Children with Autism Spectrum Disorder in Manitoba: Population Characteristics and Psychotropic Medication Use

by

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Abstract

Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental disability diagnosed in an increasing number of children. ASD has few effective treatment options. This study describes ASD prevalence and use of psychotropic medications among children and youth in Manitoba.

Methodology: Administrative data from the Repository at the Manitoba Centre for Health Policy (MCHP) were used to create a cohort of children born in Manitoba. Diagnoses of ASD were based on medical claim records, hospital abstracts, or special education funding data.

Results: Between 2010 and 2014, 3079 Manitoba children aged 0-14 had an ASD diagnosis (1.2% prevalence). Child demographic, health and education, and family environmental characteristics were compared between children with ASD and children in the general population; children with ASD with and without psychotropic medications; and among all children with psychotropic medications. Children with ASD were more likely to have a psychotropic medication than children in the general population. Children with ASD were more likely to receive a psychotropic medication if they were older than age 4, were diagnosed with ASD later than age 4, received special education funding, had participated in behavioural programming, had a co-occurring psychiatric condition, had a sibling diagnosed with ASD or had ever been in the care of child welfare. This study demonstrated that children with ASD received a greater number and intensity of psychotropic medications than children in the general population with similar demographic and psychiatric conditions.

Conclusions: In Manitoba, the prevalence of ASD is increasing and differences exist between children with ASD and children in the general population. Future research and treatment planning for children with mental disorders and developmental disabilities should consider the appropriateness of the patterns of medication use and equity of treatment interventions found in this study.

Disclaimer

The author acknowledges the Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository under project #2015-013 (HIPC#2014/2015-40). The results and conclusions are those of the author and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Seniors and Active Living, or other data providers is intended or should be inferred. Data used in this study are from the Populations Health Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba, and were derived from data provided by Manitoba Health, Seniors and Active Living, Manitoba Education and Training, Winnipeg Regional Health Authority, Manitoba Families and the Manitoba Adolescent Treatment Centre.

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Dedication

This work is dedicated to the memory of my mother, Layla Louise Plastino,
who taught me the importance of learning and discovery.

And to my cousins William and Benjamin, and all children and youth
who live with Autism Spectrum Disorder or other developmental disabilities.

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Chapter 1: Introduction

The prevalence of Autism Spectrum Disorder (ASD) among children in Canada is increasing, concurrent with an increased awareness of developmental disabilities and early symptoms of autism (Fombonne, 2009; Nassar et al., 2009; Ouellette-Kuntz et al., 2012; Ouellette-Kuntz et al., 2014). Current epidemiological studies have not determined if this is a true prevalence increase or due to greater awareness of the disorder (Fombonne, 2009); regardless, there remains an increasing population of children eligible for and requiring accessible and appropriate intervention strategies for behaviour and symptoms associated with ASD. At present, there is little information regarding the extent of treatment of core symptoms for children with ASD in Manitoba, or the additional mental disorders that they may experience. However, anecdotal evidence suggests that many children in Manitoba must wait to access the services and treatments that may help them to achieve their full potential. The dual aim of this research was to determine the prevalence and characteristics of children and youths diagnosed with ASD in Manitoba and to establish the prevalence of psychotropic prescriptions in this population. Furthermore, this study determined whether there was a relationship between the use of psychotropic medication and medical, demographic, regional and socioeconomic characteristics of children and youths with ASD. This study therefore provides a better understanding of the population of children and youths diagnosed with ASD in Manitoba through an epidemiological description utilizing secondary data analysis of population-based health and social services records.

Psychotropic, specifically antipsychotic, medication prescriptions are increasing for children in Canada despite a lack of strong evidence for use in this population and without approval from Health Canada (Di Pietro, Illes, & Canadian Working Group on Antipsychotic Medications and Children, 2014). These medications have typically been used for children with challenging behaviour problems. Two antipsychotics (risperidone and aripiprazole) are approved for use in the United States for controlling serious behavioural problems in children with ASD (Scahill, Koenig, Carroll, & Pachler, 2007). Psychotropic medications are associated with the development of serious side effects such as sedation, excessive weight gain, development of metabolic syndrome, tardive dyskinesia, tremor and other extrapyramidal adverse events (Canitano & Scandurra, 2011; McPheeters et al., 2011; Pringsheim et al., 2011; Scahill et al., 2016). As such, monitoring medication use, metabolic changes and motor function is important to manage possible adverse events and to ensure that these medications are used only in situations where it is necessary. There has not previously been a detailed population-based study of psychotropic medication use in Canadian children with ASD. This study will therefore fill this gap and add to a broader understanding of the characteristics of children with ASD who are prescribed psychotropic medications and the intensity of their medication use.

1.1 Research Questions and Hypotheses

The purpose of this research was to determine the prevalence of ASD for children and youths in Manitoba and the prevalence and intensity of psychotropic medication prescription use for this population. The specific research questions were:

1. What is the prevalence of ASD for children and youths in Manitoba as measured using health and education records?

Hypothesis: The prevalence of ASD in children and youths in Manitoba will be higher in 2009/10 – 2013/14 than the previously reported prevalence in 2001/02 – 2005/06.

2. What is the prevalence of psychotropic medication use among identified children with ASD, and what are the patterns of medication use in this population?

Hypothesis: The prevalence of psychotropic medication use among children and youths in Manitoba with ASD will be greater than previously reported North American values.

3. What are the demographic, socioeconomic, geographic and medical characteristics of children and youths in Manitoba with ASD and how do these characteristics differ between:
    a. children with ASD and children in the general population?
    b. children with ASD who are prescribed psychotropic medications and those who are not prescribed psychotropic medications?

Hypothesis: Compared to children with ASD who have not been prescribed a psychotropic medication, children with ASD and psychotropic medications are expected to more likely be male, older, live in a rural area or an urban area with high SES, experience a co-morbid psychiatric condition, have their mother experience a psychiatric condition and receive special educational funding and behavioural therapies. It is expected that they will be less likely to have a sibling with ASD.

    c. children with psychotropic medications who are diagnosed with ASD and children with psychotropic medications in the general population?

Hypothesis: Compared to children without ASD, children with ASD and a psychotropic medication are expected to more likely be male and younger. It is expected that children with

ASD will be less likely to experience a co-morbid psychiatric condition and have their mother experience a psychiatric condition. It is expected that children with ASD and those without will not be significantly different in the areas where they live and socioeconomic status.

4. How does psychotropic medication use and intensity differ between children with ASD and children without ASD or any other developmental disability?

Hypothesis: Medication use by children with ASD will not differ greatly from children without ASD or any other developmental disability, and any variation will correlate with comorbid psychiatric diagnoses. It is anticipated that children with ASD may experience more polypharmacy.

Justifications for the above hypotheses are provided in the following literature review, particularly in Section 2.5: Factors that Influence ASD Prevalence, Early Childhood Development and Health System Use.

Chapter 2: Literature Review

2.1 Prevalence

Diagnostic prevalence of autism spectrum disorder has been documented to be as high as 1 in every 68 children, with reports suggesting prevalence has been increasing in recent years (CDC, 2014). An overall prevalence for Canada has not been published. Prevalence of ASD in Canada are measured and reported in each province or territory differently, and in some not at all. Prevalence in some of these regions have been calculated using administrative data from education and psychiatric treatment centres or through surveys of regional birth cohorts. Due to differences in data sources, years available for analysis and varying levels of surveillance, it is

difficult to combine provincial prevalence rates to establish a national estimate. Some examples of provincial rates include a prevalence of 1 in 77 (2010 data) children aged 2 – 14 in southeastern Ontario, 1 in 110 (2010 data) in Prince Edward Island and 1 in 120 (2008 data) in Newfoundland and Labrador (Ouellette-Kuntz et al., 2014). Prevalence rates in Manitoba are estimated as 1 in 114 for children aged 5-9 from physician diagnosis and educational data spanning 2001/2002 – 2005/2006 (Brownell et al., 2008). Many researchers and clinicians have discussed the origins for the increases observed in ASD prevalence, commenting on the evolution of diagnostic practices, childhood exposure to environmental changes, increased awareness of ASD symptoms and diagnosis of previously undetected cases (Nassar et al., 2009). An important component of measuring prevalence is the diagnostic reclassification of ASD that occurred in 2013 and will be discussed in further detail in Section 2.2.

2.2 Defining Autism Spectrum Disorder

Autism Spectrum Disorder is characterized as a condition where individuals experience difficulties in communication, responding and interacting in social situations and conversations, reading nonverbal communication and forming relationships that are appropriate for their age (American Psychiatric Association, 2013). These symptoms may be present from an early age and occur on a continuum with some individuals demonstrating mild expressions and others more severe. In the Diagnostic and Statistical Manual of Mental Disorders – IV (2000) (DSM-IV-TR) children could be diagnosed with one of four pervasive childhood developmental disorders: Autism disorder, childhood disintegrative disorder, Asperger's Disorder and Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS) (Mcpartland & Volkmar, 2012). These diagnoses were based on the three domains of impaired social interaction, abnormal

communication, and restricted and repetitive behaviours and interests. More recently the Diagnostic and Statistical Manual of Mental Disorders - 5 (DSM-5) (2013) has redefined ASD as impairments in the two domains of social communication and restricted/repetitive behaviours and interests. The DSM-5 uses a single diagnosis of Autism Spectrum Disorder (ASD), which includes all individuals with the previously named conditions, or allows for reassignment to another more appropriate diagnosis (American Psychiatric Association, 2013).

The recent revision of ASD defines the condition with two symptom clusters – impairments in social communication and restricted/repetitive behaviours. These two clusters replaced the previous three, through the combination of socialization and language deficits into the social communication domain (Matson, Hattier, & Williams, 2012; Sipes & Matson, 2014). There is no differentiation between verbal and nonverbal communication in this definition. Impairment of communication was determined to be an inherent deficit in socialization and therefore these domains were combined. Studies have since supported both the two (Sipes & Matson, 2014) and three factor definitions (Snow, Lecavalier, & Houts, 2009) using methods of factorial analyses of diagnostic tools such as the Modified Checklist for Autism in Toddlers (M-CHAT), Baby and Infant Screen for Autistic Traits (BISCUIT) and, the diagnostic standard for research, the Autism Diagnostic Interview-Revised (ADI-R). Despite this support for the new ASD definition, the DSM-5 diagnostic criteria have been criticized as being significantly more rigid than DMS-IV-TR, undermining the uniqueness of an Asperger's diagnosis and threatening access to services for these children (Matson 2012). However, the DSM-IV-TR criterion that children exhibit symptoms before age 3 has been removed, which will likely allow for a greater number of diagnoses among adolescents and adults.

The revised definition of ASD could potentially have a profound impact on the number of children that are diagnosed with ASD and therefore the prevalence rate. The new criteria have been criticized for sacrificing sensitivity to gain specificity and in response were tested by both proponents and detractors to determine reliability. The DSM-5 definition criteria have been field tested and found to have high reliability when compared to other pediatric ASD definitions (Frazier et al., 2012; Kaufmann, 2012). The diagnostic criteria have also been tested in four studies against those provided in DSM-IV-TR for ASD. These studies found that 30-45% of children, adolescents and adults who had been classified as having ASD by DSM-IV-TR no longer met the DSM-5 criteria (McPartland 2012, Matson, Belva 2012, Matson, Kozlowski 2012 and Worley, Matson 2012). Another study comparing ICD-10R (International Statistical Classification of Diseases and Related Health Problems 10th Revision), DSM-IV-TR and DSM-5 diagnostic criteria in a population of "intellectually able" adults in an ASD Diagnostic Clinic found that of those diagnosed with ASD with DSM-IV-TR criteria, only 78% also met DSM-5 ASD criteria (Wilson et al., 2013).

The inconsistencies observed between DSM-IV-TR and DSM-V criteria diagnoses should be considered along with the results of a national American study in 2007 that found 40% of children (aged 3-17) who had ever received an ASD diagnosis from a health-care provider no longer had that diagnosis at the time of a parent reported survey (Kogan et al., 2009). Another study found that more than 10% of children diagnosed with ASD at age 2 had "lost" this diagnosis at age 9 (Lord et al., 2006). The "loss" of diagnosis could also be attributed to convergent symptomology of co-occurring developmental or psychiatric conditions in early childhood. The revised DSM-5 definition may reduce the number of children "temporarily

diagnosed" with ASD in early childhood – that is, provide a more accurate diagnoses and therefore more accurate prevalence rates.

Changes in the diagnostic definition of ASD and the inconsistencies described above are likely to lead to changes in prevalence over time. In the coming years, it will be important to determine if there has been a marked change in prevalence rates and diagnoses and if diagnoses of ASD are more likely to persist through the life course for more individuals. Furthermore, it is not known when possible changes in prevalence could be detected at a population level, as diagnostic practices may change slowly, unpredictably, and unevenly across geographic regions. The current study was unable to address questions related to possible changes in prevalence caused by a diagnostic shift among children at a population level because medical and hospital diagnostic records were only considered up to early 2014. It is assumed that most practicing physicians had not fully integrated these diagnostic changes into their practices at this time, as the DSM-5 was published only the previous year.

2.2.1 Common Co-occurring Psychiatric Conditions

Psychiatric disorders are highly prevalent among children with ASD and diagnosis of comorbid conditions should consider overlapping symptoms and an individual's intellectual, communication and behaviour abilities (McGuire et al., 2016). A follow-up study among a subgroup of a population-based cohort of adolescents diagnosed with ASD found that 70% had at least one co-occurring psychiatric disorder (Simonoff et al., 2008). Some of the most common co-occurring conditions in children with ASD include attention-deficit/hyperactivity disorder (ADHD), anxiety disorder, obsessive-compulsive disorder (OCD), and oppositional defiant disorder (McGuire et al., 2016; Simonoff et al., 2008; Spencer et al., 2013). Some of

these disorders may include shared symptoms with ASD diagnostic criteria. The definitive behaviours in ASD of impaired social interaction and restricted and repetitive behaviour may also be observed among children with an anxiety disorder or OCD. Fetal Alcohol Spectrum Disorder (FASD), a condition not commonly found in children with ASD, has also been analyzed for shared symptoms with ASD, with results showing commonality in socially inappropriate behaviours and difficulty with peers (Bishop, Gahagan, & Lord, 2007). Furthermore, challenging behaviours that are the target of psychotropic medication use, such as aggression, irritability and self-injurious behaviour, may stem from a comorbid condition. There is currently little evidence to guide treatment and management of comorbid psychiatric disorders, with the exception of ADHD, in children with ASD (McGuire et al., 2016). A recently published pathway for managing self-injurious behaviour among individuals with ASD provides a psychopharmacological treatment pathway that accounts for the presence of common comorbid psychiatric conditions (Minshawi, Hurwitz, Morriss, & McDougle, 2015). This pathway suggests trials of psychotropic medications for the following conditions: anxiety disorder, OCD, depression, catatonia, bipolar disorder and psychotic disorder (Minshawi et al., 2015). ASD and the commonly occurring comorbid conditions discussed here are often addressed and treated through many multidisciplinary interventions that include the integration of psychological, pharmacological and behavioural treatment options.

2.3 Current Treatments for Symptoms of ASD

Children diagnosed with ASD and treated within the medical model of autism, which considers ASD as a series of symptoms or deficits to be managed, often experience behavioural

therapies and medical interventions intended to help them develop skills, learn communication strategies and to assist with diminishing challenging behaviours. The types of treatments available may be categorized into several broad categories such as biomedical, behavioural, communication, and sensory, among others. Some of these methods have been shown to help individuals diagnosed with ASD, enabling them to express themselves better and to engage with their environment. Although some options have been documented as effective, others have little or no evidence to support utilization (Matson, Adams, Williams, & Rieske, 2013; Miller, Schreck, Mulick, & Butter, 2012). The type of intervention that has been found to be the most successful for some individuals is early intensive behavioural intervention (EIBI) methods (Matson & Konst, 2013). Recent reviews of EIBI programs have repeatedly shown the effectiveness of this method for children to gain and improve skills (Dawson & Burner, 2011; Reichow, Barton, Boyd, & Hume, 2012; Warren et al., 2011). One review found that EIBI had an impact on improving adaptive behaviour, communication, socialization and daily living skills (Reichow et al., 2012). EIBIs are often provided in a comprehensive and intensive manner with support from many types of professionals and clinicians who can monitor development and skill acquisition (Matson & Konst, 2013). In Manitoba, a form of EIBI called Applied Behaviour Analysis (ABA) is available to children through St.Amant, a service provider for individuals with developmental disabilities and autism in Winnipeg (http://stamant.ca/programs/autism-services). Children in Manitoba may have access to up to three years of pre-school ABA services and three years of support to transition to school programming through the St.Amant ABA program (http://www.gov.mb.ca/fs/thrive/abanalysis.html). This method tends to be the

costliest and most difficult to implement for many children due to accessibility issues and a lack of quality, skilled providers.

2.3.1 Medication Use

Psychotropic medications are provided as a medical intervention for children with ASD as an option for symptom management to control such symptoms as anxiety, irritability, aggression, stereotypic behaviours and other difficult and challenging behaviours (Bryson, Rogers, & Fombonne, 2003; McPheeters et al., 2011). Psychotropic medications are often used with children in difficult and urgent situations where there is pressure to act quickly to resolve challenging symptoms (Paris, 2010). These medications may also relate to co-occurring mental disorders, as described above. As such, several classes of medications are used to manage these symptoms including antipsychotics, ADHD medications, antidepressants, neuroleptics and stimulants (McPheeters et al., 2011; Rosenberg et al., 2010). While these medications are often used in combination, there have been few studies to show either safety or effectiveness of these regimens in children with ASD (Logan et al., 2012; Rosenberg et al., 2010; Spencer et al., 2013). In fact, there is currently very little published on the long-term safety of any of these medications for children with ASD (Pringsheim et al., 2011). One of the few studies examining adverse events for a period longer than 6 months, reported developments of excessive weight gain (mean increase of 58% from baseline), and atypical involuntary muscle contractions such as tardive dyskinesia, akathisia, and tremor that are associated with medication use (Hellings, Cardona, & Schroeder, 2010). Sedation is another commonly experienced side effect, one which could reduce a child's ability to interact with his/her environment (Bryson et al., 2003; Pringsheim et al., 2011).

