The Manitoba Mothers and Fetal Alcohol Spectrum Disorder Study:

A Retrospective Population-Based Cohort Study Using Linked Administrative data

By

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A thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfillment of the requirements of the degree of

Doctor of Philosophy

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Abstract

Background: Identifying maternal risk factors associated with giving birth to children with Fetal Alcohol Spectrum Disorder (FASD) is integral to the development of effective prevention strategies, however, there are no Canadian data in this area. The objective of this dissertation was to utilize population-based linked data to generate a large, representative sample of mothers whose children were diagnosed with FASD to investigate: (1) maternal risk factors associated with giving birth to children with FASD; (2) maternal physical and health outcomes; and (3) maternal usage of health services of the study population.

Methods: A cohort of mother-infant dyads from a population of all children born in Manitoba between April 1, 1984 and March 31, 2012 who had an FASD diagnosis from the Manitoba FASD Centre from April 1, 1999 to March 31 2012, with follow-up until December 1, 2013 (study group: n=702). A control group (n=2097) matched 1:3 on date of birth of index child, region of residence, and socioeconomic status was generated to compare exposures and outcomes. Logistic regression analyses were run to determine maternal risk factors for giving birth to children with FASD, and adjusted relative rates for all mental and physical health outcomes, as well as rate of prenatal care, were calculated using generalized estimating equations with a Poisson or Negative Binomial distribution.

Results: The following maternal characteristics were identified as having a statistically significant association with giving birth to children with FASD: history of teen pregnancy, being a single mother at birth of the index child, higher gravidity and parity, having a psychiatric disorder and/or physical health disorder up to three years before the birth of the child, and having inadequate prenatal care. Women who gave birth to children with FASD were also more likely to

be involved with the child welfare system and the justice system, and to take antidepressants during pregnancy. Study group women had higher adjusted rates of substance use disorder, personality disorder, and mood and anxiety disorders before pregnancy, as well as higher adjusted rates of maternal psychological distress during pregnancy and postpartum, and antidepressant prescriptions before, during, and after pregnancy. Adjusted rates were higher among the study group for suicide completion, number of women attempting suicide, and number of attempts after the birth of the child until the end of the study period, as well as for inadequate and low prenatal care.

Conclusion: Women giving birth to children with FASD face significant social complexity, as well as a high psychiatric burden, increased risk of suicide, and are at risk for inadequate prenatal care. FASD prevention strategies are needed that address these maternal risk factors to help reduce the incidence of FASD.

Acknowledgements

Dedication

This work is dedicated to families affected by Fetal Alcohol Spectrum Disorder and for women

who need compassionate, empathic support to overcome their issues of addiction

and alcohol use.

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List of Abbreviations

aRR: Adjusted relative rate

aOR: Adjusted odds ratio

ARND: Alcohol related neurodevelopmental disorder

ARBD: Alcohol related birth defects

CFSIS: Child and Family Services Information System

CI: Confidence interval

DPIN: Drug Program Information Network

FASD: Fetal Alcohol Spectrum Disorder

FAS: Fetal Alcohol Syndrome

R-GINDEX: Graduated Index of Prenatal Care Utilization

HSU: Health services utilization

ICD-9-CM: International Classification of Disease, Ninth Revision, Clinical Modification

ICD-10-CA: International Classification of Disease, Tenth Revision, Canada

MB FASD Moms: Manitoba Mothers and FASD Study

MCHP: Manitoba Centre for Health Policy

OR: Odds Ratio

pFAS: Partial Fetal Alcohol Syndrome

PNC: Prenatal Care

RR: Relative rate

SD: Standard Deviation

SES: Socioeconomic status

Authorship Declaration

This thesis contains work that has been published and prepared for publication. All studies in this dissertation were conceptualized and executed by the candidate (Deepa Singal) in collaboration with her thesis advisory committee and thesis advisor: Dr. Marni Brownell, Dr. Dan Chateau, Dr. Ana Hanlon-Dearman, Dr. Sally Longstaffe, and Dr. Leslie L. Roos. Deepa Singal takes full responsibility for the accuracy of this thesis and was responsible for statistical analysis and interpretation. All authors on the manuscripts included in this thesis provided intellectual input on the study design, participated in the interpretation of results, and assisted with preparation of manuscript drafts. All authors approved final manuscripts.

Manuscripts generated from this thesis:

(1) Chapters 1 and 3 were used to generate a protocol paper that is located in appendix 1: Singal D, Brownell M, Chateau D, Hanlon-Dearman A, Longstaffe S, Roos LL. Manitoba mothers and fetal alcohol spectrum disorders study (MBMomsFASD): protocol for a population-based cohort study using linked administrative data. *BMJ Open 2016;6:e013330.doi:10.1136*

(2) Chapter 4: Singal D, Brownell M, Chateau D, Hanlon-Dearman A, Longstaffe S, Roos LL. Maternal risk factors for giving birth to children with FASD: A matched case-control study of the Manitoba Mothers and FASD Cohort utilizing linked administrative data. [*Prepared for publication to the Canadian Journal of Public Health*].

(3) Chapter 5: Singal D, Brownell M, Chateau D, Hanlon-Dearman A, Longstaffe S, Roos LL. The psychiatric morbidity of women who give birth to children with Fetal Alcohol Spectrum

Disorder (FASD): Results of the Manitoba Mothers and FASD Study. *The Canadian Journal of Psychiatry.* Jan 01 2017:706743717703646.

(4) Chapter 6: Singal D, Brownell M, Chateau D, Hanlon-Dearman A, Longstaffe S, Wall-Wieler E, Roos LL. Suicide and suicide attempts among women in the Manitoba Mothers FASD Cohort Study: A retrospective cohort analysis utilizing linked administrative data. CMAJ Open. IN PRESS. Accepted: July 6 2017.

(5) Chapter 7: Singal D, Brownell M, Chateau D, Hanlon-Dearman A, Longstaffe S, Wall-Wieler E, Roos LL. Prenatal care of women who give birth to children with Fetal Alcohol Spectrum Disorder in a universal health care system: A population-based retrospective cohort study utilizing linkable administrative data.

[Submitted for publication to BMC Pregnancy and Childbirth June 27, 2017]

Preface: Dissertation Organization

This dissertation is presented as a collection of studies and includes published manuscripts and manuscripts prepared for publication. This dissertation is a manuscript style thesis, thus there is some repetition of content, particularly pertaining to the methods sections. Chapters are slightly modified from the form they were prepared for publication to maintain consistency throughout this dissertation. At the start of each chapter a brief preface will provide readers with a logical link that facilitates the integration of information throughout this body of work.

Chapter 1 presents an introduction to this work, as well as pertinent background information. This chapter begins with an overview of the definition and impact of FASD, a brief overview of the FASD diagnostic process, and the prevalence of FASD. It then discusses the current data on the characteristics of women whose children are diagnosed with FASD, highlights evidence gaps in the current literature, and concludes with the study rational and a theoretical model that grounds this work, as well as specific study objectives.

Chapter 2 presents a detailed literature review of all studies investigating maternal risk factors associated with giving birth to children with FASD and highlights gaps in the literature.

Chapter 3 presents the methodology for the study, and includes details regarding ethics approvals, a description of data sources housed at the Manitoba Centre for Health Policy that were used for this dissertation, and an overview of the data linkage process. The chapter includes detailed descriptions of the exclusion and inclusion criteria, the final population, the study

designs used to address each research objective, and the approach to data analysis. This chapter

concludes with a detailed discussion regarding the limitations and strengths of the data.

Chapter 4 investigates maternal risk factors associated with giving birth to a child with FASD

and presents baseline characteristics of study groups.

Chapter 5 investigates rates of psychiatric morbidity of women who give birth to children with

FASD relative to women who have not given birth to children with FASD, including: rates of

substance use disorder; personality disorder; mood and anxiety disorders; maternal psychological

distress during pregnancy and postpartum; and antidepressant use before, during, and after

pregnancy.

Chapter 6 investigates rates of suicide attempts and completions before, during, and after

pregnancy of women who give birth to children with FASD relative to women who have not

given birth to children with FASD.

Chapter 7 investigates quality of prenatal care of women who give birth to children with FASD

relative to women who have not given birth to children with FASD utilizing the revised Gradated

Index of Prenatal Care Utilization.

Chapter 8 provides a summary of findings of each chapter providing empirical results and

presents policy implications of results including how the results of this dissertation can be

integrated into the CanFASD FASD Prevention Framework. This chapter also presents

suggestions for using the evidence generated in this thesis to address the social determinants of women's health in clinical practice. This chapter concludes with a brief summary of the strengths and limitations of this work in the context of common biases inherent in observational and descriptive studies, and areas for future research.

Preface: Chapter 1

This chapter will provide background about Fetal Alcohol Spectrum Disorder (FASD), including a description of the disorder, its impact on patients and society, and a brief overview of the diagnostic process and prevalence. A summary of what is currently known about women whose children are diagnosed with FASD will be presented, as well as a discussion about evidence gaps in the current literature. The chapter will conclude with the study rational, the theoretical model that guides this work, and specific research objectives.

Chapter 1: Introduction and Background

1.1   Defining FASD and its impact

Fetal Alcohol Spectrum Disorder (FASD) is a major global heath concern[1]. FASD encompasses

a range of effects associated with prenatal exposure to alcohol (PAE)[2-5]. Specific diagnoses that

span the continuum of FASD include: Fetal Alcohol Syndrome (FAS); Partial Fetal Alcohol

Syndrome (pFAS); Alcohol-Related Birth Defects (ARBD); and Alcohol-Related

Neurodevelopmental Disorder (ARND)[4]. Persons affected by FASD often face a wide spectrum

of challenges and disabilities which are can persist throughout childhood and adulthood, as

FASD is a life long disorder[5]. While FASD is primarily characterized by facial anomalies and

neurodevelopmental impairment[5], people affected by this disorder also experience

communication, behavioural, emotional, and social difficulties[6-8]. As a result of these disabilities,

people with FASD may develop secondary disabilities, such as mental health problems (e.g.

mood and anxiety disorders, conduct disorder, oppositional defiance disorder) and substance

abuse, and may experience poor social outcomes such as trouble with the law, withdrawal from

school, unemployment, and homelessness [9,10].

These health and social issues are associated with increased emotional and financial burden on

patients, families, and health and social systems[11-16]. Several studies that have assessed the

economic impact of FASD in general populations in Canada[13,16-19]. A recent analysis estimated

the annual health services utilization (HSU) cost for people diagnosed with FASD in Alberta to

be $259 million in 2012[19]. The annual HSU cost per person with FASD was $5,600, and the

lifetime HSU cost per person with FASD was $245,000[19]. Another study calculated the total

direct health care cost of acute care, day surgery, emergency department services, and psychiatric care associated with FASD using data from the Canadian Institute for Health Information in Canada in 2006-2009 to be approximately $6.7 million[13]. Easton et al, (2015)[20] investigated the cost of lost productivity due to FASD-related premature mortality and morbidity in Canada. Authors reported there were 2,977 years of potential employment loss based on premature mortality of individuals with FASD, resulting in a productivity loss ranging from $88 million to $126 million[20]. The same authors also investigated productivity losses due to morbidity attributable to FASD in Canada[21]. They reported losses ranging from $418 million to $1.08 billion annually[21]. These studies demonstrate the significant economic burden FASD has on Canadian society and reinforces the urgent need for systematic prevention strategies.

1.2   Diagnosing FASD

Diagnosing FASD is a challenging process as patients with prenatal alcohol exposure have a wide range of symptoms that are not caused only by prenatal alcohol exposure and manifest throughout the lifespan[2]. The severity and expression of symptoms are dependent on the timing, frequency and quantity of prenatal alcohol exposure[2], and are often confounded by other prenatal and postnatal exposures and co-morbid diagnoses[5]. Historically, diagnoses varied widely between clinics and regions based on which diagnostic criteria were being utilized. These inconsistencies can lead to inappropriate patient care and the poor management of secondary disabilities[22]. Currently there are four major clinical diagnostic guidelines commonly used in practice: The Revised Institute of Medicine FASD guidelines; the Centres for Disease Control FAS guidelines; the Canadian FASD Guidelines; and the FASD-4Digit Diagnostic Code[2]. The criteria for FASD diagnosis have been described comprehensively and are available in current

literature[2,4,5,22-24]. The field is currently working to adopt a single set of diagnostic guidelines for FASD in the interest of accuracy and consistency, as well as to facilitate accurate estimates of incidence and prevalence at national and international levels.

The FASD diagnostic process involves a multidisciplinary assessment including physicians (developmental paediatricians, clinical geneticists, psychiatrics or neurologists), speech-language pathologists, psychologists, occupational therapists and physiotherapists[4,5,23,24]. The diagnosis of FASD generally involves the following assessments: (1) physical examination to identify sentinel facial features related to prenatal alcohol exposure, including thinness of upper lip, length of palpebral fissure, and philtrum smoothness[12]; (2) neurobehavioral assessment investigating pervasive brain dysfunction, including impairment in: language, cognition, school performance, motor skills; attention; and hyperactivity; affect regulation; and adaptive behaviour social skills or social communication[5]; (3) confirmation of prenatal alcohol use (generally obtained through interviews with birth mother, through medical records, or through a reliable source such as a child welfare agency)[5]. A person can only be diagnosed with FASD if there is a confirmation of prenatal alcohol exposure. A person may be diagnosed with FASD if they have, or do not have sentinel facial features, but must have impairment in three of more of the neurodevelopmental domains mentioned above[5].

Popova et al. (2013) investigated the annual cost of FASD diagnosis and estimated that an FASD evaluation results in a total cost of approximately $3,110 to $4,570 per person per year, with the total cost of FASD diagnostic services in Canada ranging from $3.6 to $7.3 million per year[12]. Due to the resource intensive nature of obtaining a full diagnostic assessment, there is limited

clinical capacity throughout Canada to diagnosis FASD. Many provinces and territories do not have interdisciplinary FASD diagnostic/assessment clinics and the need across Canada is greater than the resources currently available[23,25]; this results in substantial under diagnosis of the disorder.

1.3   The Prevalence of FASD

A significant gap in accurately demonstrating the impact of FASD has been the lack of precise population and national FASD prevalence estimates in Canada. Establishing population-based prevalence of FASD is a challenging and complex undertaking[26]. Researchers have struggled with issues of variable diagnostic criteria, evolving terminology, different methodologies in case ascertainment, and underreporting of prenatal exposure to alcohol due to stigmatization[17,27,28]. Due to the complex health effects and range of expression and disability related to prenatal alcohol exposure, FASD is a difficult condition to diagnose and often goes under reported[4,28]. Children are often not diagnosed in infancy, but later in life when symptoms begin to show. These methodological issues, differences in diagnostic criteria, and lack of diagnostic capacity contribute to the lack of epidemiological data on FASD in Canada and across the world[26,29].

The incidence and prevalence of FASD varies greatly depending on what country, study population and study methodology is being utilized[30]. For example, studies using active case ascertainment such as diagnosing children in school settings have calculated higher rates than those using passive surveillance systems[30]. Prevalence estimates of FASD also tend to be higher in high risk populations, such as First Nations populations in Canada[30]. Over the past decade, Canadian and international FASD prevalence estimates have ranged from 2% to 5% in the

general population[31] and up to 23.3% in high-risk populations[6,28,32-36]. In the United States the most frequently cited rate of FASD is 9.1 per 1000 births (estimated from Sampson et al., 1997[37]). In 2009, May et al. re-estimated the prevalence of FASD in the United States at 20 to 50 per 1000 people[28]. In Canada, no specific incidence and prevalence rates of FASD have been calculated for the general population[30]. Canadian government reports and studies often cite the 9.1 per 1000 births reported in the United States, however caution needs to be taken when generalizing the rates of FASD from other countries or populations[30]. Recently, researchers in Alberta have calculated an incidence of 14.2 to 43.8 per 1000 births and have estimated the prevalence of FASD to be 11.7 per 1000 population (ranging from 8.2 to 15.1)[38].

In the most recent effort to provide an estimate of the prevalence of FASD, Popova et al (2016) conducted a systematic review and meta-analysis to generate the pooled prevalence of FAS and FASD among the general and Indigenous populations in Canada and the United States[29]. Among the general population of Canada, the pooled prevalence of FAS was estimated to be approximately 1 per 1000, and 5 per 1000 for FASD[29]. The prevalence of FAS and FASD was estimated to be 38 times and 16 times higher for Indigenous populations, respectively[29]. In the United States the pooled prevalence of FAS and FASD was approximately 2 per 1000 and 15 per 1000, respectively, among the general population, and 4 per 1000 and 10 per 1000, respectively, among Indigenous populations[29].

Roozen et al (2016) conducted a meta-analysis on the worldwide prevalence of FASD in several countries outside North America. Rates of FASD were estimated to be 113.33 per 1000 in South Africa, and rates of partial FAS to be 43.01 per 1000 in Croatia, 36.89 per 1000 in Italy and

28.29 per 1000 in South Africa[26]. While there is great heterogeneity in study methodologies and populations used to ascertain FASD prevalence and incidence estimates, these high rates indicate the significant global burden of this disorder. Prevalence rates of FASD are higher than the prevalence of Autism or Down Syndrome in North America, making FASD an important public health priority in Canada and throughout the world. Reducing the rates of FASD begins with supporting women from abstaining from alcohol consumption during pregnancy.

1.4   What is known about women whose children are diagnosed with FASD?

Approximately 80% of women of childbearing age consume alcohol in Canada, and women with planned pregnancies report prevalence of alcohol consumption before recognizing pregnancy of up to 50%[39]. The Canadian Maternity Experiences Survey (2009) indicated that approximately 63% of women reported drinking alcohol during pre-conception, and 11% reported alcohol consumption during pregnancy[40]. In a recent meta-analysis of the prevalence of alcohol consumption during pregnancy it was reported that 10% to 15% of pregnant women in the general population in Canada and the United States consume alcohol[26]. This indicates that a substantial proportion of women are at risk for giving birth to children with FASD.

FASD has been cited throughout the literature as the world's only entirely preventable birth defect[1]. Since the identification of FAS in the 1970s, women who drink during pregnancy have been made to feel stigmatized and responsible for causing this "preventable" condition[41]. The notion that this disorder can be easily prevented is rooted in the theory that the exposure can be easily eliminated[41]. However, this response does not account for the many complex factors that influence women to engage in this detrimental behaviour such as poverty, poor housing, a history

of physical and sexual abuse, mental health disorders, and lack of education[42,43]. The use of alcohol during pregnancy cannot be separated from other issues in the lives of women, and from other harmful behaviours such as poor health practices, poor nutrition and the use of other harmful substances such as tobacco and illicit drugs[42,43].

