities (Billstedt et al., 2005; Howlin, Goode, Hutton, & Rutter, 2004; Seltzer, Shattuck, Abbeduto, & Greenberg, 2004; Shattuck et al., 2007). In addition, adolescence tends to be a particularly vulnerable period, with many individuals developing serious mental health, behavioural and emotional problems during this time, and many individuals never regaining their pre-puberty phenotype (Billstedt et al., 2005).

The added burden of a mental health concern in adolescence may further complicate the developmental course of an individual with ASD and further compromise adult outcomes, particularly if comorbid mental health concerns are not recognized and treated (Joshi et al., 2010). Predicting adolescent and adult outcomes for children with ASD can help service providers anticipate future needs, and offer individual and family-oriented services to build resilience designed to mitigate the impact of any mental health problems that eventually develop. One aspect of predicting adolescent and adult outcomes is identifying those individuals who are at greatest risk for comorbidities, including mental health concerns.

The core symptoms of ASD are impairments in reciprocal social interaction and communication, and restricted, repetitive and stereotyped patterns of behaviour. These core impairments of ASD have been studied as predictors of various adult outcomes, including ASD symptom change over time (Seltzer, Krauss, Shattuck, Orsmond, Swe, & Lord, 2003; Shattuck et al., 2006), social functioning, linguistic abilities, and stereotyped behaviours (Howlin et al., 2004) and challenging or maladaptive behaviours (Matson, Wilkins, & Macken, 2008). Matson et al. (2008) evaluated a group of 176 individuals with ASD, to determine if severity of ASD symptoms (categorized as mild, moderate, or severe) affected the types of challenging behaviours displayed in the study population, and to identify the symptoms of ASD that best predict specific challenging behaviours (Matson et al., 2008).

The severity of ASD symptoms in this study sample was significantly correlated with the severity of problem behaviours, and individuals with severe ASD symptoms were more likely to present with stereotypic or repetitive behaviour, self-injurious behaviour and aggressive or destructive behaviours (Matson et al., 2008). Furthermore, eight of the challenging behaviours investigated were significantly predicted by specific ASD symptoms. The results of this study provide initial evidence that specific groupings of ASD symptoms can predict problematic behaviours that require intervention or further assessment (Matson et al., 2008). Since there was a significant amount of previously collected data on early childhood ASD symptomatology available for potential study participants in this current study, we chose to use childhood ASD symptomatology as our exposure variable. By linking early childhood ASD symptoms to adolescent mental health outcomes, this study will build on the work of Matson et al. (2008), which looked at challenging and maladaptive behaviours, rather than specific psychiatric diagnoses, and will enable us to contribute to the literature on the developmental trajectory of ASD, with a specific focus on mental health outcomes.

2.10 Public Health Implications of Mental Health Concerns in ASD

Mental health concerns are increasingly being recognized as major contributors to poor quality of life for individuals with ASD and their families (Joshi et al., 2010), just as they have been increasingly recognized as problematic in typical individuals (Mental Health Commission of Canada, 2012). The *Changing Directions, Changing Lives* report from the Mental Health Commission of Canada highlights the importance of recognizing mental health concerns in childhood and adolescence, with special attention paid to youth at increased risk, as adolescence is a critical period for the development of mental health concerns, and children and youth in particular face many barriers to treatments and services.

The 2011 report from the National Coalition on Dual Diagnosis in Canada indicates that individuals with a dual diagnosis (used here to indicate any Intellectual Disability and cooccurring mental health concerns) have more severe mental health symptoms and are more likely to have other co-occurring medical conditions than the general population, and have access to fewer resources, including education, social and economic support (National Coalition on Dual Diagnosis, 2011). Due to their complex needs and lack of community or specialized supports, individuals with dual diagnoses are more likely to visit emergency departments for treatment and are more likely to be re-hospitalized than the general population, creating a significant economic burden on the healthcare system (Lunsky et al., 2011). The National Action on Dual Diagnosis in Canada report stresses the need for early intervention, namely early recognition of mental health concerns, in childhood and throughout the life course. Other needs the report identifies include the need for preventative programs, for example, mental illness screening guidelines for people with ID, and better guidelines for primary care providers for the recognition and treatment of dual diagnoses (National Coalition on Dual Diagnosis, 2011). The research presented in this thesis attempted to build on previous studies by focusing specifically on mental health challenges that occur in the pre-teen and adolescent years. We chose to use early childhood ASD symptomatology as the exposure of interest in this thesis as we had access to previously collected data for a large number of potential participants, and we attempted to improve upon Matson et al.'s (2008) previous study of the relationship between ASD symptomatology and maladaptive behaviour by looking at mental health concerns in a manner that aligned with DSM diagnoses. Furthermore, we were able to consider a number of possible risk factors for the development of mental health concerns, such as ID, family history of mental health concerns, and individual medical history in a community-based sample, and provide initial prevalence estimates of mental health concerns in a sample of Canadian adolescents with ASD.

2.11 References

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Chapter 3

Considerations for use of the Autism Diagnostic Interview-Revised (ADI-R) in Retrospective Studies

3.1 Abstract

Objectives: As a standard diagnostic tool, the Autism Diagnostic Interview-Revised (ADI-R) can potentially be used in retrospective studies to establish ASD symptomatology at a standard age across a study sample, as many questions query behaviour at age four. However, since the ADI-R is not always administered at the same age in each individual, the age at which the ADI-R assessment is conducted may bias scores on domains containing both items queried at age four and items queried at any point. The purpose of this study was to determine if there was a correlation between ADI-R diagnostic algorithm scores and age at assessment that would need to be controlled for in subsequent analyses using ADI-R data.

Methodology: 339 verbal individuals between the ages of 10 and 19 were selected for inclusion in the study population. All ADI-R data were previously collected for research purposes (nondiagnostic). Kendall tau *b* correlation coefficients were calculated to examine the association between age at assessment with the ADI-R and total score on each ADI-R domain.

Results: A weak positive correlation was detected between age at assessment and total score on both the reciprocal social interaction and communication domains. No correlation was found between age at assessment and score in the repetitive behaviours and stereotyped interests domain. When the population was stratified into two age groups based on the median age at assessment, there were significant differences in the median scores on the reciprocal social interaction and communication domains, indicating a possible cohort effect. **Conclusions:** Researchers should use caution and control for age at assessment when using the ADI-R diagnostic algorithm to ascertain early childhood levels of ASD symptomatology in retrospective studies.

3.2 Introduction

The Autism Diagnostic Interview-Revised (ADI-R) is a psychological assessment tool developed to evaluate children for ASD. It contains 96 items that probe parents for information about the child's verbal and non-verbal communication and social interaction, and investigates behaviours that are rare in individuals without ASD. Due to the wealth of information collected during an ADI-R interview, the results of this interview provide an excellent clinical portrait of an affected individual and a rich data source for researchers. Currently, the ADI-R is often used in research to develop ASD symptom profiles of study participants (Billstedt, Gillberg, & Gillberg, 2005; Howlin, Good, Hutton, & Rutter, 2004; Shattuck et al., 2007). In addition to questions about the individual's current functioning, two types of items are included the diagnostic algorithm for the ADI-R. The first type queries the individual's development and symptoms at age four. The second type of items are specific to behaviours that are abnormal at any stage in development and interviewees are asked whether these behaviours have occurred at any point in the individual's life (Rutter, Le Couteur & Lord, 2008).

Since many of the ADI-R items query the individual's behaviour at age four, the ADI-R may be particularly well-suited for use in retrospective studies, as it allows researchers to establish a baseline of symptomatology at a specific age that can be standardized across participants, and ameliorates the issue of recall error, particularly if previously collected data is used. Retrospective studies are extremely useful- they are less labour- and cost-intensive than prospective studies, and can make use of larger, community-based samples (Seltzer et al., 2004). Retrospective studies with an established baseline also avoid the challenge of cohort effects (Seltzer et al., 2004). This is particularly relevant in studies of ASD, where changes in diagnostic practice can create profound cohort effects.

3.2.1 ADI-R Diagnostic Algorithm

For each ADI-R item, the informant is asked to rate the child's behaviour on a numerical scale, with zero representing no impairment or total absence of unusual behavior, and two indicating the definite presence of the abnormal behaviour queried (Rutter, Le Couteur, & Lord, 2008). A score of one is given when the behaviour in question is present in an abnormal form, but is not severe enough to meet the criteria for a score of two (the ADI-R is administered by highly trained interviewers and scoring requires judgment on the part of the interviewer) (Rutter, Le Couteur, & Lord, 2008). Items are scored either on the basis of the child's appearance at age four, or whether a particular behaviour occurred at any point in the child's life (Rutter, Le Couteur, & Lord, 2008). Scores on domains that contain these "ever" or lifetime items may, therefore, not be reliable measures of ASD symptomatology at age four.

The ADI-R diagnostic algorithm is divided into three domains: qualitative abnormalities in reciprocal social interaction; qualitative abnormalities in communication; and restricted, repetitive and stereotyped patterns of behaviour. There are 35 items in these three domains. The communication and social reciprocity domains contain both age four and "ever" items, while the repetitive and stereotyped patterns of behaviour domain contains only "ever" items. The rationale for this scoring system is described in the ADI-R manual (Rutter, LeCouteur, & Lord, 2008). The items with a current and ever score are behaviours that would be abnormal regardless of the age at which they occurred, for example, echolalia or abnormal preoccupation with objects or parts of objects. The items that utilize a current score and an additional score for ages 4-5 are behaviours that are likely to be influenced by maturation level, for example, imaginative play. The reasons for choosing ages 4-5 are twofold. Firstly, severe developmental delays may impede the development of some of these behaviours in children younger than four, and older children may

have outgrown some of these behaviours by the time the ADI-R is administered (Rutter, Le Couteur, & Lord, 2008). Age 4-5 years is a reasonable compromise where children are less likely to be impeded by severe developmental delay, but young enough to not have outgrown maturation-influenced behaviours such as imaginative play (Rutter, Le Couteur, & Lord, 2008). Secondly, ASD symptoms tend to be the most severe and most clearly reflective of ASD at this point in time (Rutter, Le Couteur, & Lord, 2008). The diagnostic algorithm, therefore, does not contain any items about the individual's current behaviour, rather it focuses on their behaviour at age four, and whether they displayed particular abnormal behaviours at any point in their lives. In using the diagnostic algorithm in this study, we were able to capture a picture of ASD symptomatology that reflects how the individual appeared at age four.

3.3 Purpose and Rationale

Since the ADI-R is not always administered at the same age in each individual, the age at which the ADI-R assessment is conducted may bias scores on domains containing both items queried at age four and items queried at any point. The purpose of this study was to determine if there was a correlation between ADI-R diagnostic algorithm scores and age at assessment that would need to be controlled for in subsequent analyses using ADI-R data.

3.4 Methods

ADI-R data used in this study had been previously collected for use by two ASD research databases located at Queen's University, Kingston, ON: the National Epidemiologic Database for the Study of Autism in Canada (NEDSAC), and the Autism Spectrum Disorders Canadian-American Research Consortium (ASD-CARC) research registry. In order to be eligible for the study, children had to have a completed ADI-R entered in one of the research databases, be between the ages of 10 and 19 as of 2012, and reside in Canada. These inclusion criteria were chosen as they correspond to those of a retrospective cohort study of adolescents with ASD to which parents of children in this sample were invited to participate.

After excluding non-verbal participants (n=74), and individuals who were assessed at less than four years of age (n=12), the final number of participants was 339. The decision to exclude individuals assessed before age four was based on the fact that the ADI-R uses a slightly different diagnostic algorithm for individuals who are between the ages of two and three years, eleven months when assessed. The ADI-R data used in this study was collected between 2003 and 2010, with most collected in 2004.

The ADI-R diagnostic algorithm is different for verbal and non-verbal individuals, making it difficult to compare scores between groups. We decided *a priori* to exclude non-verbal individuals from our analysis due to the relatively small number of non-verbal individuals (n=74) in this sample. Individuals were judged to be non-verbal on the basis of item 30 of the ADI-R. Item 30 evaluates the individual's overall level of language, including the number of words and phrases they use, whether they use verbs, and if other people understand their speech (Rutter, Le Couteur & Lord, 2008). Individual with a score of one or two on this item are considered nonverbal according to the ADI-R instruction manual provided by Western Psychological Services (Rutter, Le Couteur & Lord, 2008).

3.4.1 Statistical Analysis

All statistical analyses were performed using SAS 9.3. Descriptive statistics were computed for the study sample. Kendall tau *b* correlation coefficients were calculated between age at assessment and scores on each of the diagnostic algorithms of the three domains of the ADI-R

(reciprocal social interaction, communication, restricted, repetitive and stereotyped patterns of behaviour). Scatter plots with 95% confidence limits and regression lines were created to provide a visual description of the correlation between age at assessment and domain scores.

Additionally, we stratified our analysis into two groups, based on the median age of assessment with the ADI-R to assess for any cohort effects in our study sample. In this study, cohort effects would have taken the form of systematic variations in ADI-R scores based on the age at which individuals were assessed. The first group consisted of those who had been evaluated at <8.9 years of age (n=169), while the second consisted of individuals who were assessed at \geq 8.9 years of age (n=170).

3.5 Results

Table 3-1 contains descriptive statistics, including median scores and ranges for each ADI-R diagnostic algorithm domain. The median age at assessment of the study sample was 8.9 years. Age at assessment and all domain scores were non-normally distributed. It is important to note that the ranges of the ADI-R scores include values that fall below diagnostic cutoffs. These interviews were non-diagnostic (i.e. they were collected by a trained interviewer for research purposes) and every individual in the study sample had a parent-confirmed ASD diagnosis.

ADI-R Domain	Median	Range	Possible Range	
Age at Assessment (in years)	8.9	4-15		
Communication Score	13	1-22	0-26	
Reciprocal Social Interaction Score	21	3-30	0-30	
Restricted, Repetitive & Stereotyped Behaviour	6	0-12	0-12	

Table 3-1: Descriptive Statistics (n=339)

3.5.1 Association of Age at Assessment and Domain Scores

As shown in Table 3-2, correlation coefficients revealed weak positive associations between age at assessment and total score in the reciprocal social interaction domain (Kendall tau b=0.23, p<0.0001; see Figure 3-1) and communication domain (Kendall tau b=0.10, p<0.001; see Figure 3-2). The correlation between age at assessment and score on the restricted, repetitive and stereotyped behaviour domain was not significant (see Figure 3-3).

ADI-R Domain	Kendall tau b	p-value
Reciprocal Social Interaction Score	.23	<0.0001
Communication Score	.10	< 0.001
Restricted, Repetitive & Stereotyped Behaviour	03	.51

 Table 3-2: Kendall tau b correlation coefficients for domain score and age at assessment

 (n=339)



Figure 3-1: Correlation between age at assessment and reciprocal social interaction score

(n=339)



Figure 3-2: Correlation between age at assessment and communication score (n=339)



Figure 3-3: Correlation between age at assessment and restricted, repetitive behaviours score (n=339)

To explore the possibility of a cohort effect, we compared the median scores in ADI-R domains between age groups, using the Wilcoxon Mann-Whitney test to compare medians (see Table 3-3), and found significant differences for the reciprocal social interaction and communication domains, where higher median scores were found in the group that was assessed at an older age.

Domain	Media	р	
	Assessed < 8.9 years	Assessed ≥ 8.9 years	
Reciprocal Social Interaction	19	22	< 0.001
Communication	13	14	0.05
Restricted, Repetitive and Stereotyped Behaviour	6	6	0.9

Table 3-3:	Comparison o	f median scores	by age at	assessment	(n=339)
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3.6 Discussion

The strongest correlation was found between age at assessment and score on the reciprocal social interaction domain, which consists mostly of items queried at age four. This might suggest that there is an element of recall bias at work in the ADI-R, in that parents of children who were older when evaluated recall worse symptoms or behaviours in this domain, perhaps influenced by perceptions of their child's current symptomatology. Alternatively, it could mean that individuals in the study sample who were assessed when they were older had more severe ASD symptoms when they were four years old.