Presently, there is a limited amount of literature that supports the use of psychotropic medications for children with ASD. In a systematic review completed in 2011, 18 unique studies were found that addressed the effectiveness, safety and impact of medication use and interventions in managing challenging behaviour and other symptoms for children with ASD (McPheeters et al., 2011). These studies tested the use of antipsychotic medications, serotonin reuptake inhibitor (SRI) medications and psychostimulant medications; 10 of the 18 studies were randomized controlled trials (RCT). The antipsychotics risperidone, aripiprazole or haloperidol with added cyproheptadine (a first-generation antihistamine) were tested in 9 of the 18 studies, including 2 prospective case series and 7 RCTs – of which 2 were considered to be good quality. Most of the RCTs used a behaviour or symptom rating scale as the outcome and measured all child participants at baseline and at the study end period, some of these were parent-reported from Aberrant Behaviour Checklist (ABC) subscales. Five of the RCT trials reported a significant, or close to significant, mean decrease in rating scale score for challenging behaviour, hyperactivity or repetitive behaviour in the treatment arm when compared to the placebo or non-treatment arm of the trial. Two of the RCTs did not report specific rating scores for challenging behaviour, but instead found that there were fewer children whose behaviour relapsed after drug-discontinuation in the treatment arm compared to placebo arm. The resulting strength of evidence for use was considered from this review to be moderate for risperidone, high for aripiprazole and insufficient for cyproheptadine (McPheeters et al., 2011). SRIs, including citalopram and fluoxetine, were tested in 2 RCTs, 1 prospective case series and 2 retrospective case series. These studies resulted in no significant difference or no clinically significant difference of reduced challenging behaviours among children receiving treatment

and therefore the strength of evidence for SRIs was considered insufficient. Psychostimulants were reviewed through 1 RCT and 3 retrospective case series which also resulted in insufficient evidence to support use for reducing hyperactivity. The RCT for psychostimulants did find an improvement in hyperactivity and noncompliance, but an increase in challenging behaviours and loss of appetite. Overall, this review found that while there were positive outcomes for children in the medication arm of the RCTs, there was little evidence to support medication use in children with ASD. Furthermore, some of the children also experienced significant adverse events including weight gain, drowsiness or sedation and involuntary muscle movements that should be considered when prescribing these medications As a result, evidence for effectiveness is only available from this review for two second-generation antipsychotic medications, risperidone and aripiprazole (McPheeters et al., 2011).

There are current Canadian guidelines for monitoring the safety of second-generation antipsychotics for children and adolescents with mental disorders (Pringsheim et al., 2011). Despite this, current published practice parameters to guide the treatment of children with ASD do not provide specific guidelines for use of psychotropic medications, as these medications are not approved for use among this sub-population (Evans & Morris, 2011; Volkmar et al., 2014). These parameters, however, do suggest that when psychotropic medications are used, their use should be done cautiously and in the context of regular monitoring (Evans & Morris, 2011). It is also important to note that only one antipsychotic medication is approved by Health Canada for use in individuals under the age of 18 and therefore prescription of these medications to children diagnosed with ASD occurs “off label” in Canada (Health Canada, 2015; Pringsheim et al., 2011) - that is for purposes that are not included in the current Health Canada

approval. Aripiprazole is approved for use in Canada among children 13-years-old or older, to treat manic-depressive disorder and schizophrenia (Health Canada, 2015). The Food and Drug Administration (FDA) in the United States has approved the use of risperidone and aripiprazole in children for reducing irritability, outbursts and aggression, that are associated with ASD (Scahill et al., 2007; Volkmar et al., 2014). Despite governmental approval, the scientific literature described above does not strongly support the use of psychotropic medication for children with ASD. Furthermore, many of the available guidelines and reviews include precautions regarding the likelihood of, and the importance of continued monitoring for, neurological and metabolic adverse events (Bryson et al., 2003; Pringsheim et al., 2011; Volkmar et al., 2014). Current recommendations state that these pharmaceuticals should only be used once other strategies have been exhausted or in combination with psychosocial strategies to improve a child's ability to participate in activities and interventions (Bryson et al., 2003; Volkmar et al., 2014).

International examples provide a useful basis for understanding expected medication prescription prevalence rates in Manitoba. The percent of children and adolescents with ASD who have prescriptions for psychotropic medication range from 10% to 65% based on studies from Australia, Germany and the United States (Bachmann, Manthey, Kamp-Becker, Glaeske, & Hoffmann, 2013; Mandell et al., 2008; McGillivray & McCabe, 2004; Schubart, Camacho, & Leslie, 2013). The lowest prevalence is from a study in the Australian state of Victoria where the use of "drugs to restrain the behavior of individuals with intellectual disability" is heavily restricted to avoid indiscriminate use (McGillivray & McCabe, 2004).The highest prevalence of

65% was found in a population of American children and adolescents with ASD from 41 states who were enrolled in a Medicaid program (Schubart et al., 2013).

2.4 Conceptual Framework

The social, demographic and other variables used in this study were chosen to describe the population of children with ASD in acknowledgement of the many factors that can influence health status and accessibility of health care for an individual, particularly one with a disability. Environmental factors can act on different levels to influence diagnostic prevalence and treatment prevalence, options and preferences. These levels of influence are demonstrated in Figure 1, a conceptual framework based on the *Total Environment Assessment Model for Early Child Development (TEAM-ECD) Schematic* (Siddiqi, Irwin, & Hertzman, 2007). While each layer and sphere of influence included in the TEAM-ECD framework would be important to explore in the context of this study and the research questions proposed, the framework has been simplified to include the factors that were considered in this project and the widest sphere of influence.

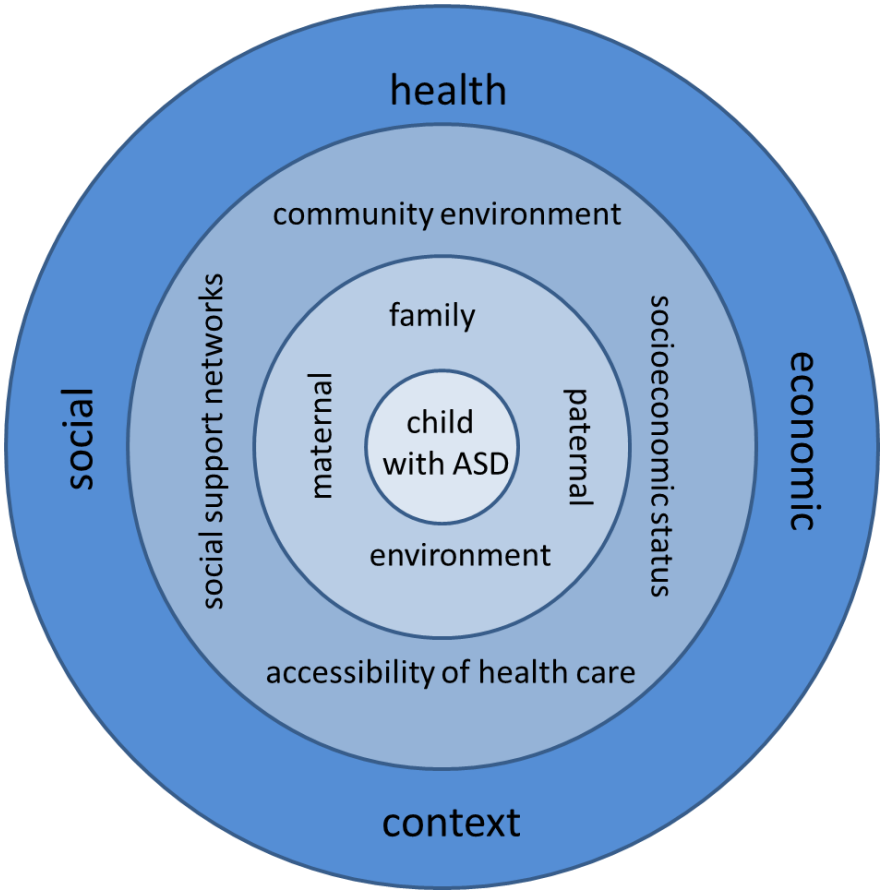

Figure 1: Conceptual framework of factors that may influence the prevalence of psychotropic medication prescriptions in the population of children with ASD in Manitoba (adapted from Siddiqi, Irwin, & Hertzman, 2007).

Child demographics, family environment influences, and health and education experiences were considered in this study for children in Manitoba and are represented in the three inner concentric circles. A child's individual characteristics such as age, sex and comorbid psychiatric conditions, are likely to have the greatest influence on whether they have a psychotropic medication. Secondly, some of the closest external influences on an individual are family and household factors, such as maternal age and presence of a sibling with ASD. These factors may additionally be influenced by environmental factors that directly interact with the family, such as socioeconomic status, the social supports that a family has access to, including

education and behavioural supports, and the community environment. Direct environmental factors that may influence whether a child with ASD receives a psychotropic medication could include the availability of behavioural intervention programs in a health region, attitudes of medical and education professionals and social acceptance of individuals with disabilities within the community. Family and social support environment can also be influenced by societal expectations of individuals with ASD. These attitudes could impact the types of treatment and intervention options that are available to children in education and health settings. Other broader influences that may impact the prevalence of psychotropic medications can include accessibility and affordability of health care, the social context and dialogue regarding disability and child behaviour, and economic factors which can influence government spending on social programs.

Community social acceptance and tolerance of individuals with disabilities and the social dialogue on disability and child behaviour may be associated with psychotropic medication use. Psychotropic medications are typically targeted at managing challenging behaviours in individuals with developmental disabilities, and a level of social inclusion and tolerance towards these behaviours may influence the prevalence and intensity of medication use. The effect of many of these factors on the use of psychotropic medications by a child with ASD is very difficult to determine using administrative data, and will not necessarily be measured by this study. However, it is important to consider and acknowledge the wide range of factors that may be influencing the prevalence rates that will be measured through this study.

This study was completed within the context of a difference-not-deficit, biocultural approach to intellectual and developmental disabilities. The biocultural perspective of disability recognizes that a defined disability consists of a complex interaction between culture and biology (Davis & Morris, 2007); that a condition is both fundamentally rooted in biology and is culturally defined. This contextual approach was used both to conceptualize disability and to consider medication use for the purpose of managing symptoms and challenging behaviour. Furthermore, this approach should be acknowledged as a consideration within the author's interpretation of the interactions and findings presented in this study.

2.5 Factors that Influence ASD Prevalence, Early Childhood Development and Health System Use

The following factors have been identified in the literature as either associated with variations in ASD population prevalence, early childhood development, interaction with service providers and intervention programs or prescriptions of psychotropic medications. These factors are some of those that were considered as independent variables within this study.

2.5.1 Health region of residence and socioeconomic status

Socioeconomic status (SES) and relative income inequality in geographic areas have been shown to be associated with population-level differences in health status (Berkman & Kawachi, 2000). Health status tends to be better in areas with higher SES and areas of more equal distribution of resources. The direct association of SES with ASD prevalence, however, has not been conclusively established, with multiple research papers finding contradictory results as discussed below.

The association between SES and ASD has been investigated in a number of studies based on American sub-populations which reported rates of autism that were positively associated with SES; that is, children in high SES groups were more likely to show symptoms of and be diagnosed with ASD (Durkin et al., 2010; Thomas et al., 2012). For instance, one study looking at ASD prevalence and SES in 12 American states found that there was a "dose-response" relationship between increasing SES and prevalence rates (Durkin et al., 2010). This study included both children who had and had not been diagnosed with ASD, but met criteria in health and education based information in order to reduce the effect of limited access to diagnostic services on prevalence. Additional population-based research has not shown this trend. A cohort study from Denmark, where there is universal health care, found that while prenatal environmental factors and parental psychopathology were associated with an increased risk of ASD diagnosis, there was no link with SES (Larsson et al., 2005). This study suggested that possible associations found in other studies could be explained by unaccounted correlations of SES and other early childhood health outcomes such as low birth weight and early gestational age (Larsson et al., 2005).

Previous research in Manitoba, Canada found that area-level income was not associated with prevalence of ASD in urban populations (Brownell et al., 2008). However, in rural areas, residence in a higher income area was associated with higher prevalence compared to the lowest rural income area. The study authors suggested that this difference may be related to unequal access to diagnostic services in rural areas (Brownell et al., 2008). Additionally, previous research in Manitoba concluded that there were regional variations in prescription use (Kozyrskyj, 2002). This could be considered as a combination of region of residence and the SES

of the area which then may be associated with differing levels of ASD prevalence and perhaps also treatment of ASD.

2.5.2 Age at diagnosis and age at study conclusion

Early identification and diagnosis of ASD has often been discussed as an important factor in the developmental trajectory of a child with ASD, as earlier exposure to education and behavioural programs can lead to better outcomes in some children (Barbaro & Dissanayake, 2009). Age at diagnosis can also vary greatly within a population and therefore have an effect on the prevalence rate in that population. If age at diagnosis and initial interactions with service providers are associated with access to more intervention and treatment options, then it may also influence whether a child receives a psychotropic medication. While there are many factors that are likely to contribute to the age at which a child is diagnosed with ASD (Mandell, Novak, & Zubritsky, 2005), a multi-jurisdictional Canadian study was unable to find consistent factors that could explain variations in age at diagnosis (Coo et al., 2012).

Age at an index date or study conclusion has previously been used to describe the population of children with ASD and psychotropic pharmacological treatment. These studies have found that older children have an increased prevalence of psychotropic medication use (Bachmann et al., 2013; McGillivray & McCabe, 2004; Spencer et al., 2013).

2.5.3 Participation in a behavioural intervention and special education funding

While early exposure to behavioural interventions for children with ASD has been suggested to improve functional outcomes, a systematic review from 2008 of interventions for children with ASD found only conflicting evidence of improvement (Ospina et al., 2008). This

review included many trials and programs directed towards preschool-aged or young children which found varying degrees of success among the wide variety of interventions directed at improving behaviour, social and communication skills (Ospina et al., 2008). Increased use of psychotropic medications may be associated with participation in a behavioural intervention or special education funding, in accordance with published symptom management strategies and practice parameters. Some of these guidelines suggest that psychotropic medications may be used in conjunction with a non-medical intervention in order to improve a child's engagement or ability to focus when involved with that intervention (Bryson et al., 2003; Volkmar et al., 2014).

2.5.4 Maternal age at birth of index child

Parental age has been found to be a risk factor for a number of developmental disabilities including ASD. Advanced parental age has been suggested to have a protective effect for some social and educational outcomes; however, it has also been associated with an increased risk for congenital anomalies. This factor is often considered in studies determining the influence of prenatal factors on the risk for ASD. Despite the number of studies that have attempted to determine the influence of advancing maternal or paternal age, the relationship has not been conclusively defined. A Swedish population-based cohort study found that advancing maternal age was associated with increased risk for ASD, however, only after the age of 30 (Idring et al., 2014). A national birth cohort study from Finland also attempted to determine the relationship between parental age and risk of ASD (Lampi et al. 2013). Maternal age was found to be associated with an increased risk of Asperger's, at age 35 or greater, and PDD, at age 40 and greater and age 19 and younger (Lampi et al., 2013). Another case-control

study from the Netherlands found no significant difference between maternal age greater than 35 years between the group of children with ASD and a control group (Visser et al. 2013). Maternal age has therefore been a complex risk factor for ASD showing great variation.

2.5.5 Maternal mental disorder history

Parental mental disorder history is a complex indicator that has been found to be associated with an increased risk of ASD diagnosis (Larsson et al., 2005), though the direct impact on prevalence rates is not well understood. A review of the prevalence of major mood disorders in families of individuals diagnosed with ASD found that there was a difference in family history between those diagnosed with ASD that show intellectual disability, or "lower functioning", and those without (DeLong, 2004). This review also found that individuals with ASD who demonstrated intellectual disabilities and fewer functional skills were more likely to have a family history of rigid personality and a "broader autistic phenotype" without a mood disorder (DeLong, 2004). These results have contributed to guiding genetic research meant to further elucidate the underlying biological mechanisms of ASD.

Maternal mental disorder history is considered in this study because of the possible underlying genetic and prenatal or early life environmental influences. Information on mothers and maternal linkages are more readily available within the Manitoba administrative data than paternal linkage, and for this reason, paternal disorders were not examined.

The medical or psychological treatment of children is dependent on their caregivers' decision-making. Children are not able to provide informed consent to medication use or diagnostic services and therefore pharmacological management occurs in relation to, and in collaboration with, family and caregivers (Carlon, Carter, & Stephenson, 2013; Paris, 2010).

Patterns of medical care use for children have been shown to be strongly associated with maternal medical care use, particularly for mental health care (Minkovitz, O'Campo, Chen, & Grason, 2002). Family and parental psychopathology have also been found to be associated with a decrease in the parents' threshold for identifying problem behaviour in their child, however, it was not associated with a change in likelihood of seeking mental health services (Verhulst & van der Ende, 1997).

Although maternal mental disorder history has not been directly linked to psychotropic medication use in children with ASD, this variable was included as a likely family factor that can influence mental health services use based on the interactions between maternal mental health and child mental health service use.

2.5.6 Diagnosed co-occurring psychiatric conditions

Diagnosed co-occurring psychiatric conditions were discussed in section 2.2.1 Common Co-occurring Psychiatric Condition, and based on this literature are expected to be strongly associated with psychotropic medication use among children with ASD.

Chapter 3. Materials and Methodology

3.1 Data Source

This study used a pediatric population from the Manitoba Population Health Research Data Repository (Data Repository) housed at the Manitoba Centre for Health Policy, University of Manitoba. The Data Repository includes administrative, survey, clinical and registry databases, many of which are population-based. All databases contain de-identified data (containing no names or addresses) that can be linked at the individual level through a

scrambled identifier. These data can only be linked for research purposes for approved research projects. The datasets used in this study were medical claims (physician visits), hospital admissions, the population registry (for demographic information), public-use census files (for area-level socioeconomic status), pharmaceutical claims, educational enrolment (for special education funding), clinical data from the Manitoba Adolescent Treatment Centre (MATC) and case file information from Child and Family Services (CFS). More information and descriptions of these databases is available on the MCHP webpage (http://umanitoba.ca/centres/mchp). Detailed descriptions of the variables that were used, and how they were defined follows. Approvals for this study were obtained from each agency that provided data, including Manitoba Health, Seniors and Active Living, Manitoba Education and Training, Winnipeg Regional Health Authority, Manitoba Families and MATC. Ethical approval was obtained from the University of Manitoba Health Research Ethics Board (HREB) (ethics #: H2015:005) and privacy approval from the Health Information Privacy Committee (HIPC) (HIPC No. 2014/2015 – 40) of Manitoba Health, Seniors and Active Living.

3.2 Study Population

The population used in this retrospective cohort study included all children aged 0-18 years who were born in the province of Manitoba, Canada on or after January 1st, 1995 and were eligible for provincial health care coverage for a period of at least two years between 1995 and 2014 (n=255,214). Individuals were included in the cohort of children with prevalent ASD (n=3,234) when there was 1 or more inpatient or outpatient diagnosis of ASD (International Classification of Diseases, 9th Revision (ICD-9-CM) diagnosis code 299 or ICD-10

diagnosis code F84), or if the child was identified as "ASD" within the Manitoba Education Special Needs data file. This definition has been used in previous studies of ASD using the Manitoba Data Repository, and other studies of medication use in a pediatric population (Brownell et al., 2008; House et al., 2015). Approximately 35% of children identified as ASD in this cohort had only one health (n= 876) or education (n= 281) claim for ASD. Children without a claim for ASD or any other intellectual disability, including Fetal Alcohol Spectrum Disorder (see Appendix A. for detailed exclusion criteria), comprised the general population cohort used for comparison (n=245,897).