Over the past two decades a shift has occurred in the lens by which women who drink during pregnancy are viewed; from a "shame and blame"/fetus-centred approach to a more woman-centred framework[11]. A woman-centred framework emphasizes the social determinants affecting women's health and encourages a respectful approach to women and alcohol use during pregnancy, in contrast to the "shame and blame" approach, which does not view women as worthy of health promotion activities and focuses only the health of the fetus[11]. Investigators are now placing importance on uncovering factors and influences that place women at risk for consuming alcohol during pregnancy[44-48]. Only through investigating the demographic, social, and economic factors that place women at risk for alcohol consumption during pregnancy can we obtain insight into the root causes of this behaviour and identify target points for prevention and support.

This important research inquiry is in line with the International Charter on the Prevention of FASD, published in the *Lancet Global Health* that places a call to action for policy makers and governments to increase awareness of FASD and highlights the importance of addressing the underlying social determinants of health in developing effective FASD prevention strategies[1]. The WHO global strategy to reduce the harmful use of alcohol also highlights the importance of identification and prevention of the use of alcohol among pregnant women across the world

through targeting the social and economic contexts of society in which in this detrimental behaviour occurs[49].

While a growing body of literature investigates maternal demographic and socioeconomic risk factors associated with FASD, limited data focus on the birth mothers of children who are diagnosed with FASD from North America, and no Canadian data. Previous studies investigating maternal factors associated with the development of FASD have utilized populations from the United States, Italy, and Australia, and the majority of the data come from studies conducted in South Africa[22,45,48,50-61]. These studies have summarized demographic factors, family and social factors, psychiatric and neuropsychological factors, and patterns of alcohol consumption and identified the following maternal factors to be associated with the development of FASD in children: older age; lower educational level; lower socioeconomic status (SES); unemployment; rural residence; higher parity and gravidity; family relatives with alcohol abuse issues; mental disorders; sexual abuse; smoking and the use of illicit drugs during pregnancy; and heavy alcohol consumption during pregnancy, including high rates of binge drinking[47]. Although maternal alcohol during pregnancy is the necessary cause of FASD, this literature highlights many other underlying social, economic, and health causes that place infants at risk for FASD.

1.5   Evidence gaps in the current literature

While these studies have laid the groundwork for investigating factors associated with giving birth to children with FASD, they have several important limitations that may preclude them from informing FASD prevention strategies for women in the general North American population:

(1) **Limited generalizability:** First, no Canadian studies and few studies from the United States are conducted at a population level. The majority of studies are from South Africa, and many focus on women who are from high risk populations, such as Indigenous populations[48,51,62,63]. Owing to differences in population demographics and cultural norms, caution should be taken when extrapolating these results to the general North American population.

(2) **Small sample sizes:** Previous studies have utilized small sizes that range from 8 to 250 birth mothers[44,48,51,55,56,62]. These sample sizes may be a function of the complexity of diagnosing children with FASD, particularly because alcohol consumption during pregnancy is underreported[28,31]. However, these sample sizes limit the generalizability of results, have decreased power to detect significant difference among comparison groups and constraint the use of powerful multivariate analyses[64].

(3) **Recall bias:** Previous studies are also limited by recall bias from self-report survey and interview data[44,53,55,61]. There are many factors that affect the validity of self-report data on alcohol use during pregnancy, including severity of alcohol use, issues of confidentiality, stigmatization, fear of disclosure, fear of involvement of child welfare services, mental disorders, and denial of alcohol use as a problem[55,56]. Moreover, the accuracy of the information provided by self-reports is questionable, especially during periods of high alcohol consumption which affects memory and judgment[65].

(4) **Limited data on diagnosed physician and mental disorders:** Few previous studies have documented clinically diagnosed physical and mental disorders in women who gave birth to children with FASD using reliable and validated clinical data, highlighting an important gap in the literature[64]. There is strong association between mental disorders and

alcohol consumption[66-70], and investigating this relationship in women who give birth to children with FASD is extremely important for the advocacy of effective support and prevention strategies.

(5) Limited data on service utilization: Few studies have investigated prenatal care in this population and have found that these women receive fewer prenatal visits compared to women in the general population, and generally begin prenatal care later in their pregnancies[44,48,51,62]. However, these results are generated from small sample sizes, do not use validated scales that assess the quality or appropriateness of prenatal care, and do not investigate any other health care utilization such as hospitalizations or social support programs. Research using reliable longitudinal data documenting health care and social system utilization throughout significant periods in these women's lives, such as the prenatal period, is needed to identify further opportunities for prevention.

1.6   Study Rationale & Theoretical Model

How administrative data help to address evidence gaps: There are no large-scale studies that comprehensively investigate the characteristics, mental and physical health, and social and health care system utilization of women whose child(ren) have been diagnosed with FASD in Canada, highlighting a gap in Canadian public health data. The Manitoba Mothers and FASD Study (MB FASD Moms) is a data linkage project that has generated a retrospective cohort of all mothers who gave birth to children diagnosed with FASD in Manitoba, Canada. In partnership with the Manitoba FASD Centre (a provincially centralized FASD assessment and diagnostic clinic) and the Manitoba Centre for Healthy Policy (MCHP), we have analyzed explanatory variables associated with giving birth to children with FASD by analyzing potential risk factors that are

present *before* giving birth to a child with FASD (e.g. socioeconomic status, marital status, prenatal psychological distress, inadequate prenatal care), as well as maternal outcomes *after* the child with FASD is born (e.g. post partum psychological distress, suicide attempts and completions).

This study makes important contributions to the literature by filling existing gaps and addressing key methodological limitations identified in previous studies by utilizing linked administrative health, social and education data housed at MCHP. The MCHP Population Research Data Repository (Repository) is one of the world's most comprehensive collections of population-level administrative databases. These data are a powerful tool to investigate factors that promote the health of populations, as well as to understand the use of health care services and social programmes of populations and specific groups[71]. The Repository consists of population-wide administrative data from health and social service agencies, education institutions and Canadian census[71-73], which allow investigation of outcomes from multiple domains in a cohort of individuals[71-73]. This approach allows for enhanced assessment of overall well-being and the impact of the multiple social determinants of health. This type of holistic investigation is particularly relevant to women who give birth to children with FASD. Women who drink during pregnancy have histories that are rooted in abuse, poverty, other substance abuse and mental and/or physical illness[43,74,75].

This study is guided by a theoretical model created by Abel and Hannigan (1995) that outlined factors associated with the development of FASD[42]. While alcohol is the only necessary factor for FASD, the authors recognized that other factors contribute to the manifestation of this

disorder, as well as to the consumption of alcohol during pregnancy. The authors categorized two categories of maternal risk factors for Fetal Alcohol Syndrome: ***provocative and permissive influences***[42]. Permissive factors are specific socio-behavioural risk factors (e.g. low socioeconomic status, stress, cultural factors) that provide the context for increased vulnerability to the teratogenic effects of alcohol[42]. Provocative factors are related to biological aspects and increase the cellular vulnerability to the teratogenic effects of alcohol, for example hypoxia, malnutrition, and free radical formation, which are related to in-utero growth retardation and cellular death[42]. The authors proposed a model hypothesizing that permissive and provocative factors increase the likelihood of FAS because "they potentiate two related mechanisms of alcohol-induced teratogenesis"[42]. This was the first paper to highlight the role of social factors that play a role in the development of FASD and how they relate to biological manifestation of this disorder in the fetus (see Figure 1.1).

Figure 1.1: Theoretical Model: Provocative & Permissive Influences (Abel & Hannigan, 1995)
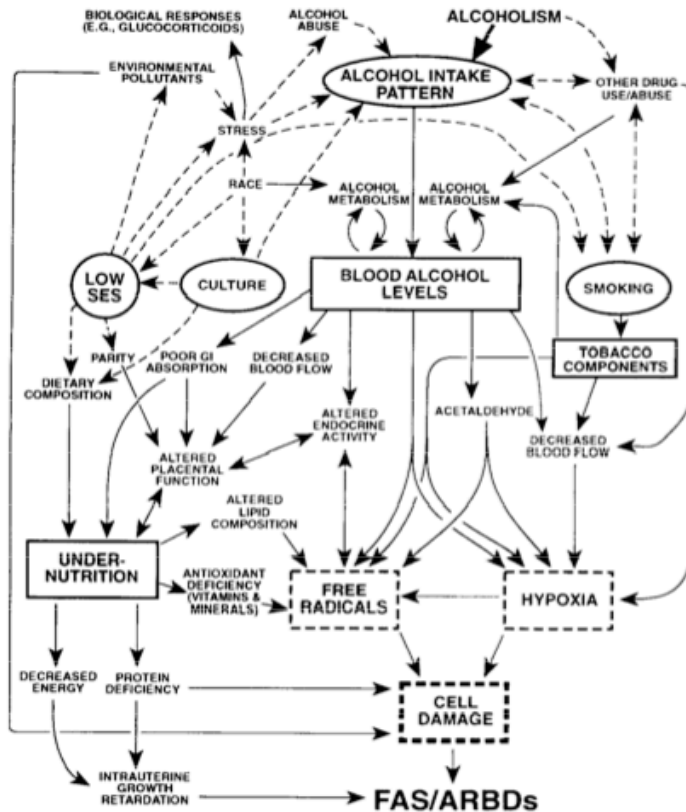
FIG. 1. Schematic summary of some of the relationships among permissive and provocative maternal risk factors, and among mechanisms underlying Alcohol-Related Birth Defects (ARBDs), including Fetal Alcohol Syndrome (FAS). Sociobehavioral Permissive Factors (inside the circles), include alcohol intake pattern, low socioeconomic status (low SES), particular aspects of culture, and smoking behavior. Permissive factors are highly correlated among themselves and increase risk for FAS/ARBDs by establishing an environment for, and/or predisposing fetuses to alcohol's direct cellular teratogenic effects by exacerbating the provocative risk factors. The key biological Provocative Factors (inside the solid squares) are peak blood alcohol levels (BALs), undernutrition and tobacco smoke constituents. Similar to the relationship between alcohol drinking pattern (permissive factor) and BALs (provocative factor), smoking is essentially both a permissive and a provocative risk factor because cigarette smoking is highly correlated with alcohol abuse and poor nutrition (permissive factor), and because tobacco smoke (provocative factor) exacerbates the effects of alcohol and directly impacts fetal development. The several pathways by which the permissive and provocative risk factors act on the maternal/placental/fetal unit are shown: The dotted-line arrows (- - - - >) show recognized, sometimes bidirectional associations among various environmental, demographic, and behavioral variables. For example, low SES is highly correlated with high parity, smoking behavior and stress. The solid-line arrows (———>) indicate biological relationships and physiological pathways. For example, binge drinking (alcohol intake pattern) increases peak BALs which in turn leads to decreased blood flow, altered placental function, undernutrition, etc. The key teratogenic mechanisms of FAS operate via hypoxia and free-radical damage (dashed squares) to converge on the necessary proximal cause of FAS, cell damage. The effects of cell damage on developing fetuses include altered cellular proliferation, differentiation, migration and/or apoptosis, as well as the regulation and timing of these events in all organ systems. Cell damage occurs because of disrupted membrane integrity (membrane order or fluidity), increased Ca^{++} influx, toxic levels of glutamate release, mitochondrial damage, as well as altered intracellular signal transduction, nuclear transcription, and gene expression. In addition to contributing to cell damage via various nutrient deficiencies, undernutrition also directly contributes to intrauterine growth retardation, a cardinal feature of FAS/ARBDs.

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The MB FASD Moms Study investigates permissive maternal factors related to FASD. Due to the wealth of social and health information within the Repository, these data are an ideal source to investigate permissive factors associated with prenatal alcohol consumption that results in the birth of a child with FASD including SES, region of residence, involvement with child welfare services, gravidity and parity, smoking and substance use, and maternal mental and physical health co-morbid diagnoses. Due to limitations in the scope of information collected in the MCHP Repository, these data do not facilitate investigation into provocative factors, indicating an area for future research utilizing other sources. However, identifying permissive factors present in women who are at risk for alcohol use during pregnancy can lead to the development of targeted intervention and prevention efforts to reduce alcohol use during pregnancy. Targeting permissive factors may improve infant outcomes, reduce the severity of FASD symptoms in children, and ultimately lead to decreasing the incidence of FASD by preventing prenatal alcohol use.

MCHP administrative data also provide the opportunity to investigate novel permissive factors that have not been studied utilizing large population-based samples. The use of health and social support systems might be important permissive factors that may have a protective effect on the detrimental effects of alcohol on the developing fetus. For example, regular prenatal care (PNC) could provide opportunities for counseling women to reduce their alcohol consumption during pregnancy and result in better infant outcomes. Administrative data are ideal to investigate the health care utilization of a population for any length of time, or specified years[71-73,76,77]. These data document health and social system utilization of women whose children have been diagnosed with FASD to provide insight into how they navigate the health, social and education

systems. Due to the longitudinal nature of the data an analysis of system utilization of women before, during, and after pregnancy can be conducted and compared to women in the general population whose children have not been diagnosed with FASD. For example, the adequacy of PNC of study groups was investigated to assess the quality of care received. The health and social service system utilization was also investigated, including receipt of social assistance and involvement with child protection services. This analysis is important to identifying points for prevention, early intervention and treatment, and effective resource allocation, as well as supporting the health and well-being of women who give birth to children with FASD. The Repository is ideal for these analyses, as the data accurately capture health care service utilization and have been validated for research purposes[71-73,76-79]. MCHP data have been used to calculate the health care utilization of related populations in the past; for example, Brownell et al. utilized MCHP data to document the health and social system utilization of children with FASD[80].

Very few studies have investigated at the possibility of physical and mental health comorbidities being important permissive maternal risk factors associated with FASD.

Our study assessed whether these women are burdened with chronic health conditions such as diabetes and heart disease that may contribute to alcohol consumption during pregnancy. Moreover, no North American studies have looked at the mental health of these women utilizing a population-level sample, which is an important area for prevention and support. We investigated the relative rates of mental disorders including substance abuse, schizophrenia, personality disorder, mood and anxiety disorder, as well as the suicidal behaviour of our study

groups. Literature shows that women who abuse alcohol have endured great emotional difficulty as well as physical, emotional, and sexual abuse that places them at high risk for mental illness[74]

This is the first population-based study in Canada to conduct this in-depth analysis on women whose child(ren) have a diagnosis of FASD and has the largest sample to date in the international literature. The study results contribute to our understanding of the life circumstances of mothers who give birth to children with FASD and provide an informed picture of the determinants of health that place women at increased risk of alcohol consumption during pregnancy that results in FASD. Moreover, study results offer insight into how women whose children have been diagnosed with FASD navigate health and social service systems during the perinatal and postnatal periods.

These results add to the international evidence base and facilitate FASD prevention efforts through identifying: (1) high risk women who should be targeted for prevention and intervention; (2) areas in health and social services that can be targeted for FASD prevention and support programs to enhance service delivery to this population. Research providing insight into the factors that place women at risk for having children with FASD is vital for effective targeting and development of policy resources that can help women cope with the influences and stresses in their lives to decrease prenatal alcohol consumption and ultimately prevent FASD.

1.7   Research Objectives:

This dissertation is organized into 5 individual publication-based documents (Chapters 3-7) aiming to meet the following research objectives:

Research Objective 1 (Chapter 2): To conduct a review of the literature investigating maternal risk factors associated with FASD.

Research Objective 2 (Chapter 4): To investigate demographic, socioeconomic, family, mental health characteristics that are associated with/predictive of giving birth to children with FASD compared to not giving birth to children with FASD.

Research Objective 3 (Chapter 5): To investigate rates of psychiatric morbidity (including: substance use disorders; schizophrenia; personality disorders; prenatal and postnatal psychological distress; and mood and anxiety disorders) of women who have given birth to children diagnosed with FASD compared to women who have given birth to children not diagnosed with FASD.

Research Objective 4 (Chapter 6): To investigate rates of suicidal behaviour (i.e. attempts and completions) of women who have given birth to children diagnosed with FASD compared to women who have given birth to children not diagnosed with FASD.

Research Objective 5 (Chapter 7): To investigate the adequacy of prenatal health care utilization of women who have given birth to children diagnosed with FASD compared to women who have given birth to children not diagnosed with FASD.

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Preface: Chapter 2

The original intention of this thesis was to conduct a systematic literature review investigating maternal factors for giving birth to children with FASD. A protocol for this was published online at PROPERSO in 2014 (Prospero registration number: 42014010763). In the same year, Epser et al[1] published a similar review focusing on the same population of women, using similar inclusion and exclusion criteria, and using the same scale to determine validity and quality of studies. In the interest of contributing novel work into the literature base, it was decided to postpone this review until there were enough new studies published after the end of the search period used by Esper and colleagues (i.e. 2013) to warrant an update of the existing review. Therefore, this chapter includes a summary of the results found by Esper et al., as well as a presentation of the results of studies published after 2013. This chapter concludes with an overview of the strengths and weakness of the overall body of evidence and highlighting gaps for future research that provide a rationale for the use of administrative data in investigating maternal risk factors for FASD and documenting health care and social services utilization in this population.

Chapter 2: A Review of the Literature Investigating Maternal Risk Factors for Giving Birth to Children with Fetal Alcohol Spectrum Disorder

2.1   Introduction

While alcohol during pregnancy is the necessary factor associated with the development of Fetal Alcohol Spectrum Disorder (FASD) in offspring, psychological, environmental, social, and biological factors can influence the development of FASD. A growing body of literature investigates these maternal risk factors that may be associated with the development of FASD in children in various populations across the world[1]. This chapter summarizes the evidence in this area. Strengths and weakness of the body of evidence are presented, and gaps for further research highlighted.

2.2   Evidence before this review

One previous systematic review summarized maternal factors associated with the development of FASD[1]. Authors of that review searched PubMed, SciELO, Lilacs, Web of Knowledge and PyscINFO for all studies that investigated statistical association of at least one or more demographic, psychological, or social maternal risk factor for FASD, until 2013[1]. Out of 736 references identified, 15 met inclusion criteria[1].

Studies were published from 2000 to 2010 and sample sizes ranged from 10 to 221 cases of mothers with children with FASD[1]. Many studies (7 out of 15) were collaborations through partnerships with researchers from the University of New Mexico and researchers from institutions in South Africa and Italy[1]. A large proportion of studies were performed in countries

outside of North America, with a majority of them conducted in different parts of rural South Africa[2-9]. Most these studies had the primary purpose of estimating the prevalence and incidence of FASD in these areas, and included secondary analysis of maternal risk factors associated with the development of FASD in children. These studies utilized a similar active case ascertainment strategy to obtain cases of children with FASD: children were screened per weight and height. Children in the 10th percentile regarding weight and height were selected for another set of diagnostic screening procedures[2-9]. Biological mothers were then invited to provide information about their alcohol intake during pregnancy using maternal interviews and surveys conducted up to seven years after the birth of children[2-9]. These interviews gathered information on socioeconomic and demographic factors as well as drinking patterns before and during pregnancy.