Furthermore, we found statistically significant differences in median scores on the communication and reciprocal social interaction domains after stratifying the sample based on median age at assessment. There are two possible explanations for this finding. The first is a cohort effect. Individuals who were assessed at an older age are generally speaking, older (median age of 18 vs. 14 for those assessed earlier than 8.9 years), and were diagnosed with ASD earlier. It may be that changes in diagnostic procedures and an increased awareness of Asperger's mean that the younger individuals in our study sample simply have less severe ASD symptoms (Fombonne, 2003).

Alternatively, there could be an element of recall error on the part of parents at work in the ADI-R. Difficulties in social interaction and communication may become more salient to parents as their child gets older and difficulties in school become more pronounced, and parents may report their child's symptoms at age four through the lens of how they perceive their child's current symptoms (Ingersoll & Hambrick, 2011). Parental stress has been shown to influence perception of child impairment (Brookman-Frazee, Baker-Ericzen, & Stahmer, 2005; Davis & Carter, 2008; Ingersoll & Hambrick, 2011), and a lack of prosocial behaviour (which would be identified in the Reciprocal Social Interaction scale) in particular has been linked to increased parental stress (Davis & Carter, 2008). Additionally, with older children, parental memory of a child's symptoms at age four may be less accurate due to the amount of time elapsed. While the results of this study do not allow us to draw any conclusions as to which explanation best accounts for our findings, the results indicate a need for caution when attempting to use the ADI-R as a standardized measure of ASD symptomatology at age four.

3.7 Strengths and Limitations

To our knowledge, this is the first study that attempts to determine if the ADI-R can be used as a measurement to predict outcomes later in life, by generating a comprehensive profile for individuals at a specific age in early childhood, regardless of what age the ADI-R was administered at. A large sample size, ensuring adequate statistical power, is an important strength of this study

One possible limitation of this study is that due to the nature of the data collected in the ASD research databases, we were not able to differentiate between individuals with Autistic Disorder, and individuals with other Autism Spectrum Disorders. The relationship between age at assessment and score on the diagnostic algorithms of the ADI-R may have differed by ASD diagnosis, however, with the DSM 5 changes to the manner in which ASD is diagnosed, any differences found in this study would have limited practical significance.

3.8 Conclusions

The results of this study suggest the need for caution in using the ADI-R diagnostic algorithm in a retrospective setting, where symptomatology at age four may be used to predict outcomes later in life. If the ADI-R data is going to be used in this manner, the age at which individuals were

assessed with the ADI-R should be controlled for in the analysis. Replication of these findings by other researchers would add strength to the conclusions drawn in this study.

3.9 References

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Chapter 4

Prevalence Estimates of Mental Health Concerns in a Canadian Sample of Pre-teens and Adolescents with Autism Spectrum Disorder (ASD)

4.1 Abstract

Objectives: The purpose of this study was to generate prevalence estimates for mental health concerns in a sample of Canadian adolescents with ASD. This is the first study to attempt to assess the burden of mental health concerns in adolescents with ASD in the Canadian context. Further, we sought to determine the degree of agreement between parent-reported diagnoses and symptoms reported on a standard psychological screening tool, the Child Behaviour Checklist (CBCL).

Methods: Four hundred and twenty-five potential participants were identified from two ASD research databases located in Kingston, Ontario. The parents of 390 individuals were invited to participate in a survey, either online or by mail, on family medical history, individual educational attainment, service utilization, drug use, mental health, and medical history. The parents of 66 individuals completed the survey.

Results: Forty-five percent of the study sample scored in the clinical range on one or more of the DSM-oriented scales of the CBCL. Anxiety problems were the most commonly reported mental health concerns in this sample, both as reported by parents and detected by the CBCL. Fifteen percent (n=10) of the study sample scored in the clinical range of two or more CBCL subscales.

Finally, kappa statistics indicated poor agreement between parent-reported diagnoses and clinical scores on CBCL subscales, with McNemar's test for matched pairs revealing that the CBCL detected more cases than reported by parents.

Conclusions: Our findings indicate that many of the adolescents in this study sample may have undiagnosed mental health concerns or psychiatric disorders. This study highlights the need for further exploration of the reasons for the discrepancy between parent-reported diagnoses and elevated levels of behavior and emotional problems detected on screening tools.

4.2 Introduction

Adolescence is a critical time for the development of psychiatric disorders and mental health concerns. Half of all lifetime cases of psychiatric disorders emerge by age 14 (Kessler et al., 2005), and psychiatric disorders represent a significant contributor to poor quality of life (Mental Health Commission of Canada, 2012). This is particularly true for individuals with Autism Spectrum Disorders (ASD), who experience greater social (and, in some cases, academic) challenges in adolescence. The prevalence of mental health concerns that do not meet DSM diagnostic criteria may be even higher than that of psychiatric disorders and may represent an equally large or larger burden on quality of life. In some cases, symptoms that do not meet diagnostic levels may present more of a challenge than a psychiatric diagnosis, as some services may be available only to those with diagnoses. Individuals with ASD and a mental health concern may require specialized treatment or support services designed to address their complex needs (National Coalition on Dual Diagnosis, 2011). Unrecognized, untreated mental health concerns can negatively affect academic performance and can also exacerbate the already wide gap between adolescents with ASD and their peers (Joshi et al., 2010).

Mental health concerns can be difficult to recognize and treat in individuals with ASD, due in part to the prevalence of ID and limited verbal ability in this population. Individuals with ASD may have limited verbal ability, no verbal ability, or difficulty with the abstract thoughts necessary to describe their fears or worries (Leyfer et al., 2006; Witwer & Lecavalier, 2010). Since many diagnostic tools require individuals to articulate their distress, clinicians may have difficulty making diagnoses and interpreting behaviours in the absence of the ability to describe one's mental state. Furthermore, there is insufficient research on the way symptoms of psychiatric disorders manifest in individuals with ASD (Joshi et al., 2010; Witwer & Lecavalier, 2010), with some experts believing that symptoms manifest differently in individuals with ASD than typical individuals (Lecavalier, 2006; Leyfer et al., 2006).

Due to difficulty in diagnosing and recognizing symptoms of mental health concerns in this population, obtaining accurate incidence and prevalence estimates is difficult. In a study of psychiatric disorders in children and youth with ASD, 108 children with ASD aged four to eighteen years who did not have an Intellectual Disability were evaluated using the eight syndrome scales of the CBCL (the syndrome scales are: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour) (Mazefsky, Anderson, Conner, & Minshew, 2011). More than 50% of the study population scored in the clinical range on the withdrawn/depressed, social, thought and attention problems scales (Mazefsky et al., 2011). One notable weakness of this study was that it did not consider individuals with ID. A second weakness is that it used CBCL scales that are not aligned with the DSM, making it difficult to infer any associations with DSM disorders.

A 2012 cross-sectional study of 2853 children aged 2 to 17 years with ASD revealed that 15.5% of the study sample had a parent-reported psychiatric disorder, and 36% met clinical criteria on the internalizing and externalizing behaviour scales of the CBCL (Coury et al., 2012). Again, this study used CBCL scales that are not aligned with the DSM, and did not collect any information on Intellectual Disability status among participants.

A recent study of mental health in Irish youth with ASD used the DSM-oriented scales of the Child Behaviour Checklist (CBCL) to evaluate the mental health of 67 youth with ASD and IQ-matched controls (Skokauskas & Gallager, 2012). In this sample, 46.2% met clinical cut-off scores for anxiety, and 44.8% of youth with ASD met clinical cut-off scores for Attention Deficit
Hyperactivity Disorder (ADHD) (Skokauskas & Gallagher (2012). This study included individuals with ID, and evaluated participants using both the DSM scales and the total problems scales of the CBCL.

These recent prevalence estimates provide some evidence that many individuals with ASD are burdened by mental health concerns, and may experience mental health concerns at a greater rate than typically developing adolescents. Specifically, these estimates are higher than those reported by Costello et al. (2003), who reported a 3-month prevalence of psychiatric disorders of 13.3% in a representative sample of 1420 typically developing American youth aged 9 to 13, and estimated that by age 16, the cumulative prevalence of psychiatric disorders in this sample would be 36.7% (Costello et al., 2003).

The current study aimed to address some gaps in the literature by evaluating individuals with the DSM-oriented CBCL scales in order to facilitate comparisons with parent-reported DSM diagnoses. This study also attempted to provide an initial prevalence estimate of mental health concerns in Canadian youth with ASD, potentially providing Canadian service providers and policy makers with information to aid in decision-making and predicting the needs of Canadian youth with ASD. We attempted to improve on previous studies by collecting information about Intellectual Disability from participants, however there was a significant amount of missing data for this variable.

4.2.1 Autism Spectrum Disorders and Psychiatric Co-Morbidities

Recognition and diagnosis of psychiatric co-morbidities in individuals with ASD has been a topic of debate amongst health professionals and experts- namely, whether DSM-IV psychiatric diagnoses should be thought of as separate from ASD, or treated as symptom clusters within the ASD diagnosis (American Academy of Child and Adolescent Psychology, 1999). While it has become accepted that individuals with ASD present with a range of symptoms indicative of psychiatric disorders (Billstedt, Gillberg, & Gillberg, 2005; Sverd, 2003), such conditions are still difficult to recognize and diagnose in this population. Three factors contributing to this difficulty are: co-occurring Intellectual Disability (ID), prevalence of non-verbal individuals with ASD, and the heterogeneity of psychiatric symptoms in individuals with ASD (Matson & Nebel-Schwalm, 2007).

Individuals with ASD may have limited verbal ability, no verbal ability, or difficulty with the abstract thoughts necessary to describe their fears or worries (Leyfer et al., 2006; Witwer & Lecavalier, 2010). Since many diagnostic tools require individuals to articulate their distress, clinicians may have difficulty making diagnoses and interpreting behaviours in the absence of the ability to describe one's mental state (Witwer & Lecavalier, 2010). Furthermore, the diagnostic criteria for some psychiatric disorders require individuals to express their worries, thoughts, or fears, which may be difficult for those with ID, or with limited verbal ability (Witwer & Lecavalier, 2010). Finally, mental health concerns may present differently in those with ASD, particularly those who also have an ID (Leyfer, 2006; Witwer & Lecavalier, 2010), and we do not yet have a clear understanding of the extent of the overlap between symptoms of ASD and symptoms of mental health concerns (Leyfer, 2006).

4.3 Purpose and Rationale

The purpose of this study was to generate prevalence estimates for mental health concerns in a population of Canadian pre-teens and adolescents with ASD. The findings from this study may be used to inform policy makers of the burden of mental health concerns in this population and to enable service providers to predict future areas of need.

4.4 Methods

Participants for this study were recruited through two ASD research databases based in Kingston, Ontario. Individuals who were invited to participate had previously given consent to be contacted for future studies and completed consent forms prior to filling out the questionnaire. The information and consent forms for this study are available in Appendix A. Ethical approval for this study was granted by the Queen's Health Science Research Ethics Board (see Appendix B). The questionnaire is presented in Appendix C. Participants were parents of children who:

- 1. Have an ASD, confirmed by parent report,
- 2. Were between the ages of 10 and 19 years in 2012,
- Had completed an Autism Diagnostic Interview-Revised (ADI-R) with the research registries and;
- 4. Lived in Canada in 2012

We invited the parents of 390 individuals to participate in this study by email and mail. Twenty survey packages were undeliverable (returned to sender). The parents of 66 individuals returned completed surveys, for a response rate of 17%.

4.4.1 Survey Design

A survey entitled "Risk factors for Mental Health Concerns and Seizures in Adolescents with Autism Spectrum Disorders (ASD)" was created using pre-existing questions from the Canadian Community Health Surveys (CCHS) (Statistics Canada, 2011), the National Longitudinal Study of Children and Youth (NLSCY) (Statistics Canada, 2008) and the Kennedy Krieger Institutes Interactive Autism Network (IAN) ASD Family History Questionnaire (Kennedy Krieger Institute, 2012). The survey consisted of 26 items on individual medical history, medication use, educational attainment and service utilization, and family medical history. The survey also contained the Child Behaviour Checklist Parent Report Form (CBCL) for children aged 6-18. The survey was made available online through the Autism Spectrum Disorders Canadian-American Research Consortium (ASD-CARC) online survey tool, and by mail.

4.4.2 Child Behaviour Checklist (CBCL)

The CBCL Parent Report Form for children aged 6-18 (Achenbach & Rescorla, 2001) is a standardized clinical screening tool for behavioural and emotional problems. The CBCL has become a commonly used screening tool in children and adolescents (Gladman & Lancaster, 2003; Matson, Belva, Hattier, & Matson, 2012). The internal consistencies of the DSM-oriented scales of the CBCL range from .71 for somatic problems to .89 for conduct problems (Nakamura, Ebesutani, Bernstein & Chorpita, 2008). In a large, clinical sample, each DSM-oriented scale demonstrated significant convergent validity, and favourable divergent validity (Nakamura et al., 2008). The CBCL also shows good sensitivity in detecting disorders in children with ASD, with syndrome scale sensitivities ranging from 83% for externalizing problems to 100% for aggressive behaviour (Pandolfi et al., 2012). As the CBCL is designed as a screening tool, the specificity of the syndrome scales is lower, ranging from 25% for total attention problems to 78% for internalizing problems (Pandolfi et al., 2012).

The CBCL consists of 113 items scored on a three-point Likert scale, with zero indicating "not true", one indicating "sometimes or somewhat true" and two indicating "very true or often true". Parents are asked to rate their child's behaviour in the previous six months, resulting in a current picture of the child's behaviour and mental health.

For this study, we used the DSM-oriented profiles for boys and girls. There are six DSMoriented scales provided by the CBCL: affective problems (Dysthymia, Major Depressive Disorder), anxiety problems (Generalized Anxiety Disorder, Separation Anxiety Disorder, Specific Phobia), attention deficit/hyperactivity problems, conduct problems, oppositional-defiant problems, and somatic problems (Achenbach & Rescorla, 2001). Scores for the DSM-oriented profiles are based on both age and gender. For each of the six DSM-oriented scales, a score of "normal", "sub-clinical" or "clinical" may be obtained. There are other scoring profiles available for the CBCL, including a total problems score, internalizing and externalizing scales, or eight individual scales that do not align with the DSM-IV. We chose to use the DSM-oriented scales for this study, as they would facilitate comparison with parent-reported diagnoses.

4.4.3 Case Definitions

Since the aim of this study was to address mental health concerns in pre-teens and adolescents, we were interested in current behaviour and emotional problems (obtained from the CBCL) and diagnoses after the age of 10 (obtained from the parent survey). Therefore, individuals were considered cases if they met clinical cutoffs on the CBCL or if their parent reported a diagnosis after age 10.

4.5 Statistical Analysis

Point prevalence estimates and 95% confidence intervals for a combined outcome of any mental health concern as well as each DSM-oriented CBCL subscale were calculated in SAS 9.3. We used McNemar's test for matched pairs to assess discordance between parent-reported diagnoses and CBCL findings.

4.6 Results

Parents of 66 individuals completed the survey online (n=40) or by mail (n=26). The mean age of the study sample was 15.2 years (SD=2.7). There were 12 female and 54 male individuals in the sample. The majority of individuals (96%, n=64) in the study sample lived at home. The two

individuals not living at home were living independently. All respondents were the biological parents of their children.

The majority of the individuals were enrolled in a public school (83%, n=55), with 39% (n=26) in regular education classrooms for the entirety of their school day, and 24% (n=16) in special education classrooms for the entire school day. Fifty-five percent of parents reported that their child had never had an IQ test (or that they were uncertain if they had), and the majority of the sample (71%, n=47) did not have a reported Intellectual Disability (ID).