3.3 Demographic, Health, Education and Family Environment Variables

Children in the ASD and general population cohorts were described using demographic variables (sex, age, health regions of residence, area-level socioeconomic status), health and education variables (age at diagnosis, receipt of special education funding, diagnosed psychiatric conditions, participation in programming at MATC and prescription claims) and family environment variables (sibling diagnosed with ASD, age of mother at birth of index child, maternal mental health history and experience in the care of Child and Family Services (CFS)).

3.3.1 Child Demographic Variables

Sex and age were obtained from the Manitoba Health Registry data which contain demographic information. Health region of residence was determined using a method of assigning regions based on the municipal codes assigned by Manitoba Health. The recorded residence location on March 31st 2014, or earlier if the individual left the province before this date, was used to assign a health region. Residence location at date of diagnosis was also

considered for use, however, some children may have moved after their diagnosis was made and before medication use began; therefore, a common date was chosen. The five current Manitoba health regions of Northern, Interlake-Eastern, Prairie Mountain, Winnipeg and Southern were used in this study.

Area-level socioeconomic status was measured in this study using the Socioeconomic Factor Index – Version 2 (SEFI-2) (Chateau, Metge, Prior, & Soodeen, 2012). This index is a score based on the following non-medical determinants of health variables available from Canadian Census data: average household income, percent of single parent households, unemployment rate and high school education rate. This continuous variable was used as a predictor variable and in an interaction term with health region of residence to account for possible regional variations of psychotropic medication use among children in Manitoba.

3.3.2 Health and Education Variables

The age at diagnosis for children with ASD was determined from the dataset which identifies the diagnosis claim, either medical or hospital. Age at diagnosis was considered from birth so as to have a completely inclusive lower limit; however, more than half of the ASD diagnoses in this sample occurred between ages 2 and 4 years inclusive (n=1614). Children (n=281) who were only identified as ASD through the special education funding data were not assigned an age at diagnosis.

Special education funding for ASD was determined from the Manitoba Education Enrollment data file using the variable of special needs status for only those children that received special education funding. This variable was used both to determine which children

were included in the ASD cohort and as a way to describe children in the ASD cohort, as not all children with diagnosed ASD received special education funding. Behavioural intervention information was available for some children using data from MATC. Children with ASD were included as participating in MATC programming if they had at least one program visit. Use of other behavioural interventions through private clinics, St.Amant Centre, or home-based interventions cannot be determined through the data that are currently available in the Repository.

Diagnosed psychiatric conditions (ICD-9-CM diagnosis codes 290-319 & V17) for all children were determined using physician visits and hospitalizations over the entire study period. ICD-10 diagnostic codes for psychiatric conditions were converted to ICD-9-CM codes using conversion files provided by MCHP. Ten categories were selected from these conditions to be analyzed for this study: the eight most commonly diagnosed psychiatric conditions in this population, excluding ASD (ICD-9 code 299); one less common disorder specific to childhood (ICD-9 code 313); and the remaining conditions (grouped as "other"). The categories used and codes included in each are described in Table 3.1. Children were included in these categories when there was 1 or more diagnostic claim in the described data.

Table 3.1: ICD-9-CM codes used to determine whether children had been diagnosed with psychiatric conditions.

Diagnosis Category	**Codes included**
Affective psychoses	296
Adjustment reaction (including depressive reaction)	309
Depressive disorder – not otherwise classified	311
Disturbance of conduct not elsewhere classified	312
Disturbance of emotions specific to childhood and adolescence	313
Hyperkinetic syndrome of childhood	314
Neurotic Disorders (including anxiety, phobic and obsessive compulsive disorders)	300

Special Symptoms not elsewhere classified	307
Specific delays in development	315
Other	290-295, 297, 298, 301-306, 308, 310, 316-319 and V17

3.3.3 Family Environment Variables

Siblings were linked through the biological mother to determine if siblings of the index child were diagnosed with ASD. Maternal and sibling data from the Manitoba Health Registry from 1984 to 2014 were used to establish family connection. Presence of at least 1 sibling diagnosed with ASD was determined for all children in the ASD and general population cohorts, using the definition of ASD used for the ASD cohort.

Maternal age at birth of index child was determined using Manitoba Health Registry data and compared across 4 age groups (≤19 years, 20-29 years, 30-39 years, and 40-49 years). There were no mothers found to be ≥50 years at the birth of the child in the study cohort. More than 98% of children in both cohorts were linked with a biological mother through the administrative data. Children with no linked biological mother were not included in the predictive modelling samples. Demographic characteristics describing this group of children can be found in Appendix B.

Maternal mental disorder history was determined using the same diagnostic codes and data sources described above for the cohort children. Medical and hospital claims from 1984 to 2014 were used for maternal mental disorder history. Diagnostic information regarding maternal mental disorder history was obtained from time periods both before and after birth of the index child and was not considered in relation to when the birth occurred. Maternal mental

disorder severity was categorized as '1' if they had ever received at least 2 psychiatric condition diagnoses in any 3-year period, '2' for at least 2 psychiatric condition diagnoses in any 3-year period with at least 1 in hospital and '0' for less than 2 psychiatric condition diagnoses in any 3-year period.

Interaction with CFS was established for this study if the child was taken into care of CFS at any point during the study period. This does not include children whose families were receiving support services from CFS, but only those who were removed from parental care. Although any involvement with CFS has been observed to impact health outcomes for children (Brownell et al., 2008), this study only considered the characteristic of being taken into care by CFS.

3.4 Prescription Claims

Outpatient psychotropic prescription claims for all children within the general and ASD cohort populations were obtained from the Drug Programs Information Network (DPIN) data. Prescription use was categorized and measured in five ways in this study: (1) category of psychotropic medications filled, (2) age at first prescription, (3) polypharmacy of filled psychotropic prescriptions by drug class, (4) number of changes in medication type, and (5) defined daily dose (DDD). These measures were compared between the ASD and general population cohorts. The final two measures were calculated only for prescriptions filled between April 1st, 2013 and March 31st 2014 for children who were in the province of Manitoba during this entire fiscal year period.

A psychotropic prescription was considered filled and used if there was at least one prescription claim in the DPIN database (Alessi-Severini, Biscontri, Collins, Sareen, & Enns, 2012; Spencer et al., 2013). The following classes of prescription medications were considered: antipsychotics, (ex. risperidone, aripiprazole, haloperidol), antidepressants, anticonvulsants/antiepileptics, anxiolytics, psychostimulants, antiparkinson, anticholinergic medications and naltrexone. Medications are classified through the Anatomical Therapeutic Chemical (ATC) Classification System codes. This system is managed by the World Health Organization Collaboration Centre for Drug Statistics Methodology (WHOCC) and classifies drugs based on where (the organ or system) and how (the chemical, therapeutic and pharmacological properties) the active ingredients act in the body. All medications considered in this study were classified as an 'N – Nervous System' type chemical. Table 3.2 lists the ATC codes that are included in each category. All psychotropic medications filled for children in the ASD and general population cohorts were categorized into these categories. Hydroxyzine, which can be used for both anxiety disorders and allergic conditions, was prescribed to 1.95% of children with ASD and 4.49% of children in the general population cohort who had a psychotropic medication prescription. Because the objective of this analyses was to examine psychotropic meds used for mental disorders/psychiatrics conditions, any hydroxyzine prescription that was prescribed by a physician with an allergy/immunology specialty was excluded.

Table 3.2. Categories of psychotropic medications used in this study and the ATC codes used to define each category.

Category	ATC Code		Category	ATC Code
Antipsychotics	N05AA		Antiepileptics	N03AB
	N05AB			N03AD
	N05AC			N03AE
	N05AD			N03AF
	N05AE			N03AG
	N05AG			N03AX
	N05AH		Antidepressants	N06AA
	N05AN			N06AB
	N05AX			N06AX
Antiparkinsons	N04BA		Anxiolytics	N05BA
	N04BC			N05BB
Anticholinergics	N04AA			N05BE
	N04AC		Psychostimulants	N06BA
Naltrexone	N07BB			

The use of medications from more than one pharmaceutical class is considered polypharmacy. Polypharmacy in this study was considered in terms of the classes of psychotropic medications previously described (see Table 3.2.) and was defined as the use of medications from more than one class. Multiclass medication use was defined as one or more filled prescription per class with at least a 30-day supply of each medication type within one year. Polypharmacy in children has been defined in a number of ways in the literature with no definitive description of the number of medications, length of supply or overlap of days (Comer, Olfson, & Mojtabai, 2010). Polypharmacy, or multiclass medication episodes, have been defined in populations of children with psychotropic medications as overlapping medication fills from at least 2 classes for at least 14 or 30 days (Logan et al., 2015; Spencer et al., 2013). The current study used a broader definition of medication use that considered multiclass use within one year. Similar outcomes were observed between the cohorts of children with and without ASD in

this study when less stringent definitions (shorter supply, over more than 1 year) for multiclass use were considered to match demographic comparison categories.

Age at first prescription was determined using the Manitoba Health Registry recorded birthdate and the recorded date of the first psychotropic medication prescription that was filled. Children were compared across 4 age groups: 0-4 years, 5-9 years, 10-14 years and ≥ 15 years old.

The number of medications, defined as a change at the 4th level of ATC classification, in the last year of the study period for both the ASD and general population cohort was counted. Medications that were used concurrently were also counted as "changes". This level of classification was used to distinguish inter-class prescription changes (WHO Collaborating Centre for Drug Statistics Methodology, 2011). It does not, however, account for changes in dose or medication format. These types of changes can be counted using the Drug Identification Number (DIN), however, this was not used in the current study because DIN codes are also assigned for medications of the same dose and type from different manufacturers – which would not appropriately describe medication changes (Health Canada, 2009).

Defined daily dose (DDD) is a method used to analyze and compare the use of different classes of medication where dose can not be directly compared (WHO Collaborating Centre for Drug Statistics Methodology, 2015b). DDD implies a maintenance dose when used for the main indicated purpose of the drug and has been validated for use with adults, though not in children. Psychotropic medication use in children may be for non-indicated purposes and

therefore the DDD may not provide an accurate measure of the dose intensity in this population. However, this study is using DDD as a comparison between two groups of children and not as a measure of appropriate medication use. As such, the limitations of using this as a measure of prescription medication use intensity are equally applied to both comparator groups and allow for a comparison of dose intensity in reference to each other.

3.5 Statistical Analysis

Chi-square and t-tests were used to determine the similarity between comparator groups of children, both between the general population and ASD cohort and within the ASD cohort. The chi-square goodness-of-fit test was used to determine if the proportions of a categorical variable in one cohort differed from those observed in the comparator cohort. The null hypothesis considered in this test is that the proportions observed in each cohort are the same. The p-value in this case is therefore the probability that the observed proportions are different due to chance.

T-tests were used to compare the difference in group means for continuous variables such as SEFI-2 scores by region, and count variables such as DDD, number of medication changes, and age. The p-value reported for these statistical tests represents the probability of the t-value (calculated test statistic) being equal or greater than the calculated value under a null hypothesis, or given no difference in means. A p-value less than 0.05 therefore represents a less than 5% probability that the difference in means is equal to 0 in two independent samples. Equal variance was assumed for the comparator groups if the variance of one group was less than twice as large as the comparator group. In cases where the variances were very different

and determined to be unequal, the Wilcoxon Rank Sum test was used to determine differences. Ordinal scaled response variables with non-normally distributed values were also tested using a Wilcoxon Rank Sum test to determine similarity between comparator groups (Stokes, Davis, & Koch, 2000). This test was used for variables such maternal mental health severity, number of mental health conditions, number of medication types and age groups.

Logistic regression analysis was used to establish the relationship between the descriptive independent variables and having ever had a prescription for a psychotropic medication, the response variable, among children with ASD. Univariate analysis was first used to asses the significance of each covariate to the outcome variable through 95% confidence intervals. Multi-level class variables that were not significant at every level were collapsed into fewer levels. All variables identified as significant in previous literature were included in the multivariable analysis. Sex and age were included in every model to adjust for variations in the two populations.

A zero-inflated negative binomial regression model was used to consider the relationship between the descriptive independent variables and the count variables of number of medication types and number of DDD in the final year of the study. The frequency distribution of these response variables fit a negative binomial distribution and the variance of each response variable was greater than the respective mean. A zero-inflated negative binomial model accounts for a frequency distribution heavily skewed towards zero (UCLA: Statistical Consulting Group). For these outcomes, the negative binomial distribution was caused by both the large number of zero responses (no medication use) and low medication use in most of the population. Furthermore, a zero-inflated regression model was appropriate to use in this

population cohort because it accounts for the multiple possible causes for a large proportion of zero-values. In this study, the excessive number of zeros in the response variables resulted from those children who did not receive a psychotropic medication in the last year of the study. This may represent both children who do not need psychotropic medications and those that do need psychotropic medications but did not use them.

In this model, the psychotropic medication use in the last year of the study for all children in the general population and ASD cohort were considered. Over 95% of children did not have a psychotropic medication prescribed that year and therefore over 95% of the response outcome values were equal to zero. Children with no medication use in the last year were included in this analysis to account for all levels of medication use intensity. Furthermore, while most children with a psychotropic medication prescription had low levels of use, such as few or no medication changes or a low DDD, a small number of children had high levels of use including many changes in medications and higher DDD.

Parameter estimates, or regression coefficients, calculated from a zero-inflated negative binomial regression model were exponentiated to calculate a rate ratio per person year. The rate ratio represents the predicted influence on the dependent variable of a one-unit change in the independent variable while all other variables in the model remain constant.

Chapter 4: Results

The purpose of this research was to determine the prevalence of ASD for children and youths in Manitoba and the psychotropic medication prescriptions for this population as outlined in the research questions.

4.1 Prevalence of Autism Spectrum Disorder

The population of children used for this study consisted of 249,131 children born in Manitoba between January 1st 1995 and March 31st 2014 who lived in the province for at least two years and were not diagnosed during this time with a developmental disability (including FASD) other than ASD. This population consists of 3,234 children diagnosed with ASD and 245,897 children with no diagnosed developmental disability. The prevalence of ASD among children aged 0-14 years old who lived in Manitoba for at least two years between April 1st, 2009 to March 31st 2014 was 2,346 from a total population of 194,277. This is approximately 1.2% of the population – or 120.8 children diagnosed with ASD per 10,000 children in Manitoba, or 1 in every 83 children.

4.2 Prevalence of Psychotropic Medication use in children with ASD

Of the 3,234 children with ASD, 1,578 (48.79%) filled at least one prescription for a psychotropic medication. Over 90% of these children were prescribed at least one psychotropic medication with a minimum 30-day supply during one year of the study. Approximately 50% of children prescribed a psychotropic medication in this study experienced polypharmacy, that is at least one prescription, with a minimum 30-day supply, from two or more medication classes

in one year. Less than 15% of the general population of children had at least one psychotropic medication during the study period (30,465 or 12.39%).

4.3 Population Characteristics of Children with ASD

Results pertaining to research question 3 will be answered in the following three sections: 4.3 (question 3.a), 4.4 (question 3.b) and 4.5 (question 3.c). The following tables show individual demographic, health and education and family environment characteristics of children in the ASD population compared to children in the general population cohort. Reported p-values were calculated to determine similarity between the two comparator groups.

4.3.1 Demographics

As shown in Table 4.1, children with ASD differ from the general population of children in frequency distribution of sex (males 79.9% vs 50.6%, p-value < 0.0001), age and health region of residence. There is a greater proportion of children over 10 years of age in the ASD cohort than in the general population cohort. Almost 60% of children in the ASD cohort received the first ASD diagnosis before age 5 (Table 4.2). More children with ASD live in Winnipeg than would be expected from the general population cohort (63.2% vs 49.0%, p < 0.0001). Comparison of SEFI-2 between children in the ASD and general population cohorts was not significantly different (0.011 vs 0.065, p=0.6741, not shown in table). However, there were significant differences between groups when considering the SEFI-2 mean scores by region. Children with ASD in the Northern health region had lower mean SEFI-2 scores compared to the general population cohort (0.84 vs 1.39, p<0.0001), indicating that they were more likely to live in areas with more

favourable socioeconomic conditions. The opposite was true in the Southern (-0.12 vs -0.19, p=0.0045) and Winnipeg (-0.06 vs -0.12, p=0.0003) health regions, where children with ASD were more likely to live in areas with less favourable socioeconomic conditions.

Table 4.1: Child demographic variables of children in the ASD and general population cohorts (1995-2014).

	Total	**ASD Cohort**	**General Cohort**	
N	249131	3234	245897	
	Count (%)	**Count (%)**	**Count (%)**	p-value
Sex				
Male	127120 (51.03)	2585 (79.93)	124535 (50.65)	<0.0001
Female	122011 (48.97)	649 (20.07)	121362 (49.35)	
Age in 2014				
0 - 4 years	56135 (22.53)	373 (11.53)	55762 (22.68)	<0.0001
5 - 9 years	69142 (27.75)	893 (27.61)	68249 (27.76)	
10 - 14 years	65059 (26.11)	1080 (33.40)	63979 (26.02)	
15 and above	58794 (23.60)	888 (27.46)	57906 (23.55)	
Health Region of Residence in 2014				
Interlake-Eastern	25438 (10.21)	276 (8.53)	25162 (10.23)	0.0013
Northern	24870 (9.98)	191 (5.91)	24679 (10.04)	<0.0001
Prairie Mountain	32341 (12.98)	279 (8.63)	32062 (13.04)	<0.0001
Southern	43931 (17.63)	444 (13.73)	43487 (17.69)	<0.0001
Winnipeg	122551 (49.19)	2044 (63.20)	120507 (49.01)	<0.0001
SEFI-2 Score by Region	**Mean Score (Std. Dev.)**	**Mean Score (Std. Dev.)**	**Mean Score (Std. Dev.)**	
Interlake-Eastern	0.135 (1.11)	0.014 (0.99)	0.137 (1.11)	0.1553
Northern	1.383 (1.37)	0.835 (1.25)	1.388 (1.37)	<0.0001
Prairie Mountain	0.065 (0.88)	0.153 (0.87)	0.065 (0.88)	0.1069
Southern	-0.185 (0.59)	-0.122 (0.62)	-0.186 (0.59)	0.0045
Winnipeg	-0.120 (1.00)	-0.056 (0.98)	-0.121 (1.00)	0.0003
All	0.065 (1.08)	0.011 (0.97)	0.065 (1.08)	0.6741

4.3.2 Health and Education Variables

Age at diagnosis and receipt of special education funding were determined for children with ASD (Table 4.2). Almost 60% of children in the ASD cohort received an ASD diagnosis before age

5, or before most children in Manitoba begin school. Special education funding is common among children in the ASD cohort, with 46.8% receiving funding for educational support at some point during the study period.

Table 4.2: Education and age at diagnosis variables of children with ASD.