Demographic factors. The review found that the majority of studies documented low socio-economic status to be a risk factor associated with the most severe forms of FASD[1,7,10]. Furthermore, low education level, low-income levels, and unemployment were associated with the development of FASD in children[4,8,11-15]. Studies also identified being unmarried as a risk factor for FASD in offspring[5,12,13,15,16], as well as living in a rural residence[1]. Nine of 11 studies investigating maternal age at birth of the child with FASD found older age as a maternal risk factor for FASD[1].

Psychiatric morbidity, suicide, and abuse. Four studies included in the review also identified a higher prevalence of psychiatric conditions among mothers of children with FASD and higher levels of stress[4,9,11,13,17]. Three studies also identified physical and sexual abuse as a maternal risk

factor for FASD[5,11,13]. One study investigating risk factors in a Northern Plains, United States population found increased odds for suicide attempts in mothers with children with Fetal alcohol syndrome (FAS) and partial-FAS (pFAS)[13].

Family and social factors. Several studies included in the review indicated that mothers of children with FASD also had family members who had heavy alcohol use, including siblings, fathers, mothers, spouses, and grandmothers[4,5,9,13]. Research documented that mothers who were identified as giving birth to children with FASD had already given birth to other children with FAS or with symptoms associated with alcohol use during pregnancy[1].

Substance use and smoking. Several studies included in the review investigated the use of illegal drugs, and the majority found a relationship between use of illegal drugs and smoking with an increased risk in the development of FASD in the children[1].

Maternal health. A few studies included in the review assessed the number of prenatal appointments during pregnancy and found that women who gave birth to children with FASD had higher rates of late initiation of prenatal care[12,13,15,16]. Studies also found women who gave birth to children with FASD had lower weight gain during pregnancy, greater restriction of uterus growth, higher rates of premature birth, and higher gravidity and parity, as well as more miscarriages and higher rates of other complications during pregnancy[12,13,15,16].

Patterns of alcohol consumption before and during pregnancy. Most studies investigated alcohol use patterns before and during pregnancy, with the large majority of studies using

maternal interviews and self-report data[1]. The majority of studies identified higher levels of use before and during pregnancy, no reduction or abstinence during pregnancy, higher frequency of binge drinking, and higher levels of alcohol consumption in second and third trimesters, as well as early age of alcohol consumption initiation among mothers who gave birth to children with FASD[1].

Linking maternal risk factors to severity of symptoms in children. A few studies investigated maternal risk factors that were associated with different levels of severity of symptoms in children., The following maternal risk factors were identified as having a relationship to children's dysmorphia: greater number of children; lower education level and income; rural residence; higher levels of alcohol consumed weekly; higher frequency of binge drinking; alcohol consumption throughout each trimester; and smoking during pregnancy. There were also associations found between maternal risk factors and behaviour and social challenges, as well as verbal and non-verbal cognitive abilities (i.e. the intelligence quotient (IQ)) of the child[5].

Summary of evidence: The systematic review of studies investigating maternal risk factors for the development of FASD in children found that mothers of children with FASD were: older at the time of the birth of the child with FASD; had lower education levels; had family members with a history of alcohol abuse; had other children diagnosed with FASD; and had inadequate prenatal care[1]. Mothers of children with FASD also had a distinct pattern of alcohol use, including use before and during pregnancy, no reduction of alcohol use during pregnancy, and frequent binge drinking[1]. This review highlighted the important message that mothers of children

with FASD experience social, economic, and behavioural disadvantages that place them at risk to consume alcohol during pregnancy[1].

Authors of this review evaluated the validity and quality of studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) and reported that very few studies included in the review were of high methodological quality according to the NOS requirements[1]. The authors of the review recommended the addition of more high-quality epidemiological studies to the literature, as well as more clinical epidemiological comparative studies performed on well-defined high-risk groups and comparison groups that are focused on the identification of maternal factors that can potentiate FASD, as well as inform evidence-based prevention efforts[1].

2.3   Methods: Updating the evidence

A search using PubMed from 2013 up to January 2017 was conducted to update the body of literature. Articles published in English, with the search terms: "Fetal Alcohol Syndrome"; "Fetal Alcohol Spectrum Disorders"; "maternal characteristics"; and "risk factors" were included in the search. All observational studies including cohort, case-control, and cross sectional studies investigating women who had given birth to children with FASD were included. Diagnoses for FASD included Fetal Alcohol Syndrome (FAS), partial Fetal Alcohol Syndrome (pFAS), Alcohol-Related Neurodevelopmental Disorder (ARND), and Alcohol-Related Birth Defects (ARBD).

The following studies were excluded: studies involving non-humans; studies assessing characteristics or drinking behaviour of women of childbearing age who have no reports of

drinking during pregnancy; studies assessing characteristics or drinking behaviour of women who report drinking during pregnancy but do not have children diagnosed with FASD; studies investigating substance abuse, smoking and illicit drug use during pregnancy without a focus on alcohol; studies exploring attitudes on prenatal alcohol use, case reports, opinion papers, editorials, or previous reviews.

2.4   Results: Summary of updated literature

Eight additional studies not included in the original review fit both the inclusion criteria of the previous review and the criteria of this literature review [18-24]. These papers were published from 2013 to 2017. Like the body of work prior to 2013, 7 out of 8 of these papers were collaborations with the research group from the University of New Mexico and researchers from South Africa. Most of the recent studies were also conducted on populations outside North America and Europe, and once again focused on high-risk populations of women from South Africa. Sample sizes ranged from 17 to 353 mothers who had given birth to children with FASD. A summary of these studies is shown in Table 2.1.

Similar to previous studies, all but one of these recent papers also had the primary purpose of estimating the prevalence and incidence of FASD in these geographic regions and included secondary analysis of maternal risk factors associated with the development of FASD in children. The majority of studies used the same active case ascertainment strategy used in previous work to obtain cases of children with FASD; that is, school children in rural communities were diagnosed and their birth mothers or proxy informants interviewed[18-22,24].

An addition to the literature with results more generalizable to North American populations was made by Cannon et al. (2015) who used population-based data from the FAS Surveillance Network to identify characteristics and behaviours of mothers of children with FAS in the United States [22]. This network included children from the following states: Arizona; New York; Alaska; and Colorado[22]. The study sample was made up of 257 confirmed cases of FAS, and 96 probable cases[22]. Results reported that mothers of children born with FAS were significantly more likely to be older, lone parents, American Indians/Alaska Natives, Black non-Hispanics, unemployed, to not have prenatal care, to smoke cigarettes during pregnancy, to have lower education, and to have higher gravidity[22]. These mothers were also more likely to have much lower socioeconomic status, as they had higher rates of public assistance, and Medicaid[22]. They also were more likely to have received treatment for alcohol abuse, to have confirmed alcoholism and substance use issues, to have used illicit drugs during pregnancy including marijuana or cocaine, to have drank heavily and engaged in binge drinking during pregnancy, and to have a history of mental illness [22].

While this study is more generalizable to North American populations, there was a high degree of missing information on key variables such as history of mental illness and the study included only mothers with children diagnosed with FAS[22], which excludes women with children with less severe forms of FASD who may have different characteristics and risk factors. This study also did not use standardized measures of documenting prenatal care, and did not include information on other social service utilization. Furthermore, information pertaining to health service use may not be generalizable to countries with universal access to health care.

The studies included in this update found very similar maternal risk factors for the development of FASD in children as reported in the previously published review, including: older maternal age at the time of birth of the child with FASD; higher gravidity and parity; lower SES; higher rates of unemployment; lower education levels; family members with a history of alcohol abuse; other children diagnosed with FASD; and low rates of prenatal care[18-24]. Mothers of children with FASD also had higher rates of mental illness[22,25], and reported illicit drug use and smoking during pregnancy[18-24]. These women also had similar patterns of alcohol use as reported in previous studies, including use before and during pregnancy, failure to reduce alcohol use during pregnancy, and frequent binge drinking episodes[18-24]. Several studies reported inadequate maternal nutrition and low body mass index (BMI) as maternal risk factors for giving birth to children with FASD[18-20,23], which was not extensively reported in previous studies. These studies reported that mothers with children with FASD had inadequate dietary intake; however, four of these studies were conducted in rural south Africa[18-20] which has high rates of malnutrition and very different rates of food insecurity and nutrition compared to a general population of women in North America[23]. Future work should be done investigating the interaction of alcohol and nutrition and BMI in pregnant women and the effect on offspring in North American populations.

Table 2.1: Studies investigating maternal risk factors for the development of FASD in offspring

Study & location	Sample	Type of study	Control group	FASD diagnostic criteria	Type of data	Results: Pattern of alcohol consumption	Results: Maternal risk factors	Results: Service utilization
1. May 2016 South Africa	68 mothers of children with FAS 89 mothers of children with partial FAS 39 mothers of children with ARND 196 total mothers of cases 207 mothers of controls	Case-control	Mothers of control children attending the school where cases were ascertained – children were not diagnosed but 41% mothers drank into pregnancy	Institute of medicine (IOM)	Maternal interview (7 years after pregnancy)	Heavy drinking – 16.5 drinks per week during pregnancy; 7.5 drinks per day Binge drinking – more than 3-5 drinks per occasion	Smoking during pregnancy Advanced maternal age Lower weight Lower BMI Higher parity Lower education Lower income Rural region Inadequate nutrition	Not investigated
2. May 2016 South Africa	168 mothers of children with FAS 106 mothers of children with partial FAS 59 mothers of children with ARND 333 total mothers of cases 212 mothers of controls	Case-control	Mothers of control children attending the school where cases were ascertained	Institute of medicine (IOM)	Maternal interview (7 years after pregnancy)	High quantity of drinks consumed per occasion Binge drinking – 3-5 drinks per occasion	Low body weight Low body mass Lower education Lower income High gravidity High parity Older age at birth of index child Rural region	Not investigated
3. Urban 2016 South Africa	156 mothers of children diagnosed with FAS and partial FAS 50 proxy informants of children diagnosed with FAS and partial FAS 206 total mothers of cases 55 mothers of controls	Case-control	Mothers of randomly selected control children of school age entry from the same populations	Maternal interviews conducted if clinical features indicated a high risk of FAS in surveys administered to mothers	Maternal interview (8 years after pregnancy)	History of ever drinking Initiation of drinking before 16 years of age Binge drinking	Smoking Low socioeconomic status Children were in foster care Malnourished – underweight, microcephalic Single marital status Lower education	Late initiation of first antenatal visit – after first trimester
4. Urban 2015	52 mothers of children with FASD	Cohort study	No controls	Active case ascertainment	Maternal interview	Heavy drinking during pregnancy	Older age at birth of index child	Not investigated

						had 5 to 9 drinks per drinking session		
5. May 2015 United States – Rocky Mountain Region	17 mothers of children with FASD 106 mothers of control children (Mothers of controls also report drinking during pregnancy)	Case-control	Randomly selected controls from same schools cases were ascertained	Active case ascertainment by an experienced dysmorpholo-gist –Hoyme guidelines	Maternal interview	Binge drinking Alcohol use during early life (drinking regularly at an earlier age) and during index pregnancy higher for case mothers	Lower education Shorter in stature Finding out about pregnancy later in index pregnancy History of sexually transmitted disease More likely to have post-partum depression Higher gravidity Use of marijuana during index pregnancy	Not investigated
6. Ceccanti 2004 Italy	40 mothers of children with FASD 108 mothers of randomly selected controls 758 community mothers	Case-control	Randomly selected controls from same schools cases were ascertained	Institute of medicine (IOM)	Maternal interview	Report more drinking three months prior to pregnancy Engage in more current drinking and drinking alone Report of high rates of drinking during second and third trimester	Shorter stature higher BMI married to partners with legal problems Family history of alcohol use issues	Not investigated
7. Pettcovic 2013 Rural Croatia	55 mothers of children with FAS/pFAS 769 mothers of children without FAS/pFAS	Case-control	Controls from same school where cases were ascertained	Institute of medicine (IOM)	Maternal survey	Higher frequency of confirmed pregnancy consumption of alcohol Higher frequency of alcohol consumption throughout pregnancy Report of high rates of drinking during second and third trimester	Lower maternal education	Not investigated

40

| 8. Cannon 2012

USA | 353 mothers of children with FAS

(compared risk factors with state-specific population dat from vial records or census) | Cohort study | Women of reproductive age in same population | Centre for Disease Control (CDC) | Fetal Alcohol Syndrome Surveillance Network data | Binge drinking during pregnancy

Drunk heavily (7days/week) during pregnancy | Older age
Unmarried
Higher unemployment
Smoked during pregnancy
Higher gravidity
Other children with suspected alcohol effects
Drug use during pregnancy
History of mental illness
Confirmed alcoholism
Use of marijuana or cocaine during pregnancy | Higher rates of no prenatal care |

2.5   Discussion

While all previous studies have laid the groundwork for investigating factors associated with giving birth to children with FASD, they have several important limitations that may preclude them from informing FASD prevention strategies for women in the Canadian population:

(1) **Limited generalizability.** There are no Canadian studies and few studies from the United States conducted at a population level. Most studies are from South Africa, and many focus on women who are from high risk populations, such as Indigenous populations. Due to differences in population demographics, cultural norms, and differences in health care coverage, caution should be taken when extrapolating these results to the general North American population, or to populations with universal access to health care.

(2) **Small sample sizes.** Previous studies have utilized small sizes that range from 8 to 353 birth mothers. These sample sizes may be a function of the complexity of diagnosing children with FASD, particularly because alcohol consumption during pregnancy is underreported. However, these sample sizes limit the generalizability of results, have limited power to detect significant differences among comparison groups and limit the ability to conduct powerful multivariate analyses.

(6) **Recall bias.** Previous studies are also limited by recall bias from self-report survey and interview data. There are many factors that affect the validity of self-report data on alcohol use during pregnancy, including severity of alcohol use disorder, issues of confidentiality, stigmatization, fear of disclosure, fear of involvement of child welfare services, mental disorders and denial of alcohol use as a problem. Moreover, the accuracy of the information provided by self-reports is questionable, especially during periods of

high alcohol consumption, which affects memory and judgment. For some of the women interviewed, information was gathered up to eight years after the pregnancy, which is a lengthy time between event and interview, potentially affecting the ability to recall events accurately.

(3) **Limited data on diagnosed physician and mental disorders.** Few previous studies have documented clinically diagnosed physical and mental disorders in women who gave birth to children with FASD using reliable and validated clinical data, highlighting an important gap in the literature. There is a strong association between mental disorders and alcohol consumption, and investigating this relationship in women who give birth to children with FASD is extremely important for the advocacy of effective support and prevention strategies.

(4) **Limited data on service utilization.** Few studies have investigated prenatal care in this population; those that have, found that these women receive fewer prenatal visits compared to women in the general population, and generally begin prenatal care later in their pregnancies. However, these results are generated from small sample sizes, do not use validated scales that assess the quality or appropriateness of prenatal care, and do not investigate any other health care utilization such as hospitalizations, or social support programs. Research using reliable longitudinal data documenting health care and social service utilization throughout significant periods in these women's lives, such as the prenatal period, is needed to identify further opportunities for prevention.

2.6   Summary: Evidence gaps and implications of available evidence

(1) No population-based studies from Canada investigate maternal risk factors for the development of FASD in children.

(2) There is a paucity of population-based research from developed countries investigating maternal risk factors for the development in children.

(3) Limited studies investigate health care utilization patterns of women who give birth to children with FASD. Such studies are important for the development of effective approaches for the prevention of FASD.

(4) Limited studies investigating the social service of women who give birth to children with FASD. This type of study is important for the development of effective approaches to prevent FASD.

(5) Limited studies explore the types of diagnosed mental disorders among women who give birth to children with FASD.

(6) The existing body of work has highlighted mothers of children with FASD from different populations throughout the world face complex social, economic, and behavioural challenges. These findings emphasize the importance of addressing the underlying social determinants of health that are associated with alcohol consumption during pregnancy to develop effective FASD prevention strategies. There is a need for high quality epidemiological studies performed on well-defined groups and controls, which use standardized and validated outcome measures that investigate maternal factors associated with FASD in children.

2.7   Conclusion: Added value of the Manitoba Mothers and FASD Study

No studies included in the review by Esper and colleges or in the updated literature search described in this chapter have investigated maternal risk factors for giving birth to children with FASD in Canada. Furthermore, very few studies have investigated the health and social service utilization of these women, and there is no comprehensive investigation into the presence/association of mental and physical disorders in this population. The MB FASD Moms study described in this thesis adds to the international literature by contributing high quality, robust evidence that supports a woman-centered approach to the prevention of FASD in Canada. The series of studies described in the following chapters investigated maternal risk factors present during the preconception period and pregnancy that may be associated with giving birth to children with FASD in a current Canadian population. The MB FASD Moms study used linkable administrative data to conduct comprehensive and accurate investigations into the social determinants of health, as well as novel analyses examining physician and medication use, and psychiatric and physical health diagnosis, addressing limitations of previous studies, including recall bias, small sample sizes, and attrition bias. The goal of this work was to provide policy makers and health care professionals responsible for developing FASD preventions strategies with high quality evidence on Canadian women who give birth to children with FASD that can be used to garner funding for prevention efforts and for the development of targeted prevention.

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Preface: Chapter 3

This chapter will provide an overview of the ethics and privacy considerations of the MB FASD Moms study[1], a description of the data sources used, an outline of the data linkage methods utilized to create the study cohort, a description of the study groups, as well as the study designs and statistical analyses used to address each research objective. It will also include a discussion of the strengths and limitations of the study.

Publication details:

    The content from chapters 1 and 3 were used to generate a protocol paper that is located in the appendices: Singal D, Brownell M, Chateau D, Hanlon-Dearman A, Longstaffe S, Roos LL. Manitoba mothers and fetal alcohol spectrum disorders study (MBMomsFASD): protocol for a population-based cohort study using linked administrative data. *BMJ Open 2016;6:e013330.doi:10.1136*

<h1 style="text-align: center">Chapter 3: Methods</h1>

3.1   Ethics and Privacy

This study was approved by the University of Manitoba's Health Research Ethics Board

(HS16460(H2013:221)) and the Manitoba Health Information Privacy Committee

(HIPC#2013/2014-20). Data access was approved by MCHP and the following data custodians:

Manitoba FASD Centre and the Winnipeg Regional Health Authority, Healthy Child Manitoba

Office, Manitoba Families, and Manitoba Education and Training. This study was conducted at

MCHP, which is a secure computing environment. Strict security measures are in place to protect

the data files and to restrict access. The data in the Manitoba Population Research Data

Repository (Repository) contain no identifiable personal information and are only used for

research purposes. Data are presented in summary form, in a fashion ensuring that the potential

for identification is minimized.