4.6.1 Point Prevalence Estimates and Confidence Intervals

Forty-five percent of the study sample (n=30) met our case definition for one or more mental health concerns. Point prevalence estimates and 95% confidence intervals for each DSM-oriented scale can be found in Table 4-1. Anxiety problems were the most prevalent mental health concerns in this population, both parent-reported and identified on the CBCL, with 33.3% of the study sample meeting case criteria for anxiety problems. This was followed by mood disorders (18%) and attention deficit/hyperactivity problems (12%).

DSM-oriented Disorders	Point Prevalence (%) (N)	95% Confidence Interval
All	45.5 (30)	33-58
Anxiety	33.3 (22)	22-46
Mood	18 (12)	9.7-29.6
Somatic	10.6 (7)	4-20.6
Conduct	4.6 (3)	0.95-12.7
Oppositional Defiant	7.6 (5)	2.5-16.8
Attention Deficit	12 (8)	5.4-22.4

Table 4-1: Point Prevalence estimates with 95% confidence intervals for all mental health concerns evaluated (n=66).

Furthermore, the frequencies of positive scores on the CBCL indicated that some individuals in the study sample scored positive on more than one DSM-oriented subscale (see table 4-2). Three individuals (4.6%) scored positive on two DSM subscales, while 10.5% scored positive on three or more subscales.

Number of CBCL Scales where clinical scores were obtained	(%) N
0	57.6 (38)
1	27.3 (18)
2	4.6 (3)
3	6 (4)
4	1.5 (1)
5	3 (2)
6	0 (0)

 Table 4-2: Frequency of clinical CBCL scores per individual (n=66)

4.6.2 Agreement between Parent-Reported Psychiatric Diagnoses and CBCL Findings Kappa statistics indicated poor or no agreement (<0.2; see Landis and Koch, 1977) between parent-reported disorders and clinical CBCL symptoms. McNemar's tests further revealed that for anxiety disorders and mood disorders, the discrepancy was due to parents reporting fewer diagnoses than problems identified by the CBCL (see table 4-3).

Scale	Kappa for Agreement between Parent- Reported Diagnoses and CBCL case status	Parent- Reported diagnoses only (n)	CBCL cases only (n)	p-value from McNemar's test for Discordant Pairs
Anxiety disorders	0.03	3	16	< 0.005
Mood disorders	0.12	2	9	< 0.05
Conduct disorder	-0.02	1	2	0.56
Attention deficit disorders	0.19	1	6	0.058

 Table 4-3: Comparison of parent-reported diagnoses and CBCL-identified cases (n=66)

4.6.3 Adjusting the Case Definition

The DSM-oriented scales of the CBCL offer three categories of score: normal, sub-clinical, and clinical. It is accepted that clinical levels of behaviour indicate a possible psychiatric disorder. Since categorical distinctions are less reliable for individuals who score close to the border between categories (Achenbach & Rescorla, 2001), the sub-clinical range was created to assist in decision-making by caregivers (Achenbach & Rescorla, 2001). A sub-clinical score indicates symptoms severe enough to be of concern, but not so severe as to typically need immediate treatment or intervention (Achenbach & Rescorla, 2001). However, sub-clinical scores on several scales may warrant further evaluation, or an individual may need to be assessed again in a

few months to determine if symptoms have moved into the clinical or normal ranges (Achenbach & Rescorla, 2001).

To investigate the practical implications of sub-clinical scores in our study sample, we repeated our analysis with an altered case definition, where a case was any individual who scored in the subclinical or clinical range on the CBCL or who had a parent-reported diagnosis after age 10. Altering our case definition resulted in 60% of our study sample (n=40) meeting case criteria. As before, anxiety, mood and attention-deficit disorders were the most common problems in this population. Table 4-4 presents point prevalence estimates and confidence intervals for this broadened case definition.

When assessing the agreement between parent-reported diagnosis and our broadened case definition, the disagreement was significant for mood disorders (p<0.01), anxiety disorders (p<0.001), conduct disorders (p<0.05), and attention-deficit disorders (p=0.05).

Psychiatric Disorders	Point Prevalence (%) (N)	95% Confidence Interval
All	60 (40)	47.8-72
Anxiety	47 (31)	35.6-59.6
Mood	29 (19)	18-41
Somatic	15 (10)	7.5-26
Conduct	13.6 (9)	6-24
Oppositional Defiant	21 (14)	12-33
Attention Deficit	22.7 (15)	13.3-34.7

 Table 4-4: Point prevalence estimates and 95% confidence intervals for broadened case definition (n=66)





Figure 4-1: Prevalence of CBCL scores, by subscale (n=66)

4.7 Discussion

The data from our parent survey indicated that 45% of the study sample met criteria for one or more mental health concern. The most common concerns in this population were anxiety problems (33.3%), followed closely by mood disorders (18%). Several studies have also reported that mood disorders are common in psychiatrically-referred ASD populations (Leyfer et al., 2006; Sverd, 2003), and mood and anxiety disorders are consistently reported as the most common disorders in individuals with ASD, along with Attention-Deficit Hyperactivity Disorder (ADHD) (Hofvander et al., 2009; Mouridsen et al., 2008; Munesue et al., 2008). We also found that 15% of the study sample met clinical criteria on 2 or more CBCL subscales, indicating levels of symptoms that may be indicative of a psychiatric disorder. This is consistent with literature reporting that in a community-based sample of 109 children and adolescents with ASD, the median number of lifetime psychiatric disorders was three (Leyfer et al., 2006), as well as evidence that some psychiatric disorders (i.e. anxiety and depression) are likely to co-occur (Herpertz-Dahlmann et al., 2013). Our prevalence estimates for anxiety and mood disorders were consistent with those found by Skokauskas and Gallagher (2012), in a sample of 67 youth with ASD and 67 IQ-matched controls. Where our findings differed was in the prevalence of attention-deficit disorders; we found a 12% prevalence in our study sample, as opposed to the previously reported 44.7% (Skokauskas & Gallagher, 2012). High rates of ADHD have been reported in other studies, including Frazier et al. (2001). It is important to note that the assessment of attention problems in individuals with ASD is complicated by the fact that many ADHD symptoms overlap with ASD symptoms, and the DSM-IV-TR officially precludes a diagnosis of both ASD and ADHD (Skokauskas & Gallagher, 2012).

There is some indication that anxiety disorders are more common in individuals with ASD who have higher intellectual functioning or milder ASD (Leyfer et al., 2006; Sukhodolsky et al., 2008). Without having administered IQ tests to study participants and with the majority of parents in our sample indicating that their child has never had an IQ test or that their child was not diagnosed with an Intellectual Disability (ID), it was not possible to fully examine the effects of IQ and Intellectual Disability in our study sample. Volkmar and Pauls (2003) indicate that more than 60% of individuals with Autistic Disorder have an Intellectual Disability, and other epidemiological estimates indicate that between 40% and 80% of individuals with ASD have an Intellectual Disability (Newschaffer & Curran, 2003; Volkmar & Pauls, 2003). The low prevalence of ID in our study sample may mean that this sample is more high-functioning than

the average group of adolescents with ASD; this could be due to ascertainment bias (if parents of children without ID were more likely to complete the survey). However, given the amount of missing data (don't know/unsure responses) for the questions on IQ tests and reported ID, the validity of our ID measure is low and the reported prevalence of ID in this sample should be viewed with caution.

Rates of psychotropic medication use in this study sample were comparable to those reported by Coury et al. (2012). We asked parents "does your child take any of the following medications on a regular basis?" and how old their child was when he/she had first been prescribed the medication in question. For the purposes of this study, we were interested in medications that had been prescribed after age 10, to reflect a more current picture of mental health. Sixteen individuals (24.2%) in the study sample were taking a psychotropic medication, with anti-depressants being the most common type of prescription (n=6, 9.1%).

The gender ratio of our study population is consistent with the overall 4:1 male to female ratio for ASD (Levy et al., 2009; Volkmar & Pauls, 2003).

While the CBCL assesses current (including the preceding 6 months) behaviour, we asked parents about any current diagnoses since age 10. It is possible (and, based on anecdotal evidence, likely) that some individuals are presenting with symptoms that result in clinical CBCL scores, but do not yet have a diagnosis, and would not be captured in parent-reported psychiatric disorder counts; however our case definition took both CBCL score and parent report into account and therefore this would not affect the final results of the study.

The CBCL is a clinical screening tool. While it is not sufficient to diagnose psychiatric disorders, clinical scores on any scale warrant further investigation. The discrepancy between parent-reported diagnoses and CBCL findings has important clinical implications. We did not

report CBCL scores to parents, or ask if they were currently seeking a mental health diagnosis for their child based on current behaviours. It is possible that parents simply see behaviours queried on the CBCL as ASD-related, or are not concerned about them. However, given anecdotal evidence from other sections of the survey (including questions on service utilization and a section for parents to add any information they feel relevant), another possibility is that parents are struggling to access diagnostic and support services for their children. Information from parents indicates that they are concerned about their child's mental health and are struggling to manage but are unable to get their child re-assessed or are having difficulty accessing services. A selection of quotes from parents is presented here:

> He has not been diagnosed with an anxiety disorder but is becoming increasingly fearful of certain things.

I wish I could get her re-assessed, last assessed at 5 years old.

We had difficulty with anxiety in grade 3 but he was a small child. Now at16, 6 feet tall and190-200lbs we are seeing the same thing but it is dangerous because of his size. He has put holes in walls and broken beds tantruming. The behaviour is like a person in an uncontrollable rage. We are feeling that he has mental health issues along with the autism, anxiety and epilepsy.

Our daughter was diagnosed with ADHD when she was 8 years of age and medicated off and on for 4 years. She showed some improvements with meds but no change with discontinuing them. We think her inattention comes more from anxiety than the ADHD. We have had testing done again and are waiting for results to determine our next course of action.

There are several places in the healthcare system where parents may be experiencing difficulty in accessing services. Several of our participants indicated that they live in remote or rural areas and certain services were not available in their small communities. Waitlists or costs for private evaluations may be prohibitive, or primary care physicians may be unwilling to provide referrals. Finally, the DSM-IV-TR has historically prohibited a diagnosis of more than one Axis-I disorder at a time (American Psychiatric Association, 2000). Axis-I disorders include ASD, as well as mood, anxiety, attention deficit, conduct and oppositional defiant disorders (American Psychiatric Association, 2000). This restriction has been eliminated in the DSM 5 and as a result some mental health professionals may now be more willing to diagnose individuals with ASD with comorbid psychiatric disorders. However, given the lack of clarity on how to differentiate ASD symptoms from symptoms of mental health concerns, better diagnostic guidelines and tools for use among individuals with ASD are still needed (Witwer & Lecavalier, 2010).

4.8 Strengths and Limitations

In any study that makes use of volunteers, the possibility of volunteer bias must be carefully considered. In this study, parents who completed our study may be those who are concerned about their child's mental health and are personally invested in this area of research. This may have resulted in an overestimation of the prevalence of mental health concerns if parents whose children were not experiencing mental health concerns were less likely to take the time to complete the survey.

Additionally, the low response rate (17%) of this study may have introduced bias into our results, leading to findings that are not representative of all Canadian adolescents with ASD. If the study results are biased, they would likely be over-estimations of the prevalence of mental health concerns in this population, as parents with a child who is experiencing mental health concerns may have been more likely to take the time to participate in this study. However, low response rates are typical when working with the ASD community (Siklos & Kerns, 2006) and clinically relevant findings should not be ignored solely on this basis.

The major strength of this study lies in using a screening tool that has been empirically tested in individuals with ASD. Using the DSM-IV oriented scoring system strengthens the results of this study by enabling a more direct comparison with parent-reported diagnoses.

Our study used a community-based sample. While much of the previous literature in mental health of individuals with ASD (Joshi et al., 2010; Leyfer et al., 2006; Matson & Nebel-Schwalm, 2007; Munesue et al., 2008) uses clinically referred populations, the community-based nature of this sample may make our results more generalizable. Finally, the findings of this study have important clinical and practical implications. They highlight the issue of mental health challenges in pre-teens and adolescents and provide evidence that more recognition and awareness from health care providers is needed.

4.9 Conclusions

A substantial number of individuals in our study sample exhibited mental health symptoms severe enough to be indicative of diagnosable psychiatric disorders, with anxiety and mood disorders being especially prevalent. In order to obtain accurate assessments of prevalence, the creation of a "gold standard" tool should be made a priority, ensuring that symptoms of mental illnesses are accurately discriminated from ASD symptoms. Ideally, a gold standard tool would take into account the prevalence of ID in people with ASD, and the varied presentation of symptoms of mental health concerns in this population (Leyfer et al., 2006). Some tools have been created in an attempt to meet this need, namely the Nisonger Child Behaviour Rating Form (Aman, Tasse, Rojahn, & Hammer, 1995), and the Autism Comorbidity Interview- Present and Lifetime Version (Leyfer et al., 2006), however these tools are not yet widely used..

Some experts have suggested behaviour equivalents- behaviours that have been empirically linked to specific psychiatric symptoms- as a way to identify symptoms of mental health concerns in individuals with reduced verbal capability and/or ID (Witwer & Lecavalier, 2010), and some medical associations, such as the Royal College of Psychiatrists, have released diagnostic guidelines for individuals with ID that incorporate the use of behaviour equivalents (Royal College of Psychiatrists, 2001). The existence of a gold standard tool will also facilitate direct comparisons between studies and more accurate prevalence estimates for psychiatric comorbidities in this population.

Future research on this topic should focus on understanding how to accurately differentiate between symptoms that are part of the ASD symptom cluster and those that are indicative of mental health concerns. Furthermore, existing studies of prevalence should be replicated in larger, community-based samples to enhance the generalizability of their findings, and to provide more accurate prevalence estimates.

In order to facilitate continued research in the field of ASD, improving response and participation rates will be critical. Participation in epidemiological research has declined in the

past 30 years, with the rate of decline increasing more recently (Galea & Tracy, 2007), having profound implications for the accuracy and generalizability of research findings. Unfortunately, there are no easy solutions for this issue.

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Chapter 5

Association of Childhood ASD Symptomatology with the Development of Mental Health Concerns in Adolescence

5.1 Abstract

Objectives: The purpose of this study was to identify risk factors for the development of mental health concerns in adolescence, in particular, to determine if early childhood ASD symptomatology was associated with the development of mental health concerns.

Methods: The parents of 390 individuals recruited to two ASD research databases located in Kingston, Ontario were invited by email and mail to participate in a survey that collected information on educational setting, demographics, individual medical history, mental health, medication use, service utilization, and family mental health history. To collect information on mental health outcomes, the Child Behaviour Checklist (CBCL) for ages 6-18 was also included. Previously collected ADI-R data was linked to survey data through participant identification codes. ADI-R scores were used as a measure of early childhood ASD symptomatology, with each ADI-R domain considered separately. Domain scores were generated using the diagnostic algorithm and divided into tertiles of most impaired, least impaired, and moderately impaired.

Results: Bivariate analysis did not reveal significant associations between ADI-R scores and developing a mental health concern in adolescence. Family history of psychiatric disorders and female gender were significantly associated with the development of mental health concerns in adolescence.

Conclusions: We did not find any relationship between early childhood ASD symptoms and the development of mental health concerns in adolescence; however, this relationship should be explored further in larger study samples. Female gender was identified as a risk factor for the development of mental health concerns. As girls are more likely to experience internalizing disorders, parents and clinicians may need to be especially attuned to the way symptoms of internalizing disorders present in individuals with ASD.

5.2 Introduction

Given the debate surrounding the diagnosis of psychiatric comorbidities in individuals with Autism Spectrum Disorder (ASD), there has been very little research on specific risk factors for the development of psychiatric disorders in this population (Ghaziuddin et al., 2002). This lack of understanding of specific risk factors ties into a poor understanding of the developmental trajectory of ASD. Predicting adolescent or adult outcomes from childhood characteristics is difficult for a variety of reasons, including the heterogeneity of ASD symptoms, associated medical conditions, a lack of standardized outcome measures, and a paucity of longitudinal research on the subject (Howlin et al., 2004).