	ASD Cohort	
N	3234	
	Count (%)	p-value
Age at diagnosis*		
0 - 4 years	1767 (59.78)	<0.0001
5 - 9 years	770 (26.05)	
10 - 14 years	351 (11.87)	
15 and above	68 (2.30)	
Special Education Funding		
Yes	1514 (46.82)	0.0003
No	1720 (53.18)	

** n = 2956 (does not include children (n=281) with only special education funding and no ASD medical diagnosis)*

Children in the ASD cohort had significantly more diagnosed psychiatric conditions and psychotropic medication use when compared to children in the general population cohort (Table 4.3). More than 80% of children with ASD had at least one other diagnosed psychiatric condition while less than 20% of children in the general population cohort have any diagnosed psychiatric condition ($p < 0.0001$). The most common concurrent conditions diagnosed in children with ASD were specific delays of development (44.3%), hyperkinetic syndrome of childhood (42.3%), conduct disturbance (27.5%) and neurotic disorders (21.7%). Every category of psychiatric conditions considered in this study was found more commonly in children with ASD than in those without a diagnosed developmental disability.

Table 4.3. Mental disorder diagnoses for children in the ASD and general population cohorts.

	Total	ASD Cohort	Manitoba Cohort	
N	249131	3234	245897	
	Count (%)	**Count (%)**	**Count (%)**	p-value
Diagnosed Psychiatric Conditions				
Adjustment reaction	2517 (0.01)	89 (2.75)	2428 (0.01)	<0.0001
Affective psychoses	1571 (0.006)	107 (3.31)	1464 (0.006)	<0.0001
Depressive disorder - not otherwise classified	3426 (0.01)	183 (5.66)	3243 (0.01)	<0.0001
Disturbance of conduct	9362 (0.04)	888 (27.46)	8474 (0.03)	<0.0001
Disturbance of emotions specific to childhood and adolescence	975 (0.004)	98 (3.03)	877 (0.004)	<0.0001
Hyperkinetic syndrome of childhood	13708 (0.06)	1368 (42.30)	12340 (0.05)	<0.0001
Neurotic Disorders	16475 (0.07)	702 (21.71)	15773 (0.06)	<0.0001
Special Symptoms	9306 (0.04)	354 (10.95)	8952 (0.004)	<0.0001
Specific delays in Development	10987 (0.04)	1432 (44.28)	9555 (0.04)	<0.0001
Other	2501 (0.01)	274 (8.47)	2227 (0.01)	<0.0001
Number of Diagnosed Psychiatric Conditions (not including ASD)				
0 conditions	200188 (80.36)	617 (19.08)	199571 (81.16)	<0.0001
1 - 3 conditions	47218 (18.95)	2275 (70.35)	44943 (18.28)	<0.0001
4 - 8 conditions	1725 (0.69)	342 (10.58)	1383 (0.56)	<0.0001

4.3.3 Family Environment Variables

Three of the four family environment variables (sibling diagnosed with ASD, maternal age at birth of index child and maternal mental disorder history) were dependent on an available linkage between each child and their biological mother. This was not available for every child in the study, with 5517 children not linkable to their biological mother (2.21%). A greater portion of children in the general population cohort could not be linked to their biological mother than in the ASD cohort (2.22% vs 1.67%). Siblings were linked through their biological mothers.

A significantly greater proportion of children in the ASD cohort had a sibling also diagnosed with ASD than children in the general population cohort (14.0% vs 1.23%, p <0.0001) (Table 4.4). A smaller percentage of children in the ASD cohort had no siblings than in the general population cohort (18.37% vs 22.82%).

Maternal age at the birth of children in the study population tended to be older for the children with ASD than for children in the general population cohort (p <0.0001). A greater portion of mothers of children with ASD were over 30 years old when their child was born (43.06% vs 38.23%). Maternal mental disorder history also showed differences between the mothers of children with ASD and those in the general population. More mothers of children with ASD experienced 2 or more diagnoses of psychiatric conditions with or without hospitalizations compared to mothers of children in the general population cohort (p <0.0001). Children with ASD were also more likely to be in the care of CFS than children in the general population (6.18% vs 4.10% p <0.0001).

Table 4.4. Family environment characteristics for children in the ASD and general population cohorts.

	Total	ASD Cohort	General Cohort	
N	249131	3234	245897	
	Count (%)	**Count (%)**	**Count (%)**	p-value
Sibling diagnosed with ASD				
Yes	3480 (1.40)	453 (14.01)	3027 (1.23)	<0.0001
No	188886 (75.82)	2133 (65.96)	186753 (75.95)	
No sibling	56711 (22.76)	594 (18.37)	56117 (22.82)	
Missing	5517 (2.21)	54 (1.67)	5463 (2.22)	
Maternal age at birth of index child				
≤ 19 years	22004 (8.83)	230 (7.11)	21774 (8.85)	<0.0001
20 - 29 years	126215 (50.66)	1558 (48.16)	124657 (50.69)	
30 - 39 years	90682 (36.40)	1305 (40.34)	89377 (36.35)	
40 + years	4717 (1.89)	88 (2.72)	4626 (1.88)	
Missing	5517 (2.21)	54 (1.67)	5463 (2.22)	
Maternal Mental Disorder History				
No history	93519 (37.54)	823 (23.98)	92696 (37.70)	<0.0001
≥ 2 diagnoses in 3 years	121446 (48.75)	1881 (54.81)	119565 (48.62)	
≥ 2 diagnoses in 3 years with ≥ 1 hospitalization	28649 (11.50)	476 (13.87)	28173 (11.46)	
Missing	5517 (2.21)	54 (1.67)	5463 (2.22)	
Child ever in the care of Child and Family Services				
Yes	10280 (4.13)	200 (6.18)	10080 (4.10)	<0.0001
No	238851 (95.87)	3034 (93.82)	235817 (95.90)	

4.4 Population Characteristics of Children with ASD with and without psychotropic medications

The following results consider children within the ASD cohort, comparing those with and without psychotropic medication. Reported p-values were calculated to determine similarity between the two comparator groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine the relationship between that variable and the outcome of having a psychotropic medication. The ORs and CIs presented in Tables 4.5 – 4.8 represent the outcomes

of univariate analyses in the full cohort of children with ASD for an outcome of a psychotropic medication

4.4.1 Demographics

Children with ASD and a psychotropic medication were more likely older than children with ASD and no psychotropic medication (see Table 4.5). Older children were significantly more likely to receive medications, with children over 15 years old having a 27 times greater odds of receiving a psychotropic medication when compared to children under the age of 5. In the ASD cohort, male and female children had similar odds of receiving psychotropic medications. Proportion of children living in each health region and SEFI2 mean scores were not significantly different between children with ASD and a psychotropic medication and those without – with the exception of children living in Winnipeg. Children with ASD and a psychotropic medication in Winnipeg had higher mean SEFI-2 scores (i.e., lower SES) than children with ASD and no psychotropic medication (0.006 vs -0.104, p=0.0338).

Table 4.5. Demographic characteristics of children in the ASD cohort, comparing children with and without psychotropic medications.

	ASD Cohort	with Psychotropic medication	without Psychotropic medication			
N	3234	1578	1656			
	Count (%)	**Count (%)**	**Count (%)**	p-value	OR	CI
Sex						
Male	2585 (79.93)	1280 (81.12)	1305 (78.80)	0.1010	1.15	0.97 - 1.37
Female	649 (20.07)	298 (18.88)	351 (21.20)		*ref*	
Age in 2014						
0 - 4 years	373 (11.53)	30 (1.90)	343 (20.71)	<0.0001	*ref*	
5 - 9 years	893 (27.61)	288 (18.25)	605 (36.53)		**5.44**	**3.65 - 8.11**
10 - 14 years	1080 (33.40)	636 (40.30)	444 (26.81)		**16.38**	**11.06 - 24.24**
15 and above	888 (27.46)	624 (39.54)	264 (15.94)		**27.02**	**18.12 - 40.31**
Health Region of Residence in 2014						
Interlake-Eastern	276 (8.53)	152 (9.58)	124 (7.49)	0.0919	1.22	0.87 - 1.70
Northern	191 (5.91)	86 (5.42)	105 (6.34)	0.1692	0.81	0.56 -1.18
Prairie Mountain	279 (8.63)	140 (8.82)	139 (8.39)	0.9523	*ref*	
Southern	444 (13.73)	195 (12.29)	249 (15.04)	0.0104	0.78	0.58 - 1.05
Winnipeg	2044 (63.20)	1005 (63.33)	1039 (62.74)	0.4520	0.96	0.75 - 1.23
SEFI-2 Score by Region	**Mean Score (Std. Dev.)**	**Mean Score (Std. Dev.)**	**Mean Score (Std. Dev.)**			
Interlake-Eastern	0.014 (0.99)	-0.0008 (0.97)	0.0308 (1.01)	0.7389	0.97	0.76 - 1.23
Northern	0.835 (1.25)	0.833 (1.21)	0.836 (1.29)	0.8576	0.99	0.79 - 1.26
Prairie Mountain	0.153 (0.87)	0.099 (0.82)	0.208 (0.91)	0.4232	0.86	0.65 - 1.14
Southern	-0.122 (0.62)	-0.105 (0.55)	-0.135 (0.67)	0.4985	1.08	0.80 - 1.46
Winnipeg	-0.056 (0.98)	0.006 (1.02)	-0.104 (0.93)	0.0338	**1.11**	**1.01 - 1.21**
All	0.011 (0.97)	0.037 (0.99)	-0.014 (0.96)	0.1109		

4.4.2 Health and Education Characteristics

Children with ASD and a psychotropic medication differ significantly from children with ASD and no psychotropic medication in their age at diagnosis and receipt of special education funding services and behavioural programming at MATC (Table 4.6). Children in the ASD cohort with a psychotropic medication had a significantly higher age at diagnosis than children without a psychotropic medication ($p < 0.0001$). Children over 15 years old at first diagnosis had an 8.94

times increased odds of receiving a psychotropic medication compared to children who are diagnosed before age 5 (Table 4.6). More children with ASD that have special education funding (<0.0001) and behavioural programming at MATC (<0.0001) also receive psychotropic medications. Children with ASD who participate in programming at MATC have 6.8 times greater odds of receiving psychotropic medications than those who do not participate in MATC programming (Table 4.6).

Table 4.6. Health and education variables of children with ASD, comparing children with and without psychotropic medications.

	ASD Cohort	**with Psychotropic medication**	**without Psychotropic medication**			
N	3234	1578	1656			
	Count (%)	**Count (%)**	**Count (%)**	p-value	OR	CI
Age at diagnosis*						
0 - 4 years	1767 (54.64)	605 (38.34)	1159 (69.99)	**<0.0001**	*ref*	
5 - 9 years	770 (23.81)	471 (29.85)	299 (18.06)		**3.02**	**2.53 - 3.60**
10 - 14 years	351 (10.85)	272 (17.24)	79 (4.77)		**6.60**	**5.04 - 8.63**
15 and above	68 (2.10)	56 (3.55)	12 (0.72)		**8.94**	**4.76 - 16.80**
Missing	281 (8.69)	174 (11.03)	107 (6.46)		-	-
Special Education Funding						
Yes	1514 (46.82)	870 (55.13)	644 (38.89)	**<0.0001**	**1.93**	**1.68 - 2.22**
No	1720 (53.18)	708 (44.87)	1012 (61.11)		*ref*	
Behaviour Programming (MATC)						
Yes	909 (28.11)	727 (45.81)	182 (10.99)	**<0.0001**	**6.86**	**5.71 - 8.23**
No	2325 (71.89)	860 (54.19)	1465 (88.47)		*ref*	

** n = 2953 (does not include children with only special education funding and no ASD medical diagnosis)*

For children with ASD, the concurrent diagnosis of additional psychiatric conditions was associated with increased odds of receiving a psychotropic medication with the exception of specific delays in development. Excluding delays in development, there was a greater proportion of children with ASD and a psychotropic medication co-diagnosed with every psychiatric condition considered in this study (Table 4.7). Almost all children with a co-diagnosis of affective psychoses ($p < 0.0001$), depressive disorder ($p < 0.0001$), disturbances of emotions

specific to childhood and adolescence ($p < 0.0001$) and adjustment reaction ($p < 0.0001$) had a psychotropic medication. The number of children with ASD and affective psychoses without a psychotropic medication is less than or equal to 5 and therefore this cell has been suppressed in Table 4.7 for privacy reasons. Children with ASD and hyperkinetic syndrome of childhood had 10 times increased odds of receiving a psychotropic medication when compared to all other children with ASD without a diagnosis of hyperkinetic syndrome (OR=10.23, CI: 8.67 – 12.07). The number of concurrently diagnosed psychiatric conditions also increased the odds of a child with ASD receiving a psychotropic medication (Table 4.7).

Table 4.7. Mental health conditions of children with ASD, comparing children with and without psychotropic medications.

	ASD Cohort	**with Psychotropic medication**	**without Psychotropic medication**			
N	3234	1578	1656			
	Count (%)	**Count (%)**	**Count (%)**	p-value	OR	CI
Diagnosed Psychiatric Conditions						
Adjustment reaction	89 (2.75)	73 (4.63)	16 (0.97)	**<0.0001**	**4.97**	**2.88 - 8.58**
Affective psychoses	107 (3.31)	*suppressed*	*suppressed*	**<0.0001**	**28.84**	**10.60 - 78.50**
Depressive disorder - not otherwise classified	183 (5.66)	168 (10.65)	15 (0.91)	**<0.0001**	**13.03**	**7.65 - 22.21**
Disturbance of conduct	888 (27.46)	611 (38.72)	277 (16.73)	**<0.0001**	**3.15**	**2.67 - 3.71**
Disturbance of emotions specific to childhood and adolescence	98 (3.03)	87 (5.51)	11 (0.66)	**<0.0001**	**8.73**	**4.64 - 16.40**
Hyperkinetic syndrome of childhood	1368 (42.30)	1079 (68.38)	289 (17.45)	**<0.0001**	**10.23**	**8.67 - 12.07**
Neurotic Disorders	702 (21.71)	521 (33.02)	181 (10.93)	**<0.0001**	**4.02**	**3.33 - 4.84**
Special Symptoms	354 (10.95)	248 (15.72)	106 (6.40)	**<0.0001**	**2.73**	**2.45 - 3.46**
Specific delays in Development	1432 (44.28)	667 (42.27)	765 (46.20)	**0.0246**	**0.85**	**0.74 - 0.98**
Other	274 (8.47)	222 (14.07)	52 (3.14)	**<0.0001**	**5.05**	**3.70 - 8.89**
Number of Diagnosed Psychiatric Conditions (not including ASD)						
0 conditions	617 (19.08)	105 (6.65)	512 (30.92)	**<0.0001**	*ref*	
1-3 conditions	2275 (70.35)	1148 (72.75)	1127 (68.06)		**4.97**	**3.96 – 6.22**
4-8 conditions	325 (10.05)	325 (20.60)	17 (1.03)		**93.22**	**54.82 – 158.52**

4.4.3 Family Environment Characteristics

As previously described, not all children could be linked to their biological mothers and therefore 1.67% of children with ASD were missing information about sibling ASD diagnosis, maternal age and maternal mental health conditions. A similar proportion of children in the ASD cohort with psychotropic medication (1.77%) and without psychotropic medication (1.57%) were missing these variables.

Sibling diagnosis with ASD was a significant predictor of psychotropic medication use for children with ASD. Compared to children with siblings that were not diagnosed with ASD, children with a sibling with ASD had a 1.26 times increased odds of receiving a psychotropic medication (Table 4.8). Children with no sibling had similar odds of receiving a psychotropic medication when compared to children with no sibling with ASD (Table 4.8).

Despite some differences in frequency distribution of maternal age at birth of the index child (ASD cohort), this family characteristic was not found to be significantly associated with the use of a psychotropic medication among children with ASD. Maternal mental disorder history did have a significant association with child psychotropic medication use for the ASD cohort, including an almost 2-fold increase in odds of receiving a psychotropic medication associated with at least 2 maternal mental health condition diagnoses in any 3 years.

Significantly more children with ASD and a psychotropic medication had ever been in the care of CFS when compared to those with ASD without a psychotropic medication. Children with ASD who had ever been in care of CFS had more than 3 times greater odds of receiving a psychotropic medication.

Table 4.8. Family environment characteristics of children with ASD, comparing children with and without psychotropic medications.

	ASD Cohort	with Psychotropic medication	without Psychotropic medication			
N	3234	1578	1656			
	Count (%)	**Count (%)**	**Count (%)**	p-value	OR	CI
Sibling diagnosed with ASD						
Yes	417 (12.89)	220 (13.94)	197 (11.90)	0.0749	**1.26**	**1.02 - 1.57**
No	1854 (57.33)	869 (55.07)	985 (59.48)		*ref*	
No sibling	909 (28.11)	461 (14.25)	448 (27.05)		1.17	0.99 - 1.37
Missing	54 (1.67)	28 (1.77)	26 (1.57)		-	-
Maternal age at birth of index child						
≤ 19 years	230 (7.11)	120 (7.60)	110 (6.64)	0.0646	1.14	0.70 - 1.87
20 - 29 years	1558 (48.16)	791 (50.13)	766 (46.26)		1.08	0.70 -1.66
30 - 39 years	1305 (40.34)	596 (37.77)	709 (42.81)		0.88	0.57 - 1.36
40 + years	88 (2.72)	43 (2.72)	45 (2.72)		*ref*	
Missing	54 (1.67)	28 (1.77)	26 (1.57)		1.13	0.57 - 2.22
Maternal mental disorder history						
No history	823 (23.98)	304 (19.26)	519 (31.34)	**<0.0001**	*ref*	
≥ 2 diagnoses in 3 years	1881 (54.81)	957 (60.65)	924 (55.80)		**1.77**	**1.50 - 2.09**
≥ 2 diagnoses in 3 years with ≥ 1 hospitalization	476 (13.87)	289 (18.31)	187 (11.29)		**2.64**	**2.09 - 3.33**
Missing	54 (1.67)	28 (1.77)	26 (1.57)		-	-
Child ever in the care of Child and Family Services						
Yes	200 (6.18)	147 (9.32)	53 (3.20)	**<0.0001**	**3.11**	**2.25 - 4.29**
No	3034 (93.82)	1431 (90.68)	1603 (96.80)		*ref*	

4.4.4 Logistic Regression – Psychotropic Medication Use Among Children with ASD

Children with ASD and a psychotropic medication had different demographic and family characteristics when compared to children with ASD and no psychotropic medications. This study used a logistic regression model to determine the characteristics that were associated with an increased likelihood of a child with ASD having a psychotropic medication. The variables were grouped in three models: Child Demographics, Health & Education, and Family Environment. For the point estimates and confidence intervals from these models see Appendix

E. All variables included in these three models were used in the full model and are presented below in Table 4.9.

Table 4.9. Results of multivariable model showing Odds Ratios and Confidence Intervals for use of a psychotropic medication among children with ASD.