3.2   Description of Data Sources

Records from the following data sources were linked together for analyses:

(1) **Manitoba FASD Centre:** This data set includes information on all children assessed at
the clinic from March 31, 1999 to March 31, 2012 and consists of children who have
received a diagnosis of FASD, children who have been assessed but do not meet the
criteria for FASD, and those who have received a deferred status, meaning they will be
assessed later, as symptoms are more apparent in older children. The clinic uses Canadian
diagnostic guidelines developed by Chudley et al[2], and the updated guidelines published
by Cook et al[3]. These guidelines include all alcohol-related disabilities included under the

FASD definition: Alcohol-Related Neurodevelopmental Disorder (ARND), Alcohol-Related Birth Defects (ARBD), Fetal Alcohol Syndrome (FAS), and partial FAS (pFAS)[3]. Diagnosis of FASD is conducted by a multidisciplinary team that typically includes: screening and referral; physical examination and differential diagnosis; neurobehavioral assessment; and treatment and follow-up[2].

(2) Manitoba Centre for Heath Policy Population Research Data Repository: The Repository is one of the world's most comprehensive collections of population-level administrative databases and includes health services data for Manitobans from 1984 onwards[13]. De-identified health records are transferred to MCHP from Manitoba Health, Seniors and Active Living (Manitoba Health, a government department that administers the health insurance program for the province) and encrypted identifiers allow for linkages across multiple databases and years of data[13]. These data present a unique opportunity for the exploration of research and policy questions at a population level[4-7], and have been widely validated for the use of population health and social services research[4-8]. Data are collected by different sectors including health, education, and social services[13]. The following databases were utilized in this study:

a) **The population registry:** A registry maintained by the provincial department of health of all Manitobans eligible to receive health services since 1970 (updated semi-annually) and includes demographic information and 6-digit residential postal code[6];

b) **Canada census information:** Social data based on the Statistics Canada Population Census. These data were used to determine area-level income, with the Manitoba population divided into quintiles per average area-level household income[13],

composed of five income groupings with Q1 being the lowest and Q5 being the highest income quintile;

c) **Employment and Income Assistance:** Data from the Social Assistance Management Information Network that provide information on Manitoba residents who receive provincial employment and income assistance, a program that provides financial assistance for meeting the basic needs of living[18];

d) **Education Data:** Education data are maintained by the provincial department of education and training and provide information on enrolment, marks and high school completion, and special funding. Special education funding is provided to children with severe to profound disabilities[18];

e) **Babies First/Families First Screening Program data:** Data collected as part of a universal screening program administered by Healthy Child Manitoba. The screen is filled out by Public Health Nurses on all families with newborns in Manitoba and captures data on biological, social, and demographic risk factors including alcohol use during pregnancy[18];

f) **Healthy Baby Prenatal Benefit:** Data from the Healthy Baby program, which provides an income supplement to help low-income women meet nutritional needs during pregnancy and connects women to programs and resources in their area[18];

g) **InSight Program Data:** Data from an outreach program where mentors provide intensive support to pregnant women who are using substances or those who have recently had a baby. This dataset includes information on women who have prenatal alcohol use[18];

h) **Justice System Data:** An incident tracking system maintained by the provincial department of justice. These data include information on incidents, charges, and involvements (e.g., Witness, accused, victim) in the justice system in Manitoba;

i) **Hospital discharge abstracts:** Consisting of all hospitalizations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before April 1, 2004 and up to 25 ICD-10-CM diagnostic codes for discharges on or after April 1, 2004[6];

j) **Medical/physician reimbursement claims:** Consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit[6];

k) **Pharmaceutical drug claims:** Containing all prescription drug claims from the Drug Programs Information Network (DPIN, an electronic, on-line, point-of-sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba)[6]. Contains information on all prescription drugs dispensed in Manitoba;

l) **Manitoba Vital Statistics mortality data:** A longitudinal population-based registry maintained by Manitoba's Vital Statistical Agency that includes all Manitobans who have died since January 1970 to present and the cause of death[6];

m) **Child and Family Services data:** A data management system that supports case tracking and reporting of services provided to children and families as they are served through the Manitoba Child and Family Services (CFS) system. This database includes information on children in care as well as information of families receiving protection and support services[18].

See Table 3.1 for descriptions and years of datasets used for analysis.

Table 3.1: Description of datasets used for analysis and types of information retrieved

Name of Dataset	Description of Dataset	Years of Data Used	Information retrieved
Population Registry	A registry maintained by Manitoba Health of all Manitobans eligible to receive health services since 1970 and includes demographic information and 6-digit residential postal code[1].	1970/71 to June 2013	Demographic information: region of residence
Canada Census Information	Social data based on the Statistics Canada Population Census. These data were used to determine area-level income, with Manitoba population divided into income quintiles according to average area-level household income, composed of five possible income groupings with Q1 being the lowest and Q5 being the highest income quintile[1].	1996, 2001, 2006, 2013	Socioeconomic status information
Employment and Income Assistance Data	Data maintained by Manitoba Families that provide information on Manitoba residents who receive provincial employment and income Assistance[1].	1995/96 to 2012/2013	Socioeconomic status information
Education data: Enrolment, Marks and Assessments	Education data maintained by Manitoba Education and Advanced Learning that provide information on enrolment, marks, and high school completion, and special funding. Special education funding is provided to children with severe to profound disabilities[1].	1995/96 to 2012/2013	High school completion, level of special education funding
Baby First/Families First Screening Program data	Data collected as part of a universal screening program administered by Healthy Child Manitoba. The screen is filled out by Public Health Nurses on all families with newborns in Manitoba and captures data on biological, social and demographic risk factors, including alcohol use during pregnancy[1].	2003 to 2013 = Families First 2000 to 2002 = Baby First	Alcohol and drug use during pregnancy Maternal education
Healthy Baby Prenatal Benefit and Healthy Baby Community Support Program	Data from the Healthy Baby programs (administered by Healthy Child Manitoba), which provide financial benefits to help women meet nutritional needs during pregnancy and connects women to programs and resources in their area[1].	2001 to 2011/2012	Demographic and socioeconomic status information Program participation
InSight Program data	Include data from an outreach program where mentors provide intensive support to women who are pregnant or have recently had a baby and use substances. This dataset includes information on women who have prenatal alcohol use[1]	1999 to 2012/2013	Alcohol and substance use during pregnancy
Hospital Abstracts	Health data maintained by Manitoba Health consisting of all hospitalizations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before April 1, 2004 and up to 25 ICD-10-CM diagnostic codes for discharges on or after April 1, 2004[1].	1984 to 2012/13	Physical and mental health diagnoses Antenatal hospitalizations Suicide attempts
Medical/Physician reimbursement claims	Health data maintained by Manitoba Health consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit[1].	1984 to 2012/13	Physical and mental health diagnoses Physician visits Prenatal care
Prescription claims data: Drug Program	Data maintained by Manitoba Health containing all prescription drug claims from the Drug Program Information Network (DPIN), an electronic, on-line,	1995/96 to 2012/13	Physical and mental health diagnoses

Information Network	point-of –sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba). Contains information on all prescription drugs dispensed in Manitoba[1].		
Manitoba FASD Centre data	Include clinical assessments and diagnoses received under the FASD umbrella for all children referred to the MB FASD Centre[1]	1999 to 2012/2013	FASD diagnosis Children diagnosed with FASD
Vital Statistics data	A longitudinal population-based registry maintained by Manitoba's Vital Statistics Agency that includes all Manitobans who have died since January 1970 to present and the cause of death[1].	1970 to 2012/2013	Cause of premature death Suicide completion
Justice System: The Prosecutions Information Management System	An incident tracking system maintained by Manitoba Justice. This data includes information on incidents, charges and involvements (e.g., Witness, accused, victim) in the justice system in Manitoba[1].	2002 to 2011/2012	Justice system involvement
Child and Family Services Information System (CFSIS)	A data management system that supports case tracking and reporting of services provided to children and families as they pass through the Manitoba Child and Family Services (CFS) system[1]. This database includes information on children in care as well as information of families receiving protective and support services[1].	1992/1993 to 2012/2013	Involvement with child and family services

[1]http://umanitoba.ca/faculties/health_sciences/medicine/units/chs/departmental_units/mchp/resources/repository/datalist.html

3.3   Data linkage

De-identified health records are transferred to MCHP from Manitoba Health and contain

scrambled identifiers that allow for linkages across multiple databases and years of data[7].

Manitoba Health acts as a third party for other non-health data providers, to develop cross-walk

files allowing individual-level linkages across different data sectors[7]. Linkages are done using

de-identified personal health identification numbers (PHIN) which are unique nine-digit numeric

identifiers assigned by Manitoba Health to every person registered for health insurance in

Manitoba[7].

The main sources of data for this work were the MB FASD Centre database and the databases

identified above from the Repository. This linkage produced a powerful tool for studying

children and families with FASD that combines the comprehensive health, social, and education

administrative data with detailed clinical information. For this study the study population was formed through linking children identified as having a clinical diagnosis of FASD to their birth mothers. Children diagnosed with FASD through the MB FASD Centre were linked to their mothers using the "Hospital Newborn to Mother Linkage" which is a Registry file in the Repository. This file contains basic demographic and hospital data on newborns born in a hospital in Manitoba from 1984/85 onward and their mothers. This file included all live and stillbirths to Manitoba residents, and babies born in out of province hospitals to Manitoba residents, if reported to Manitoba Health. Babies not included are those: born out of hospital; born in Manitoba hospitals to out-of-province residents; and those born out of province to Manitoba residents who are not reported to Manitoba Health. A baby's birth record is matched to the mother's obstetrical delivery record using PHINs. The study population was then linked to several other Repository datasets (hospital, physician, drug, and the social and educational databases specified above) through one-to-one links between PHINs and data records. For example, a woman in the Repository identified as having given birth to a child diagnosed with FASD from the MB FASD dataset was linked to her individual hospital abstract records, physician claims records and prescription data records.

3.4   Study Population

Women were drawn from the entire population of women whose child was born in Manitoba between April 1, 1984 and March 31, 2012; two groups were generated to address research objectives:

Group 1: Study group: Mothers whose children received a clinical diagnosis of FASD:

Clinical data from the MB FASD Centre were used to ascertain all children and youth

(birth to 21 years of age) who were diagnosed with FASD between 1999 and 2012. The MB FASD Centre is one of the first and only provincially centralized FASD diagnostic clinics in Canada, and thus one of the largest. Children are diagnosed according to the Canadian FASD diagnostic guidelines[2,3]. The clinic database was linked to administrative data from the MCHP Repository to identify these children's birth mothers. Only mothers who could be linked to their children, who had postal code information, and who were Manitoba residents registered to receive health care in the province and covered from the birth of their child until December 31st, 2013 were included. If a mother had multiple children diagnosed with FASD, the first child diagnosed with FASD was used as the index child.

Group 2: Comparison group: Mothers whose children have not received a clinical diagnosis of FASD: Women whose children have never received an FASD diagnosis from the MB FASD Centre, and with no known record of prenatal alcohol use in the databases available, and whose children have had no evidence of FASD from the Repository were matched to the study group on date of month of birth of the index child, SES, and region of residence. Matching was performed without replacement, at a ratio of 3 controls for each case. To decrease the likelihood that the comparison women had children with undiagnosed FASD the following exclusion criteria was used: (1) women with any children assessed at the Manitoba FASD Centre; (2) women with children who had a diagnosis of FASD as recorded in hospital or physician claims data using the following ICD codes: a hospital visit with ICD 9CM code 760.71, ICD 10CCA code of 86.0 or a physician visit with any ICD 9 code 760; (3) women who had children who had prescriptions for psychostimulants or risperidone; (4) women with children diagnosed

with ADHD (due to high comorbidity with a diagnosis of FASD and ADHD[9,10]); (5)

women involved in the InSight Mentoring program (a program that provides support for

women with alcohol and substance abuse issues); (6) women with a history of substance

abuse disorder (including alcohol) during pregnancy as indicated by the physician and

hospital claims; (7) women whose newborn risk screen indicates they had used alcohol

during pregnancy; and, (8) women whose children received special education funding

indicating that they had severe to profound disabilities. See figure 3.1 for study flow

chart.

Figure 3.1: Study cohort formation
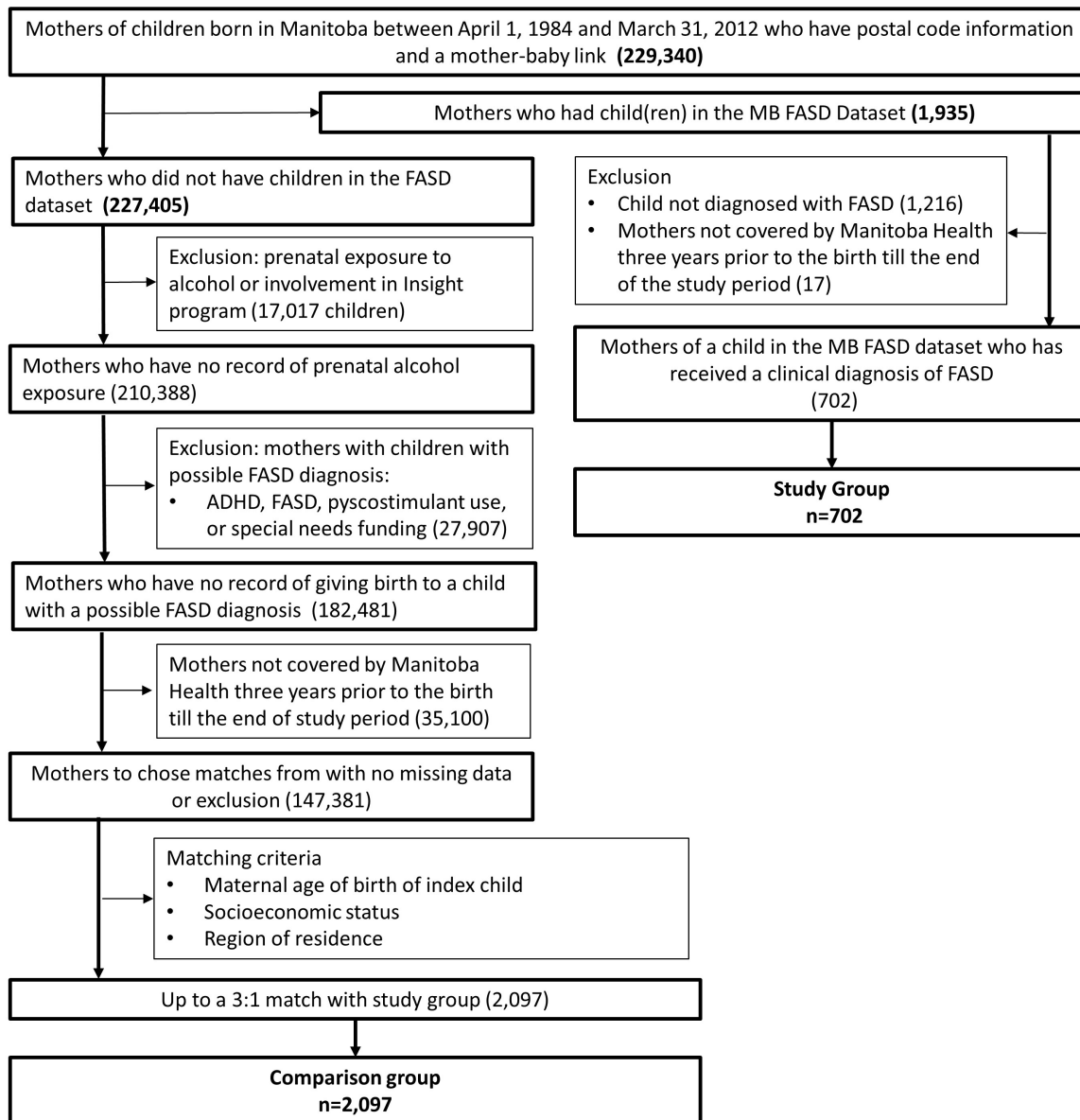
3.5   Study Design

Four research objectives of this dissertation require statistical analysis:

Research Objective 2 (Chapter 4): To investigate demographic, socioeconomic, family, mental and health characteristics associated with/predictive of giving birth to children with FASD compared to not giving birth to children with FASD.

Research Objective 3 (Chapter 5): To investigate rates of psychiatric morbidity (including: substance use disorders, schizophrenia, personality disorders, prenatal and postnatal psychological distress, and mood and anxiety disorders) of women who have given birth to children diagnosed with FASD compared to women who have given birth to children not diagnosed with FASD.

Research Objective 4 (Chapter 6): To investigate rates of suicidal behaviour (including attempts and completions) of women who have given birth to children diagnosed with FASD compared to women who have given birth to children not diagnosed with FASD.

Research Objective 5 (Chapter 7): To investigate the adequacy of prenatal health care utilization of women who have given birth to children diagnosed with FASD compared to women who have given birth to children not diagnosed with FASD.

Two study designs were used based on the different research objectives being addressed.

Research objective 2: A **retrospective matched case-control** design was utilized to investigate potential risk factors (exposure variables) associated with giving birth to a child with FASD (outcome) (See Figure 3.2). Our case group (group 1) was compared to our comparison group (group 2) to investigate if they had the following risk factors *before* the birth of the child and if these factors were associated with giving birth to children with FASD: demographic and socioeconomic factors, family history, mental disorder diagnoses, physical health diagnosis, health care utilization, and social service utilization.

Research Question 3,4,5: A **retrospective matched cohort study** design was utilized to investigate differences in rates of psychiatric morbidity, suicide attempts and completion,

physical health disorders and health and social services utilization (outcome variables)

(see Figure 3.3) between our study group (group 1) and our comparison group (group 2)

before and after the birth of the index child.