A longitudinal study of 241 individuals with ASD aged 10 to 52 followed participants for a 4.5 year period, assessing changes in ASD symptoms and maladaptive behaviour (Shattuck et al., 2007). This study reported overall improvements in both ASD symptomatology and maladaptive behaviour throughout adolescence and into adulthood, but found that individuals with Intellectual Disabilities (ID) made fewer improvements overall; individuals with ID also displayed more maladaptive behaviours in adulthood (Shattuck et al., 2007). This study also found that verbal ability predicted better outcomes in terms of ASD symptoms; however, individuals with verbal ability were found to display more asocial maladaptive behaviours, which included socially offensive and uncooperative behaviour (Shattuck et al., 2007).

A second study followed 68 individuals with Autistic Disorder. Individuals were first evaluated at a mean age of seven (with a range from three to 15 years), and had a mean age of 29 (range from 21 to 48 years) at follow-up (Howlin, Goode, Hutton, & Rutter, 2004). All individuals in the study sample had a childhood IQ of 50 or greater, which would include individuals with an Intellectual Disability (the DSM 5 describes ID as an IQ of less than 70, with significant impairment in adaptive functioning (cognitive, social and self-care skills)) (American Psychiatric Association, 2013). At follow-up, social, communication and behavioural problems were evaluated with the Autism Diagnostic Interview Revised (ADI-R), and language and cognitive abilities were evaluated with other standardized tests (Howlin et al., 2004). As in the previous study, the majority of individuals in this study had poor adult outcomes, including persistent stereotyped behaviours and communication impairments. Howlin and her colleagues found that similar to the findings of Shattuck et al. (2007), individuals with a childhood IQ of at least 70 had significantly better outcomes than those with an IQ of less than 70; however outcomes within the higher IQ group were quite variable. Similar to Shattuck et al. (2005), childhood verbal ability also predicted better adult outcomes (Howlin et al., 2004).

In a 2005 study on long-term outcomes for individuals with ASD, a population-based cohort of 120 individuals with ASD was followed for a period of 13 to 22 years and re-evaluated between 17 and 40 years of age (Billstedt, Gillberg, & Gillberg, 2005). Re-evaluation involved measures of ASD symptomatology, adaptive behaviour, IQ, medical and psychiatric examinations, and took into account markers of quality of life such as employment, peer relationships, and independent living. Overall outcome was poor for 78% of the study cohort (Billstedt et al., 2005). Similar to the findings of Shattuck et al. (2007) and Howlin et al. (2004), higher childhood IQ was predictive of better adult outcomes, as was the ability to speak in phrases by age six (Billstedt et al., 2005). At follow-up, eight individuals (7%) in the study cohort had been diagnosed with psychosis (Billstedt et al., 2005). Half of the study sample was reported to have engaged in moderate or severe levels of self-injurious behaviour during the study period, and 33% displayed signs of severe hyperactivity (Billstedt et al., 2005). Furthermore, 23% exhibited violent behaviour severe or frequent enough for concern, and 19% of the study

sample displayed extremely severe violent behaviour (Billstedt et al., 2005). At follow-up, 32% of the study sample was prescribed a psychotropic medication; all of these individuals displayed behavioural problems including self-injurious, violent or hyperactive behaviour (Billstedt et al., 2005).

Altogether, the findings from these studies suggest that individuals with ASD typically face poor adult outcomes, in terms of independence, educational attainment, employment attainment, friendships and social well-being, communication abilities and repetitive, stereotyped, and maladaptive behaviours (Billstedt et al., 2004; Howlin et al., 2004; Shattuck et al., 2007). Having an ID leads to worse outcomes in adulthood, however the absence of ID alone is not enough to guarantee good outcomes (Howlin et al., 2004). In these studies, verbal ability in childhood and childhood IQ were the only indicators that were found to predict adult outcomes, however even these predictors were not associated with all outcome measures (Billstedt et al., 2005; Howlin et al., 2004; Shattuck et al., 2007).

One of the weaknesses of the existing literature on long-term outcomes for individuals with ASD is that existing studies typically do not look closely at psychiatric comorbidities other than Schizophrenia (Selzter, Shattuck, Abbeduto, & Greenberg, 2004). In particular, there is a paucity of longitudinal research on the development of psychiatric comorbidities in individuals with ASD. Shattuck et al. (2007) did consider "maladaptive behaviour", which was broadly defined as behaviours that interfere with everyday activities, including self-injury, withdrawal, aggression, and destruction of property (Shattuck et al., 2007). Shattuck et al. (2007) noted that these behaviours are considered to be "associated features" of ASD; however, more recent studies suggest that behaviours like these may be symptoms of mental health concerns (Witwer & Lecavalier, 2010). Billstedt, Gillberg, and Gillberg (2005) also assessed mental health outcomes,

but again, looked at specific maladaptive behaviours (Billstedt et al., 2005). Maladaptive behaviours are a good starting point in the investigation of mental health outcomes for individuals with ASD, as they can impact quality of life (Matson et al., 2008) and are often cause for referral to intervention services (Plant & Sanders, 2007). However, with increasing awareness of the prevalence of psychiatric comorbidities in individuals with ASD (Brereton, Tonge, and Einfeld, 2006; Joshi et al., 2010) it is also be important to begin investigating mental health outcomes that are aligned with DSM diagnoses, which this study attempts to do.

The 2011 report from the National Coalition on Dual Diagnosis in Canada indicates that individuals with a dual diagnosis (used in this report to indicate ID and co-occurring mental health concerns) have more severe mental health symptoms and are more likely to have other cooccurring medical conditions than the general population (National Coalition on Dual Diagnosis, 2011). The added burden of a mental health concern in adolescence may further complicate the developmental course of an individual with ASD and further compromise adult outcomes, particularly if comorbid mental health concerns are not recognized and treated (Joshi et al., 2010).

Predicting adolescent and adult outcomes for children with ASD can help service providers anticipate future needs, and offer individual and family-oriented services to build resilience designed to mitigate the impact of any mental health concerns that eventually develop. One aspect of predicting adolescent and adult outcomes is identifying those individuals who are at greatest risk for mental health concerns.

5.2.1 Using the ADI-R to Predict Adolescent or Adult Outcomes

The core symptoms of ASD are impairments in reciprocal social interaction and communication, and restricted, repetitive and stereotyped patterns of behaviour. These core impairments of ASD have been studied as predictors of various adult outcomes, including ASD symptom change over time (Seltzer, Krauss, Shattuck, Orsmond, Swe, & Lord, 2003; Shattuck et al., 2006), social functioning, linguistic abilities, and stereotyped behaviours (Howlin et al., 2004) and challenging or maladaptive behaviours (Matson, Wilkins, & Macken, 2008). Matson et al. (2008) evaluated a group of 176 individuals with ASD, to determine if severity of ASD symptoms (categorized as mild, moderate, or severe) affected the types of challenging behaviours displayed in the study population, and to identify the symptoms of ASD that best predict specific challenging behaviours (Matson et al., 2008). Challenging behaviours that were evaluated in this study included:

- Stereotypic behaviours (repeated and unusual vocalizations, repeated and unusual body movements, unusual play with objects)
- Aggression towards others
- Elopement (running away)
- Yelling or shouting
- Property destruction
- Banging on objects with hands
- Throwing objects at others
- Removal of clothing at inappropriate times
- Self-harm
- Kicking objects
- Playing with own saliva

- Inappropriate sexual behaviour
- Mouthing or swallowing objects causing bodily harm
- Pulling others' hair
- Smearing or playing with feces
- Poking himself/herself in the eye

(Matson et al., 2008).

These challenging behaviours do not directly align with mental health concerns, but can be extremely severe and have a significant impact on quality of life of individuals with ASD and their families (Matson et al., 2008). They are also frequently cited as reasons for referrals to intervention services (Plant & Sanders, 2007).

The severity of ASD symptoms in this study sample was significantly correlated with the severity of problem behaviours, and individuals with severe ASD symptoms were more likely to present with stereotypic or repetitive behaviour, self-injurious behaviour and aggressive or destructive behaviours (Matson et al., 2008). Furthermore, eight of the challenging behaviours investigated were significantly predicted by specific ASD symptoms. For example, removal of clothing at inappropriate times was predicted by a group of 20 ASD symptoms: eight communication items, eight social interaction items and four restricted and repetitive behaviour items, while banging on objects with hands was predicted by body posture and gestures, displaying a range of socially appropriate facial expressions, use of facial expressions, and responding to others' distress (Matson et al., 2008). While this study was unable to identify individuals with an ID, and was also unable to identify individuals with comorbid mental health concerns, the results provide initial evidence that specific groupings of ASD symptoms can

predict problematic behaviours that require intervention or further assessment (Matson et al., 2008).

5.2.2 Risk Factors for the Development of Mental Health Concerns

While there is very little published information on specific risk factors for the development of psychiatric disorders in individuals with ASD, many potential risk factors in typically developing individuals have been well identified. Genetics play a role, although the degree of influence depends on the disorder (Gadow et al., 2008; Green et al., 2010). Environmental factors are also extremely important. "Childhood adversities" are strongly associated with the development of psychiatric disorders; these include "maladaptive family functioning" (parental mental illness, parental substance abuse, parental criminality, family violence, physical or sexual abuse, and neglect) (Green et al., 2010; Herpertz-Dahlmann et al., 2013), parental loss (through divorce or death) (Green et al., 2010), experiencing a serious illness in childhood (Green et al., 2010), social ties to delinquent peers (Herpertz-Dahlmann et al., 2013), economic adversity (Gadow et al., 2008; Herpertz-Dahlmann et al., 2013), living in a deprived environment, and coming from an immigrant family (Herpertz-Dahlmann et al., 2013) have all been identified as childhood risk factors for the development of psychiatric disorders. Age and sex are also risk factors; older individuals are more likely to have experienced a psychiatric disorder at some point in their lives (Gadow et al., 2008), and sex-specific risk factors exist at both the biological and social levels (Herpertz-Dahlmann et al., 2013). Girls are more likely to experience internalizing mental health problems such as eating disorders, mood disorders and anxiety. Boys are more likely to experience externalizing or disruptive mental health problems such as Conduct Disorder and Oppositional-Defiant Disorder (Herpertz-Dahlmann et al., 2013).

We also know that adolescence is a critical period for the development of psychiatric disorders (Herpertz-Dahlmann et al., 2013), both in typically developing individuals and those with ASD (Mouridsen et al., 2008; Munesue et al., 2008). The social gap between individuals with ASD and their peers can increase during adolescence, as typically developing peers begin dating, driving, getting part-time jobs, establishing independence from their parents, and participating in increasingly complex social hierarchies (Herpertz-Dahlmann et al., 2013); the added challenge of a mental health concern can exacerbate this gap. While identifying risk factors for the development of a mental illness in adolescence cannot prevent mental health concerns from occurring, it can help identify those individuals at greatest risk. With more research, identifying risk factors for psychiatric comorbidities may also contribute to a better understanding of the developmental trajectory of ASD.

5.3 Study Rationale and Objectives

This study aimed to identify risk factors for the development of psychiatric disorders in adolescence, in particular, whether the severity of early childhood ASD symptomatology (measured by a standardized diagnostic tool, the ADI-R) predicts the development of a mental health concern in adolescence. We wanted to explore whether individuals with more severe early childhood ASD symptomatology would be more likely to develop a mental health concern in adolescence and if there was a positive relationship between severity of ASD symptomatology and adolescent outcome, where individuals with more severe early childhood ASD symptomatology were more likely to develop mental health concerns in adolescence. Early childhood ASD symptomatology was chosen as the exposure variable for this study for several reasons. First, by linking early childhood ASD symptomatology to adolescent outcomes, we hoped to add to the existing literature on the developmental trajectory of ASD. Secondly, data on early childhood ASD symptoms had been previously collected for a large volume of NEDSAC and ASD-CARC registry participants, via the Autism Diagnostic Interview-Revised (ADI-R). Given that we used a questionnaire to collect outcome data, using previously collected ADI-R data eliminated the need to also collect exposure data, significantly shortening the length of the questionnaire. The ADI-R was an ideal data source for this study because it represents a rich source of information on ASD symptomatology. Furthermore, it collects much of the information based on the individual's symptoms at age four, which represents an ideal standardized age for early childhood ASD symptomatology.

5.4 Methods

Participants for this study were recruited through two ASD research databases held in Kingston, Ontario, the National Epidemiologic Database for Autism in Canada (NEDSAC), and Autism-Spectrum Disorders Canadian-American Research Consortium (ASD-CARC) research registry. Respondents were parents of children who:

- 1. Had an ASD, with diagnosis confirmed by parents,
- 2. Were between the ages of 10 and 19 years,
- Had completed an Autism Diagnostic Interview-Revised (ADI-R) with the research registries and;
- 4. Lived in Canada in 2012

Information letters and consent forms are available in Appendix A. The ethics approval for this project is presented in Appendix B. The full questionnaire is presented in Appendix C. All invited participants had previously completed consent forms indicating they were willing to be contacted for further research.

Parents who were invited to complete the survey were encouraged to complete it online, with a mailing option available for those who were unable to be reached by email (i.e. they did not have an email address on file with the research group, or the email they had provided was invalid). Any surveys that were completed by mail were manually entered into the online form for ease of data organization. We invited the parents of 390 individuals to participate. Twenty individuals were lost to follow-up, as they had moved and not provided an updated address. We received 65 completed surveys, for a response rate of 18%².

5.4.1 Exposure Measurement

The Autism Diagnostic Interview-Revised (ADI-R) (Rutter, Le Couteur & Lord, 2008) is a standardized interview for diagnosing Autism. Informants are typically parents or long-term guardians who are familiar with the individual's developmental course. There are 96 items on the ADI-R, and 35 of these items are divided into three domains that reflect impairments characteristic of ASD. These domains are: reciprocal social interaction, communication, and restricted, repetitive and stereotyped patterns of behaviour. There is no upper age limit for use of the ADI-R, and it is valid for use in any individual with a mental age of greater than 2 years, 0 months (Rutter, Le Couteur & Lord, 2008).

² We received 67 responses to the survey for this objective, however as the online survey was available to anyone with an ASD-CARC username and password, two individuals whose parents completed the survey did not have a completed ADI-R on file and were excluded from the analyses using the ADI-R.

A unique feature of the ADI-R is that some items collect information on the child's symptomatology specifically at age four, while others ask about behaviours at any point in the child's life. This age (four) was chosen by the creators of the ADI-R because by this point, children with even severe developmental delays should have developed the symptoms of interest and are not yet old enough to have outgrown behaviours influenced by maturation (Rutter, Le Couteur & Lord, 2008). Additionally, ASD symptoms tend to be most severe at this age (Rutter, Le Couteur & Lord, 2008).

The ADI-R manual provides two different scoring algorithms: a current behaviour algorithm, and a diagnostic algorithm. We used the diagnostic algorithm for this study, since the current behaviour algorithm is reflective of the child's symptoms at the age the ADI-R was conducted, and this was different for all the participants in our study sample. The diagnostic algorithm, in many cases, queries the individual's behaviour at age four, and by adjusting for age at assessment in accordance with the results presented in Chapter Three, we were able to use age four as a standardized age for early childhood ASD symptomatology, regardless of the age at which participants were assessed with the ADI-R.

For this study, individual scores for each domain were calculated in accordance with instructions provided by the ADI-R Manual (Rutter, Le Couteur & Lord, 2008). Since a diagnosis of Autism with the ADI-R is based on meeting cutoffs in each domain and there is no total score, we decided to assess each domain individually.

The communication domain presented a challenge as it is scored differently for verbal and non-verbal individuals. There are four sections for verbal individuals, and only two for those who are non-verbal. To preserve sample size, rather than exclude non-verbal individuals (n=5), we used only the non-verbal communication items for this analysis, as done by Bennett et al.
(2012). The internal consistency of this modified ADI-R domain was 0.85 for this sample. The study sample was divided into score tertiles for each domain: "most impaired", "moderately impaired" and "least impaired". This conceptualization of ASD symptoms neatly aligns with the DSM 5. In the DSM-IV, each autism spectrum disorder was treated as a specific diagnosis (American Psychiatric Association, 2000). In the DSM 5, these individual diagnoses have been eliminated in favour of a single autism spectrum disorder diagnosis, with this spectrum reflecting a range of severity, assessed according to the level of support needed by the individual (American Psychiatric Association, 2013).