N	2889				
Sex	OR	CI	**Diagnosed Psychiatric Conditions**	OR	CI
Male	0.99	0.78 - 1.27	Adjustment reaction	1.81	0.84 - 3.86
Female	*ref*		Affective psychoses	**7.27**	**2.33 - 22.76**
Age in 2014			Depressive disorder - not otherwise classified	**2.86**	**1.42 - 5.74**
0 - 4 years	*ref*		Disturbance of conduct	**1.73**	**1.37 - 2.18**
5 - 9 years	**2.04**	**1.30 - 3.21**	Disturbance of emotions specific to childhood and adolescence	**6.08**	**2.38 - 15.55**
10 - 14 years	**3.04**	**1.90 - 4.87**	Hyperkinetic syndrome of childhood	**5.33**	**4.32 - 6.56**
15 and above	**3.50**	**2.14 - 5.72**	Neurotic Disorders	**1.99**	**1.53 - 2.58**
Health Region of Residence in 2014			Special Symptoms	**1.52**	**1.09 - 2.12**
Interlake-Eastern	0.94	0.59 - 1.49	Specific delays in Development	1.05	0.86 - 1.28
Northern	0.88	0.53 - 1.47	Other	**3.20**	**2.10 - 4.87**
Prairie Mountain	*ref*		**Sibling Diagnosed with ASD**		
Southern	0.71	0.47 - 1.08	Yes	**1.56**	**1.18 - 2.08**
Winnipeg	0.76	0.53 - 1.07	No sibling	1.22	0.96 - 1.54
SEFI-2 Score by Region			No	*ref*	
All	1.10	0.99 - 1.23	**Maternal age at birth of index child**		
Age at diagnosis			≤ 19 years	1.09	0.53 - 2.26
0 - 4 years	*ref*		20 - 29 years	1.03	0.55 - 1.94
5 - 9 years	**1.39**	**1.10 - 1.78**	30 - 39 years	0.93	0.50 - 1.75
10 - 14 years	**2.00**	**1.38 - 2.92**	40 + years	*ref*	
15 and above	**2.95**	**1.30 - 6.70**	**Maternal Mental Disorder History**		
Special Education Funding			No history	*ref*	
Yes	**1.87**	**1.50 - 2.34**	At least 2 diagnoses in 3 years	1.15	0.91 - 1.45
No	*ref*		At least 2 diagnoses in 3 years with at least 1 hospitalization	1.27	0.91 - 1.78
Behaviour Programming (MATC)			**Child ever in the care of Child and Family Services**		
Yes	**2.72**	**2.12 - 3.50**	Yes	**1.87**	**1.19 - 2.95**
No	*ref*		No	*ref*	

The logistic regression model shown in Table 4.9 indicates which demographic, health and education and family environment characteristics are associated with an increased likelihood of a child with ASD receiving a psychotropic medication. Most of the characteristics that were significant in the univariate analysis remained significant when considered simultaneously with other variables in the multivariable model, with the exception of concurrent diagnosis of adjustment reaction disorder and specific delays in development, and maternal mental disorder history. Children with ASD who were older at the end of the study period, older at the time of diagnosis, had special education funding, participated in behavioural programming at MATC, had a sibling diagnosed with ASD, were ever in the care of CFS and were concurrently diagnosed with a psychiatric condition were more likely to have a psychotropic medication.

4.5 Comparison of Population Characteristics among All Children with a Psychotropic Medication

The following tables show the population characteristics of all children with a psychotropic medication in the ASD and general population cohorts. The p-value of a test statistic (Chi-square or T-test) was used to determine similarity between these two groups.

4.5.1 Demographics

More children with ASD and a psychotropic medication are male, compared to the general population cohort of children with no developmental disabilities ($p < 0.0001$). This is consistent with the general population demographics of children with ASD. The age group frequency distribution of children with a psychotropic medication differed between children with ASD and those in the general population cohort ($p < 0.0001$). There was a greater

proportion of children with a psychotropic medication between the ages of 5 and 14 with ASD than in the general population (Table 4.10). A greater proportion of children in the general population who received psychotropic medications received these before age 5 compared to the ASD cohort.

Comparing all children with psychotropic medications, there was a smaller portion of children with ASD in the Northern ($p < 0.0001$) and Prairie Mountain ($p < 0.0001$) health regions compared to the general population cohort. Conversely, there was a greater proportion of children with ASD and a psychotropic medication living in Winnipeg ($p < 0.0001$). There was no significant difference between the mean SEFI-2 scores for children with psychotropic medications with and without ASD in the Interlake-Eastern ($p = 0.0599$), Northern ($p = 0.1821$), Prairie Mountain ($p = 0.7521$) and Southern ($p = 0.0533$) health regions. Children with ASD and a psychotropic medication had a mean SEFI-2 score that indicates more favourable neighbourhood socioeconomic status, on average, than children in the general population in Winnipeg ($p = 0.0044$) and in the aggregate analysis of all children with a psychotropic medication ($p = 0.0002$).

Table 4.10. Demographic characteristics of children with psychotropic medications, comparing children in the ASD and general population cohorts.

		ASD Cohort	General Cohort	
N	32043	1578 (4.92)	30465 (95.08)	
	Count (%)	**Count (%)**	**Count (%)**	p-value
Sex				
Male	17968 (56.07)	1280 (81.12)	16688 (54.78)	**<0.0001**
Female	14075 (43.93)	298 (18.88)	13777 (45.22)	
Age in 2014				
0 - 4 years	1435 (4.48)	30 (1.90)	1405 (4.61)	**<0.0001**
5 - 9 years	5611 (17.51)	288 (18.25)	5323 (17.47)	
10 - 14 years	10590 (33.05)	636 (40.30)	9954 (32.67)	
15 and above	14407 (44.96)	624 (39.54)	13783 (45.24)	
Health Region of Residence in 2014				
Interlake-Eastern	2954 (9.22)	152 (9.58)	2802 (9.20)	0.5603
Northern	2874 (8.97)	86 (5.42)	2788 (9.15)	**<0.0001**
Prairie Mountain	3863 (12.06)	140 (8.82)	3723 (12.22)	**<0.0001**
Southern	3891 (12.14)	195 (12.29)	3696 (12.13)	0.7892
Winnipeg	18461 (57.61)	1005 (63.33)	17456 (57.30)	**<0.0001**
SEFI-2 Score by Region	**Mean Score (Std. Dev.)**	**Mean Score (Std. Dev.)**	**Mean Score (Std. Dev.)**	
Interlake-Eastern	0.198 (1.15)	-0.0008 (0.97)	0.209 (1.16)	0.0599
Northern	1.051 (1.40)	0.833 (1.21)	1.057 (1.40)	0.1821
Prairie Mountain	0.140 (0.94)	0.099 (0.82)	0.142 (0.94)	0.7521
Southern	-0.166 (0.61)	-0.105 (0.55)	-0.170 (0.61)	0.0533
Winnipeg	0.093 (1.05)	0.006 (1.02)	0.099 (1.05)	**0.0044**
All	0.161 (1.08)	0.037 (0.99)	0.168 (1.08)	**0.0002**

4.5.2 Health and Psychiatric Condition Variables

Children with ASD tend to be older at the time of their first prescription for a psychotropic medication than the general population cohort of children ($p < 0.0001$), with almost 75% of children receiving their first medication between the ages of 5 and 14. Comparing the diagnosed psychiatric conditions of these two groups of children, there was a larger proportion of children with ASD concurrently diagnosed with each other considered

condition (Table 4.11) with the exception of adjustment reaction which had similar proportions ($p = 0.2685$). Furthermore, children with ASD were diagnosed with a greater number of psychiatric conditions, where almost 94% diagnosed with at least one other concurrent condition. In the general cohort population of children, just over 50% of children with a psychotropic medication were diagnosed with at least one psychiatric condition.

Table 4.11. Health and psychiatric condition variables for children with psychotropic medications, comparing children in the ASD and general population cohorts.

		ASD Cohort	**General Cohort**	
N	32043	1578 (4.92)	30465 (95.08)	
	Count (%)	**Count (%)**	**Count (%)**	p-value
Age at First Prescription				
0 - 4 years	12874 (40.18)	471 (29.85)	12403 (40.71)	**<0.0001**
5 - 9 years	10775 (33.63)	847 (53.68)	9928 (32.59)	
10 - 14 years	5373 (16.77)	217 (13.75)	5156 (16.92)	
15 and above	3021 (9.43)	43 (2.72)	2978 (9.78)	
Diagnosed Psychiatric Conditions				
Adjustment reaction	1310 (4.09)	73 (4.63)	1237 (4.06)	0.2685
Affective psychoses	1217 (3.80)	*suppressed*	*suppressed*	**<0.0001**
Depressive disorder - not otherwise classified	2314 (7.22)	168 (10.65)	2146 (7.04)	**<0.0001**
Disturbance of conduct	4220 (13.17)	611 (38.72)	3609 (11.85)	**<0.0001**
Disturbance of emotions specific to childhood and adolescence	569 (1.78)	87 (5.51)	482 (1.58)	**<0.0001**
Hyperkinetic syndrome of childhood	9863 (30.78)	1079 (68.38)	8784 (28.83)	**<0.0001**
Neurotic Disorders	5849 (18.25)	521 (33.02)	5328 (17.49)	**<0.0001**
Special Symptoms	2792 (8.71)	248 (15.72)	2544 (8.35)	**<0.0001**
Specific delays in Development	3042 (9.49)	667 (42.27)	2375 (7.80)	**<0.0001**
Other	1259 (3.93)	222 (14.07)	1037 (3.40)	**<0.0001**
Number of Diagnosed Psychiatric Conditions (not including ASD)				
0 conditions	14656 (45.74)	105 (6.65)	14551 (47.76)	**<0.0001**
1-3 conditions	15848 (49.46)	1148 (72.75)	14700 (48.25)	
4-8 conditions	1539 (4.80)	325 (20.60)	1214 (3.99)	

4.5.3 Family Environment Variables

A similar proportion of children with a psychotropic medication in the ASD cohort (1.77%) and in the general population cohort (1.37%) were missing variables due to an unidentified biological mother. Sibling diagnosis of ASD was significantly greater among children with ASD (13.94%) than in the general population cohort (1.78%). Both groups of children with psychotropic medications had a similar proportion of children with no recorded sibling (Table 4.12).

The frequency distribution of maternal age at birth of the index child was significantly different between the ASD and general population cohorts of children with a psychotropic medication, with moms of children with ASD tending to be older ($p < 0.0001$). Maternal mental disorder history was also significantly different in these two groups of children ($p = 0.0003$). There was a greater proportion of mothers with no history of mental disorders among children in the general population cohort (Table 4.12).

There was no difference in the proportion of children with a psychotropic medication, with and without ASD, who had ever been in the care of CFS ($p = 0.9825$). Approximately 9% of all children with a psychotropic medication had ever been in the care of CFS.

Table 4.12: Family environment variables for children with psychotropic medications, comparing children in the ASD and general population cohorts.

		ASD Cohort	General Cohort	
N	32043	1578 (4.92)	30465 (95.08)	
	Count (%)	**Count (%)**	**Count (%)**	p-value
Sibling diagnosed with ASD				
Yes	761 (2.37)	220 (13.94)	541 (1.78)	**<0.0001**
No	22402 (69.91)	869 (55.07)	21533 (70.68)	
No sibling	8436 (26.33)	461 (29.21)	7975 (26.18)	
Missing	444 (1.39)	28 (1.77)	416 (1.37)	
Maternal age at birth of index child				
≤ 19 years	3973 (12.40)	120 (7.60)	3853 (12.65)	**<0.0001**
20 - 29 years	16884 (52.69)	791 (50.13)	16093 (52.82)	
30 - 39 years	10202 (31.84)	596 (37.77)	9606 (31.53)	
40 + years	540 (1.69)	43 (2.72)	497 (1.63)	
Missing	444 (1.39)	28 (1.77)	416 (1.37)	
Maternal Mental Disorder History				
No history	7589 (23.68)	304 (19.26)	7285 (23.91)	**0.0003**
≥ 2 diagnoses in 3 years	18419 (57.48)	957 (60.65)	17462 (57.32)	
≥ 2 diagnoses in 3 years with ≥ 1 hospitalization	5591 (17.45)	289 (18.31)	5302 (17.40)	
Missing	444 (1.39)	28 (1.77)	416 (1.37)	
Child ever in the care of Child and Family Services				
Yes	2990 (9.33)	147 (9.32)	2843 (9.33)	0.9825
No	29053 (90.67)	1431 (90.68)	27622 (90.67)	

4.6 Psychotropic Medication Use and Intensity Among All Children

All children in Manitoba who received at least one psychotropic medication were considered in the following analyses, stratified by ASD diagnosis.

4.6.1 Psychotropic Medication Use During the Full Study Period

Children in the ASD cohort were older at the age of first prescription than those in the general population cohort. The greatest proportion of children with ASD (53.7%) received a psychotropic medication at ages 5 – 9 years whereas the greatest proportion of children in the general cohort (40.7%) received their first psychotropic medication at ages 0 – 4 years (Table

4.13). Children with ASD received fewer prescriptions for anxiolytic, antidepressant and psychostimulant medications than children in the general population (all $p < 0.0001$ Table 4.13). However, children with ASD had more prescriptions for antipsychotic and antiepileptic medications (both $p < 0.0001$) and naltrexone was only given to children with ASD (Table 4.13). Few prescriptions for naltrexone, anticholinergic and antiparkinson medications were filled for children in Manitoba – with all three types comprising less than 1% of total prescriptions in this cohort (Table 4.13).

A greater proportion of children with ASD used multiple classes of medication in one year than those in the general population (Table 4.13). Less than 15% of children in the general Manitoba population cohort with a psychotropic medication met the polypharmacy medication use criteria of at least two prescriptions with at least 30-day supply in two drug classes in one calendar year, compared to 50% in the ASD cohort. Half of children in the ASD cohort with a psychotropic medication experienced polypharmacy of two or more medication classes in at least one year of the study period (Table 4.13).

Table 4.13: Population Characteristics, total ever psychotropic medication prescriptions and polypharmacy of children with a psychotropic medication prescription in the ASD and general population cohorts.

	Total	ASD Cohort	General Cohort	
N	32043	1578	30465	
	Count (%)	**Count (%)**	**Count (%)**	p-value
Sex				
Male	17968 (56.1)	1280 (81.1)	16688 (54.8)	**<0.0001**
Female	14075 (43.9)	298 (18.9)	13777 (45.2)	
Age at First Prescription				
0 - 4 years	12874 (40.18)	471 (29.85)	12403 (40.71)	**<0.0001**
5 - 9 years	10775 (33.63)	847 (53.68)	9928 (32.59)	
10 - 14 years	5373 (16.77)	217 (13.75)	5156 (16.92)	
15 and above	3021 (9.43)	43 (2.72)	2978 (9.78)	
Total Psychotropic Medication Prescriptions				
Total	588214	116919	471295	**<0.0001**
Anticholinergics	249 (0.04)	88 (0.08)	161 (0.03)	**<0.0001**
Antidepressants	81060 (13.8)	14616 (12.5)	66444 (14.1)	**<0.0001**
Antiepileptic	54056 (9.2)	15463 (13.23)	38593 (8.19)	**<0.0001**
Antiparkinson	134 (0.02)	19 (0.02)	115 (0.02)	0.0983
Antipsychotic	104614 (17.8)	39738 (34.0)	64876 (13.8)	**<0.0001**
Anxiolytic	43371 (7.4)	4547 (3.9)	38824 (8.2)	**<0.0001**
Naltrexone	50 (0.01)	50 (0.04)	0 (0)	**<0.0001**
Psychostimulant	304680 (51.8)	42398 (36.3)	262282 (55.7)	**<0.0001**
Suspected Antihistamine*	4559	177	4382	
Number of Psychotropic Medications				
Does not meet criteria	9327 (37.9)	150 (9.5)	12131 (39.8)	**<0.0001**
1 medication type	11601 (47.2)	647 (41.0)	14210 (46.6)	
2 medication types	2587 (10.5)	402 (25.5)	3056 (10.0)	
3 medication types	782 (3.2)	234 (14.8)	826 (2.7)	
4 medication types	209 (0.8)	92 (5.8)	190 (0.6)	
5 medication types	63 (0.2)	33 (2.1)	40 (0.1)	
6 + medication types	26 (0.1)	20 (1.3)	12 (0.04)	

* number of suspected antihistamine prescriptions that were excluded from the analysis for each cohort – these values were not included in percentage totals

4.6.2 Intensity of Psychotropic Medication Use in 2013/2014

Children with ASD had a significantly greater number of psychotropic medications in the final year of this study period. Over half (54.1%) of children with ASD who had a psychotropic

medication in the last year received a prescription for more than one type of medication in a one-year period, whereas only 26.8% of children in the general cohort received more than one type of psychotropic medication in this same time period (Table 4.14). Approximately 10% of children in the ASD cohort received 4 or more types of psychotropic medication in the final year of this study period, compared to just over 2% of children in the general population cohort.

Table 4.14 Number of psychotropic medications for the ASD and general population cohorts of children in Manitoba with at least one medication in the last year of this study period (2013/2014).

	Total	**ASD Cohort**	**General Cohort**	
N	9871	935	8936	
	Count (%)	**Count (%)**	**Count (%)**	p-value
Number of Psychotropic Medications				
1 medication type	6969 (70.6)	429 (45.9)	6540 (73.2)	**<0.0001**
2 medication types	1936 (19.6)	262 (28.0)	1674 (18.7)	
3 medication types	658 (6.7)	146 (15.6)	512 (5.7)	
4 medication types	195 (2.0)	56 (6.0)	139 (1.6)	
5 medication types	73 (0.7)	20 (2.1)	53 (0.6)	
6 + medication types	40 (0.4)	22 (2.4)	18 (0.2)	

The mean DDD received in 2013/2014 was compared for children in the ASD and general population cohorts by user per medication class. The total for each class, mean and standard deviations are presented in Table 4.15. Children with ASD received a significantly greater mean DDD of antiepileptic medications and anxiolytics compared to children in the general cohort. Comparatively, children in the general population cohort received a significantly greater mean DDD of antidepressants and psychostimulants. There were no significant differences between the two cohorts for the mean DDD for anticholinergic, antiparkinson and antipsychotic medications.

Table 4.15 Total, mean and standard deviations of the DDD per psychotropic medication class for the ASD and general population cohorts of children in Manitoba with at least one medication in the last year of this study period (2013/2014).

Amount of Defined Daily Dose per user by Medication Class	**Total**	**ASD Cohort**		**General Cohort**		
	9871	935		8936		
	Total	**Total**	**Mean (Std Dev)**	**Total**	**Mean (Std Dev)**	p-value
Anticholinergic	1488.8	487.0	48.7 (40.0)	1001.8	58.9 (90.6)	0.7822
Antidepressant	55547975.3	5258694.8	15935.4 (89136)	50289280.5	17565.2 (73497)	**<0.0001**
Antiepileptic	219850096.8	76569661.3	539223 (1086681)	143280435.5	200673 (308264)	**<0.0001**
Antiparkinson	498.6	182.7	60.9 (86.4)	315.9	105.3 (79.4)	0.5480
Antipsychotic	40039989.4	20541413.5	47549.6 (180703)	19498575.9	13957.5 (45336)	0.3903
Anxiolytic	60948.2	14578.8	104.1 (199)	46369.4	28.3 (77)	**0.0109**
Naltrexone	2040.0	2040.0	*suppressed*	0.0	0	-
Psychostimulant	485727.1	242863.5	449.7 (350.4)	242863.5	454.1 (4267.0)	**<0.0001**

p-values were determined using a t-test or Wilcoxon rank-sum test for classes with unequal variance.