Figure 3.2: A retrospective matched case-control design to investigate potential risk factors associated with giving birth to a child with FASD
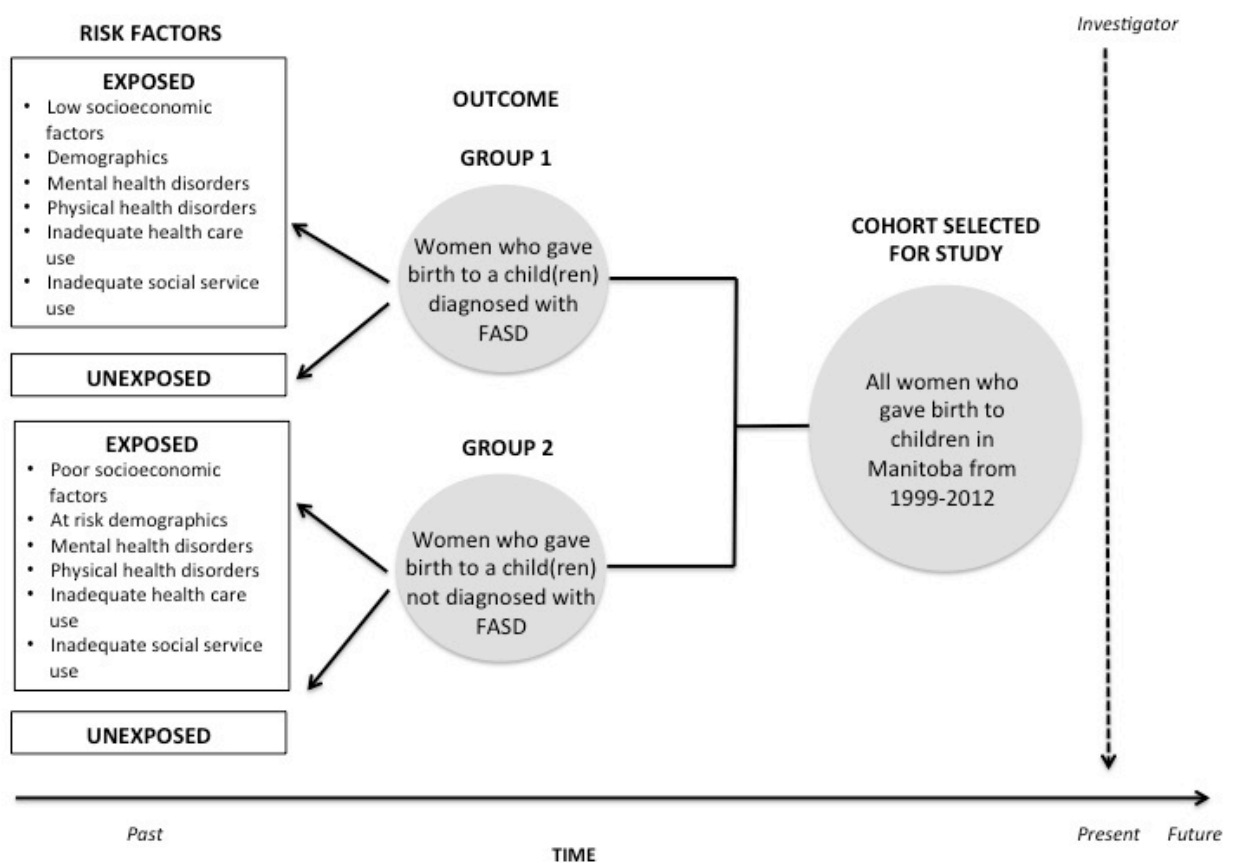
Figure 3.3: A retrospective matched cohort design to investigate differences in rates of psychiatric morbidity, suicide attempts and completions, physical health disorders, and health and social service utilization between study group and comparison group before and after the birth of the index child
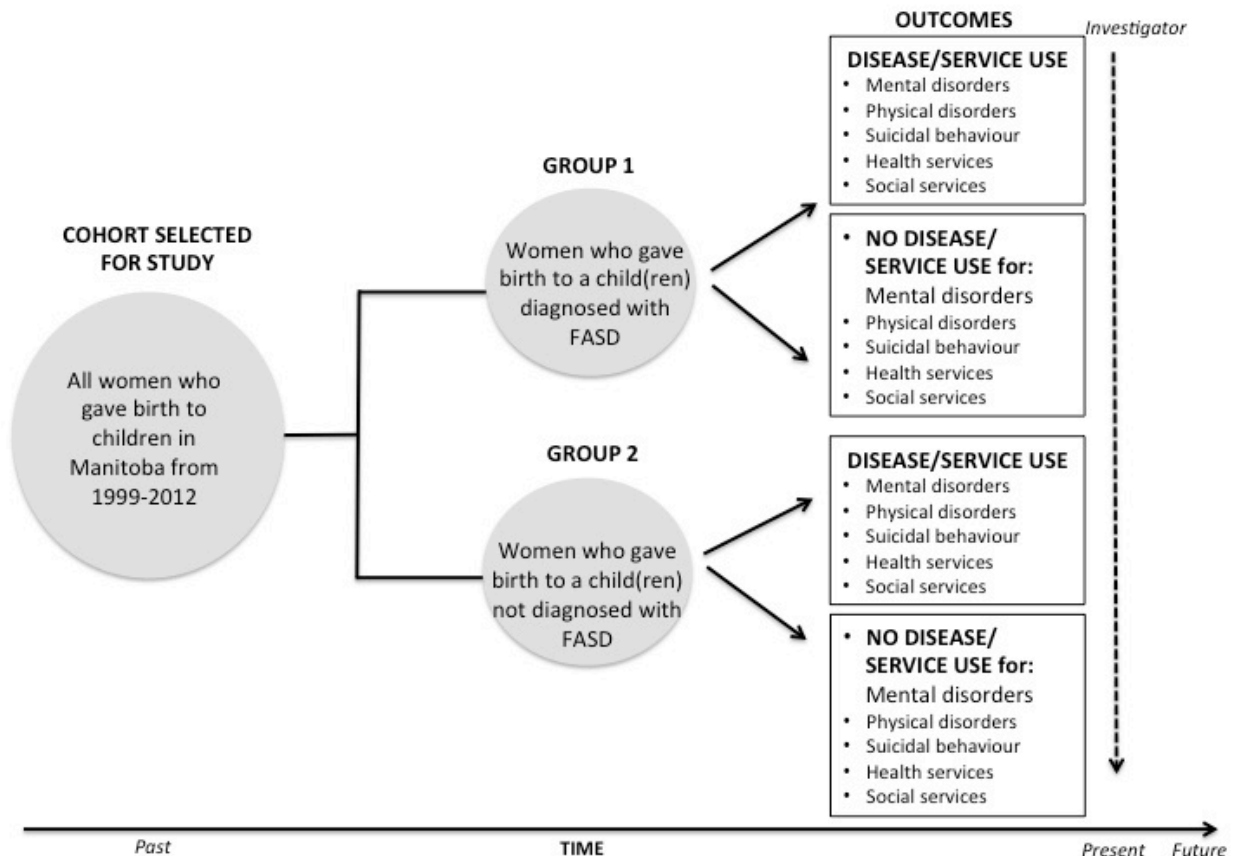
3.6   Definition of study variables for research objective 2

Outcome variable: The outcome investigated was giving birth to a child diagnosed with FASD, as identified in the MB FASD Centre data. FASD diagnoses included: Fetal Alcohol Spectrum Disorder, Fetal Alcohol Syndrome (FAS), partial-FAS, alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (ARBD).

Maternal risk factors: To investigate potential risk factors associated with giving birth to a child with FASD, the following variables were investigated three years prior to the birth of the index child for the study group and comparison group:

(a) **Demographic and socioeconomic factors:** Maternal age at birth of index child, maternal age at first birth, history of teen pregnancy, region of residence, mean household income, socioeconomic status (as measured by income quintiles), receipt of income assistance (see Table 3.2 for definitions);

(b) **Family history:** Marital status, gravidity, parity, birth order of the index child (first, middle, last), involvement with Child and Family Services, type of FASD diagnosis of child, involvement with the justice system (see Table 3.3 for definitions);

(c) **Diagnosis of a mental disorder:** Substance abuse disorder, personality disorder, mood and anxiety disorder, schizophrenia, prenatal psychological distress (Table 3.4), suicide attempts and completions (Table 3.5)

(d) **Diagnosis of a physical health disorder:** Diabetes, hypertension, ischemic heart disease, Total Respiratory Morbidity (Table 3.6);

(e) **Quality of prenatal care:** Late initiation of prenatal care, no prenatal care, low number of prenatal visits, inadequate prenatal care (Table 3.7).

3.7   Definition of study variables for research objectives 3,4,5

To investigate health outcomes and service utilization of the exposed and unexposed groups the following outcomes were investigated:

(a) **Psychiatric morbidity:** Diagnosis of substance abuse disorder, personality disorder, mood and anxiety disorder, and schizophrenia three years prior to the birth of the index

child. Prenatal psychological distress (8 months prior to the birth of the index child) and postnatal psychological distress (from birth to 12 months after the birth of the index child) (see Table 3.4 for definitions)

(b) **Suicidal Behaviour**: Suicide attempts (three years before the birth of the index child, during pregnancy, during the postpartum period, until the end of the study period) and completion (from birth to the end of the study period) (Table 3.5).

(c) **Physical health disorders:** Diabetes, hypertension, Ischemic Heart Disease, Total Respiratory Morbidity (three years prior to the birth of the index child) (see Table 3.6 for definitions).

(d) **Health Care Service Utilization:** Average number of physician/ambulatory visits one year before the pregnancy with the index child, average number of physician/ambulatory visits during the pregnancy with the index child, average number of all hospitalizations three years before the birth of the index child, average number of antenatal hospitalizations three years before the birth of the index child, late initiation of prenatal care, no prenatal care, low number of prenatal visits, inadequate prenatal care (see Table 3.7)

(e) **Social Services Utilization:** Receipt of Healthy Baby Prenatal Benefit (one year prior to the birth of the index child), participation in Healthy Baby Support Program (one year prior to the birth of the index child), participation in InSight Mentoring Program (one year prior to the birth of the index child), record of a Families First/Baby First Screen (after the birth of the index child). (See Table 3.8).

Table 3.2: Definitions of Demographic and Socioeconomic Exposure/Outcome variables

Variable	Time Frame	Database	Operation Definition/ ICD Codes
Mother's age at birth of index child	Year of birth of index child	Registry	A woman's age at birth of index child was determined by subtracting the date of conception of the index child by the birth date of the mother
History of a teen birth or pregnancy	Prior to the birth of the index child	Hospital Abstracts	A woman was identified has having a history of teen pregnancy or birth if they had the following diagnostic codes from the ages 15-19: • live birth: ICD-9-CM code V27, ICD-10-CA code Z37 • missed abortion: ICD-9-CM code 632, ICD-10-CA code O02.1 • ectopic pregnancy: ICD-9-CM code 633, ICD-10-CA code O00 • abortion: ICD-9-CM codes 634-637 ICD-10-CA codes O03-O07 • intrauterine death: ICD-9-CM code 656.4, ICD-10-CA code O36.4 Or, a hospitalization with one of the following procedures: • surgical termination of pregnancy: ICD-9-CM codes 69.01, 69.51, 74.91; CCI codes 5.CA.89, 5.CA.90 • surgical removal of extrauterine (ectopic) pregnancy: ICD-9-CM codes 66.62, 74.3; CCI code 5.CA.93 • pharmacological termination of pregnancy: ICD-9-CM code 75.0; CCI code 5.CA.88 • interventions during labour and delivery, CCI codes 5.MD.5, 5.MD.60
Region of residence – Urban/Rural	Year of birth of index child	Registry	Region of residence is categorized as being rural or urban as determined by the postal code registered with Manitoba Health. Those who are registered to Winnipeg or Brandon are categorized as urban, while the rest of Manitoba is considered rural.
Region of residence – Regional Health Authority	Year of birth of index child	Registry	In Manitoba, a Regional Health Authority (RHA) is a regional governance structure set up by the provincial government to be responsible for the delivery and administration of health services in a specified geographic area. From July 2002 to June 2, 2012 Manitoba consisted for the following RHAs: Winnipeg, Brandon, South Eastman, Assiniboine, Central, Parkland, North Eastman, Interlake, Burntwood, NOR-MAN, and Churchill. On June 1, 2012 these existing 11 RHAs were amalgamated into five larger regions. The new RHAs are listed below, with the old RHAs listed in brackets: (1) Winnipeg (Winnipeg, Churchill); (2) Interlake-Eastern (Interake, North Eastman); (3) Prairie Mountain (Assiniboine, Brandon, Parkland); (4) Southern (Central, South Eastman); (5) Northern (Burntwood, NOR-MAN)
Income Quintiles	Five years prior to the birth of the index child	Census Data	Income quintile is an aggregate, area-level measure of the average household income of residents in small areas, ranking them from poorest to wealthiest, and then grouping the population into five equal categories (1 being the poorest and 5 being the wealthiest). Each quintile contains approximately 20% of the population. The income quintile measure is derived from the 2006 Statistics Canada Census data by aggregating household income to the dissemination area and then ranking neighborhoods by income. Income quintiles

			are produced separately for urban and rural populations and are used as a proxy measure of individual socio-economic status. If the postal code is missing for a study subject, income quintiles cannot be calculated.
Receipt of income assistance	Five years prior to the birth of the index child	Social Assistance Management Information Network (SAMIN)	A woman was identified as having received income assistance if she was coded as having received income assistance from the SAMIN database anytime during the period of five years before the birth of the child.
Socioeconomic status (SES)	Year of birth of index child	Census Data	Socioeconomic status was defined according to income quintiles and income assistance data. A woman was considered to have: • Low SES if she was categorized as being in income quintile 1 or had a receipt of income assistance • Middle SES if she was categorized as being in income quintile 2 or 3 • High SES if she was categorized as being in income quintile 4 or 5
Involvement with the Justice System	5 years before birth of the child	Manitoba Justice	A woman was considered to have involvement with the justice system if she had a record of an incident in the Prosecutions Information Management System. Involvement type was classified by the following categories: (1) Witness; (2) Victim; (3) Accused

Table 3.3: Definitions of Family History Exposure/Outcome Variables

Variable	Time Frame	Database	Operation Definition/ ICD Codes
Marital status	Time of birth of index child	Registry	A woman was considered married if her marital status variable in the Registry was indicated as "married" or if she could be linked to a spouse through family linkages developed at MCHP.
Gravidity	Entire study period	Hospital abstracts	Gravidity is defined as the number of pregnancies, regardless of the duration, including the present pregnancy. Multiple fetuses (twins, triplets) count as one pregnancy. Gravidity was calculated using the hospital abstract data and was categorized as: 0-3 pregnancies, 4-9, 10-14.
Parity	Entire study period	Hospital abstracts	Parity is defined as the number of births a mother has had after 20 weeks gestation. A multiple birth is counted as one and stillbirths are included. Parity was calculated using the hospital abstracts data and was categorized as: 0-3, 4-9, 10-14.
Birth Order of the Child	Time of birth of the index child	Registry	Birth order of the child was defined by the variable "Birth Order" in the Registry Centre data and was categorized as: First, middle or last.
Any Child & Family Services involvement	5 years prior to the birth of the index child	Child and Family Services Information System (CFSIS)	A woman was defined as having any contact with Child and Family Services (CFS) 5 years prior to the birth of the index child if a record of any contact with CFS existed CFSIS, including: (1) Ever in Care – if a child was in care; (2) Ever received CFS Services – if there were no children in care but the family received protection or support services from CFS.
Children in care	5 years prior to the birth of the index	CFSIS	A woman was defined as having children in care if she had a child who had been removed from the home due to a situation where authorities deemed their family unable or unfit to look after them

	child		properly. In some cases, children are voluntarily placed into care by their parents, or they come into care for a variety of reasons including abuse and neglect, illness, death of a parent, addiction issues or conflict in the family, or disabilities.
Children receiving services from Child and Family Services	5 years prior to the birth of the index child	CFSIS	A woman was defined as having received protection or support services from CFS five years prior to the birth of the index child. Both involvement of children of the mother with CFS, as well as her own involvement as a minor with CFS were examined.
FASD diagnosis of index child	Entire study period	Manitoba FASD Centre data	The type of FASD diagnosis of the index child was determined by the diagnosis variable in the Manitoba FASD Centre data and was categorized as the following: (1) Alcohol related neurodevelopmental disorder (ARND); (2) Alcohol related birth defects (ARBD); (3) Fetal Alcohol Syndrome (FAS); or (4) Partial FAS (pFAS).
Other FASD affected children	At time of birth of index child	Manitoba FASD Centre	A mother was identified as having other children affected by FASD by a variable in the Manitoba FASD Centre dataset "other affected children".