5.4.2 Outcome Measurement

A parent questionnaire was used to collect information on individual's demographic information, family and individual psychiatric history and medication use (see Appendix C for the full questionnaire). This questionnaire consisted, where possible, of questions from the Canadian Community Health Survey (CCHS) (Statistics Canada, 2011), the National Longitudinal Survey of Children and Youth (NLSCY) (Statistics Canada, 2008) and the Interactive Autism Network (IAN) Family History survey (Kennedy Krieger Institute, 2012). The questionnaire was piloted by two NEDSAC staff members and the parent of a potential study participant who had expressed interest in being involved in the development process, and went through several revisions before being finalized.

The questionnaire also contained the Child Behaviour Checklist (CBCL) 6-18, a standardized screening tool (Achenbach & Rescorla, 2001) for mental health problems. The CBCL consists of 113 items, with items rated on a 3-point Likert scale, with zero being "never" or "not true", one indicating "somewhat or sometimes true" and two indicating "very true or often true". Parents are asked to rate their child's behaviour over the past six months. The CBCL is a commonly-used screening tool for mental health problems (Matson et al., 2012) and is frequently used in individuals with ASD although it was not specifically developed for this population (Gladman & Lancaster, 2003). There are different scoring profiles available for the CBCL; for this study we used the DSM-oriented scales. These are six scales that align well with clinical diagnostic categories of the DSM (Ebesutani et al., 2010); affective (mood) problems, anxiety problems, somatic problems, conduct problems, oppositional-defiant problems and attention deficit problems (with or without hyperactivity) (Achenbach & Rescorla, 2001). Individuals receive a score for each scale, based on age and gender. Individuals may receive a normal score, subclinical score, or clinical score for each scale.

The internal consistencies of the DSM-oriented scales of the CBCL range from .71 for somatic problems to .89 for conduct problems (Nakamura, Ebesutani, Bernstein & Chorpita, 2008). In a large, clinical sample, each DSM-oriented scale demonstrated significant convergent validity, and favourable divergent validity (Nakamura et al., 2008). There are also eight syndrome scales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour, but these were not used as we were interested in DSM diagnoses and these scales do not align directly with DSM diagnostic categories (Achenbach & Rescorla, 2001; Pandolfi et al., 2012).

We also collected data on several covariates of interest through our parent questionnaire. We asked parents to provide their postal code, with the plan of using neighbourhood socioeconomic status as a proxy measure for individual socioeconomic status, a known risk factor for the development of mental health concerns in individuals with ASD (Gadow et al., 2008). Other previously studied risk factors we collected information on included: living with at least one biological parent; psychotropic medication use; other medical conditions; individual history of mental illness; family history of mental illness; family history of ASD; and current school placement (regular vs. special education) (Gadow et al., 2008).

Most of our respondents lived in Southeastern Ontario, Manitoba, and Newfoundland and Labrador. Canadian census data on ethnic diversity and immigration indicates that Newfoundland and Labrador and Manitoba do not have a high degree of ethnic diversity (Statistics Canada, 2011). While Ontario is a diverse province, much of this diversity is located in the Greater Toronto Area (Statistics Canada, 2011). Therefore, we did not ask respondents questions about immigration status and ethnicity under the assumption that there would be few recent immigrants in our study sample.

We opted not to ask questions about other known risk factors, such as family violence, parental criminality, parental substance abuse, physical or sexual abuse and neglect (Green et al., 2010; Herpertz-Dahlmann et al., 2013); due to the sensitive nature of these topics, questions about them are vulnerable to social desirability bias. Social desirability bias causes participants to under-report undesirable behaviours (include drug use, neglect, and criminal behaviour) and would result in unreliable measurements of these behaviours and possibly lead to drawing incorrect conclusions of the relationship between childhood ASD symptomatology, adolescent mental health, and these behaviours (King & Bruner, 2000).

5.5 Statistical Analysis

First, a binary outcome was created, where cases were participants who had a parent-reported diagnosis of a psychiatric illness after age 10 or a clinical score on one or more CBCL subscales. The association between outcome (case vs. control) and score tertile was evaluated for each ADI-

R domain using the Cochrane Armitage test for trend. We also evaluated the association between adolescent mental health concerns and several covariates of interest using Pearson's Chi-squared test or Fisher's Exact test when appropriate. These covariates were: gender, Intellectual Disability (ID), family history of psychiatric disorders, and age.

An *a priori* decision was made to assess outcomes only if they were present in 20% or more of the study sample, due to an anticipated small sample size. Therefore we considered only a combined outcome (clinical score on one or more CBCL subscales or any parent-reported diagnosis after age 10) and anxiety disorders. Individuals met case criteria for an anxiety disorder if they had a parent-reported diagnosis after age 10, or if they scored in the clinical range of the anxiety scale of the CBCL.

To generate effect estimates (odds ratios) for score tertiles, and to account for other covariates, logistic regression modeling was used. The "least impaired" (lowest score) tertile for each ADI-R domain was set as the reference group for the modeling procedure. For the reciprocal social interaction and communication domains of the ADI-R, we controlled for age at assessment with the ADI-R, based on the findings from Chapter Three of this thesis that indicated a significant relationship between age at assessment and score on these domains, where individuals who were older when they were assessed with the ADI-R were more likely to have a higher score (see Chapter Three).

The "family history of mental illness" covariate is a composite measure created from answers to questions 21 to 23 of the "Risk Factors for Mental Health Concerns and Seizures in Pre-teens and Adolescents with an Autism Spectrum Disorder" questionnaire (Appendix C). Due to the small sample size we were unable to create multiple measures of family history of mental illness (i.e. considering first-degree relatives, second-degree relatives and second cousins separately); we therefore created a composite family history of mental illness variable that combined first and second-degree relatives and second cousins. In our analysis, we considered Intellectual Disability as a binary variable, treating only parent-confirmed ID (answering "yes" to the question of "has your child ever been diagnosed with an intellectual disability?") as cases.

The logistic regression models included gender, age, ID, and family history of mental illness as covariates of interest. The models for the communication and reciprocal social interaction domains of the ADI-R were adjusted for age at assessment with the ADI-R in accordance with our findings from the first manuscript of this thesis. We had initially planned to include other covariates of interest, such as class type (special education vs. regular education) opportunities for inclusion with typically developing peers, and living with biological parents in in our models, in addition to neighbourhood socioeconomic status (using postal codes). However, given the small sample size of the study, the decision was made to exclude these covariates.

5.6 Results

The mean age of the study sample was 15.2 years (SD=2.75). The mean age at assessment with the ADI-R was 8.6 years (SD=2.6) with a range of 3.6 to 14.8 years. There were 55 male and 12 female individuals in this study sample. The parents of 55% (n=37) of the study sample indicated that their child had never had an IQ test or that they were not sure if they had, and 54% (n=36) reported that their child did not have an Intellectual Disability. The parents of an additional 18% of the study sample indicated that they did not know or were unsure if their child had an

Intellectual Disability. Table 5-1 provides some additional information on the educational environment of study participants.

Our bivariate analysis did not detect any association between score on any of the ADI-R domains and our composite outcome (clinical CBCL score on one or more scales or parent-reported diagnosis after age 10) or the presence of an anxiety disorder. There was a significant association between the composite outcome and gender, with being male having a slight protective effect. Family history of mental illness was significantly associated with both the composite outcome and anxiety (see table 5-2).

Education Characteristics	Frequency (%)	
Type of School		
Home schooled	1 (1.5)	
Not in school	2 (3)	
Private school, regular education classes	3 (4.5)	
Public school	56 (84)	
Specialized private school for children with special needs	2 (3)	
Specialized public school for children with special needs	3 (4.5)	
Classroom Setting		
More time in regular education classes than special education classes	3 (4.5)	
More time in special education classes than regular education classes	9 (13.4)	
Regular education classes for all of school day	26 (39)	
Same amount of time in regular and special education classes	6 (9)	
Special education classes for all of school day	16 (24)	
N/A	3 (4.5)	
Grade		
Four	1 (1.6)	
Five	4 (6.5)	
Six	7 (11)	
Seven	8 (13)	
Eight	5 (8)	
Nine	5 (8)	
Ten	13 (21)	
Eleven	4 (6.5)	
Twelve	15 (24)	
N/A	5 (8)	

	Any Mental Hea	Any Mental Health Concern		Anxiety	
	Yes (%)	No (%)	Yes (%)	No (%)	Total (%)
Sex (M)	20 (30)	35(52)	16 (24)	39 (58)	55 (82)
Sex (F)	10 (15)*	2 (3)	6 (9)	6 (9)	12 (18)
Intellectual Disability	8 (12)	11 (16)	5 (7)	14 (21)	19 (28)
Family History	26 (39)*	24 (36)	21 (31)*	29 (43)	50 (75)
Reciprocal Social					
Interaction					
Least Impaired	12 (18)	11 (17)	10 (15)	13 (20)	23 (35)
Moderately Impaired	10 (15)	14 (22)	5 (8)	19 (29)	24 (37)
Most Impaired	8 (12)	12 (18)	7 (11)	13 (20)	20 (31)
Communication					
Least Impaired	12 (18)	14 (22)	10	16 (25)	26 (40)
			(15)		
Moderately Impaired	7 (11)	14 (22)	5 (8)	16 (25)	21
					(33)
Most Impaired	11 (17)	9 (14)	7 (11)	13 (20)	20 (31)
Repetitive Behaviours and					
Stereotyped Interests					
Least Impaired	14 (22)	13 (20)	10 (15)	17 (26)	27 (42)
Moderately Impaired	5 (8)	10 (15)	4 (6)	11 (17)	15 (23)
Most Impaired	11 (17)	14 (22)	8 (12)	17 (26)	25 (38)

Table 5-2: Frequency distributions for exposures and covariates of interest (n=67 for sex, intellectual disability and family history, n=65 for ADI-R domains).

*statistically significant at p<0.05

We then used logistic regression modeling to assess the relationship between ADI-R scores and mental health concerns in adolescence while controlling for certain covariates of interest. These covariates were: Intellectual Disability, gender, age, and family history of mental illness. Table 5-3 shows the unadjusted and adjusted odds ratios with associated 95% confidence intervals for the relationship between composite outcome and score on each ADI-R domain, after controlling for covariates of interest. Table 5-4 shows the same results for the relationship between anxiety and score on ADI-R domains.

	Unadjusted	95% C.I.	Adjusted	95% C.I
	OR		OR	
Communication				
Age	1.1	.93-1.3	0.88	0.62-1.3
Gender (F)	8.7*	1.7-43.9	14.8*	1.9-111.6
Family History of mental illness	3.5*	1-12.3	5.2*	1.15-23
Intellectual Disability	0.86	0.29-2.5	0.5	0.1-2.17
Moderately Impaired vs. least impaired	0.58	0.17-1.9	0.34	0.08-1.5
Most impaired vs. least impaired	1.4	0.4-4.6	2.67	0.53-13.5
Reciprocal Social Interaction				
Age	1.1	.93-1.3	0.94	0.67-1.32
Gender (F)	8.7*	1.7-43.9	7.7*	1.4-42.1
Family History of mental illness	3.5*	1-12.3	3.19	0.78-13
Intellectual Disability	0.86	0.29-2.5	0.82	0.2-3.3
Moderately Impaired vs. least impaired	0.65	0.2-2.0	0.47	0.12-1.8
Most impaired vs. least impaired	0.61	0.18-2.1	0.43	0.1-1.9
Restricted, Repetitive and Stereotyped				
Behaviours				
Age	1.1	0.9-1.3	1.18	0.94-1.5
Gender (F)	8.7*	1.7-43.9	8.4	1.6-45.1
Family History of mental illness	3.5*	1-12.3	2.92	0.7-12
Intellectual Disability	0.86	0.29-2.5	0.60	0.16-2.3
Moderately Impaired vs. least impaired	0.47	0.13-1.7	0.50	0.09-2.3
Most impaired vs. least impaired	0.73	0.25-2.2	0.72	0.20-2.6
	1			

Table 5-3: Composite outcome, adjusted and unadjusted ORs (n=65)

*statistically significant at p<0.05

Unadjusted	95% C.I.	Adjusted	95% C.I
OR		OR	
0.99	0.82-1.2	1.0	0.8-1.6
2.4	0.68-8.7	2.1	0.47-9.7
9.0*	1.1-73	13.5*	1.5-121
0.59	0.17-2.1	0.58	0.1-2.5
0.50	0.14-1.8	0.42	0.1-1.7
0.86	0.25-2.9	1.4	0.3-6.7
0.99	0.82-1.2	1.1	0.8-1.6
2.4	0.68-8.7	2.0	0.47-8.9
9.0*	1.1-73	11.4*	1.4-99
0.59	0.17-2.1	0.5	0.1-2.4
0.34	0.1-1.2	0.26	0.06-1.1
0.7	0.2-2.4	0.83	0.18-3.9
0.99	0.82-1.2	1.18	0.9-1.5
2.4	0.68-8.7	2.3	0.57-9.0
9.0*	1.1-73	9.9*	1.2-85
0.59	0.17-2.1	0.54	0.1-2.3
0.6	0.2-2.4	0.57	0.1-3.1
0.8	0.3-2.5	0.72	0.2-2.6
	Unadjusted OR 0.99 2.4 9.0* 0.59 0.50 0.86 0.99 2.4 9.0* 0.59 0.34 0.7 0.99 2.4 9.0* 0.59 0.34 0.7	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Unadjusted95% C.I.Adjusted OR OR OR 0.990.82-1.21.02.40.68-8.72.19.0*1.1-7313.5*0.590.17-2.10.580.500.14-1.80.420.860.25-2.91.40.990.82-1.21.12.40.68-8.72.09.0*1.1-7311.4*0.590.17-2.10.50.340.1-1.20.260.70.2-2.40.830.990.82-1.21.182.40.68-8.72.39.0*1.1-739.9*0.590.17-2.10.540.60.2-2.40.570.80.3-2.50.72

Table 5-4: Anxiety, adjusted and unadjusted ORs (n=65)

*statistically significant at p<0.05

5.7 Discussion

Our analysis did not find any associations between early childhood ASD symptoms, represented by diagnostic algorithm score on each ADI-R domain and the development of a mental health concern in adolescence.

The majority of individuals in this study sample (72%) did not have a reported Intellectual Disability (ID). This differs from previously reported population prevalence estimates of 40% to 60% of individuals with ASD having an ID (Volkmar & Pauls, 2003). Additionally, 18% of respondents reported that they did not know if their child had an ID, and 55% indicated that their child had never had an IQ test, or that they were not sure if they had. The amount of missing data for this variable does call into question the validity of our ID measure and makes it difficult to draw any conclusions about the relationship between Intellectual Disability, childhood ASD symptomatology and adolescent mental health outcome in this study sample. Intellectual Disability has been reported to be a predictor of overall adolescent and adult outcomes in individuals with ASD; individuals with ASD who also have an ID make fewer improvements in communication, social interaction, independence, repetitive behaviours and maladaptive behaviours as they age (Billstedt et al., 2005; Shattuck et al., 2007). Our study findings were different from those of Billstedt et al. (2005) with respect to violent and selfinjurious behaviour. In this previous study, 42% of the sample displayed violent behaviour and half of the sample engaged in self-injurious behaviour (Billstedt et al., 2005), where we found a high prevalence of mood and anxiety problems. These differences can likely be explained by the age of the Billstedt et al. (2005) study participants and the era in which they were diagnosed; the older participants in this study would have been diagnosed under very different criteria than DSM-IV-TR or DSM 5 criteria, and likely had more severe ASD than our study sample.