4.6.3 Regression Model – Number of Psychotropic Medication Types

A zero-inflated negative binomial regression model was used to determine the relationship between the number of psychotropic medication types a child received and the following child characteristics – ASD diagnosis, sex, age, sibling diagnosed with ASD, history of being in the care of CFS and diagnosed psychiatric conditions. All other variables that were used in the previous logistic regression (Section 4.4.4) (such as region of residence, SEFI-2, maternal age at birth and maternal mental disorder history) were attempted for inclusion in the regression model. Addition of these variables prevented the model from converging and therefore were excluded from the regression analysis.

The final model is presented in Table 4.16, showing the resultant rate ratio and p-values for all included variables. A childhood diagnosis of ASD was associated with an increased rate of number of medication types per person year (RR = 1.69, $p < 0.0001$). A diagnosed psychiatric condition of affective psychoses (RR = 1.53, $p < 0.0001$), depressive disorder (RR = 1.50, p <

0.0001), disturbance of emotions (RR = 1.32, p < 0.0001), neurotic disorders (RR = 1.31, p < 0.0001), conduct disorder (RR = 1.29, p < 0.0001), other conditions (RR = 1.29, p < 0.0001), special symptoms (RR = 1.25, p < 0.0001) or hyperkinetic syndrome (RR = 1.19, p < 0.0001) were all associated with significantly increased rates of number of medication types used. Male children and children with a sibling with ASD also had increased rates of number of medication types. Children who had ever been in care of CFS also had a 1.30 (p <0.0001) increase in rate of number of medication types used per person year.

Table 4.16 Rate Ratios and p values for associations between child characteristics and the number of psychotropic medication types, final year of the study.

Child Characteristic Variables					
ASD Diagnosis	RR	p-value	**Diagnosed Psychiatric Conditions**	RR	p-value
Yes	**1.69**	**<0.0001**	Adjustment reaction	1.05	0.2935
Sex			Affective psychoses	**1.53**	**<0.0001**
Male	**1.11**	**<0.0001**	Depressive disorder - not otherwise classified	**1.50**	**<0.0001**
Female	*ref*		Disturbance of conduct	**1.29**	**<0.0001**
Age in 2014			Disturbance of emotions specific to childhood and adolescence	**1.32**	**<0.0001**
Continuous	0.98		Hyperkinetic syndrome of childhood	**1.19**	**<0.0001**
Sibling Diagnosed with ASD			Neurotic Disorders	**1.31**	**<0.0001**
Yes	**1.18**	**0.0016**	Special Symptoms	**1.25**	**<0.0001**
No siblings	0.97	0.3210	Specific delays in Development	1.01	0.6974
No siblings with ASD	*ref*		Other	**1.29**	**<0.0001**
Ever in Care of CFS					
Yes	**1.30**	**<0.0001**			

4.6.4 Regression Model – Total Defined Daily Dose per User

A zero-inflated negative binomial regression model was also used to determine the association between total DDD per user in the final year of the study period and the following child characteristics – ASD diagnosis, sex, health region of residence, SEFI-2 score, maternal

diagnoses of psychiatric condition, history of being in the care of CFS, diagnosed psychiatric conditions, sibling diagnosed with ASD and maternal age at birth of index child (Table 4.17). The model converged with all variables included.

ASD diagnosis was associated with a 3.68 increase in the rate of DDD used in the final year of the study. Larger significant associations were found for diagnosis of depressive disorder (RR=8.25, $p = 0.0009$), hyperkinetic syndrome (RR=23.30, $p < 0.0001$) and for each one-year increase in age (RR=3.84, $p < 0.0001$). Diagnosis with the psychiatric conditions of disturbance of emotions, other conditions, neurotic disorders, conduct disturbance, special symptoms and delays in development were all also associated with increased rate ratios for DDD. Health region of residence was also associated with a significant difference in DDD, with children in Interlake-Eastern, Northern and Southern all experiencing reduced rate ratios for DDD and Winnipeg having an increased rate ratio for DDD when compared to children in Prairie Mountain. A significant, though very small, increase in rate ratio for DDD was found to be associated with an increase in SEFI-2 score – suggesting that children living in lower SES areas had a greater DDD per person year. Unlike the regression model showing association with number of medication types, having a sibling diagnosed with ASD was not associated with DDD. However, being an only child (no sibling) was associated with a small but significant (RR = 1.06, $p < 0.0001$) increase in DDD per person year. Maternal diagnosis of a psychiatric condition and maternal age at birth of the index child (20-29 and 30-39-year-old age groups compared to 40-49 year olds) were also found to be associated with an increased DDD per person year. History of being in the care of CFS also increased DDD by 1.31, similar to the previous model.

Table 4.17 Rate Ratios and p values for associations between child characteristics and number of DDDs, final year of the study.

Child Characteristic Variables

ASD Diagnosis	RR	p-value
Yes	**3.68**	**<0.0001**
Sex		
Male	**1.12**	**<0.0001**
Female	*ref*	
Age in 2014		
Continuous	**3.84**	**<0.0001**
Health Region of Residence in 2014		
Interlake-Eastern	**0.97**	**<0.0001**
Northern	**0.94**	**<0.0001**
Prairie Mountain	*ref*	
Southern	**0.96**	**<0.0001**
Winnipeg	**1.06**	**<0.0001**
SEFI-2 Score		
Continuous	**1.01**	**<0.0001**
Maternal Diagnoses of Psychiatric Condition		
Yes	**1.13**	**<0.0001**
Ever in Care of CFS		
Yes	**1.31**	**<0.0001**

Diagnosed Psychiatric Conditions	RR	p-value
Adjustment reaction	1.60	0.5949
Affective psychoses	11.61	0.2150
Depressive disorder - not otherwise classified	**8.25**	**0.0009**
Disturbance of conduct	**1.61**	**<0.0001**
Disturbance of emotions specific to childhood and adolescence	**2.55**	**<0.0001**
Hyperkinetic syndrome of childhood	**23.30**	**<0.0001**
Neurotic Disorders	**1.71**	**<0.0001**
Special Symptoms	**1.25**	**<0.0001**
Specific delays in Development	**1.13**	**<0.0001**
Other	**2.40**	**<0.0001**
Sibling Diagnosed with ASD		
Yes	1.16	0.1421
No sibling	**1.06**	**<0.0001**
No sibling diagnosed with ASD	*ref*	
Maternal Age at Birth of Index Child		
≤ 19 years	1.01	0.1286
20 - 29 years	**1.08**	**<0.0001**
30 - 39 years	**1.07**	**<0.0001**
40 - 49 years	*ref*	
≥ 50 years	0.81	0.8407

Chapter 5: Discussion

This study described the characteristics of children with ASD in Manitoba, exploring and comparing psychotropic medication use within this population and to a general child population cohort. While previous research on the topic of psychotropic medication use in children with ASD has described patterns of use, it has not closely considered the characteristics of children who receive these medications. This study demonstrated how demographic, social and family factors were associated with psychotropic medication use

among children in Manitoba with ASD and how these characteristics and medication use and intensity differ between children with ASD and the general population of children in Manitoba. This discussion will review the results from the research questions in relation to appropriate literature and the conceptual framework.

The main findings of this study are a higher measured prevalence of ASD among children and youth in Manitoba than that which was previously reported and that a greater proportion of children with ASD used psychotropic medications during this period than children in the general population. Upon consideration of demographic, social and family environmental factors, the population of children with ASD was found to be different from the population of children without ASD. Furthermore, among children with ASD, those who use psychotropic medications are different from those who do not use psychotropic medications and among all children who use psychotropic medications, children with ASD are different from those in the general population. Lastly, this study found that children with ASD use medication differently and with a greater intensity than children in the general population cohort.

5.1 Prevalence of ASD for children and youths in Manitoba

The prevalence of children and youths in Manitoba with ASD aged 0 to 18 years old was 1.28% (1 in 78 children) during the five-year period of 2009/10 – 2013/14. A similar percentage of children diagnosed with ASD was observed when considering other commonly reported age groups, such as 1.21% of children (1 in 82 children) 0- to 14-years-old and 1.25% of children (1 in 80 children) 5- to 9-years-old. This is an increase from the previously reported prevalence for Manitoba children aged 5- to 9-years-old of 0.49% in 1996/97 – 2000/01 and 0.88% in 2001/02 – 2005/06 (Brownell et al., 2008).

The prevalence determined in this study was, as hypothesized, higher than previously reported in Manitoba. The current Manitoban prevalence of 1.21% falls within the previously reported Canadian ranges of 0.83% and 1.30% (Ouellette-Kuntz et al., 2014) for children aged 0 to 14 years old. The Manitoba prevalence for 5- to 9-year-olds remains below the most recently reported CDC prevalence of 1.47% among 8-year-olds in the United States (CDC, 2014).

Comparing the previously reported Manitoba prevalence with that produced in this study demonstrates that the overall prevalence of ASD increased in Manitoba. This study, has not, however, established the cause for this increase and whether it is a true increase in the population prevalence of ASD or is due to changes in diagnostic practices, increased ASD awareness or increased access to diagnostic services. Previous studies comparing ASD prevalence rates have been criticized for not accounting for changes in diagnostic criteria in a population or comparing results that were obtained using different ASD diagnostic rating scales or definitions (Matson & Kozlowski, 2011). The current study used the same ASD definition from the same administrative database in the same geographic population as Brownell et al. and therefore the prevalence of ASD from these studies can be compared. The current study considered a later time period than the previous study, and it is possible that diagnostic shifts may have occurred over time due to changes in physician practice, including changes in competency or anticipation of DSM-5 diagnostic changes. The presence, likelihood and influence of these possible changes were not addressed.

The current prevalence rate for ASD in Manitoba is important to establish in the time period considered in this study. As previously discussed, the diagnostic prevalence of ASD may change with the new definitions released in the DSM-5. The 2009/10 – 2013/14 prevalence rate

and the characteristics of children currently diagnosed with ASD will be a useful comparison for future studies to determine if there has been a change in diagnosis patterns or a diagnostic drift among children with ASD.

5.2 Prevalence of psychotropic medication use among children with ASD

Almost half of all children with ASD considered in this study were found to have ever had a psychotropic medication. Published prevalence values for psychotropic medication use among children with ASD range widely. A recent study from the North American Autism Speaks Autism Treatment Network (ATN) of almost 3000 children aged 2 to 17 years who were diagnosed with ASD, found that 27% received one or more psychotropic medications (Coury et al., 2012). The period prevalence of ever having used a psychotropic medication in the cohort of children with ASD in Manitoba examined in this study was much greater than this published value. Psychotropic medication use was determined in the ATN study by parent report in an intake questionnaire of current psychotropic medication use (Coury et al., 2012), while the current study considered all available administrative medication data during the lifetime of each child diagnosed with ASD. The ATN study sample consisted of children whose families chose to participate and enroll in the network registry and whose diagnosis was confirmed using a consistent set of assessments, while the current study considered all children with a health or education record of ASD. These study variations are important to consider because the Manitoba sample may include children with non-confirmed ASD diagnoses and the ATN study missed medication use that occurred before and after study enrollment, likely influencing the predicted population medication use prevalence. Furthermore, the current study included all children in Manitoba with a diagnosis of ASD and therefore was not influenced by selection

bias. This difference in study sample and medication use reporting is likely to account for some of the variation in drug use prevalence.

While there are differences in the reporting of medication use that could skew this comparison, it is important to consider that almost half of all children in Manitoba with ASD have ever received a psychotropic medication. Furthermore, this study showed that 44% of all children in Manitoba with ASD used one or more psychotropic medications for at least 30 consecutive days during their lifetime. As discussed in the introduction, while these medications can have a positive effect on improving and managing challenging behaviour and mental health conditions, they are not specifically approved for use in children with ASD and can have serious lasting side effects. These results contribute valuable insight into the number of children with ASD that are using psychotropic medications and point to directions for future analyses required to determine whether this level of use is appropriate.

5.3 Comparisons among all children and youth in Manitoba – with and without ASD

As outlined in section 4.3, the population of children with ASD in Manitoba has unique characteristics compared to the general population cohort of children. A greater proportion of children with ASD are male, have a co-occurring mental disorder diagnosis, have a sibling diagnosed with ASD or a mother with a history of mental disorders when compared to children in the general population cohort. These two groups of children also varied in age distribution and their level of SES, when considered on a regional level. Each of these differences in characteristics between the two cohorts of children are discussed in greater detail below.

5.3.1 Demographic Characteristics

The population of children with ASD was significantly different from the general population in the proportion of males and females and the age distribution (Table 4.1). It is well described that ASD is significantly more common among males than females; the current study further demonstrated this, with 80% of children diagnosed with ASD recorded as males in population registry data (Table 4.1). The male (2.03%) and female (0.53%) specific prevalence values in Manitoba are similar to those reported in the United States by the Centre for Disease Control (male: 2.37%, female: 0.53%) (CDC, 2014). Compared to the general population cohort, there was a larger proportion of children with ASD over the age of 10 (Table 4.1). The proportion of children in the youngest age group was smaller than in the general population cohort, likely because children are diagnosed with ASD at all ages and not just as preschoolers. Furthermore, some children with ASD in the 0- to 4- years-old age group may have not received a diagnosis yet, and were therefore included in the general population cohort.

While the mean SEFI-2 scores comparing all children with ASD to the general population of children in Manitoba were not significantly different ($p = 0.6741$, Table 4.1), differences were noted when SES was considered by region. For example, in Winnipeg and the Southern health region, children with ASD generally tended to live in less favourable socioeconomic conditions than the general population cohort ($p=0.0003$ and $p=0.0045$, respectively). However, children with ASD in Northern Manitoba tended to live in more favourable conditions when compared to the general population of children ($p <0.0001$, Table 4.1). These results are not entirely consistent with previous population research in Manitoba, which found that area-level income was not associated with ASD prevalence in urban areas whereas higher ASD prevalence was associated with higher income in rural areas (Brownell et al., 2008). The results of these two

studies can not be directly compared, however, as Brownell et al. used income/area to stratify the population and compared prevalence rates whereas the current study stratified the population by ASD diagnosis and compared mean SES indicator scores. Interestingly, both studies describe a similar characteristic in the Manitoba population at different time points with conflicting results.

The results of this study contribute to the broader inconclusive discussion of whether there are inequalities in SES among children with ASD and if these inequalities match those observed in the general population of children. This study shows that while there is no significant difference in the overall Manitoba mean SES index score between children with ASD and those in the general population, there are significant differences when considered at a regional level. The differences shown in Northern Manitoba, where children with ASD have a lower mean SEFI-2 score, and therefore live in higher SES areas, may suggest that there is inequity in access to diagnostic services in this region. Northern Manitoba includes large remote areas where access to specialist services can be challenging and infrequent. It is possible that this barrier to diagnostic services for children who live in lower SES areas of Northern Manitoba has contributed to the prevalence difference. Children in lower SES areas of Northern Manitoba may also be under the care of salaried physicians who may not be submitting claims, which would lead to an underestimation of ASD prevalence in this population.

Additionally, previous studies have found that there were financial implications for a family with a child with ASD. Two American studies, one based on a national survey and the other a cohort study, considered the associations of a family with a child with ASD and

household income and parental employment (Cidav, Marcus, & Mandell, 2012; Montes & Halterman, 2008). These studies found that parents of children with ASD were less likely to both be working, or work less if they were employed and that these families experienced a loss in annual household income as a result of having a child with ASD (Cidav et al., 2012; Montes & Halterman, 2008). This pattern may be experienced by parents of children with ASD in Winnipeg and the Southern health region, leading to the results found in this research. Access to diagnostic services in these two areas of Manitoba are likely more equitable than in more remote areas and therefore other factors, such as parental employment and income, could influence the association of region and SES with ASD diagnosis.

The association of ASD diagnosis and area level SES demonstrates the bi-directional nature of the individual, family and area levels of the conceptual framework. This association could manifest in a lower prevalence of ASD diagnosis among children whose families have fewer resources and variable access to diagnostic services, or families who experience a reduction in annual household income after an ASD diagnosis. This relationship could be further elucidated in future research through consideration of ASD diagnosis and changes in SES over time.

5.3.2 Psychiatric Conditions

In this study of children and youth in Manitoba, more children with ASD had a diagnosed psychiatric condition when compared to the general population cohort. Children with ASD in Manitoba experience a large number of diagnosed psychiatric conditions, with most children (70.4%) having 1 – 3 diagnosed psychiatric conditions and 10.6% with 4 or more diagnosed

psychiatric conditions additional to ASD (Table 4.7). This is significantly greater than among children in the general population cohort, where over 80% of children do not have a diagnosed psychiatric condition (Table 4.3). Although the population prevalence of children with ASD in Manitoba is just over 1%, the prevalence of children with ASD among all children in Manitoba with at least one diagnosed psychiatric condition is 5%. The association of mental disorders and ASD will be discussed in more detail in section 5.4.2.

5.3.3 Family Environment

The impact of family environment conditions on the prevalence of ASD has been widely discussed and researched with little true consensus. This study outlined a few of these characteristics and found that they all differed between the population of children with ASD and those in the general population cohort. As expected, more children with ASD have siblings also diagnosed with ASD, when compared to children in the general population (Table 4.4). ASD is generally understood as a heritable disorder that is associated with some unique genetic features (Miles, 2011). While the genetic etiology of ASD is not completely understood, it is well accepted that siblings and family members of individuals with ASD have an increased risk of experiencing similar symptoms and of receiving an ASD diagnosis. One prospective longitudinal cohort found that over 18% of siblings of children with ASD also received an ASD diagnosis (Ozonoff et al., 2011). The current study found a slightly lower proportion of siblings with ASD (14.01%), which was significantly different from the general population (1.23%, $p < 0.0001$). Ozonoff et al. considered siblings that had been actively screened for ASD using standardized measures and expert clinicians. Inclusion in the current study was not dependent on either standardized measures nor that expert clinicians were involved in the diagnostic process,

although it is assumed that most children in Manitoba receive an ASD diagnosis, or some consultation, at the Child Development Clinic in Winnipeg. These differences in inclusion criteria could contribute to the different sibling recurrence rate.

Increased maternal age has been suggested in the literature to be a risk factor for a childhood diagnosis of ASD, though the link is not well characterized nor has it been found to be true in all populations (Idring et al., 2014; Lampi et al., 2013). The distribution of maternal ages for children in the two Manitoba cohorts considered in the current study was significantly different ($p < 0.0001$), with mothers of children with ASD tending to be older at the birth of the index child (Table 4.4). The current study did not consider the risk for ASD diagnosis associated with increased maternal age however, this observed difference in the Manitoba population follows current published trends.