Table 3.4: Definitions of Mental Disorders Exposure/Outcome Variables

Variable	**Time Frame**	**Database**	**Operation Definition/ ICD Codes**
Diagnosis of a mental health disorder	3 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	**A woman was considered to have a psychiatric disorder if she had one or more of the following (see specific definitions below):** Substance abuse disorder, personality disorder, mood and anxiety disorder, schizophrenia or pre- or postnatal psychological distress
Substance Abuse Disorder	3 years prior to the birth of the index child	Physician claims Hospital Abstracts Prescription claims	**A woman was considered to have a substance use disorder if in the five years prior to the birth of the child she had:** 1) one or more hospitalizations with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, or nondependent abuse of drugs (ICD-9-CM codes 291, 292, 303, 304, 305, ICD-10-CM codes: F10-F19 and F55) **OR** 2) one or more physician visits with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, or nondependent abuse of drugs using the same ICD-9-CM codes listed above.
Personality Disorder	3 years prior to the birth of the index child	Physician claims Hospital abstracts	**A woman was considered to have a personality disorders if in the five years prior to giving birth to the child she had the following:** 1) one or more hospitalizations with a diagnosis of personality disorder (ICD-9-CM code 301 or ICD-10- CA codes F34.0, F60, F61, F62, F68.1, F68.8, or F69) **OR** 2) one or more physician visits with a diagnosis of personality disorder: (ICD-9-CM code 301)
Mood & Anxiety Disorder	3 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	**A woman was considered to have mood or anxiety disorder if in the five years prior to giving birth to the child she had the following:** 1) one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction: ICD-9-CM codes 296.1-296.8, 300.4, 309 or 311; ICD-

			10-CA codes F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0 or with a diagnosis for an anxiety state, phobic disorders or obsessive-compulsive disorders: ICD-9-CM codes 300.0, 300.2, 300.3, 300.7; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42, F45.2; **OR** 2) F48, F68.0, or F99 AND one or more prescriptions for an antidepressant or mood stabilizer, including medications with the ATC codes N05AN01, N05BA, N06A; **OR** 3) one or more physician visits with a diagnosis for depressive disorder or affective psychoses: ICD-9-CM codes 296, 311; **OR** 4) one or more physician visits with a diagnosis for anxiety disorders: ICD-9-CM code 300 AND one or more prescriptions for an antidepressant or mood stabilizer, including medications with the ATC codes N05AN01, N05BA, N06A; **OR** 5) three or more physician visits with a diagnosis for anxiety disorders or adjustment reaction: ICD-9-CM code 300, 309
Schizophrenia	3 years prior to the birth of the index child	Physician claims Hospital abstracts	**A woman was considered to have schizophrenia if in the five years prior to giving birth to the child had the following:** 1) one or more hospitalizations or physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295 or ICD-10-CA codes F20, F21, F23.2, F25; **OR** one or more physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295.
Prenatal psychological distress	8 months prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	**A woman was considered to have prenatal psychological distress if in the eight months prior to giving birth she had:** 1) one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296.2–296.8, 300.4, 309, 311; ICD–10–CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8,F53.0, F93.0); **OR** 2) one or more physician visits with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296, 309 or 311); **OR** 3) one or more hospitalizations with a diagnosis for anxiety disorders (ICD-9-CM code 300l ICD-10-CD codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99); **OR** 4) one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR** 5) one or more physician visits with a diagnosis of anxiety disorders one or more physician visits with a diagnosis for anxiety disorders (ICD–9–CM code 300) and one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR** 6) one or more hospitalizations with a diagnosis for anxiety states, phobic disorders, or obsessive–compulsive disorders (ICD–9–CM codes 300.0, 300.2, 300.3; ICD–10–CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42); **OR** 7) two or more physician visits with a diagnosis for anxiety disorders (ICD--CM code 300).
Postnatal	12 months	Physician	**A woman was considered to have postnatal psychological**

| psychological distress | after the the birth of the index child | claims Hospital abstracts Prescription claims | **distress if in the 12 months after giving birth she had:**
1) one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296.2–296.8, 300.4, 309, 311; ICD–10–CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8,F53.0, F93.0); **OR**
2) one or more physician visits with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296, 309 or 311); **OR**
3) one or more hospitalizations with a diagnosis for anxiety disorders (ICD-9-CM code 300l ICD-10-CD codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99); **OR**
4) one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
5) one or more physician visits with a diagnosis of anxiety disorders one or more physician visits with a diagnosis for anxiety disorders (ICD–9–CM code 300) and one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
6) one or more hospitalizations with a diagnosis for anxiety states, phobic disorders, or obsessive–compulsive disorders (ICD–9–CM codes 300.0, 300.2, 300.3; ICD–10–CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42); **OR**
7) two or more physician visits with a diagnosis for anxiety disorders (ICD--CM code 300) |

Table 3.5: Definitions of Suicide Behaviour Exposure/Outcome Variables

Variable	Time Frame	Database	Operation Definition/ ICD Codes
Suicide attempts	5 years prior to the birth of the index child During pregnancy During the postpartum period From one year after the birth of the child till the end of the study period	Physician claims Hospital abstracts	**A woman was considered to have attempted suicide if in the five years prior to the birth of the child she had:** 1) one hospitalization with a diagnosis for suicide and self-inflicted injury: ICD-9-CM codes E950-E959, ICD-10-CA codes X60-X84; **OR** 2)one hospitalization with a diagnosis code for accidental poisoning: ICD-9-CM codes 965, 967, 969, 977.9, 986, E850-E854, E858, E862, E868; ICD-10-CA codes T39, T40,T42.3, T42.4, T42.7,T43, T50.9, T58, X40-X42, X44, X46, X47, Y10-Y12, Y16, Y17, only if there is a physician visit with a diagnosis code for accidental poisoning and a psychiatric tariff code either during the hospital stay or within 30 days post-discharge. Psychiatric tariff codes are as follows: From the **psychiatric schedule:** 8444 Psychotherapy - group of two to four patients 8446 Psychotherapy - group of five or more patients 8472 Child and Youth Management Conference 8475 Psychiatry - Patient Care Family Conference 8476 Psychiatric Social Interview 8503 Complete history and psychiatric examination - adult 8504 Complete history and psychiatric examination - child 8553 Psychiatry Consultation - adult 8554 Psychiatry Consultation - child

			8581 Psychotherapy - individual
			8584 Psychiatric care - individual
			8588 Electroshock therapy
			8596 Consultation - Unassigned patient – child
			From the **general schedule:**
			8580 Psychotherapy - individual
			8587 Electroshock therapy
			8589 Psychotherapy - group
Suicide completion	From birth till the end of the study period	Vital Statistics Mortality Data	**A woman was considered to have completed suicide if the following ICD codes were used in the "cause of death" field in the Vital Statistics Mortality Data (our definition including accidental poisonings):** 1) accidental poisoning: ICD-9 codes E850-E854, E858, E862, E868; ICD-10 codes X40-X42, X46, X47; **OR** 2) poisoning with undetermined intent: ICD-10 codes Y10-Y12, Y16, Y17; **OR** 3) self-inflicted poisoning: ICD-9 codes E950-E952, ICD-10 codes X60-X69; **OR** 4) self-inflicted injury by hanging, strangulation and suffocation: ICD-9 code E953, ICD-10 code X70; **OR** 5) self-inflicted injury by drowning: ICD-9 code E954, ICD-10 code X71; **OR** 6) self-inflicted injury by firearms and explosives: ICD-9 code E955, ICD-10 codes X72-X75; **OR** 7) self-inflicted injury by smoke, fire, flames, steam, hot vapours and hot objects: ICD-9 codes E958.1, E958.2; ICD-10 codes X76, X77; **OR** 8) self-inflicted injury by cutting and piecing instruments: ICD-9 code E956; ICD-10 codes X78, X79; **OR** 9) self-inflicted injury by jumping from high places: ICD-9 code E957, ICD-10 code X80; **OR** 10) self-inflicted injury by jumping or lying before a moving object: ICD-9 code E958.0, ICD-10 code X81; **OR** 11) self-inflicted injury by crashing of motor vehicle: ICD-9 code E958.5, ICD-10-CA code X82; **OR** 12) self-inflicted injury by other and unspecified means: ICD-9 codes E958.3, E958.4, E958.6-E958.9; ICD-10 codes X83, X84; **OR** *13)* late effects of self-inflicted injury: ICD-9 code E959

Table 3.6: Definitions of Physical Health Disorders Exposure/Outcome Variables

Variable	Time Frame	Database	Operation Definition/ ICD Codes
Hypertension	3 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	**A woman was considered to have a history of hypertension if 5 years prior to the birth of the child she had:** 1) At least one physician visit or one hospitalization with an ICD–9–CM code of 401–405 (ICD–10–CA codes I10–I13, I15); **OR** 2) two or more prescriptions for hypertension drugs
Total Respiratory Morbidity	3 years prior to the birth of the index child	Physician claims Hospital abstracts	**A woman was considered to have a history of total respiratory morbidity if 5 years prior to the birth of the child she had:** one physician visit or hospitalization in one year with: asthma, acute bronchitis, chronic bronchitis, bronchitis not specified as

Variable	Time Frame	Database	Operation Definition/ ICD Codes
			acute or chronic, emphysema, or chronic airway obstruction (ICD–9–CM codes 466, 490, 491, 492, 493, 496; ICD–10 codes J20, J21, J40–J45).
Diabetes	3 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	**A woman was considered to have a history of diabetes if 5 years prior to the birth of the child she had:** 1) At least two physician visits or one hospitalization with a diagnosis of diabetes (ICD–9–CM code 250; ICD–10–CA codes E10–E14); **OR** 2) one or more prescriptions for medications to treat diabetes
Ischemic Heart Disease	3 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	**A woman was considered to have a history of total respiratory morbidity if 5 years prior to the birth of the child she had:** 1) at least two physician visits or one hospitalization for IHD (ICD–9–CM codes 410–414, ICD–10 codes I20–I22, I24, I25); **OR** 2) at least one physician visit with a code listed above and two or more prescriptions for IHD medications

Table 3.7: Definitions of Health Services Exposure/Outcome Variables

Variable	Time Frame	Database	Operation Definition/ ICD Codes
Physician Visits			
Ambulatory care visits	3 year prior to birth of index child	Physician claims	Ambulatory visits are defined as all contacts with physicians (family practitioner and specialists) that do not include hospitalizations. These visits include: office visits, walk-in clinics, home visits, personal are home/nursing home visits and outpatient department's visits. They do not include emergency department visits. The type of visit is determined by a tariff code in the physician claims data.
Hospital Visits			
Hospitalizations	3 years before the birth of the child	Hospital Abstracts	A woman was considered to have a hospitalization if a billing claim was submitted to the provincial government for services a hospital had provided in order to receive reimbursement for care, these services include: physician visits, lab/pathology, x-ray/radiology, surgical services, anesthesia, post-operative care.
Antenatal hospitalizations	During the pregnancy of the index child	Hospital Abstracts	An antenatal hospitalization is a hospitalization in which a woman was pregnant but did not deliver during the hospitalization of the index child. Reasons include: threatened preterm labor, hemorrhage, diabetes, hypertensive disorders, abdominal pain etc. A woman was considered to have an antenatal hospitalization if there was a record of hospitalization not resulting in delivery in the hospital abstracts database.
Prenatal Care			
Prenatal care visit	During the pregnancy of the index child	Physician claims	A prenatal care visit was defined as the following physician tariff codes from the physician claims data: 8400 (complete Prenatal Assessment), 8401 (Prenatal visits subsequent), 8501 (office visits, regional history and examination), 8507, 8509 (office visits), 8529 (regional intermediate visit or well baby care), 8540 (office visits complete history and physician examination, new patient), 8550 (consultation).
Late initiation of prenatal care	During the pregnancy of the index child	Physician claims	A woman was considered as having late initiation of prenatal care if she began care after the first trimester of pregnancy (date of conception-91 days). This was determined by assessing when the first prenatal care tariff date was.
No care	During the	Physician	A woman was considered as having no prenatal care if she had no

Variable		Database	
	pregnancy of the index child	claims	visits with a prenatal care tariff during her pregnancy.
Care initialized in first trimester	During the pregnancy of the index child	Physician claims	A woman was considered as having care initialized in the first trimester if her first prenatal visit was between the date of conception to 91 days.
Care initialized in 2nd trimester	During the pregnancy of the index child	Physician claims	A woman was considered as having care initialized in the second trimester if her first prenatal visit was between 92 to 189 days.
Care initialized in 3rd trimester	During the pregnancy of the index child	Physician claims	A woman was considered as having care initialized in the third trimester if her first prenatal visit was between 189 days to the birth of the child.
Low number of prenatal visits	During the pregnancy of the index child	Physician claims	A woman was considered to have a low number of prenatal visits if she had less than five prenatal care visits as determined by counting the number of prenatal care tariffs she had during the pregnancy of the index child.
Quality of pre-natal care by the R-GINDEX	During the pregnancy of the index child	Physician claims Hospital Abstracts	The adequacy of prenatal care was determined using the R-GINDEX (Revised-Graduated Prenatal Care Utilization Index). The following three variables were calculated using Hospital and Physician claims data: (1) gestational age of the newborn, (2) the trimester that prenatal care began; (3) the total number of prenatal visits during the pregnancy. The G-INDEX classifies prenatal care into the following categories: (1)Inadequate prenatal care; (2) Intermediate prenatal care; (3) Adequate prenatal care; (4) Intensive prenatal care; (5)No care; (6) Missing information

Table 3.8: Definitions of Social Services Exposure/Outcome Variables

Variable	Time Frame	Database	Operation Definition/ ICD Codes
Healthy Baby Program Services			
Receipt of Healthy Baby Prenatal Benefit	One year prior to the birth of the child	Healthy Baby Community Support Program dataset	The Healthy Baby Prenatal Benefit is income supplement for pregnant women who live in Manitoba and have a net family income of less than $32,000. A woman was considered to have received the prenatal benefit if at any time during the eligibility period of the benefit (14 weeks, until delivery) she received the benefit as coded in the Healthy Baby Prenatal Benefit Dataset.
Participation in Healthy Baby Support Program	One year prior to the birth of the child	Healthy Baby Community Support Program dataset	The Healthy Baby Program is a support program delivered by the province of Manitoba to offer social support and learning opportunities that encourage prenatal care and promote healthy infant development. A woman was considered to have participated in this program if she had a file in the Healthy Baby Community Support Program dataset.
InSight Mentoring Program Participation	One year prior to the birth of the child	InSight database	The InSight program is an outreach program where mentors provide intensive support to women who are pregnant or have recently had a baby and use substances. A woman was considered to have participated in this program if she had a file in the Insight Program Database.
Baby	After the	BabyFirst	Public health nurses in Manitoba attempt to assess all families with

First/Families First Screen	birth of the index child	screen data Families First Screen data	newborns (using a validated screen) within a week of discharge from the hospitals. Families are asked about support and challenges including parents' alcohol and drug use, mental health, education etc. Three or more risk factors indicate that a family may require additional supports such as intensive home visiting, financial supports, support programs etc. Before 2003, this program was known as the BabyFirst home visiting program.
Record of a Families First screen for the index child	After the birth of the index child	Families First Screen data	A woman was identified as having a Families Frist Screen if she had a record of a screen after the birth of the index child in the Families First Dataset.
Record of a Baby First Screen for the index child	After the birth of the index child	BabyFirst screen data	A woman was identified as having a Baby Frist Screen if she had a record of a screen after the birth of the index child in the BabyFirst Dataset.

3.8   Data Analysis: Research Objective 2

Descriptive statistics (means, standard deviations, percentages) were generated to describe the study groups. Two-tailed tests were conducted, and statistical significance was defined as $p<0.05$ for all analyses. Variables found to be significant were included in multivariate regression. Multivariate regression analysis using conditional logistic regression was used, which facilitates the analysis of a binary dependent variable (giving birth to a child with FASD diagnosis and giving birth to a child with no FASD diagnosis) and various predictor variables. Conditional logistic regression as opposed to binary logistic regression was used because the observations were matched and not independent.

Study groups were matched on region of residence, SES, and date of birth of index child. It is important to note that matching was not done to control for confounding variables; all possible variables were used as potential risk factors in the logistic model to facilitate an exploratory analysis that investigates all potential risk factors for giving birth to children with FASD. Matching in this study was used to establish an accurate comparison sample from a large sample of population data (n > 100,000) of women who have given birth to children without FASD over

the study time, relative to the sample of women who have given birth to a child with FASD (n= 702). Because the outcome is rare in the population (giving birth to a child with FASD), using the entire population of women giving birth to children in Manitoba could overwhelm the model. This could result in inaccurate prediction or quasi-complete separation of data. Quasi-complete separation can occur when a logistic model perfectly predicts the response, for example, in the general population the majority of women would not have given birth to a child with FASD and unique maximum likelihood estimates would not exist. Conditional logistic regression allows for the analysis of correlated observations by accounting for the between strata variance. Each matched pair of women serves as a somewhat different population from one another because women who give birth in 1997 may have more similarities than the pairs of women who give birth to children in 2009. The focus was not in estimating or modeling this baseline risk and but in estimating the effect of the hypothesized risk factors. Conditional logistic regression "conditions out" this between variance.

All hypothesised risk factors were adjusted for in the multivariate models, and reported as adjusted odds ratios (aORs) and 95% confidence intervals (CI). The analyses were conducted using SAS version 10 (SAS Institute Inc., Cary, NC, USA).

Missing data and sensitivity analysis: Proportions of missing data for those variables with missing data were determined. Study group women with missing values and their matches were dropped from the analysis. A sensitivity analysis was conducted by imputing the creation of a missing value (99) so that all women were included in the analysis.

Model Fit: A c-statistic (ranging from 0.5 to 1) was used to assess model fit, specifically to

measure the models ability to discriminate between those with and without the outcome. The model was deemed to perform well when all predictors were included and the c statistic was above 0.7[11].

3.9   Data Analysis: Research Objectives 3,4,5

Univariate statistics, including proportions and means, were calculated for all outcome variables (i.e., events). Adjusted relative rates for all outcomes were calculated using Generalized Estimating Equations (GEE) with a Poisson distribution. A Negative Binomial distribution was used if data were over-dispersed. Both models are suitable for non-normally distributed data such as counts. GEEs are the most appropriate statistical test to handle the complexity of the clustered/correlated data present in this study and repeated measurements of the time-varying outcomes used for this analysis. For example, one of the objectives of this study was to investigate the health care utilization of women who have given birth to child(ren) diagnosed with FASD compared to women who have given birth to child(ren) without an FASD diagnosis over time. Because the time frame of the study spans over 15 years, it is important to acknowledge the rates of health care utilization have changed (risk of outcome has changed) over time in the general population. Women who gave birth in 1990 are more likely to be more similar in their health care utilization than women in 2005 due to changes in access and types of health care services available. This hypothesis is verified by trends reported in the Regional Health Authority Atlas published by the Manitoba Centre for Health Policy in 2013, which shows an increase in hospitalizations and physician visits over the past decade[12]. These data demonstrate that the risk of this outcome changes over time; therefore, women who gave birth in 1990 are more likely to be more similar in their health care utilization than women who gave

birth 15 years later. Because study data comes from strata of matched pairs of women across time, and there may be repeated measures from the same women (number of hospitalization over time), observations are not independent and underlying correlation needs to be addressed in the analysis. GEE accounts for the longitudinal and clustered design by producing parameter estimates that are more efficient and unbiased than in ordinary least square regression.

All analyses tested for differences between study groups and adjusted for the following covariates: socioeconomic status (using income quintiles), age of mother at birth of child, and other covariates that were thought to be appropriate depending on the outcome being investigated. A summary dataset for the total number of events (e.g., total number of mothers with mood and anxiety disorder) was produced to model the rate of events comparing women with children with FASD and those with children without FASD. The log of the total number of events was included as an offset in the model to produce an analysis of rates of events, rather than simple counts, and to generate estimates of adjusted RRs of events.

3.10 Discussion

The MB FASD Moms study is a large, comprehensive, in-depth investigation into the characteristics, health and mental health, and service utilization of women whose children have been diagnosed with FASD to date. This study offers numerous methodological advantages over studies utilizing primary data collection[7]:

Strengths:

(1) The use of linked clinical and administrative data is the study's greatest strength. It is difficult to ascertain and follow large groups of women whose children have a clinical

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diagnosis of FASD using primary data collection due to challenges of attrition and length of follow-up time needed to obtain longer term outcomes of mothers (e.g., suicide)[7]. In this study, mothers were identified through children who were diagnosed at the Manitoba FASD Centre, which is one of the first and only provincially centralized FASD diagnostic clinics in Canada, and thus one of the largest. Using linked clinical and administrative data, the large sample size generated in this study enhances the generalizability of the study results.