There is some evidence that individuals without ID or milder ID may be at higher risk for anxiety, in particular (Leyfer et al., 2006; Sukhodolsky et al., 2008). One possible reason for individuals without ID presenting with high levels of anxiety is increased self-awareness and perception of oneself as "different" from typically developing peers. A quote from a parent respondent provides anecdotal evidence for this:

> Our son is very self-aware and we believe this is a significant contributor to his depression. He understands that he is different and feels as though he fails at his many attempts to fit in and be accepted.

We also found a statistically significant relationship between gender and composite outcome, with being male having a slightly protective effect. These findings are consistent with literature indicating that girls are more likely to experience mood and anxiety disorders (the most common in our sample) than boys (Herpertz-Dahlmann et al., 2013). However, this finding should be interpreted with some caution as there were only 12 female participants in the sample and the wide confidence intervals surrounding odds ratio estimates indicate a lack of precision. It is possible that pre-teen and adolescent girls with ASD and mental health concerns are especially at risk of failure to recognize symptoms of mental health concerns; symptoms of internalizing problems are especially difficult to recognize in ASD, as individuals may have difficulty describing their emotions or thoughts or articulating many of the symptoms of mood, anxiety or other disorders (Leyfer et al., 2006). Gender differences in types of mental health concerns and the way in which they present should be taken into consideration by clinicians and parents. It may be that special attention should be paid to watching for the signs and symptoms of mental health concerns in girls with ASD.

Finally, as reported in other studies, we found that family history of mental illness was an important risk factor for developing a mental health concern in adolescence. Although there is little that can be done to mitigate genetic risk factors, this information may be useful in identifying individuals with ASD who are at greatest risk of developing mental health concerns in adolescence, an important aspect of the developmental trajectory of ASD.

Unfortunately, this analysis was in many ways limited by our small sample size. Only 65 individuals were included in this analysis (out of a total number of 67 respondents). Twenty-nine individuals met our composite case definition, and 21 met the anxiety case definition. We recruited study participants based on a defined set of participation criteria, which was restricted by the information needed for the analysis- i.e. ADI-R, valid consent form, and age. Ideally, participants would have been recruited in a case-control study manner, recruiting cases first and matching controls based on age, IQ, or other variables. Low participation rates are a problem in the field of epidemiology and low participation rates are a particular concern in populations with ID (Siklos & Kearns, 2006). Increasing participation in epidemiological research is a challenge with no easy solution (Galea & Tracy, 2007).

5.8 Strengths and Limitations

This study appears to be one of the first studies to use early childhood ASD symptoms to predict later-in-life outcomes. A major strength of this study is the use of the CBCL, a standardized clinical screening tool. We asked parents about diagnoses after age 10, which may have been up

to nine years earlier and therefore may not be an accurate representation of current presentation. The CBCL provides an objective measure of current mental health symptoms.

Due to the way information about ASD diagnoses was collected and stored in the research databases participants were recruited from, we were unable to determine individuals' specific ASD diagnosis, i.e. Autistic Disorder vs. Asperger's. While our measurement of Intellectual Disability is admittedly weak, the low reported prevalence of intellectual disability in our sample could indicate that this sample may be more high-functioning than the average group of adolescents with ASD. Alternatively, the reported prevalence of ID our sample may be a result of misclassification due to the number of missing responses ("don't know/unsure" responses) for our questions on ID, and it is possible that, due to this missing data, some individuals with ID were incorrectly classified as not having a reported ID. The low reported prevalence of ID in our sample likely reduces the generalizability of our findings as the prevalence of ID in this sample is not reflective of the overall prevalence of ID in individuals with ASD (Volkmar & Pauls, 2003).

Furthermore, without examining each autism spectrum disorder individually, we may have lost some of the nuance in the relationship between childhood ASD symptomatology and mental health in adolescence. With the DSM 5 and the elimination of specific diagnoses within the autism spectrum, this may be irrelevant in future research, which may focus instead on conceptualizing ASD symptomatology as mild, moderate, or severe, as we did in this study.

The analysis in this study was severely limited by a low response rate, small sample size, and a resulting lack of statistical power. When assessing anxiety, in particular, very small cell sizes resulted in extremely wide confidence intervals surrounding odds ratio estimates and results should be interpreted with this in mind. Response rates of around 20% are typical in research involving individuals with developmental disabilities (Siklos & Kerns, 2006) and small sample

sizes are often seen in studies involving individuals with ASD. While findings should not be ignored solely on the basis of low response rates, low response rates can easily introduce bias into a study (Galea & Tracy, 2007). In the case of this study, bias may have occurred in the form of parents with a child experiencing mental health issues being more likely to take the time to participate in our study, which would result in overestimation of the prevalence of mental health concerns in pre-teens and adolescents with ASD.

Increasing participation in ASD research is critical for the continued production of quality research. However, participation in epidemiologic research as a whole has declined in the last 30 years (Galea & Tracy, 2007) and there are no guaranteed solutions to improve participation rates. People are more likely to participate in research that is relevant or of personal interest to them, and financial incentives as well as offering different methods of survey completion (i.e. mail, web, phone) may improve participation rates by a small amount (Galea & Tracy, 2007). Individuals with ASD and their families may be a particularly difficult group to reach as they may be overwhelmed with the demands of caring for a child with ASD and have little time to participate in research (Davis & Carter, 2008).

Another limitation of the study is that we did not include information on all possible covariates. We had initially planned to include socioeconomic status (using neighbourhood-level data) and classroom setting (as a measure of intellectual ability and interaction with typicallydeveloping peers) as additional exposure variables. However, due to the low response rate and small sample size, it was decided that only essential covariates would be included. Future research should utilize more reliable measures of ID, in addition to investigating other covariates, including socioeconomic status and childhood adversities such as parental loss, family violence, parental abuse or neglect, parental criminality and drug use, and removal of children from the family home (Green et al., 2010; Herpetz-Dahlmann et al., 2013).

5.9 Conclusions

This study did not detect a relationship between childhood ASD symptomatology and the development of mental health concerns in adolescence. Further research is needed to generate a clear understanding of the relationship between early childhood ASD symptomatology and adolescent mental health.

This study confirms previous findings that gender and having a family history of mental illness are significant risk factors for the development of mental health concerns, particularly internalizing disorders. Although familial risk factors cannot be prevented or changed, identifying individuals at elevated risk is important for service providers and assists in predicting individual adult outcomes. Understanding the developmental trajectory of ASD is important for researchers, clinicians, individuals with ASD, and their families. Before symptoms appear, families can engage in activities to build family and individual resilience, designed to mitigate the impact of any mental health problems that eventually develop. However, given that the developmental trajectory of ASD is only beginning to be understood, it will take a great deal of further research before we are able to predict outcomes with any degree of certainty. In the meantime, a better understanding of the manifestations of mental health concerns in individuals with ASD, as well as risk factors for their development is necessary to improve recognition of symptoms by clinicians and ultimately improve quality of life.

This study provides evidence that girls with an ASD and mental health concerns may be particularly disadvantaged by a lack of understanding of the way mental health symptoms manifest in individuals with ASD. Girls, who are more likely to develop an internalizing, nondisruptive disorder (Ghaziuddin et al., 2002; Herpertz-Dahlmann et al., 2013), and who may, because of ASD have difficulty articulating thought patterns or emotions, could have problems that go unrecognized for much longer than disruptive behaviours typically associated with male mental health concerns. Parents and clinicians should be aware that girls with ASD may experience symptoms of mental health concerns that can be difficult to recognize or assess. Researchers should continue to identify behaviours that are indicative of mental health concerns, particularly internalizing ones, to aid in prompt detection and treatment. Researchers should also investigate the way symptoms of mental health concerns manifest in individuals with ID, to facilitate the early diagnosis and treatment of mental health concerns.

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Chapter 6

Overall Discussion and Conclusions

6.1 Summary of Findings

6.1.1 Objective one

The first objective of this study was to determine if age at assessment with the Autism Diagnostic Interview-Revised (ADI-R) was associated with scores on any of the ADI-R diagnostic algorithm domains. The ADI-R is a rich source of data for researchers and may be particularly useful in retrospective study designs as it captures a great deal of information about the individual's autism spectrum disorder (ASD) symptoms at age four, however since it also contains some items that ask if a particular behaviour ever occurred at any point in the individual's life, the age at which the ADI-R assessment is conducted may bias scores on domains containing both items queried at age four and items queried at any point, with older individuals being likely to receive a higher score in these domains.

In a sample of 339 individuals aged 10-19 with ASD, we determined that there was a significant correlation between age at assessment and score in the communication (p<0.001) and reciprocal social interaction domains (p<0.0001), indicating that individuals who were older when assessed with the ADI-R were more likely to receive a higher score (indicative of worse ASD symptoms) in these domains. Items on the ADI-R are scored in one of two ways: a lifetime or "ever" score (i.e. has the child ever displayed this particular behaviour) or a score for their symptoms at age four. Initially, we hypothesized that these "ever" items may be more likely to occur in individuals who were older when assessed, as they would have more time to develop 122

these behaviours, and that this would lead to older individuals receiving a higher score on items with more "ever" items. The strongest correlation was detected in the reciprocal social interaction domain, which contains mostly age four items, indicating that it may be these items that have the strongest effect on total domain score. To determine if a cohort effect existed in our study sample, we stratified the study sample into two groups based on the median age at assessment (8.9 years) and compared median scores in each domain. Significant differences in median scores between age groups were found in the reciprocal social interaction and communication domains, indicating that there is a possible cohort effect at work. Individuals who were older when they were assessed are also older, and diagnosed earlier, and due to changes in diagnostic practices (Fombonne, 2003), may have more severe ASD symptoms than the younger age group. Alternatively, this finding could be explained by recall bias, where issues with social interaction and communication become more salient to parents as their children get older, and parents may report their child's age four symptoms through the lens of their current perception of their child's symptoms, (Brookman-Frazee, 2003), or parents of older children may simply have a less accurate memory of their child's age four symptoms as more time has elapsed since their child was four.

The findings of this study have important research implications because the ADI-R is a rich source of data and a potentially valuable tool for researchers. While the ADI-R has been used in longitudinal research to measure ASD symptom stability over time (see Shattuck et al., 2007), it has been used less frequently in retrospective settings as a measure of ASD symptomatology to predict other outcomes later in life. Our findings indicate that if researchers are attempting to use the ADI-R as a baseline measurement of ASD symptoms, they should be

prepared to control for the effects of age at assessment on score in the reciprocal social interaction and communication domains, and to evaluate if these effects exist in their study sample.

6.1.2 Objective two

The second objective for this thesis was to provide a Canadian prevalence estimate of mental health concerns in pre-teens and adolescents with ASD. Study participants were recruited from the National Epidemiologic Database for the Study of Autism in Canada and the Autism Spectrum Disorders Canadian-American Research Consortium, both housed in Kingston, and invited to participate in a survey on risk factors for mental health concerns and seizures in pre-teens and adolescents with ASD. This study sample consisted of 66 individuals with ASD, aged 10-19. We found that 45% of our study sample met our case definition for mental health concerns; that is, they had scored in the clinical range of one or more CBCL subscales, or their parent had reported a diagnosis occurring after age 10, and that 15% of the sample met case criteria on two or more CBCL subscales. When we broadened the case definition to include subclinical CBCL scores, the prevalence increased to 60%. The subclinical scales on the CBCL were designed to help parents and clinicians make informed decisions about children's needs for services by identifying levels of symptoms that are not yet severe enough to require immediate intervention, but may require further investigation or re-assessment at a later time (Achenbach & Rescorla, 2000).

Mood disorders (18%) and anxiety disorders (33%) were the most common mental health concerns in our study sample, consistent with findings from a recent study of 67 youth with ASD and 67 IQ-matched controls (Skokauskas & Gallagher, 2012). Our prevalence estimates for mood and anxiety disorders were also consistent with the findings from this earlier study; however, we found a lower prevalence of attention deficit problems in our study population.

This study also detected discrepancies between the number of individuals receiving clinical scores on the CBCL and the number of parent-reported diagnoses, with parents consistently reporting fewer diagnoses than clinical CBCL scores. The level of agreement (Kappa) between parent-reported diagnoses and CBCL findings was poor for all scales

This is not to say that parents are not seeking proper treatment for their children. On the contrary, parents seem to recognize their children's behaviours as being abnormal (or occurring more frequently than would be normal), based on their answers to the CBCL. Anecdotal evidence from parents indicates they would like to get their children assessed, and may be waiting for psychological assessments or unable to access this service.. The difficulties of detecting and diagnosing psychiatric disorders in individuals with ASD have been described in this thesis; comments from parents reveal how these difficulties affect the quality of life of individuals with ASD and their families. With the release of the DSM 5, and the elimination of the restriction on diagnosing more than one Axis I disorder at a time, it will be interesting to see how the incidence and prevalence of psychiatric comorbidities in individuals with ASD change. However, we are still in need of a better understanding of how symptoms of mental health concerns manifest in individuals with ASD, particularly in those who also have an Intellectual Disability. Furthermore, better screening and diagnostic guidelines to identify mental health concerns in individuals with ASD are necessary, especially those that account for the ways in which ID and limited verbal ability impact symptom manifestation and assessment.

6.1.3 Objective three

The third objective was to identify risk factors for the development of mental health concerns in adolescence, in particular, if the severity of early childhood ASD symptoms (measured with the ADI-R) was associated with the development of mental health concerns in adolescence. We

considered each ADI-R domain individually, and divided the domains into score tertiles of "most impaired", "moderately impaired" and "least impaired", with higher score indicating more severe impairment. An *a priori* decision to assess only disorders with a prevalence rate of 20% or more in the study sample was made due to concerns about low response rate. Therefore, we tested a composite outcome of any mental health concern and we also tested anxiety disorders. Bivariate analysis did not detect any associations between ADI-R score tertiles and the development of mental health concerns in adolescence. When examining the relationship between the outcomes and other covariates of interest (Intellectual Disability, gender, age, family history of mental illness), significant associations between gender and composite outcome (p<0.005) and family history and both any mental health concern (p=0.05) and anxiety specifically (p<0.005) were found.

An important finding of this study was the association between female gender and the development of mental health concerns in adolescence. While this finding should be interpreted with some caution, as there were only 12 girls in the study sample, the confidence intervals surrounding odds ratio estimates were quite large, and the statistical power of the study was low, this study provides preliminary evidence that girls with an ASD and mental health concerns may be particularly disadvantaged by a lack of understanding of the way mental health symptoms manifest in individuals with ASD. Girls are more likely to develop an internalizing, non-disruptive disorder (Ghaziuddin et al., 2002; Herpertz-Dahlmann et al., 2013). Girls with ASD may have difficulty articulating thought patterns or emotions, that are critical to the detection and diagnosis of internalizing mental health concerns and could therefore have problems that go unrecognized for much longer than the disruptive behaviours typically associated with male

mental health concerns. Parents and clinicians should be aware that girls with ASD do experience symptoms of mental health concerns that may not be immediately apparent.

6.2 Strengths and Limitations

6.2.1 Volunteer bias

In any study that uses volunteer respondents, the issue of volunteer bias must be addressed. In this study, parents who agreed to take the time to complete our survey may have been more interested in this particular topic than those who did not. They may be parents who have children who have struggled with mental health issues and feel strongly about this topic, or they may be increasingly concerned about their child's mental health. This bias may have affected the composition of our study sample, resulting in estimates of prevalence of psychiatric disorders that are higher than the true population prevalence.

6.2.2 Generalizability

Low response rates are consistently a challenge in working with individuals with developmental disabilities (Siklos & Kearns, 2006). Low response rates and corresponding small sample sizes decrease the representativeness of study samples, and make findings less generalizable. A major strength of this study was that it used a community-based study sample, rather than a clinically-referred sample (i.e. referred to services or clinicians due to mental health concerns). In the context of mental health concerns in ASD, individuals who are referred to clinicians usually present with symptoms of mental health issues severe enough to warrant attention and parental concern, and therefore the prevalence of psychiatric disorders in clinical samples may be higher

than the prevalence in the entire population, while prevalence estimates generated from a community-based sample are likely to be closer to the true population prevalence.