Mothers of children with ASD in Manitoba have different levels of mental disorder history than mothers of children in the general population cohort. More than half of all mothers of children with ASD experienced at least two mental disorder diagnosis within any three-year period, with 13.9% experiencing at least 1 hospitalization and 1 medical claims visit within any three-year period for a mental disorder (Table 4.4). This study also found high rates (60.1%) of mental disorder diagnoses among mothers of children in the general population. Maternal mental disorder prevalence often focuses on perinatal anxiety and depression (Bennett, Einarson, Taddio, Koren, & Einarson, 2004) and does not have as wide and broad a scope and timeframe as this study. One recent study in Manitoba found that approximately 20% of children have a mother who has experienced a mood or anxiety disorder (Brownell et al., 2012). The significantly higher rates found in the current study are likely due to the use of a broader

definition of mental disorder used, which included more disorders and considered more years of data. Furthermore, this variable was not designed to provide a comprehensive representation of experienced maternal mental disorder history. Standardized measures of maternal mental disorders specific to severity, recurrence and persistence, are not captured in the administrative databases that were used for this study. Instead this study relied on a recorded mental health condition diagnosis for a wide range of mental disorders. There are different patterns of presentation of severity, recurrence and persistence which likely vary among the population of mothers in Manitoba, which is why this broader definition was considered.

As previously discussed, the mechanism by which maternal mental disorder and child ASD diagnosis are related is not understood – with genetic, prenatal and family environmental factors, including the stress associated with having a child with a developmental disability, as possible influences on both mother and child. Previous research has found an association with child ASD diagnosis both when a parental mental disorder diagnosis occurs before and after the child's diagnosis and/or birth (Daniels et al., 2008). The current study did not determine which diagnosis occurred first, the mother's or the child's. As such, the consideration of maternal mental disorder history in this study is a non-specific and broad measurement that is meant to add to the discussion of possible influential factors. It was beyond the scope of this study to determine the direct impact of maternal mental disorders on childhood ASD diagnosis and psychotropic medication use, and therefore was considered in this broad manner. The results demonstrate that there is a significant difference in this broad measure of mental disorder

history between mothers of children with ASD and mothers of children in the general population and therefore this may be an area of future research.

A greater proportion of children with ASD (6.18%) had been taken into care by CFS than of children in the general population (4.10%, Table 4.4). This result is in line with previous findings that children in the care of CFS in Manitoba had a higher proportion of both developmental disabilities and mental disorders when compared to children that had never been in the care of CFS (Brownell et al., 2015). Children in Manitoba can be taken into care by CFS because a child has a disability or emotional or behavioural difficulties that may be more difficult for parents to manage in the home (Brownell et al., 2015) and therefore this difference is expected.

Some populations of children may be under increased health or social surveillance due to geographic setting, maternal or family characteristics or interaction with child welfare services. This study found that more children with ASD had mothers with a history of mental disorders, had a sibling with ASD and had been taken into care by CFS. While these findings may suggest that children with ASD are more likely to have these family or social experiences, they may also point to populations of children that are more exposed to health and social systems and therefore are under increased surveillance for ASD or other mental health conditions. These connections and surveillance could lead to recognition of ASD symptoms and an eventual diagnosis. Therefore, such interactions between the health and social systems environment and the family/parental environment of a child, as diagrammed in the conceptual framework, could contribute to a child receiving an ASD diagnosis.

5.4 Comparisons among children with ASD, with and without psychotropic medications

In section 4.4, the population of children with ASD in Manitoba who had received a psychotropic medication was compared to children with ASD who had never received a psychotropic medication. Children with ASD were more likely to receive a psychotropic medication if they were older at the age of diagnosis, had a co-occurring mental health diagnosis, received special education funding, interventions at MATC, had a sibling with ASD or had been taken into care by CFS. Children with ASD with and without a psychotropic medication did not differ by sex, region, SES, maternal age at birth of index child or maternal mental disorder characteristics. Each of these differences between the cohorts are described in more detail below.

5.4.1 Demographic Characteristics

Sex differences among children with ASD have been studied with few consistent findings, and therefore it is not well understood if male and female children with ASD differ in social, language or communication deficits (Reinhardt, Wetherby, Schatschneider, & Lord, 2015). The current study found that male children with ASD were not more likely to receive psychotropic medications than female children (OR = 0.99, CI = 0.78 – 1.27, Table 4.5). Previous studies considering psychotropic medication use among children with ASD have also found non-significant associations with male sex (Logan et al., 2015; Spencer et al., 2013). As such, the absence of sex differences in psychotropic medication use found in this study may be attributable to the similarity of challenging behaviour and comorbid conditions experienced by female and male children with ASD in Manitoba.

Children with ASD were more likely to receive a psychotropic medication if they were older, with adolescents over the age of 15 having a 3.5 times greater odds of receiving a psychotropic medication compared to children with ASD between ages 0 and 4 (CI = 2.14 – 5.72, Table 4.5). This age-related increase in medication use has also been observed in previous studies of children with ASD (Bachmann et al., 2013; Spencer et al., 2013) and may be associated with an increase in challenging behaviours including aggression (Logan et al., 2015) that become more difficult to manage as a child ages.

The percentage of children in the ASD cohort with a psychotropic medication closely mirrored the number of children with ASD and without a psychotropic medication in all health regions of Manitoba with the exception of Southern. In the Southern health region significantly fewer children received a psychotropic medication ($p = 0.0104$, Table 4.10). When compared to children in Prairie Mountain, where almost the same number of children with ASD received a psychotropic medication as did not, none of the other regions were associated with a significantly increased or decreased odds of psychotropic medication use (Table 4.10).

The influence of socioeconomic factors was also considered by health region and was not found to significantly influence the odds of psychotropic medication use, except for Winnipeg where children with ASD and psychotropic medications were more likely live in lower SES areas (OR: 1.11, CI: 1.01-1.21, Table 4.10). Previous studies have found no difference in psychotropic medication use between rural and urban children with ASD (Logan et al., 2015). However, children in Manitoba living in rural areas have been previously found to have different health outcomes when compared to urban children, including higher rates of some poor outcomes (Brownell et al., 2008). This difference in health outcomes was expected to be

reflected in some difference in medication use across the health regions, however, it was not found.

5.4.2 Psychiatric Conditions

Children with ASD in Manitoba experience high levels of delays in development (44.3%), hyperkinetic syndrome of childhood (42.3%), conduct disturbance (27.5%) and neurotic disorders (21.7%) (Table 4.7). However, children in the ASD cohort of this study had lower rates of neurotic disorders (including anxiety or phobic disorders) than those previously reported (41.9%) (Simonoff et al., 2008). These levels of psychiatric conditions likely influence rates of psychotropic medication use and the types of medications that are prescribed in this population.

Hyperkinetic syndrome of childhood was one of the most common co-occurring conditions among children with ASD in this study – it is best characterized by the common condition ADHD. ADHD has been widely found to have high prevalence among children diagnosed with ASD, despite previous diagnostic criteria excluding concurrent diagnosis of ADHD and ASD (Simonoff et al., 2008; Taurines et al., 2012). The current study found a higher rate of ever diagnosed comorbid hyperkinetic syndrome diagnosis (42.3%, Table 4.7) than a previously reported rate of 21.5% (Close, Lee, Kaufmann, & Zimmerman, 2012). One other previous study reported a weighted 3-month period prevalence of close to 30% (Simonoff et al., 2008). These previous studies have also commented on the similarity of symptoms or behavioural challenges experienced by children with ASD and/or ADHD, suggesting that although the core diagnostic symptoms of these two conditions do not overlap, children with ASD commonly experience inattention and hyperactivity and those with ADHD may have

challenges with social interactions (Taurines et al., 2012). Furthermore, a previous study that measured ASD and ADHD symptom severity in children using standardized rating scales concluded that children with co-morbid conditions experienced a higher severity of ASD symptoms (Sprenger et al., 2013). The population of children in Manitoba with ASD and hyperkinetic syndrome is large and may present an opportunity to better understand these common conditions.

The current study did not establish if the prevalence of ASD with other co-occurring psychiatric conditions reflects mild or severe symptoms in each condition, nor has it considered which diagnosis occurred first. Furthermore, this study was not able to determine if an ASD condition was "lost" over time due to misdiagnosis and reclassification with a different psychiatric condition, as has been suggested to occur (Close et al., 2012). These are important considerations when determining psychotropic medication use, as increased symptom severity may be correlated with increased medication use and the diagnosis of a co-morbid psychiatric condition and subsequent "loss" of ASD diagnosis should exclude children from the ASD population. These same considerations must be made when considering psychotropic medication use among children without ASD – they too may experience increasing severity of symptoms, diagnosis of co-morbid conditions, or shifting diagnoses.

Most of the co-morbid diagnosed psychiatric conditions were associated with increased odds of receiving psychotropic medications among children with ASD. Affective psychoses (OR = 7.27, CI = 2.33 – 22.76), emotional disturbance (6.08, 2.38 – 15.55) and hyperkinetic syndrome (5.33, 4.32 – 6.56, Table 4.7) had the greatest association with a child receiving a psychotropic medication. The mental disorder category of affective psychoses includes conditions such as

manic-depressive psychosis and schizophrenia. These conditions along with other mood disorders are effectively treated with psychotropic medications, such as atypical antipsychotics and antidepressants (Ben Amor, 2012; Doey, 2012; Hazell & Jairam, 2012). Hyperkinetic syndrome is also commonly managed in children through the use of psychostimulants and some antipsychotic medications (Gorman et al., 2015). These comorbid conditions that are effectively and commonly treated with psychotropic medications could therefore be a consideration and causative factor for medication prescription in the population of children with ASD. In the current study population of children with ASD and a psychotropic medication, only 6.7% did not have a diagnosed co-morbid psychiatric condition, thus supporting the possibility that psychotropic medications were used to manage co-morbid conditions (Table 4.7).

5.4.3 Health and Education Variables

Children with ASD who were older at the age of diagnosis, received special education funding or behavioural programming at MATC were all significantly more likely to receive psychotropic medications (Table 4.6). These three variables may all suggest more complex or severe symptoms or diagnoses that result in a child receiving additional school-aged services and psychotropic medications. Additionally, resource guides for psychotropic medication prescribing practices strongly suggest that psychosocial interventions that serve to improve communication, social and language skills should be available and in place for children when providing psychotropic medications (Rosenberg & Gerson, 2002). Although not all children with ASD and a psychotropic medication were found to be receiving special education funding or MATC programing, it is important that there was an association with these interventions and

use of psychotropic medications. This suggests that some children are receiving a form of non-pharmacological intervention to assist with social and communication skills in addition to psychotropic medications to help manage challenging, aggressive or potentially harmful behaviours. The results from the current study highlight the association between exposure to education and behavioural treatment interventions and medication use, and provides an example of how the education and intervention environment a child is in can influence whether they receive a psychotropic medication, as outlined in the conceptual framework.

One previous study of youths involved with mental health services found that the education system was an important source of referrals into mental health services, including psychotropic medication use (Farmer, Burns, Phillips, Angold, & Costello, 2003). This may also be occurring in the population of children and youth in Manitoba with ASD and could contribute to the association between the use of psychotropic medication and special education funding. The current study did not consider which of the three severity specific levels of special education funding each child received. Further analysis of funding levels may help to clarify the relationship between special education funding and psychotropic medication use.

Previous literature has not determined consistent factors associated with age at diagnosis; one study demonstrated that children with typically presenting ASD symptoms, such as severe language deficits and hand flapping, have been found to receive diagnoses at a younger age (Mandell et al., 2005). It is possible that children who are diagnosed before age 5 are able to receive EIBI, such as ABA, prior to entering formal education and therefore do not go on to receive psychotropic medications. Children with more complex behaviours and those

who do not demonstrate these typical ASD symptoms may be more likely to receive a later diagnosis and in turn a psychotropic medication.

5.4.4 Family Environment

Maternal age at birth of the index child and maternal mental disorder history were not found to be significantly associated with psychotropic medication use among children with ASD. Maternal mental disorder history did significantly increase the odds of a child receiving a psychotropic medication in the univariate analysis (Appendix Table D.3), but once other factors were adjusted for it was no longer significant in the multivariable model (Table 4.9). It is possible that underlying genetic, prenatal or family environmental factors that could be represented in an analysis of maternal mental disorder history were also associated with the occurrence of a child's comorbid psychiatric conditions or other characteristics which could account for the influence of maternal mental disorder history.

While co-occurring mental disorders was shown in this study to be very strongly associated with psychotropic medication use among children with ASD, family and intervention factors were also found to increase the likelihood of this outcome. As discussed in section 5.3.3, interactions with health, education and social supports and interventions may influence if a child receives a psychotropic medication due to increased surveillance or improved access to services through these connections.

5.5 Comparisons among children with psychotropic medications - with and without ASD

Section 4.4 describes the population of children in Manitoba who have ever received a psychotropic medication, comparing children with a diagnosis of ASD to those in the general population cohort. In this population of children, those diagnosed with ASD were significantly

different from those without ASD in the description of each group by sex, age, mental health conditions, age at first prescription and the family characteristics of maternal age at index birth, maternal mental disorder history and presence of a sibling with ASD. The proportion of children in each region varied in Northern, Prairie Mountain and Winnipeg health regions. Mean area-level SES was different when comparing all children, and when comparing those children who lived in Winnipeg. There was no difference in the proportion of children with a psychotropic medication who had ever been in the care of CFS when stratified by ASD diagnosis. Each of these differences is discussed in detail below.

5.5.1 Demographics

A significant difference persisted in the proportion of males in the cohort of children with ASD and a psychotropic medication compared to children with a psychotropic medication in the general population ($p < 0.0001$, Table 4.10). A difference in age distribution was also seen in the comparison of all children with a psychotropic medication, with a greater proportion of children with ASD aged 10- to 14-years-old ($p < 0.0001$) than in the population of children without ASD (Table 4.10). The percent of children with ASD with a psychotropic medication was lower among children aged 0- to 4-years-old, likely due to fewer children being diagnosed at this age and therefore receiving medications (Table 4.10).

The proportion of children with ASD and a psychotropic medication was different from the proportion of children without ASD and a psychotropic medication in the Northern, Prairie Mountain and Winnipeg health regions ($p <0.0001$ for these three regions, Table 4.10). Considering all children with a psychotropic medication, in the Northern and Prairie Mountain health regions there was a smaller proportion of children with ASD than of children in the

general population. The opposite was true in Winnipeg, where there was a greater proportion of children with a psychotropic medication and ASD living in Winnipeg then was seen in the general population.

Little variation in SES was observed among the population of all children with a psychotropic medication. Children with ASD in this population, on average, tended to live in areas of higher SES ($p = 0.0002$, Table 4.10). However, within all regions except Winnipeg, children with psychotropic medications did not have different average SEFI-2 scores when comparing children with an ASD diagnosis to those without an ASD diagnosis. In Winnipeg, children with ASD tended to live in areas with higher SES when compared to other children with a psychotropic medication ($p = 0.0044$, Table 4.10).

5.5.2 Psychiatric Conditions

Among all children with a psychotropic medication, children with ASD had a higher proportion of diagnosed psychiatric conditions, with 94.3% experiencing at least one co-morbid condition compared to 52.3% experiencing at least one psychiatric condition in the general population cohort (Table 4.11). Children with ASD and psychotropic medication had higher proportions of co-occurring conditions such as depressive disorder – not otherwise classified ($p<0.0001$), disturbance of conduct ($p<0.0001$), disturbance of emotions specific to childhood and adolescence ($p<0.0001$), hyperkinetic syndrome of childhood ($p<0.0001$), neurotic disorders ($p<0.0001$), special symptoms ($p<0.0001$) and other conditions. The influence of some of these conditions on psychotropic medication use has been discussed in section 5.4.2, however these results suggest a significant burden of psychiatric conditions among children with ASD. Furthermore, while psychotropic medications have been prescribed for ASD

symptoms and co-occurring conditions, it is important to emphasize that, as previously established, pharmacological treatment of comorbid conditions in children with ASD has not been well studied (McGuire et al., 2016). Given that it has been suggested that children with ASD may be more sensitive to possible adverse effects of these medications (Rosenberg & Gerson, 2002), prescriptions should be provided with caution.

5.5.3 Family Environment

Children with ASD and a psychotropic medication had different family environment characteristics when compared to children with a psychotropic medication without ASD. Mothers of children with ASD were older than mothers of children with out ASD ($p < 0.0001$, Table 4.12). There was also a significant difference in the maternal mental disorder history between children with ASD and a psychotropic medication and children without ASD and with a psychotropic medication ($p = 0.0003$, Table 4.12). These differences reflect those observed in the initial comparisons of all children with ASD and the general population cohort, and therefore it is likely an extension of the overall population characteristics.

In the comparison of all children with a psychotropic medication, there was no difference between the proportion of children who had been in care in the cohort of children with ASD and those without ASD ($p = 0.9825$, Table 4.12). Increased use of psychotropic medications among children involved in child welfare services has been found in several North American populations (Calleja & Alavi, 2012). In a qualitative Canadian study of youths involved in child welfare services, 70% of participants reported using psychotropic medications (primarily psychostimulants), while in care (Lambe, McLennan, & Manser, 2009). Previous analyses have suggested possible explanations of these high rates of psychotropic medication use, such a

child's experience of depression, grief or challenging behaviour in response to being apprehended, an increased prevalence of mental disorders and behaviour problems among children in care, and an overreliance on psychotropic medications in a reactive, instead of proactive, treatment environment (Calleja & Alavi, 2012; Lambe et al., 2009). Children in care with and without ASD are experiencing higher rates of psychotropic medication use than children who are not in care – suggesting another important area for future research to determine the cause of these variations.

5.6 Psychotropic medication use and intensity among children with ASD and children without ASD

Psychotropic medication use and intensity were determined during the final year of this study period (2013/2014) for all children considered in the study population. The strengths and limitations of this method are highlighted in section 5.8. Of those children who received a psychotropic medication during this time period, children with ASD were more likely to receive more than one psychotropic medication when compared to children in the general population. The regression model used in this study demonstrated an association between an increased rate of number of psychotropic medication types and diagnosed psychiatric conditions (including ASD diagnosis), male sex, sibling diagnosed with ASD and a child having ever been in care of CFS (Table 4.16).

This regression model found that a diagnosis of ASD had the largest RR, such that children with the same psychiatric conditions and child demographic characteristics had a 69% increased rate of number of medications used if they also had a diagnosis of ASD. This analysis demonstrated that children with ASD are receiving a greater number of types of medications

than children without ASD, even when demographic, family and co-morbid psychiatric conditions are considered. Furthermore, this regression model demonstrated that diagnosed psychiatric conditions are associated with an increased number of psychotropic medications. As previously discussed, these conditions are commonly and effectively treated with psychotropic medications and therefore this association with psychotropic medication use supports the conclusion that the presence of co-morbid conditions is likely contributing to psychotropic medication prescribing practices for children in Manitoba.