(2) The Manitoba FASD Centre offers a valid and reliable clinical diagnosis of FASD, and thus, certainty that women in this sample have given birth to children with FASD. Previous studies investigating characteristics of women who have consumed alcohol during pregnancy cannot confirm a clinically corroborated diagnosis of FASD in children. Therefore, these women may have different characteristics, health, and service utilization from those women whose children had FASD.

(3) Access to information on the whole population of Manitoba was available through the Repository[7]. These data facilitate the creation of clinically relevant comparison groups and accurate comparative analysis[13]. Using the multiple available databases, comparison groups were created using matched characteristics including: age; sex; SES; and geographic location[13]. These comparative analyses are difficult to perform using primary data recruitment methods as both controls and cases can be difficult to identify, can take years to recruit, and are subject to attrition[7]. Moreover, using hospital, physician, educational and social administrative data to develop exclusion criteria, the likelihood that women in the comparison group had children with undiagnosed FASD can be

decreased. This is potentially a major limitation in previous studies as FASD is an extremely under diagnosed condition.

(4) Through leveraging the comprehensive, longitudinal databases available at MCHP novel health outcomes not yet studied were investigated. Specifically, the mental disorder diagnoses of women who give birth to children with FASD were documented and rates of prenatal and postnatal anxiety and depression were determined, as well as suicide attempts and completions. Women with alcohol and substance use issues are at higher risk for prenatal and postpartum depression[14-16]; investigating these outcomes specifically in mothers who give birth to children with FASD can provide evidence to policy makers responsible for optimizing FASD prevention and support resources. Furthermore, maternal suicide is an increasing public health issue[17] and investigating whether women who give birth to children with FASD are at increased risk for suicide is also important to optimize support resources to ensure these women get the services they need, rather than slipping through the cracks.

(5) Due to the longitudinal nature of the data[7], an analysis of system usage of women before, during and after pregnancy was conducted and compared to women in the general population whose children were not diagnosed with FASD. This type of analysis is important to identify points for prevention, early intervention, and treatment and effective resource allocation, as well as supporting the health and well-being of women who give birth to children with FASD. The Repository is ideal for these analyses, as the data accurately calculate the usage of the healthcare services among related populations in the past. For example, Brownell et al. used MCHP data to document the usage of health and social systems among children with FASD[18].

(6) Administrative data eliminate recall bias and offer accurate information that can be isolated in critical periods of time throughout a study participant's lifespan[7]. It is difficult to conduct studies on mothers with children with FASD due to stigmatization and attrition of study subjects. Furthermore, studies utilizing primary data collection may be conducted after a significant time period has passed since these women's pregnancies. This makes the recall of specific diagnoses, events, and health service utilization during the pregnancy difficult and increases the likelihood of inaccuracy. The use of these data is an important opportunity to ascertain accurate, unbiased information on these mothers, their use of health and social services, and co-morbid diagnoses before and during pregnancy and the post-partum period.

While the use of routinely collected population data has numerous advantages, there are also limitations that warrant discussion:

Limitations:

(1) The use of a clinically referred FASD sample may limit the generalizability of findings, as women and children not referred to this clinic may be excluded. Owing to the complex nature of FASD, the multiple co-morbidities associated with the disorder, underreporting, coding patterns of physicians, and the complex multidisciplinary teams required to diagnose FASD, there is no algorithm that has been developed to identify children with FASD in the MCHP Repository using other data sources. Therefore, record linkage with the Manitoba FASD Centre is necessary to confirm a clinical diagnosis of FASD in children in Manitoba. However, the referrals to the clinic come from a wide variety of

sources and from all regions in the province, strengthening the representativeness across populations.

(2) While great care was taken in excluding all mothers with possible prenatal alcohol exposure and children with a diagnosis of FASD, there still could be women in the comparison group who have un-reported prenatal alcohol use or children with undiagnosed FASD. However, this would serve to weaken rather than strengthen any of the findings

(3) As in all studies using administrative databases, this study is reliant on the accuracy of data submitted by the organizations that deliver services[7], and may have variations in data collection methods and compliance rates in the recording of information that may result in data errors[7]. However, as previously stated, MCHP data have been extensively validated for conducting this type of research[13,6,7].

(4) Outcome data are dependent on the individual making contact with the health care system and are therefore a report of treatment prevalence; thus, this study could undercount physical health or mental health disorders for women who do not receive treatment.

(5) The Repository does not capture information on interpersonal relationships, violence and abuse, psychological trauma, or patient insight which are important for understanding the underlying causes of the drinking during pregnancy and would provide context to results. However, data collection methods are often resource and time intensive, and studies with patient insight often have small sample sizes, limiting generalizability. Although these types of data are not readily available in the Repository, the results of this study have the potential to lay the groundwork for the development of future work in this area.

(6) Due to the exploratory nature of this study, there were multiple comparisons performed, potentially inflating the risk of type 1 error. Future research should be conducted that corroborates the results from this study.

3.11 Conclusion

The databases brought together for this study and the results produced generated a significant amount of longitudinal outcome data that contribute to our understanding of the life circumstances of mothers who give birth to children with FASD. Study results provide an informed picture of the determinants of health that place women at increased risk of alcohol consumption during pregnancy, and giving birth to children with FASD. Moreover, study results offer insight into how women whose children have been diagnosed with FASD navigate health and social service systems during the perinatal and postnatal periods. These results add to the evidence base and facilitate FASD prevention efforts through identifying: (1) high risk women who should be targeted for prevention and intervention; (2) areas in health and social services that can be targeted for FASD prevention and support programs to enhance service delivery to this population. Research providing insight into the factors that place women at risk for having children with FASD is vital for effective targeting and developing of policy resources that can help women cope with the influences and stresses in their lives to decrease prenatal alcohol consumption and ultimately prevent FASD.

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Preface: Chapter 4

The first research objective of this thesis was to identify maternal risk factors associated with giving birth to children with FASD during the preconception and pregnancy period (3 years before the birth of the index child) using linked administrative data. Identification of targeted areas for interventions to support women who give birth to children with FASD is crucial to the success of FASD prevention, yet there is a paucity of data investigating maternal risk factors associated with giving birth to children with FASD from North America. Chapter 4 presents the first empirical results of this dissertation. To the best of our knowledge, this study is the first to use a large, representative, Canadian sample of mothers to determine demographic, socioeconomic, and health and service utilization characteristics that may be associated with giving birth to children with FASD.

Publication details:

Singal D, Brownell M, Chateau D, Hanlon-Dearman A, Longstaffe S, Roos LL. Maternal risk factors for giving birth to children with FASD: A matched case-control, retrospective study of the Manitoba Mothers and FASD Cohort utilizing linked administrative data. [*Prepared for submission to the Canadian Journal of Public Health*].

Chapter 4: Maternal Risk Factors for Giving Birth to Children with FASD: A matched case-control retrospective study of the Manitoba Mothers and FASD Cohort utilizing linked administrative data

4.1   Abstract

Background: The identification of targeted areas for interventions to support women who give birth to children with FASD is crucial to the success of FASD prevention, yet there is a paucity of data investigating maternal risk factors associated with giving birth to children with FASD from North America. The objective of this study was to identify maternal characteristics and service utilization associated with giving birth to children with FASD in a large Canadian sample.

Methods: We used data from the Manitoba Mothers and FASD study cohort, a sample of all children born in Manitoba between April 1, 1984 and March 31, 2012 who have an FASD diagnosis from the Manitoba FASD Centre from April 1, 1999 to March, 31, 2012, with follow-up until December 1, 2013 (study group, n=702). A comparison group of women (n=2097) matched 1:3 on date of birth of index child, region of residence, and SES was generated. Regression modelling produced odds ratios for maternal risk factors associated with giving birth to a child with FASD.

Results: Study group women were significantly more likely to: have a history of teen pregnancy (adjusted OR 4.79, 95% Confidence interval (CI) 3.09, 7.45); be lone parents at birth of the index child (adjusted OR 6.15, 95% CI 3.78, 10.01); have higher gravidity (adjusted OR 7.73, 95% CI 4.70, 12.70) and parity (adjusted OR 9.33, 95% CI 3.64, 23.89); have a diagnosis of a psychiatric disorder (adjusted OR 14.18, 95% CI 9.80, 20.52) and/or physical health disorder

(adjusted OR 2.34, 95% CI 1.51, 3.65) up to three years before the birth of the child; and have inadequate prenatal care (adjusted OR 3.09, 95% CI 2.10, 4.55) versus women in the comparison group. Women who gave birth to children with FASD were also more likely to be involved with the child welfare system (adjusted OR 9.59, 95% CI 4.78, 19.17) as well as the justice system (adjusted OR 6.61, 95% CI 1.45, 29.97) and to take antidepressants during pregnancy (adjusted OR 2.54, 95% CI 1.18, 5.43).

Conclusion: These findings suggest Canadian women who give birth to children with FASD are at increased risk for a number of social complexities, as well as mental and physical illness before the birth of their children and during pregnancy. FASD prevention strategies are needed that address these maternal risk factors to help reduce the incidence of FASD.

4.2   Introduction

Despite universal education campaigns, women around the world continue to consume alcohol during pregnancy, which can lead to Fetal Alcohol Spectrum Disorder (FASD) in offspring[1]. FASD is a diagnostic term comprising a range of effects associated with prenatal alcohol exposure, including: facial dysmorphology, growth restriction, central nervous system and neurodevelopmental abnormalities, as well as behavioural, emotional, and social difficulties[2,3]. The global incidence of FASD is approximated at one in every 100 births[4]; the prevalence of this disorder makes FASD prevention an important public health concern[1].

The investigation of maternal risk factors associated with alcohol consumption during pregnancy is central to the prevention of FASD[1]. In the past decade, there has been a growing body of literature that investigates maternal risk factors associated with FASD[5]. While alcohol consumption during pregnancy is the necessary exposure associated with the development of FASD, other factors including demographic, socioeconomic, and biological factors can modify the effects of alcohol on the developing fetus[1]. Not all women who drink during pregnancy will give birth to children who are diagnosed with FASD. Furthermore, some children will be significantly more affected than others, even if their mothers consumed similar amounts of alcohol[3].

The International Charter on the Prevention of FASD issued an urgent call to action to prevent FASD in 2013[1]. The charter identified lack of awareness of the cultural and social context, and the social determinants of health that cause women to drink during pregnancy as a major obstacle to preventing FASD[1]. The perception that FASD prevention is solely a woman's responsibility

during pregnancy is a significant barrier to prevention efforts; women who drink during pregnancy have been stigmatized and held responsible for causing this 'preventable condition'[6]. The notion that this disorder can be easily prevented arises from the idea that the exposure can be eliminated[6]. However, this response does not account for the complex biological and social determinants of health that influence women to engage in this detrimental behaviour, such as poverty, poor housing, poor nutrition, physical and sexual abuse, mental health disorders, lack of education, and issues of substance dependence[7-10]. Identifying social, health, and economic risk factors that place women at risk for heavy alcohol consumption during pregnancy is essential to obtain insight into the underlying causes for drinking during pregnancy, to identifying key target points for effective prevention efforts, and to raise awareness that society shares responsibility for ensuring the support of pregnant women to abstain from alcohol consumption during pregnancy[1].

Previous studies have identified a number of maternal risk factors for giving birth to children with FASD, including: substance use disorders, low socioeconomic status, smoking, older age, lower education, lower income, and a history of trauma and abuse[8-14]. While these studies highlight underlying important social determinants of health that place infants at risk for FASD, these studies have several limitations that may preclude them from informing FASD prevention strategies in Canada and other developed nations with access to universal health care. The majority of studies come from South Africa and other international populations[9,14-20], and utilize small sample sizes and surveys that are limited by recall bias[11]. Furthermore, many studies focus on high-risk populations such as Indigenous populations and women from lower socioeconomic status (SES)[21], which limits generalizability of results. Due to differences in population

demographics and cultural norms, caution should be taken when extrapolating results to the general North American population. Recent larger studies conducted in the United States cannot confirm a clinical diagnosis of FASD in children and take place in a country without universal access to health care[8,22], further limiting generalizability of results, specifically pertaining to health care services utilization. Moreover, previous studies do not use validated service utilization data to investigate health service utilization. In a country with universal access to and coverage for primary health care, physicians in Canada are in a unique position to provide targeted, brief interventions during preconception counselling or prenatal care visits to help reduce prenatal alcohol use.

The objective of this study is to use linkable administrative data to investigate demographics, mental and physical health, and health care service utilization of women who give birth to children with FASD in a large Canadian sample, and compare these characteristics to women in the general population who have not given birth to children with FASD. Through the linking of novel population-level health and social data this study addresses methodological limitations of previous studies including recall, selection and attrition bias, and enhances the generalizability of results to developing nations, particularly those with access to universal health care. To the best of our knowledge, this is the first Canadian population-based study in this field. Results will facilitate Canadian FASD prevention efforts through identifying maternal health and social factors present in the preconception period and pregnancy period (3 years before birth) which may be addressed in developing prevention efforts, and the identification of key groups of women who should be targeted for such interventions as well as services that may be key to reaching them.

4.3 Methods

4.3.1 Setting

This study was conducted in Manitoba, a central Canadian province with approximately 1.2 million residents who have access to universal health care insurance. The demographics of Manitoba are similar to other provinces throughout Canada, however there are high rates of FASD reported among specific populations throughout Manitoba[23].

4.3.2 Study Design

This is a retrospective cohort study of the Manitoba Mothers and FASD (MB FASD Moms) cohort[24], which consists of mothers of children born in Manitoba between April 1, 1984 and March 31, 2012 who had an FASD diagnosis between April 1, 1999 to March 31, 2012, with follow-up until December 30, 2013. The year 1999 was chosen as the first year to ascertain FASD diagnosis as this is when accurate FASD diagnosis data was attainable. Potential risk factors were investigated three years before the birth of the child, resulting in a total study period of April 1, 1981 to December 30, 2013.

4.3.3 Data Linkage and Sources

This study utilized linkable administrative health, social, and educational data from the Manitoba Population Research Data Repository (Repository) housed at the Manitoba Centre for Health Policy (MCHP) and clinical assessment data from the Manitoba FASD Centre, which is the only referral/diagnostic centre for FASD in the province. The MCHP Repository is one of the world's most comprehensive collections of population-based administrative databases and contains province-wide, routinely collected individual level health, social, and educational data for

Manitobans[25]. De-identified health records are transferred to MCHP from the government department that administers the universal health insurance programme for the province and contain scrambled unique identifiers that allow for linkages across multiple databases and years of data. The linkages of these databases have very high accuracy[25-32]. The following databases were utilized in this study: (1) the population registry, (2) Canada census information, (3) Employment and Income Assistance; (4) education data; (5) Babies First/Families First Screening Program data, (6) InSight Program Data, (7) justice system data, (8) hospital discharge abstracts, (9) medical/physician reimbursement claims, (10) pharmaceutical drug claims, (11) Manitoba Vital Statistic mortality data. See Table 4.1 for descriptions and years of datasets used for analyses. The data in the Repository have been widely utilized for health and social research and the reliability and validity of the databases have been well established[25-32].

Table 4.1: Description of datasets used for analysis

Name of Dataset	Description of Dataset	Years of Data Used	Information retrieved
Population Registry	A registry maintained by the provincial department of health of all Manitobans eligible to receive health services since 1970 and includes demographic information and 6-digit residential postal code[1].	1970/71 to June 2013	Demographic information: region of residence
Canada Census	Social data based on the Statistics Canada Population Census. These data were used to determine area-level income, with Manitoba population divided into income quintiles according to average household income, composed of five possible income groupings with Q1 being the lowest and Q5 being the highest income quintile[1].	1996, 2001, 2006, 2011	Socioeconomic status information
Employment and Income Assistance	Data maintained by Department of Families that provide information on Manitoba residents who receive provincial income assistance[1].	1995/96 to 2012/2013	Receipt of income assistance
Babies First/Families First Screening Program	Newborn risk screen data collected as part of a home visiting program conducted by Healthy Child Manitoba. The screen is filled out by Public Health Nurses on all families with newborns in Manitoba and captures data on biological, social and demographic risk factors and alcohol use during pregnancy[1].	2003 to 2013 = Families First 2000 to 2002 = Baby First	Alcohol and drug use during pregnancy, social isolation
InSight Program	Includes data from an outreach program where mentors	1999 to	Alcohol and

	provide intensive support to women who are pregnant or have recently had a baby and use substances. This dataset includes information on women who have prenatal alcohol use[1]	2012/2013	substance use during pregnancy
Hospital Discharge Abstracts	Health data maintained by Manitoba Health consisting of all hospitalizations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before April 1, 2004 and up to 25 ICD-10-CA diagnostic codes for discharges on or after April 1, 2004[1].	1981 to 2012/13	Physical and mental health diagnoses, antenatal hospitalizations, suicide attempts
Medical/Physician reimbursement claims	Health data maintained by Manitoba Health consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit[1].	1981 to 2012/13	Physical and mental health diagnoses, physician visits, prenatal care
Prescription claims: Drug Programs Information Network	Data maintained by Manitoba Health containing all prescription drug claims from the Drug Programs Information Network (DPIN, an electronic, on-line, point-of –sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba). Contains information on all prescription drugs dispensed in Manitoba[1].	1995/96 to 2012/13	Physical and mental health conditions
Manitoba FASD Centre	Include clinical assessments and diagnoses received under the FASD umbrella for all children referred to the MB FASD Centre[1]	1999 to 2012/2013	FASD diagnosis, children diagnosed with FASD
Vital Statistics	A longitudinal population-based registry maintained by Manitoba's Vital Statistics Agency that includes all Manitobans who have died since January 1970 to present and the cause of death[1].	1970 to 2012/2013	Cause of premature death. suicide completion
Education: Enrolment, Marks and Assessments	Education data maintained by the Department of Education and Training that provide information on enrolment, marks, and high school completion, and special funding. Special education funding is provided to children with severe to profound disabilities[1].	1995/96 to 2012/2013	High school completion, level of special education funding
Child and Family Services Information System (CFSIS)	A data management system that supports case tracking and reporting of services provided to children and families as they pass through the Manitoba Child and Family services (CFS) System. This database includes information on children in care as well as information of families receiving protective and support services[1].	1992/1993 to 2012/2013	Involvement with CFS
Justice System: The Prosecutions Information Management System	An incident tracking system maintained by Manitoba Justice. This data includes information on incidents, charges and involvements (e.g., Witness, accused, victim) in the justice system in Manitoba[1].	2002 to 2011/2012	Justice system involvement

[1]http://umanitoba.ca/faculties/health_sciences/medicine/units/chs/departmental_units/mchp/resources/repository/datalist.html

4.3.4   Cohort formation

Women were drawn from the entire population of women whose child was born in Manitoba between April 1, 1984 and March 31, 2012; two groups were generated (Figure 4.1):

Group 1: Study group: Mothers whose children received a clinical diagnosis of FASD:
Clinical data from the MB FASD Centre were used to ascertain all children and youth (birth to 21 years of age) who were diagnosed with FASD between 1999 and 2012. The MB FASD Centre is one of the first and only provincially centralized FASD diagnostic clinics in Canada, and thus one of the largest. Children are diagnosed per the Canadian FASD diagnostic guidelines[3]. The clinic database was linked to administrative data from the MCHP Repository to identify these children's birth mothers. Only mothers who could be linked to their children, who had postal code information, and who were Manitoba residents registered to receive health care in the province and covered from the birth of their child until December 2013 were included.