One finding of our study that may indicate a lack of representativeness of the sample is the prevalence of Intellectual Disability in this study sample. While the majority of parents reported that their child had not had an IQ test (or were unsure if they had), for the individuals who did have a known IQ score, 71% did not have a parent-reported Intellectual Disability (ID). Previous epidemiological estimates of the prevalence of ID in those with ASD are has high as 60% (Volkmar & Pauls, 2003).

The sources of participants for this study may also have impacted the generalizability of the study findings. Participants recruited from NEDSAC were identified on the basis of receipt of services, which may mean that individuals with mild ASD who do not meet criteria for services would be under-represented. Furthermore, the regions from which NEDSAC recruited participants represent limited ethnic diversity, reducing the representativeness of the study sample. It is possible that this sample was less diverse in other ways, such as socioeconomic status and ASD severity. Recruitment from the ASD-CARC database relies heavily on volunteer enrollment, rather than systematic identification of cases, and as such, individuals enrolled in the ASD-CARC study may be systematically different from those who are not enrolled. We did not assess non-response bias in this study, and it is possible that our study sample is not representative of the Canadian population of adolescents with ASD.

6.2.3 Misclassification based on Intellectual Disability Status

The amount of missing data ("don't know" or "unsure" responses) to our Intellectual Disability and IQ test questions creates the possibility of misclassification. We considered individuals as ID cases only if their parents reported a diagnosed ID. It is possible that some individuals who 128 actually have an ID were misclassified as not having one because their parents indicated that they were unsure about an ID diagnosis. This misclassification could have introduced error into the prevalence estimate of ID in our study population, and makes it difficult to draw any conclusions about the relationship between ID and the development of mental health concerns in adolescence in our study sample.

6.2.4 Survey Quality

Due to time constraints, we were unable to test the validity and reliability of the "Risk Factors for Mental Health Concerns and Seizures in Pre-teens and Adolescents with an ASD" survey. However, the questionnaire was made of questions adapted from three sources: the Canadian Community Health Survey (CCHS) (Statistics Canada, 2011), the National Longitudinal Study of Children and Youth (NLSCY) (Statistics Canada, 2008) and the Interactive Autism Network's family history questionnaire (Kennedy Krieger Institute, 2012). Using previously created and tested questions in our survey lends strength to our findings. Furthermore, the questionnaire was also piloted before being released, to obtain feedback on the questionnaire layout, length, and clarity. The use of the CBCL in addition to parent-reported diagnoses strengthened the accuracy of our findings of prevalence of mental health concerns by providing an objective measure of mental health symptoms.

6.2.5 Statistical Power

The small sample size for this study left our analysis for objective three underpowered. An *a priori* power calculation for this objective indicated that, in order to compare the most impaired and least impaired tertiles on the basis of adolescent outcomes, 100 responses would be needed to ensure adequate statistical power (>80%).

The power of a study is the probability that the study will reject the null hypothesis when the null hypothesis is false, in other words, the probability of finding a difference that truly exists (Rosner, 2011). Statistical power is a function of sample size, the magnitude of the effect, and the significance criteria used in the test (Rosner, 2011). The results of our analysis in manuscript three should be interpreted with caution in light of the lack of statistical power of this study. Given that this analysis was underpowered, our finding of no discernable relationship between severity of childhood ASD symptomatology and adolescent mental health concerns may be a true finding, or may be due to a lack of statistical power to detect true associations.

Given the difficulty in recruiting participants for epidemiologic studies (Galea & Tracy, 2007; Hartge, 2006) and the low response rates characteristic of studies involving individuals with developmental disabilities (Siklos & Kerns, 2006), alternative study designs must be considered to maximize sample sizes in ASD research. Using case-control study designs and recruiting participants based on case status may prevent some issues with lack of statistical power, however this may not be practical in all cases. Meta-analysis can strengthen statistical power (Cohn & Becker, 2003), as can repeated measures designs (i.e. collecting measurements from the same individuals multiple times) (Guo, Logan, Glueck, & Muller, 2013). Repeated measures designs are also a cost-effective method of reducing sample size (Guo et al., 2013). Meta-analyses and repeated measures designs should be explored in future studies of individuals with ASD to increase the strength of the literature.

6.3 Future Research Directions

There are several requirements for future research on mental health in individuals with ASD. First and foremost, a better understanding of how to differentiate between symptoms of mental health concerns and symptoms or behaviours associated with ASD is imperative (Leyfer, 2006; Witwer & Lecavalier, 2010). Secondly, better diagnostic tools that can accurately discriminate between ASD symptoms and mental health symptoms must be developed and tested (Leyfer, 2006). The Nisonger Child Behaviour Rating Form (NCBRF) (Aman, Tasse, Rojahn, & Hammer, 1995) is one such tool, however, before it needs further evaluation and testing before it can be used with confidence (Matson et al., 2012).

Thirdly, understanding the ways in which Intellectual Disability and limited verbal ability interact with mental health concerns and alter the way mental health concerns present, or the ability of individuals to articulate their mental health is critical to the development of better assessment and screening tools, and better diagnostic procedures for individuals with ASD and ID (Witwer & Lecavalier, 2010). Behaviour equivalents are one possibility for the accurate evaluation and diagnosis of individuals with ASD and ID, however their specificity will need to be evaluated before they can be reliabily incorporated into diagnostic guidelines (Tsiouris, Mann, Patti, & Sturmey, 2003).

6.4 Public Health Implications

Adolescence has been established as a critical period for the development of psychiatric disorders for typically developing individuals and individuals with ASD. Social changes in adolescence can separate individuals with ASD further from their peers, and this isolation can exacerbate existing mental health issues. While there is still ongoing debate on the best way to detect symptoms of psychiatric disorders in individuals with ASD, it seems that psychiatric comorbidities are under-recognized and under-diagnosed in this population. Mental health concerns can severely impact quality of life, and disorders that develop in adolescence are likely to persist into adulthood if they are not addressed promptly. Poor mental health is increasingly recognized as being a serious problem in Canada (see the "Changing Directions, Changing Lives" report from the Mental Health Commission of Canada), and should be recognized as a problem for individuals with ASD as well. More recognition must be given to the complex needs of individuals with dual diagnoses (ASD and psychiatric comorbidity), and service providers must adapt to meet these needs. Positive changes are slowly being made: the DSM 5 makes it easier for health professionals to diagnose psychiatric disorders in individuals with ASD, for example. However, with the increasing prevalence of ASD in Canada, it will be extremely important for clinicians to be aware of the symptoms of psychiatric disorders in this population as children with ASD reach adolescence.

The parents who responded to our survey indicated they were frequently concerned about their child's mental health, but also that they were struggling; in many cases, they were waiting for diagnostic or support services for their child, or were unable to access these services; in other cases, they were struggling to cope with severe behaviour problems or mental health concerns. The struggles of parents of adolescents with ASD and comorbid mental health concerns may be best exemplified by the following quotes:

> We had difficulty with anxiety in grade 3 but he was a small child. Now at 16, 6 feet tall and 190-200lbs we are seeing the same thing but it is dangerous because of his size. He has put holes in walls and broken beds tantruming. The behaviour is like a person in an uncontrollable rage. We are feeling that he has mental health issues along with the autism, anxiety and epilepsy.

He has had a rough couple of years. Behaviour has escalated. Moods have been more explosive. He tried to kill himself last year.

Better access to services that have been specifically designed to meet the complex needs of youth with ASD and comorbid mental health concerns are essential for the well-being of individuals as well as their families.

Furthermore, extensive research must be done to determine the ways symptoms of mental health concerns manifest in adolescents with ASD, and whether these manifestations are different than in typical individuals. This will lead to the creation of better screening tools and easier diagnoses, which will, ideally, lead to better epidemiological estimates of prevalence and incidence, and better quality of life through accurate diagnosis and specialized treatment programs.
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Appendix A

Information Letter and Consent Forms

Email Introduction

Dear _____,

As a parent of a child with an Autism Spectrum Disorder you may be aware that adolescence and early adulthood can be a period of difficult adjustment. In particular, there may be an increased risk of mental health challenges during this time period. To study this, we need information about children who DO and who DO NOT show signs of mental health concerns. You are invited to participate in a study entitled *"Risk Factors for Mental Health Concerns and Seizures in Pre-Teens and Adolescents with an Autism Spectrum Disorder"* conducted by Queen's University, NEDSAC (National Epidemiologic Database for the Study of Autism in Canada) and ASD-CARC (Autism Spectrum Disorders Canadian-American Research Consortium). An online questionnaire consisting of a demographic survey and the Child Behaviour Checklist (CBCL) Parent Report Form is accessible at the following link:

Please enter this code _____ (NEDSAC or ASD-CARC ID code) when prompted.

Further information about the survey is provided below. If you choose to participate, you will be asked to complete a consent form before beginning to answer the survey questions. All information you provide will be kept confidential and you may terminate your participation at any time.



Risk Factors for Mental Health Concerns and Seizures in Pre-Teens and Adolescents with an Autism Spectrum Disorder Information Letter and Consent Form

Introduction

Queen's University, in partnership with the National Epidemiologic Database for the Study of Autism in Canada (NEDSAC) and Autism Spectrum Disorders Canadian-American Research Consortium (ASD-CARC) is conducting a study to investigate mental health challenges and concerns in pre-teens and adolescents with an Autism Spectrum Disorder. For more information on NEDSAC and ASD-CARC, including links to published research, please visit <u>www.nedsac.ca</u> or <u>www.asdcarc.com</u>. Funding for this project has been provided by Queen's University and the Empire Life Foundation.

What is the purpose of this project?

The goal of this project is to estimate the prevalence of mental health concerns in Canadians aged 10-19 with an Autism Spectrum Disorder. In order to capture an accurate estimate, we need information from families of individuals with ASD regardless of whether or not their child has a mental health diagnosis. We would additionally like to determine if early childhood behaviours or symptoms (from previously collected ADI-R information) are associated with the development of mental health challenges later in adolescence. Finally, we are interested in the types of services adolescents with ASDs are using, and if parents feel those services meet the needs of their children.

Can I participate?

We are recruiting all families with children born between 1993 and 2002 who have completed an Autism Diagnostic Interview-Revised (ADI-R) for either a NEDSAC study or the ASD-CARC research program to participate.

If I participate, what do I have to do?

We are asking parents and guardians of recruited individuals to complete a parent questionnaire and to give permission for us to use data from the ADI-R already on file with NEDSAC or ASD-CARC. The questionnaire consists of two parts: demographic information and the Child Behaviour Checklist (CBCL) Parent Report Form. The questionnaire will take approximately 25 minutes to complete. Since some of the questions concern your child, we encourage you to discuss this project with him/her and respect his/her wishes.

What are the benefits of participation?

There are no direct benefits to participating in this study, but we hope that information from this study may help parents, guardians and service providers in identifying children at greatest risk for mental health challenges in adolescence so that they can begin planning services and interventions early on.

What are the risks of participation?

The risks of participating in this study are minimal. See the next section for more information on confidentiality.

What about confidentiality?

All information collected in the questionnaire will remain confidential and will be stored in a secure database. All individuals participating in the study will be identified by a code, so that no names or geographic identifiers appear in the questionnaire forms or in the database. All findings will be reported in a group manner so that no individual participant can be identified. The master lists linking codes to names are maintained in password-protected files on password-protected hard drives in a secure building in Kingston, Ontario and are only accessible to members of the research team. At the end of the study, all data related to the study will be disposed of in accordance with Queen's Health Sciences Research Ethics Board protocols.

What are my rights if I choose to participate?

If you choose to participate and at a later date decide you no longer wish to be involved in this study, you may withdraw participation by contacting the project team at any time.

Who do I contact if I have questions or concerns?

Please feel free to contact the research team at any time with any questions or concerns you may have.

Hélène Ouellette-Kuntz, Project Director National Epidemiologic Database for the Study of Autism in Canada Associate Professor, Department of Community Health & Epidemiology Queen's University c/o Ongwanada Resource Centre 191 Portsmouth Avenue Kingston, ON, K7M 8A6 helene.kuntz@queensu.ca telephone: 613-548-1198 ext. 1198 fax: 613-548-8135

Dr. Xue Dong Liu Director, Queen's Genomics Lab at Ongwanada Co-Director, ASD-CARC Assistant Professor, Department of Psychiatry Queen's University Kingston, ON <u>liux@queensu.ca</u> telephone: 613-548-4419 x1192

Caitlin McGarry, Graduate Student

Queen's University, Department of Community Health & Epidemiology c.mcgarry@queensu.ca

If you have any questions or concerns about your rights as a research participant, please contact Dr. Albert Clark, Chair of the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board at (613) 533-6081.

CONSENT FORM (MAILED)

I have read the information describing this project and understand what is required of my participation. I understand that the information from this project will be used to help researchers better understand the association between early childhood autism symptoms and pre-teen and adolescent mental health challenges and estimate the prevalence of mental health challenges in Canadian pre-teens and adolescents with Autism Spectrum Disorders. I understand that all results of this study will be published in grouped format so that no individual participants can be identified. I understand that I can withdraw my participation from this study at any time. My child does not object to participation in this study.

If you would like to participate, please complete this form by placing a check mark in the box next to the following statement and fill in the following information.

I agree to complete a written questionnaire in order to provide researchers with information

about my child with an autism spectrum disorder and give them permission to link this information to the ADI-R data on file for my child.

I would like to receive a copy of the study's report.

Name of parent/legal guardian (please print):
Signature of parent/legal guardian:
Date:
Signature of project coordinator:
Date:

Please return this consent form and completed questionnaire in the envelope provided. A copy of this questionnaire, signed by the project coordinator, will be returned to you.

CONSENT FORM (ONLINE)

I have read the information describing this project and understand what is required of my participation. I understand that the information from this project will be used to help researchers better understand the association between early childhood autism symptoms and pre-teen and adolescent mental health challenges and estimate the prevalence of mental health challenges in Canadian pre-teens and adolescents with Autism Spectrum Disorders. I understand that all results of this study will be published in grouped format so that no individual participant can be identified. I understand that I can withdraw my participation at any time. My child does not object to participation in this study.

Please check the appropriate box. By clicking on the first option, you will be taken directly to the online survey and asked to enter the participant code provided in the invitation email.

I agree to complete an online questionnaire in order to provide researchers with information

about my child with an autism spectrum disorder and give permission for the researchers to link this information to the ADI-R data already on file for my child.

I would like to receive a copy of the study report.

I do not wish to participate in this study.

Appendix B

Ethics Approval Forms



QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW June 25, 2012

Ms. Caitlin McGarry Department of Community Health and Epidemiology Queen's University

Dear Ms. McGarry Study Title: EPID-388-12 Risk Factors for Psychiatric Comorbidities in Adolescents with Autism Spectrum Disorders- Feasibility Study File # 6007085

Co-Investigators: Dr. H. Ouellette-Kuntz

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # 6007085 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file **6007085** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

albert F. Clark.

Chair, Research Ethics Board June 25, 2012

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete



QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW September 05, 2012

Ms. Caitlin McGarry Department of Community Health and Epidemiology Queen's University

Dear Ms. McGarry Study Title: EPID-393-12 Risk Factors for Mental Health Concerns in Pre-teens and Adolescents with Autism Spectrum Disorder. File # 6007219 Co-Investigators: Mrs. H. Ouellette-Kuntz

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol, parent questionnaire, invitation letter (email), information letter, consent form (mailed) and consent form (online) for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # 6007219 in your Researcher Portal (<u>https://eservices.queensu.ca/romeo_researcher/</u>)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file **6007219** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

albert F. Clark.