Intensity of psychotropic medication use was also measured by comparing mean DDD received in the final year of the study for all children. Although DDD has not been validated as a measure of medication intensity among children, it was used as a comparative measure in this analysis in a population of children. This comparison showed that children with ASD received a greater mean DDD of antiepileptic medications ($p < 0.0001$) and anxiolytics ($p = 0.0109$, Table 4.15) compared to children without ASD. The current study did not consider the prevalence of epilepsy in this population, yet, one previous retrospective prevalence study reported that a greater proportion of hospitalized children with ASD experienced epilepsy when compared to a general youth hospital population (Kohane et al., 2012). If a similar trend in epilepsy prevalence exists among children with ASD in Manitoba, then this could explain the increased DDD of antiepileptic medications. The anxiolytic class includes lorazepam, diazepam and hydroxyzine medications which are used to treat anxiety and tension (WHO Collaborating Centre for Drug Statistics Methodology, 2015a) - symptoms of neurotic and other mental disorders. Comparing all children with a psychotropic medication, a greater proportion of children with ASD experience neurotic disorders (Table 4.11). Additionally, in the multivariable zero-inflated

negative binomial regression model, neurotic disorders were associated with an increase in DDD (RR = 1.71, $p < 0.0001$, Table 4.17). This further supports the conclusion that children with ASD are receiving medications to treat symptoms associated with co-morbid conditions.

Antipsychotic medications have demonstrated effectiveness in managing symptoms of challenging behaviour in children with ASD and were the most commonly used medication among children with ASD (Table 4.13). Among children with a psychotropic medication, those with ASD had a greater proportion of antipsychotic medications than children in the general population (Table 4.13), however, there was no significant difference ($p = 0.3903$, Table 4.15) between the mean DDD of antipsychotic medications between these groups. Some antipsychotics are used in children for other non-indicated conditions, which could be influencing measured DDD. For example, one recent American study of national trends in the use of atypical anti-psychotic medications among 4-to 18-year-olds found that the majority of physician visits that resulted in a prescription of an atypical anti-psychotic medication were for a non-indicated conditions (Sohn, Moga, Blumenschein, & Talbert, 2016). The most commonly non-indicated mental disorder diagnoses associated with atypical antipsychotics were found to be hyperactivity disorder, psychoses, disturbances and neurotic disorders. This study also determined that 15% of these visits were not associated with a mental disorder (Sohn et al., 2016).

When compared to children with ASD, children without ASD received a greater mean DDD and a greater percentage of total number of prescriptions of antidepressant (both $p < 0.0001$) and psychostimulant medications (both $p < 0.0001$, Table 4.14, and 4.15)). Among all children with a psychotropic medication however, children with ASD were more likely ($p <$

0.0001) to be diagnosed with depressive disorder (not otherwise classified) and hyperkinetic syndrome of childhood – psychiatric conditions that are typically treated with antidepressant and psychostimulant medications respectively. Adjustment reaction, which includes both brief and prolonged depressive reaction, was not significantly different between children with ASD and children in the general population. This discrepancy could be due to the large proportion (47.8%, Table 4.11) of children in the general population who were receiving psychotropic medications yet did not have a diagnosed psychiatric condition. It is possible that some diagnoses, including those for depressive disorder or hyperkinetic syndrome, were not captured in this study, that a formal diagnosis was not made for these conditions or that antidepressant and psychostimulant medications were used in the general population for non-psychiatric indications, leading to the observed results.

The regression model considering DDD in the final year of the study showed that there were significant associations of increased DDD for the child characteristics of male sex, increased age, ever having been in care of CFS and having no siblings (Table 4.17), demonstrating that individual and family environment factors are associated with the use of psychotropic medications among children. Increases of DDD associated with increases in age likely correspond to increases in body weight and therefore an increase in medication dose. SEFI-2 score, maternal diagnoses of psychiatric conditions, region of residence and maternal age of 20 – 29 years and 30 – 39 years at the birth of the index child were also associated with increased rates of DDD. Diagnosed psychiatric conditions, including ASD, had the largest RRs and therefore have the greatest associations with increased DDD. Hyperkinetic syndrome had the largest adjusted RR, so that children with a diagnosis of hyperkinetic syndrome had a 23.30

times increased DDD in the final year of the study ($p < 0.0001$, Table 4.17). Children with depressive disorder (not otherwise classified) also had a large RR of 8.25. A diagnosis of ASD was associated with a 3.68 times increased rate of DDD ($p < 0.0001$, Table 4.17) in this analysis. Along with the outcomes from the previous regression model, these results support the conclusion that children with ASD receive a greater number and intensity of psychotropic medications than children in the general population with similar demographic and psychiatric conditions.

5.7 Understanding psychiatric medication in children with ASD within the context of a culture of Autism.

Increased prevalence of ASD, a broad range of intellectual and social capabilities, and improved accessibility to media sharing platforms for individuals with ASD, has led to both an understanding of Autism as a distinct culture, and the neurodiversity movement. This movement and manner of conceptualizing ASD as a disability, a difference and a culture provides a unique perspective to understanding the context in which children with ASD are provided with a greater number and intensity of psychotropic medications than children without ASD. Joseph Straus argues in his essay “Autism as Culture” that medical models of ASD, which change in relation to technology and medical paradigms, have led to a narrowed deficit view of autism and people diagnosed with ASD, such that current intervention strategies may attempt to diminish or eliminate autistic characteristics in an individual. As an alternative, Straus presents a social model of autism where “autistic” is viewed as a valued identity to be claimed and celebrated (Straus, 2013). He argues that the traits used to define and diagnose ASD can be reframed as local coherence (detail-focused processing), fixity of focus (a

preference for repetition, orderliness, system and ritual), and private meanings (associations without reference to social convention and communication styles). Straus exemplifies these traits through high-culture works of writing, music and art created by individuals self-identified or diagnosed with autism – noting, however, that these traits also exist in the "culture of the everyday" for people along the autism spectrum.

The viewpoints of supporters of the neurodiversity movement and the medical model of autism treatment have been detailed well elsewhere (a concise explanation can be found in Kapp, Gillespie-Lynch, Sherman, & Hutman, 2013). In brief, individuals with ASD who are able to self-advocate and their supporters within the neurodiversity movement are opposed to practices that seek to prevent, cure or eliminate autism. Instead, these individuals celebrate autism as an inseparable component of a complex identity. Medical models are typically seen in opposition and are often championed by parents of children with ASD and health researchers. Proponents of this counterpoint seek to elucidate etiology to prevent ASD and treatment strategies to stabilize behaviour and reach an improved level of functioning, or "normalcy". This perspective can be seen in most of the medication effectiveness and prevalence studies cited in the current study. There are, however, significant intersections between these approaches to autism. Both viewpoints include the perspective that while negative aspects of autism may exist, it is also possible to place emphasis on the "deficit-as-difference" concept of autism. This concept promotes autism, and other neurologically complex conditions, as valid variations within human cognitive diversity. Importantly, it allows for both a recognition of autism as a unique identity and treatment to ameliorate of symptoms that can diminish quality of life.

Psychotropic medication use among children with ASD will be considered within this context of understanding ASD, disability and behavioural interventions. Prominent use of psychotropic medications that primarily sedate or diminish 'autistic traits' that are valued by an individual with ASD, would be considered as inappropriate within the neurodiversity model. This type of psychotropic medication use could be damaging to an individual's self-determination and acceptance of autism as an inherent and important component of their own complex identity. Psychotropic medication use, and other treatment interventions, would be considered allowable within this model if they are used in a way that promotes individual self-expression while managing negative or harmful symptoms such as aggression, anxiety and depression, that can diminish quality of life. This study provides evidence that psychotropic medications are being used for some children with ASD in this manner, to help manage detrimental behaviours and co-morbid conditions. Given this context, and the importance of recognizing self-determination and identity for individuals with disabilities, pharmacological and non-pharmacological interventions should be managed and planned such that they support quality of life and individuality as defined by each person.

5.8 Strengths and Limitations

The increasing prevalence of ASD is frequently measured in child and youth populations and is of interest to health, psychiatric and education service providers. The current study contributes a comparable prevalence rate to this body of research, using a standard definition applied to a whole population of children without selection bias. While the definition used in this study has previously been used, it has not been validated within the study population of children. While the prevalence described in this study is comparable to previously published

results and is based on the actual number of children diagnosed with ASD in Manitoba in this study period, it does not account for possible misdiagnoses or other possible variations that could cause a difference between the prevalence calculated using the health and education data and the 'true' population prevalence.

The study population used for this analysis included all children who had lived in Manitoba for at least two years since birth. This allowed for the estimation of children with ASD to include all children who may have required services in Manitoba, even if for a short time, during the study period. A limitation of this population definition is that children who were diagnosed with ASD outside of Manitoba and had no further health or education claims associated with ASD while living in Manitoba would incorrectly be included in the general population cohort of this study. In a similar way, those children who do not receive a diagnosis within the medical system, do not have access to diagnostic services for ASD or whose medical diagnosis was from a salaried physician who does not submit claims would also not be identifiable through the administrative data used in this study.

The administrative data used in this study to compare outcomes for the population of children with ASD and the general population of children provided a wealth of linkable demographic, health, education and family environment data. The use of administrative data facilitated the breadth of this study, which otherwise would not have been feasible given the time and financial constraints.

Family health outcomes, generated through linkable databases, provided an additional and important level of understanding the environmental factors that can influence child health

outcomes and psychotropic medication use as outlined in the conceptual framework. This study utilized family information spanning 30 years of administrative data, allowing for a comprehensive measurement of maternal mental disorder history and sibling diagnoses of ASD. Additional family measures such as parental education and paternal mental disorder history could have also provided useful insights into the family environment, however, at present the available databases do not have sufficient information regarding these variables for all children.

Psychotropic medication use was defined and explored in this study without a restrictive focus on medication types commonly prescribed in other ASD populations. This allowed for a wide range of analyses including comparisons of types and numbers of medication used. Prescription data from the administrative database is limited to those medication prescriptions that were filled within the network of data providers. Prescriptions that were written, but not filled are not included. This study also did not determine the likelihood of a filled prescription being used by an individual. Future inquiry into medication use among children should analyze the specific types of medications used, with consideration for the non-indicated, but commonly accepted, uses for individual psychotropic medications.

A strong and validated measure of psychotropic medication intensity, similar to DDD for adults, is not available for use in child and youth populations. The use of a non-validated measure such as DDD in a population of children limits the interpretation of mean values. Acknowledging this limitation, DDD was primarily considered as a comparative variable. This measure is a difficult parameter to interpret in a pediatric population, and as such the specific DDD values were not interpreted in this study.

Analysis of medication use in the final year of the study was used to define a constant time period for comparison among all children with a psychotropic medication. The intention of this analysis was to be inclusive of all children with and without an ASD or other diagnosis, but with a psychotropic medication prescription. Use of the same time period for all children limited the variations in broad environmental factors that change over time and could influence medication use, such as the sale and marketing of medications, physician prescribing practices and available funding within the education system. However, use of this final year as the measurement point allows for unmeasured differences in the amount of time that has passed since events such as ASD or other psychiatric diagnosis, receipt of behavioural programming or special education funding that contribute to medication use. These factors were not applicable to all children considered in this study as children without an ASD or other mental health diagnosis were included in the analyses of medication use intensity. In future work, children with these characteristics could be selected for, and analyses could account for the amount of time that had passed between these events and the prescription of a psychotropic medication.

5.9 Conclusion

The population of children with diagnosed ASD in Manitoba is growing and therefore so is the number of children and youths that may require appropriate treatment interventions to manage challenging behaviour. This study characterized the population of children with ASD in relation to the general population of children. It also described the population of children with ASD using psychotropic medications and demonstrated that children with ASD use these medications more than children in the general population. The results and conclusions of this study have highlighted important areas where further research is required and determined the

population level psychotropic medication use for children with ASD. Future research and treatment planning in this area should consider the appropriateness of these patterns of medication use and equity of treatment interventions for all children experiencing mental disorders and developmental disabilities such as ASD.

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Appendix A.

Exclusion Criteria from the General Population Cohort

Children with a developmental disability: These children were identified as having at least one diagnosis claim for a specific developmental or intellectual disability, born in Manitoba on or after January 1st 1995 and with provincial health coverage since birth. These children were excluded from the comparison group. Children with any of the above ASD codes or any of the following developmental disability codes will be excluded from this sample.

- children with an approved status for special education funding due to "Multiple Handicaps" (MH) in the school enrolment data.
- Identified within the Manitoba Fetal Alcohol Spectrum Disorder Centre database as having an FAS diagnosis
- Children with any one of these diagnostic claims, at any time, in the Hospital Discharge Abstracts Data or Medical Services Data

ICD9	**ICD9 Label**
317	Mild Mental Retardation (MR)
318	Other MR
319	Unspecified MR
758.0 – 758.3	Chromosomal Anomalies (includes Down's, Patau's and Edward's syndromes)
759.81 – 759.89	Other and unspecified congenital anomalies (includes Fragile X and Prader-Willi syndromes)
760.71	Fetal Alcohol Syndrome (FAS)
ICD10	**ICD10 Label**
F70 – F73, F78, F79	Mental Retardation
F84	Pervasive Developmental Disorders
P04.3	Fetus and newborn affected by maternal use of alcohol
Q86	Congenital malformation syndromes due to known exogenous causes
Q87	Other specified congenital malformation syndromes affecting multiple systems
Q89	Other specified congenital malformations
Q90	Down's syndrome
Q91	Edward's syndrome and Patau's syndrome
Q93	Monosomies and deletions from the autosomes, not elsewhere classified
Q99	Fragile X chromosome

Source: http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1365

Appendix B.

Table B.1 Child demographic characteristics of children with no linked biological mother

	N	5517
		Count (%)
Sex		
	Male	2754 (49.92)
	Female	2763 (50.06)
Age in 2014		
	0 - 4 years	1609 (29.17)
	5 - 9 years	1629 (29.53)
	10 - 14 years	1427 (25.87)
	15 and above	851 (15.43)
Health Region of Residence in 2014		
	Interlake-Eastern	396 (7.18)
	Northern	500 (9.06)
	Prairie Mountain	928 (16.82)
	Southern	1158 (20.99)
	Winnipeg	2535 (45.95)
SEFI-2 Score		**Mean Score (Std. Dev.)**
	All	0.056 (1.06)

Table B.2 Psychiatric condition variables for all children with no linkable biological mother

	N	5517
		Count (%)
Diagnosed Psychiatric Conditions		
	Adjustment reaction	27 (0.49)
	Affective psychoses	18 (0.33)
	Depressive disorder - not otherwise classified	37 (0.67)
	Disturbance of conduct	137 (2.48)
	Disturbance of emotions specific to childhood and adolescence	16 (0.29)
	Hyperkinetic syndrome of childhood	211 (3.82)
	Neurotic Disorders	229 (4.15)
	Special Symptoms	122 (2.21)
	Specific delays in Development	191 (3.46)
	Other	32 (0.58)
	0 conditions	4777 (86.59)
	1-3 conditions	543 (9.84)
	4-6 conditions	136 (2.47)
	7 + conditions	61 (1.10)

Table B.3 Psychotropic medication and social service use variable for children with no linkable biological mother.

	N	5517
		Count (%)
Psychotropic Medication Use		
	Yes	444 (8.05)
	No	5073 (91.95)
Ever in care of CFS		
	Yes	213 (3.86)
	No	5304 (96.14)
Receipt of Special Education Funding*		
	Yes	23 (42.59)
	No	31 (57.41)

* Only includes children with ASD

Appendix C

Table C.1 Distribution of MATC behavioural programming users by region

	ASD Cohort	MATC	not MATC	
N	3234	909	2325	
	Count (%)	**Count (%)**	**Count (%)**	p-value
Health Region of Residence in 2014				
Interlake-Eastern	276 (8.53)	62 (6.82)	214 (9.20)	<0.0001
Northern	191 (5.91)	41 (4.51)	150 (6.45)	
Prairie Mountain	279 (8.63)	41 (4.51)	238 (10.24)	
Southern	444 (13.73)	77 (8.47)	367 (15.78)	
Winnipeg	2044 (63.20)	688 (75.69)	1356 (58.32)	

Appendix D.

Table D.1 Child demographics multivariable logistic regression model for children with diagnosed ASD.

N	3219	
Sex	OR	CI
Male	**1.25**	**1.04 – 1.52**
Female	*ref*	
Age in 2014		
0 - 4 years	*ref*	
5 - 9 years	**5.47**	**3.67 – 8.16**
10 - 14 years	**16.68**	**11.25 – 24.72**
15 and above	**28.19**	**18.86 – 42.13**
Health Region of Residence in 2014		
Interlake-Eastern	1.07	0.74 – 1.54
Northern	0.83	0.55 – 1.25
Prairie Mountain	*ref*	
Southern	0.71	0.51 – 0.99
Winnipeg	0.96	0.73 – 1.28
SEFI-2 Score		
All	**1.13**	**1.04 – 1.22**

Table D.2 Health and education multivariable logistic regression model for children diagnosed with ASD.

N	2953	
Age at diagnosis	OR	CI
0 - 4 years	*ref*	
5 - 9 years	**1.65**	**1.32 – 2.07**
10 - 14 years	**2.72**	**1.91 – 3.87**
15 and above	**4.70**	**2.14 – 10.31**
Special Education Funding		
Yes	**2.36**	**1.93 – 2.88**
No	*ref*	
Behaviour Programming (MATC)		
Yes	**2.87**	**2.27 – 3.65**
No	*ref*	

Diagnosed Psychiatric Conditions	OR	CI
Adjustment reaction	1.79	0.87 – 3.68
Affective psychoses	**8.00**	**2.56 – 25.02**
Depressive disorder - not otherwise classified	**3.65**	**1.82 – 7.36**
Disturbance of conduct	**1.78**	**1.43 – 2.23**
Disturbance of emotions specific to childhood and adolescence	**5.68**	**2.35 – 13.73**
Hyperkinetic syndrome of childhood	**5.33**	**4.32 - 6.56**
Neurotic Disorders	**1.96**	**1.52 – 2.53**
Special symptoms	**1.62**	**1.17 – 2.23**
Specific delays in Development	1.02	0.84 – 1.23
Other	**4.00**	**2.66 – 6.01**

Table D.3 Family environment multivariable logistic regression model for children diagnosed with ASD.

N	3180	
Sibling Diagnosed with ASD	OR	CI
Yes	**1.24**	**1.00 – 1.55**
No sibling	**1.23**	**1.04 – 1.45**
No	*ref*	
Maternal age at birth of index child		
≤ 19 years	0.95	0.58 – 1.58
20 - 29 years	1.03	0.67 – 1.60
30 - 39 years	0.88	0.56 – 1.36
40 + years	*ref*	
Maternal Mental Disorder History		
No history	*ref*	
At least 2 diagnoses in 3 years	**1.73**	**1.46 – 2.05**
At least 2 diagnoses in 3 years with at least 1 hospitalization	**2.24**	**1.76 – 2.84**
Child ever in the care of Child and Family Services		
Yes	**2.57**	**1.83 – 3.60**
No	*ref*	