Chair, Research Ethics Board September 05, 2012

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

Appendix C

Parent Questionnaire

Risk Factors for Mental Health Concerns and Seizures in Pre-Teens and Adolescents with an Autism Spectrum Disorder



A study conducted by:



c/o 191 Portsmouth Avenue Kingston ON K7M 8A6



Risk Factors for Mental Health Concerns and Seizures in Pre-Teens and Adolescents with an Autism Spectrum Disorder

Thank you for your participation in this study. We understand that some information may be sensitive. Please answer to the best of your ability. All data collected will be kept strictly confidential and will only be identifiable by a participant code.

If you have any questions or concerns please contact Caitlin McGarry (c.mcgarry@queensu.ca).

Please enter your participant code:

1. What is your full postal code? _____

2. Does your child live at home with you? (please circle the correct response)

1. YES 2. NO

↓ If yes, go to question 4

3. If not, which best describes your child's living arrangement?

- 1. GROUP HOME
- 2. INDEPENDENTLY
- 3. WITH OTHER FAMILY MEMBERS
- 4. OTHER (please explain)

3a) What is your child's postal code? _____

4. What type of school does your child attend?

- 1. NOT IN SCHOOL; go to question 8.
- 2. HOME SCHOOL
- 3. PUBLIC SCHOOL
- 4. PRIVATE SCHOOL WITH REGULAR EDUCATION CLASSES
- 5. SPECIALIZED PRIVATE SCHOOL (for children with special needs)
- 6. SPECIALIZED PUBLIC SCHOOL (for children with special needs)

5. What school grade is your child in?

- 1. GRADE 4
- 2. GRADE 5
- 3. GRADE 6
- 4. GRADE 7
- 5. GRADE 8
- 6. GRADE 9
- 7. GRADE 10
- 8. GRADE 11
- 9. GRADE 12

6. How would you best describe your child's classroom setting?

- 1. REGULAR EDUCATION CLASSROOM FOR ALL OF SCHOOL DAY
- 2. MORE TIME IN REGULAR EDUCATION CLASSROOM THAN SPECIAL EDUCATION CLASSROOM
- 3. SAME AMOUNT OF TIME IN REGULAR EDUCATION CLASSROOM AND SPECIAL EDUCATION CLASSROOMS
- 4. MORE TIME IN SPECIAL EDUCATION CLASSROOM THAN REGULAR EDUCATION CLASSROOM
- 5. SPECIAL EDUCATION CLASSROOM FOR ALL OF SCHOOL DAY

7. Does your child have classroom opportunities for inclusion with typically developing peers?

1. YES 2. NO

Go to question 9.

8. If your child is not in school, are they enrolled in any educational or social programs, such as a trade or vocational program or day program for individuals with special needs?

1. YES 2. NO 3. OTHER (please explain):

9. Has your child ever been given an IQ or intelligence test?

YES
 NO; go to Question 11
 DON'T KNOW; go to Question 11

10. What was your child's most recent IQ test score?

DON'T KNOW
 40 OR BELOW
 41-55
 56-70
 71-85
 86-115
 116-130
 ABOVE 130

11. Has your child ever been diagnosed with an Intellectual Disability (ID)? (An intellectual disability is characterized by significant limitations in intellectual functioning and in adaptive behaviour).

1. YES 2. NO 3. DON'T KNOW/UNSURE

The next section of this survey asks about certain long-term health conditions your child may have. We are interested in "long term" conditions which are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional.

12. Does your child have a mood disorder such as depression, bipolar disorder, mania or dysthymia?

1. YES 2. NO 3. DON'T KNOW

12a) How old was your child when he/she was first diagnosed?

LESS THAN 10 YEARS OLD
 10 OR OLDER

13. Does your child have an anxiety disorder such as a phobia, obsessive-compulsive disorder, or a panic disorder?

1. YES 2. NO 3. DON'T KNOW

13a) How old was your child when he/she was first diagnosed?

LESS THAN 10 YEARS OLD
 10 OR OLDER

14. Does your child have attention deficit disorder, with or without hyperactivity?

1. YES 2. NO 3. DON'T KNOW

14a) How old was your child when he/she was first diagnosed?

LESS THAN 10 YEARS OLD
 10 OR OLDER

15. Does your child have a conduct disorder?

1. YES 2. NO 3. DON'T KNOW

15a) How old was your child when he/she was first diagnosed?

LESS THAN 10 YEARS OLD
 10 OR OLDER

16. Does your child have an oppositional defiant disorder?

1. YES 2.NO 3. DON'T KNOW

16a) How old was your child when he/she was first diagnosed?

LESS THAN 10 YEARS OLD
 10 OR OLDER

17. Does your child have any other disorders? (please describe)

1. YES 2. NO 3. DON'T KNOW

17a) How old was your child when he/she was first diagnosed?

LESS THAN 10 YEARS OLD
 10 OR OLDER

	Yes	No	Don't Know
Food/Digestive Allergies			
Respiratory allergies such as hay fever			
Any other allergies (specify):			
Fragile X			
Tuberous Sclerosis			
Heart condition or disease			
Epilepsy			
Cerebral Palsy			
Learning Disability			
Eating Disorder			
Migraines			
Any other long- term condition (please specify):			

18. Has a health professional diagnosed any of the following long-term health conditions for your child?

19. Has your child ever had a seizure?

1. YES 2. NO \rightarrow If no, go to question 20

19a) How old was your child when the first seizure occurred?

- 1. LESS THAN 10 YEARS OLD
- 2. 10 OR OLDER

19b) How old was your child when the most recent seizure occurred?

- 1. LESS THAN 10 YEARS OLD
- 2. 10 OR OLDER

20. Are you the genetic parent of your child? (i.e. your child was NOT conceived through egg or sperm donation).

- 1. YES
- 2. NO; child is adopted
- 3. NO; child was conceived through egg or sperm donation

The following questions ask about family history. It is important to answer these questions in relation to <u>your child's genetic family</u>. We understand that some information may be unknown, especially in the case of adoption or conception by egg or sperm donation, however please answer to the best of your ability.

	Yes	No	Don't Know/Unsure
Autism Spectrum Disorder			
Seizure Disorder or Epilepsy			
Schizophrenia			
Mood Disorder (including Bipolar/ manic-depressive)			
Attention Deficit Disorder			

21. Does your child have any <u>first degree relatives</u> (that is, parents and siblings) who have been diagnosed with the following?

22. Does your child have any <u>second-degree relatives</u> (that is, aunts and uncles by blood, and grandparents) who have been diagnosed with the following?

	Yes	No	Don't Know/Unsure
Autism Spectrum Disorder			
Seizure Disorder or Epilepsy			
Schizophrenia			
Mood Disorder (including Bipolar/ manic-depressive)			
Attention Deficit Disorder			

	Yes	No	Don't Know/Unsure
Autism Spectrum Disorder			
Seizure Disorder or Epilepsy			
Schizophrenia			
Mood Disorder (including Bipolar/ manic-depressive)			
Attention Deficit Disorder			

23. Does your child have any first cousins who have been diagnosed with the following?

24. Does your child take any of the following prescribed medications on a regular basis?

24a) Ritalin or similar medications

1. YES 2. NO 3. DON'T KNOW

24a.1) If yes, how old was your child when he/she was first prescribed this medication?

- 1. LESS THAN 10 YEARS OLD
- 2. 10 OR OLDER

24b) Tranquilizers or nerve pills such as Valium or Ativan

1. YES 2. NO 3. DON'T KNOW

24b.1) If yes, how old was your child when he/she was first prescribed this medication?

- 1. LESS THAN 10 YEARS OLD
- 2. 10 OR OLDER

24c) Anti-depressants such as Prozac, Effexor or Paxil

1. YES 2. NO 3. DON'T KNOW

24c.1) If yes, how old was your child when he/she was first prescribed this medication?

- 1. LESS THAN 10 YEARS OLD
- 2. 10 OR OLDER

24d) Mood Stabilizers such as Lithium or Tegretol

1. YES 2. NO 3. DON'T KNOW

24d.1) If yes, how old was your child when he/she was first prescribed this medication?

- 1. LESS THAN 10 YEARS OLD
- 2. 10 OR OLDER

24e) Anti-Psychotics such as Haldol or Abilify

1. YES 2. NO 3. DON'T KNOW

24e.1) If yes, how old was your child when he/she was first prescribed this medication?

- 1. LESS THAN 10 YEARS OLD
- 2. 10 OR OLDER

24f) Anticonvulsant or anti-epileptic pills

1. YES 2. NO 3. DON'T KNOW

24f.1) If yes, how old was your child when he/she was first prescribed this medication?

- 1. LESS THAN 10 YEARS OLD
- 2. 10 OR OLDER

25. For each service listed, please check the appropriate box:

	Receiving	Needs but Not Receiving	Doesn't Need
Speech Therapy			
Assisted Communication Technology			
Behaviour Therapy			
Occupational Therapy			
Life Skills/Independent Living Instruction			
Vocational Training			
Social Inclusion or Recreational Programs			
Support Groups			
Individual Counseling			
Individual Psychotherapy			
Employment Support			
Psychiatric/ Mental Health Services			
Other (please specify):			
Other (please specify):			
Other (please specify):			

26. If you checked "needs but not receiving" for any of the services listed in question 25, please indicate, in your opinion, the two main reasons your child is not receiving a needed service:

1			
2			

The following questions are taken from the Child Behaviour Checklist (CBCL) Parent Report Form, published by Achenbach Systems of Empirical Behaviour Assessment and reproduced here with permission under agreement **#728-07-06-12**.

Below is a list of items that describe children and youths. For each item that describes your **child now or within the past 6 months**, please circle the **2** if the item is **very true or often true** of your child. Circle the **1** if the item is **somewhat or sometimes true** of your child. If the item is **not true** of your child, circle the **0**. Please answer all items as well as you can, even if some do not apply to your child.

0= Not True (as far as you know)	1= Somewhat or Sometimes True	2=Very True or Often True

				0	1	2	11. Clings to adults or too dependent
0	1	2	1. Acts too young for his/her age	0	1	2	12. Complains of loneliness
0	1	2	2. Drinks alcohol without parents' approval (describe):	0	1	2	13. Confused or seems to be in a fog
				0	1	2	14. Cries a lot
0	1	2	3. Argues a lot	0	1	2	15. Cruel to animals
0	1	2	4. Fails to finish things he/she starts	0	1	2	16. Cruelty, bullying, or meanness to others
0	1	2	5. There is very little he/she enjoys	0	1	2	17. Daydreams or gets lost in his/her thoughts
0	1	2	6. Bowel movements outside toilet	0	1	2	18. Deliberately harms self or attempts suicide
0	1	2	7. Bragging, boasting	0	1	2	19. Demands a lot of attention
0	1	2	8. Can't concentrate, can't pay attention for long	0	1	2	20. Destroys his/her own things
0	1	2	9. Can't get his/her mind off certain thoughts; obsessions (describe):	0	1	2	21. Destroys things belonging to his/her family or others
			10. Con't sit still rostlass, or	0	1	2	22. Disobedient at home
0	1	2	hyperactive	0	1	2	23. Disobedient at school
				0	1	2	24. Doesn't eat well

0	1	2	25. Doesn't get along with	0	1	2	43. Lying or cheating
			outer klus	0	1	2	44. Bites fingernails
0	1	2	26. Doesn't seem to feel guilty after misbehaving	0	1	2	45. Nervous, high-strung, or tense
0	1	2	27. Easily jealous				46 Nomence more more an
0	1	2	28. Breaks rules at home, school, or elsewhere	0	1	2	twitching (describe):
0	1	2	29. Fears certain animals, situations, or places, other then school (describe):	0	1	2	47. Nightmares
			than school (describe).	0	1	2	48. Not liked by other kids
0	1	2	30. Fears going to school31. Fears he/she might think	0	1	2	49. Constipated, doesn't move bowels
0	I	2	or do something bad	0	1	2	50. Too fearful or anxious
0	1	2	32. Feels he/she has to be perfect	0	1	2	51. Feels dizzy or lightheaded
0	1	2	33. Feels or complains that no one loves him/her	0	1	2	52. Feels too guilty
			34 Feels other are out to get	0	1	2	53. Overeating
0	1	2	him/her	0	1	2	54. Overtired without good reason
0	1	2	35. Feels worthless or inferior	0	1	2	55. Overweight
0	1	2	36. Gets hurt a lot, accident prone		56. Ph medica	ysical al cau	problems <i>without known</i> se:
0	1	2	37. Gets in many fights				a Aches or pains (not
0	1	2	38. Gets teased a lot	0	1	2	stomach or headaches)
Ū		2		0	1	2	b. Headaches
0	1	2	39. Hangs around with others who get in trouble		1	2	a Nausaa faala siak
			40. Hoors counds or voices	U	1	2	c. Nausea, leels sick
0	1	2	that aren't there (describe):	0	1	2	d. Problems with eyes (<i>not</i> if corrected by glasses)(describe):
			41 Impulsive or acts				
0	1	2	without thinking			2	e. Rashes or other skin
0	1	2	42. Would rather be alone	0	1	2	problems
	-	-	than with others	0	1	2	f. Stomachaches

0	1	2	g. Vomiting, throwing up	0	1	2	72. Sets fires
0	1	2	h. Other (describe):	0	1	2	73. Sexual problems (describe):
0	1	2	57. Physically attacks people	0	1	2	74. Showing off or clowning
			58. Picks nose, skin, or other	0	1	2	75. Too shy or timid
0	1	2	parts of body (describe):	0	1	2	76. Sleeps less than most kids
0	1	2	59. Plays with own sex parts in public		1	2	77. Sleeps more than most kids during day and/or night
0	1	2	60. Plays with own sex parts too much		1	2	(describe):
0	1	2	61. Poor school work	0	1	2	78. Inattentive or easily
0	1	2	62. Poorly coordinated or clumsy				distracted 79. Speech problem
0	1	2	63. Prefers being with older kids	0	1	2	(describe):
0	1	2	64. Prefers being with	0	1	2	80. Stares blankly
			younger kids	0	1	2	81. Steals at home
0	1	2	65. Refuses to talk	0	1	2	82. Steals outside the home
0	1	2	66. Repeats certain acts over and over; compulsions (describe):	0	1	2	83. Stores up too many things he/she doesn't need (describe):
0	1	2	67. Runs away from home				
0	1	2	68. Screams a lot	0	1	2	84. Strange behaviour (describe):
0	1	2	69. Secretive, keeps things to self				
0	1	2	70. Sees things that aren't there (describe):	0	1	2	85. Strange ideas (describe):
				0	1	2	86. Stubborn, sullen, or irritable
0	1	2	71. Self-conscious or easily embarrassed				

0	1	2	87. Sudden changes in mood or feelings									105. Uses drugs for nonmedical purposes (don't
0	1	2	88. Sulks a lot	0	1	2	include alcohol or tobacco)(describe):					
0	1	2	89. Suspicious									
0	1	2	90. Swearing or obscene language	0	1	2	106. Vandalism					
0	1	2	91. Talks about killing self	0	1	2	107. Wets self during day					
			92. Talks or walks in sleep	0	1	2	108. Wets the bed					
0	1	2	(describe):	0	1	2	109. Whining					
				0	1	2	110. Wishes to be of opposite sex					
0	1	2	93. Talks too much			2	111. Withdrawn, doesn't get					
0	1	2	94. Teases a lot		1	2	involved with others					
0	1	2	95. Temper tantrums or hot temper	0	1	2	112. Worries					
0	1	2	96. Thinks about sex too much		113. I child	Please has tha	write in any problems your at were not listed above:					
0	1	2	97. Threatens people	0	1	2						
0	1	2	98. Thumb-sucking	0	1	2						
0	1	2	99. Smokes, chews, or sniffs tobacco	0	1	2						
0	1	2	100. Trouble sleeping (describe):	Plea	ase be	sur	e you answered all items.					
0	1	2	101. Truancy, skips school									
0	1	2	102. Underactive, slow									

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moving, or lacks energy 103. Unhappy, sad, or

2 depressed2 104. Unusually loud

0

0 1

Is there anything else you feel we should know that would be relevant to our study?

Thank you so much for taking the time to fill out this information!