Group 2: Comparison group: Mothers whose children did not receive a diagnosis of FASD: Women whose children did not receive an FASD diagnosis from the MB FASD Centre, with no record of prenatal alcohol, whose children had no evidence of FASD from data in the Repository were matched to the women in the study group of women on month of birth of the index child, socioeconomic status (SES), and region of residence. SES was defined per area-level data from census information. Area-level quintiles were ranked from 1(low) to 5 (high) on the basis of ranges of mean household income from census information, and grouped into five categories, with approximately 20% of the population assigned to each quintile[33]. Matching was done at a ratio of up to 3 women in the comparison group for every 1 woman in the study group. To decrease the likelihood

that the comparison women had children with undiagnosed FASD the following exclusion criteria were used: (1) women with any children assessed at the Manitoba FASD Centre; (2) women with children who had a diagnosis of FASD as recorded in hospital or physician claims data using the following ICD codes: a hospital visit with ICD-9-CM code 760.71, ICD-10-CA code of 86.0 or a physician visit with any ICD 9 code 760; (3) women who had children who had prescriptions for psychostimulants or risperidone; (4) women with children diagnosed with ADHD (due to high comorbidity of FASD and ADHD diagnoses[34,35]; (5) women involved in the InSight Mentoring program (a program that provides support for women with alcohol and substance abuse issues); (6) women with a history of substance abuse disorder (including alcohol) during pregnancy as indicated by the physician and hospital claims; (7) women whose newborn risk screen indicated they had used alcohol during pregnancy; and, (8) women whose children received special education funding indicating they had severe to profound disabilities.

Figure 4.1: Study Cohort Formation

Mothers of children born in Manitoba between April 1, 1984 and March 31, 2012 who have postal code information and a mother-baby link **(229,340)**

Mothers who had child(ren) in the MB FASD Dataset **(1,935)**

Mothers who did not have children in the FASD dataset **(227,405)**

Exclusion
- Child not diagnosed with FASD (1,216)
- Mothers not covered by Manitoba Health three years prior to the birth till the end of the study period (17)

Exclusion: prenatal exposure to alcohol or involvement in Insight program (17,017 children)

Mothers who have no record of prenatal alcohol exposure (210,388)

Mothers of a child in the MB FASD dataset who has received a clinical diagnosis of FASD (702)

Exclusion: mothers with children with possible FASD diagnosis:
- ADHD, FASD, pyscostimulant use, or special needs funding (27,907)

Study Group
n=702

Mothers who have no record of giving birth to a child with a possible FASD diagnosis (182,481)

Mothers not covered by Manitoba Health three years prior to the birth till the end of study period (35,100)

Mothers to chose matches from with no missing data or exclusion (147,381)

Matching criteria
- Maternal age of birth of index child
- Socioeconomic status
- Region of residence

Up to a 3:1 match with study group (2,097)

Comparison group
n=2,097

4.3.5 Definition of study variables

Outcome variable: The outcome investigated was giving birth to a child diagnosed with FASD, as identified in the MB FASD Centre data. FASD diagnoses included: Fetal Alcohol Spectrum

Disorder, Fetal Alcohol Syndrome (FAS), partial-FAS, alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (ARBD).

Maternal risk factors: Study groups were followed up to three years before the birth of the index child (i.e., the first child diagnosed with FASD) to determine if the following characteristics were possible risk factors for giving birth to a child with FASD: history of teen pregnancy, region of residence, low SES, receipt of income assistance, involvement with the justice system, lone parent, multiparous, multigravida, involvement with child and family services (CFS), history of mental disorder (substance use disorder, personality disorder, mood and anxiety disorder, schizophrenia, prenatal psychological distress, suicide attempts), history of physical disorder (diabetes, hypertension, ischemic heart disease, total respiratory morbidity). See Appendix Table 4.1 for definitions of variables. Adequacy of prenatal care was assessed using the Revised Graduated Index of Prenatal Care Utilization (R-GINDEX), a validated and commonly used index to measure utilization of prenatal care[36]. This index uses the number and timing of prenatal care visits present from hospital discharge abstracts and physician claims files[37].

4.4   Data Analysis

Descriptive statistics (means, standard deviations, percentages) were generated to describe the baseline characteristics of both study groups. Univariate analysis was conducted to identify variables that reached statistically significant associations with giving birth to a child with FASD. Variables found to be significant ($p<0.05$) were included in a multivariate analysis.

Conditional logistic regression was used to calculate unadjusted (UOR) and adjusted odds ratios (AOR) with 95% confidence intervals (CIs) for association with giving birth to a child with FASD. Analysis was conducted using the clogit procedure in SAS version 10 (SAS Institute Inc., Cary, NC, USA).

Three multivariate models were generated to account for differing years of data availability and to ensure there were three years of data before the birth of the child available for each study subject. The following were the population restrictions placed on each model: (1) the first model utilized the entire study population; (2) the second model was restricted to women who had children born during or after 1998 to account for availability of CFS data and income assistance data; (3) the third model was restricted to women who had a baby during or after 2003 to account for data availability from the justice system.

A c-statistic was used to examine model validity. The c-statistic measures discrimination, and indicates the "probability that a randomly selected subject who experienced the outcome will have a higher predicited probability of having the outcome occur compared to a randomly selected subject who did not experience the event"[38]. The c-statistic ranges from 0.5 to 1.0; a reasonable model has a c of at least 0.7 and a strong model has a c over 0.8[39]. All models had c statistics over 0.8.

4.4.1 Missing data & sensitivity analysis

The following variables had <10% missing values: age at birth of index child; SES; gravidity; parity; and marital status. Study group women with missing values and their matched controls

were dropped from the analysis. A sensitivity analysis was conducted by imputing the creation of a missing value (99), this ensures all cases and controls were included in the analysis. This analysis found that the inclusion or exclusion of missing values had no significant effect on the overall results.

4.5   Results

4.5.1   Characteristics of the sample

Demographic & Socioeconomic Characteristics: Demographic and socioeconomic characteristics of our study and comparison group women are shown in Table 4.2. Our study groups consisted of women who were born from 1946 to 1992 with ages ranging from 14 to 46 years. Most women from both the study and comparison groups were from an urban location. Mothers in the study group had a mean age at delivery of 24 years (SD 6.15, range 14-43) compared to 29 years (SD 5.69, range 14-46) for comparison group women. Mothers in the study group had both the child with FASD and their first child at younger ages (<24 years of age). More mothers in the study group had a higher rate of history of teen pregnancy compared to mothers in the comparison group (38% versus 12%, respectively). Due to baseline matching for SES between study and comparison group women, there was no significant difference in income quintile or SES. However, most study group mothers were in the lowest income quintile (66%), indicating that many women giving birth to children with FASD in Manitoba have low SES. Moreover, the study group also had a higher proportion of mothers who received income assistance (18%) three years before the birth of the index child, despite matching for SES, indicating a high level of poverty among these mothers.

Table 4.2: Demographic & socioeconomic characteristics of women who have given birth to children with FASD and a matched sample of women who have given birth to children without FASD

Characteristic	Study group N = 702 (%)	Comparison group N = 2097 (%)
Maternal age at birth of index child		
Mean year, (SD)	24.59 (6.15)	29.24 (5.69)
Range	14 - 43	14 - 46
Maternal age at birth of index child		
< 18 years	72 (10.26)	231 (11.02)
18-24 years	333 (47.44)	831 (39.63)
25- 29 years	146 (20.80)	525 (25.04)
30-34 years	96 (13.68)	367 (17.50)
35 + and missing[1]	55 (7.83)	143 (6.82)
Maternal age at first birth		
< 18 years	266 (37.89)	246 (11.73)
18-24 years	340 (48.43)	903 (43.06)
25- 29 years	54 (7.69)	530 (25.27)
30-34 years	29 (4.13)	306 (14.59)
35	13 (1.85)	112 (5.34)
History of teen pregnancy	266 (37.89)	246 (11.73)
Region of residence		
Rural	251 (35.75)	764 (36.43)
Urban	451 (64.24)	1333 (63.57)
Mean household income		
Q1 (lowest)	466 (64.38)	1398 (66.67)
Q2	104 (14.81)	312 (14.88)
Q3	57 (8.12)	171 (8.15)
Q4	36 (5.13)	108 (5.15)
Q5 (highest)	26 (3.70)	78 (3.72)
Missing	13 (1.85)	30 (1.43)
Receipt of Income assistance three years before birth of the index child	N = 345[2] 63 (18.26)	N=1026[2] 98 (9.55)
SES		
Low (Q1)	466 (66.38)	1398 (66.67)
Middle (Q2 & Q3)	161 (22.93)	483 (23.03)
High (Q4 & Q5)	62 (8.83)	186 (8.87)
Missing	13 (1.85)	30 (1.43)
Involvement with the justice system three years before the birth of the index child[3]	N = 116[4] 41 (35.34)	N = 341[4] 56 (16.42)

[1]Number of missing women was <6, therefore the number of missing women was combined with the "over 35 age group" to adhere to MCHP privacy rules (events less than 6 should be suppressed)

[2]Income assistance data are available after 1995, therefore the denominator was limited to women who had babies after 1998 to ensure three years of data were available before the birth of the child; 345 women in the study group and 1026 women in the control group had babies after 1998

[3]Includes accused, victim or witness of a crime.

[4]Justice data are available from 2000, therefore the denominator was limited to women who had babies after 2003 to ensure three years of data were available before the birth of the child; 116 women in the study group and 341 women in the control group had babies after 2003

Involvement with the justice system: Over 35% of women who gave birth to children with FASD were involved with the justice system, as a witness, victim and/or accused of a crime, versus 16% of comparison group mothers (Table 4.2).

Family Characteristics: Study group mothers were more likely to be lone parents, with only 9% of cases who were married at the time of the birth versus 54% of controls (Table 4.3). Study group mothers also had higher gravidity and parity than comparison mothers. Study group mothers had more involvement with CFS before the birth of the index child (66% versus 13%). This includes voluntary or involuntary involvement with CFS with any child(ren) that the women may have had prior to the birth of the index child; or if the mother was under 18, it could include her own involvement as a minor with the system. CFS services could include in-home support and/or protection services or out-of-home placements.

Mental Health: Over 82% of women in the study group had a diagnosis of a psychiatric disorder three years before the birth of the index child, versus 27% of women in the comparison group (Table 4.4). Study group mothers had significantly higher proportions of the following mental disorders: substance use disorder (25% versus 1%), personality disorders (3% versus <1%), mood and anxiety disorders (34% versus 19%), prenatal psychological distress (75.36% versus 51%). Women in the study group also had more antidepressant use during pregnancy (10% versus 2%) (Table 4.5).

Table 4.3: Family characteristics of women who have given birth to children with FASD and a matched sample of women who have given birth to children without FASD

Characteristic	N = 702 (%)	N = 2097 (%)
Married at the birth of index child		
Yes	66 (9.40)	773 (36.86)
No	603 (85.90)	1324 (63.14)
Missing	33 (4.70)	0
Gravidity		
0-3	357 (50.85)	1966 (93.75)
=>4	306 (43.59)	113 (5.39)
Missing	39 (5.56)	18 (0.86)
Parity		
0-3	524 (74.64)	2063 (98.38)
=>4	139 (19.80)	16 (0.76)
Missing	39 (5.56)	18 (0.86)
Birth Order of the index child		
First born - yes	201 (28.63)	1869 (89.13)
No	501 (71.37)	228 (10.87)
Involvement with CFS three years before the birth of the child[1]	N = 345[2] 228 (66.09)	N = 1026[2] 136 (13.26)
Breastfeeding initiation at birth		
Yes	246 (35.04)	1539 (73.39)
No	391 (55.70	460 (21.94)
Missing	65 (28.76)	98 (4.67)
FASD Diagnosis of the index child		
ARND	414 (58.97)	N/A
FAS	42 (5.98)	
Partial FAS	189 (26.92)	
Unknown	57 (8.12)	
Siblings with an FASD diagnosis	104 (14.81)	N/A
Mean age of diagnosis of child (years)	8.2 SD=4.89 range = 0-26.43	N/A

[1] Includes voluntary or involuntary involvement with CFS of any children of the mother or the mother herself (if she was under the age of 18 at the time).

[2] CFS data is available after 1995, therefore, the denominator was limited to women who had babies after 1998 to ensure three years of data were available before the birth of the child; 345 women in the study group and 1026 women in the control group had babies after 1998

Physical Health & Service Utilization: Study group women had more diabetes (16% versus 7%), and respiratory morbidity (36% versus 23%) compared to women in the comparison group (Table 4). Study group women were also more likely to receive inadequate prenatal care (41% versus 15%).

Table 4.4: Mental and physical health of women who have given birth to children with FASD and a matched sample of women who have given birth to children without FASD

Characteristic	Study group = 702 (%)	Comparison group = 2097 (%)
Diagnosis of psychiatric disorder three years before the birth of the child	580 (82.62)	566 (26.99)
Prenatal psychological distress[2]	529 (75.36)	293 (13.97)
Substance abuse[1]	179 (25.50)	41 (1.96)
Personality Disorder[1]	22 (3.13)	6 (0.29)
Mood & Anxiety Disorder[1]	237 (33.76)	397 (18.93)
Schizophrenia[1]	s[4]	7 (0.33)[4]
Postnatal psychological distress[3]	528 (75.21)	923 (44.02)
Diagnosis of physical health disorder three years before the birth of the child	130 (18.52)	216 (10.30)
Diabetes[1]	115 (16.38)	163 (7.73)
Hypertension[1]	22 (3.13)	68 (3.24)
Ischemic heart disease[1]	0	0
Total respiratory morbidity[1]	253 (36.13)	486 (23.10)
Inadequate Prenatal care	289 (41.17)	324 (15.45)

[1] Diagnosis three years before the birth of the index child

[2] Diagnosis 8 months before the birth of the index child

[3] Diagnosis 12 months after the birth of the index child

[4] Crude rate suppressed if n <6

Table 4.5: Prescription drug use of women who have given birth to children with FASD and a matched sample of women who have given birth to children without FASD during pregnancy

Medication	Study group = 476 (%)	Comparison group = 1421(%)
Antidepressants	48 (10.08)	29 (2.04)
Narcotic analgesic	81 (17.02)	66(4.64)
NSAID prescriptions	67 (14.08)	38 (2.67)
Antibiotic prescriptions	274 (57.56)	531(37.37)

Note: prescription drug data are available after 1995; therefore, the denominator was limited to women who had babies after 1998

4.5.2 Maternal risk factors associated with giving birth to children with FASD

Results from the first multivariate model (Table 4.6): The following maternal

characteristics were associated with giving birth to children with FASD (Table 6): history

of teen pregnancy (adjusted OR (aOR) 4.79, 95% confidence interval (CI) 3.09, 7.45);

being a lone parent (aOR 6.15, (3.78, 10.01)); higher gravidity (aOR 7.73 (4.70, 12.70));

higher parity (aOR 9.33, (3.64, 23.89)); having a diagnosis of a psychiatric disorder prior

to the birth of the index child (aOR 14.18 (9.80, 20.52)); physical health disorder prior to

the birth of the index child (aOR 2.34 (1.51, 3.65)) and; having inadequate prenatal care

(aOR 3.09 (2.10, 4.55)).

Table 4.6: Association between maternal demographic & socioeconomic risk factors and giving birth to children with FASD

Characteristic	Study group N = 663[1] (%)	Comparison group N = 1963[1] (%)	Unadjusted OR	Adjusted OR (95% CI)
Maternal age at birth of index child				
< 20 years	162 (24.43)	491 (25.01)	1.03 (0.84, 1.27)	1.23 (0.81, 1.87)
>= 20 years	501 (75.57)	1472 (74.99)		REF
History of teen pregnancy				
Yes	261 (39.37)	233 (11.87)	**5.01 (4.01, 6.26)***	**4.79 (3.09, 7.45)***
No	402 (60.63)	1730 (88.13)		REF
Region of residence				
Rural	234 (35.29)	703 (35.81)	0.59 (0.27, 1.30)	0.55 (0.10, 2.77)
Urban	429 (64.71)	1260 (64.19)		REF
Married at the birth of index child				
Yes	66 (9.95)	701 (35.71)		REF
No	597 (90.05)	1262 (64.29)	**5.18 (3.93, 6.82)***	**6.15 (3.78, 10.01)***
Gravidity				
0-3	357 (53.85)	1855 (94.50)	**15.52 (11.55, 20.87)***	**7.73 (4.70, 12.70)***
=>4	306 (46.15)	108 (5.50)		REF
Parity				
0-3	524 (79.03)	1947 (99.18)	**36.41 (19.69, 67.31)***	**9.33 (3.64, 23.89)***
=>4	139 (20.97)	16 (0.82)		REF
Diagnosis of psychiatric disorder three years before the birth of the child	550 (82.96)	528 (26.90)	**13.71 (10.54, 17.83)***	**14.18 (9.80, 20.52)***
Diagnosis of physical health disorder three years before the birth of the child	121 (18.25)	201 (10.24)	**1.98 (1.54, 2.54)***	**2.34 (1.51, 3.65)***
Inadequate or no prenatal care	252 (38.01)	306 (15.59)	**3.84 (1.54, 4.79)***	**3.09 (2.10, 4.55)***

[1]All mothers with any missing data were removed from the cohort, as were their matches, resulting in these denominators.

*p<0.05

Note: C statistic = 0.96

Results from the second multivariate model (Table 4.7): A restricted model of women who gave birth after 1998 was run to investigate whether or not involvement with child and family services, receipt of income assistance, and use of antidepressants, narcotic analgesics, and NSAIDs during the preconception and pregnancy period were associated with giving birth to children with FASD. Women who gave birth to children with FASD were more likely to be involved with CFS (aOR 9.59 (4.78, 19.17)), as well as the justice system (aOR 6.61 (1.45, 29.97)), and to take antidepressants during pregnancy (aOR 2.54, (1.18, 5.43)). Maternal characteristics that were significant in the full model were also significant in this restricted model with the additional variables in it.

Results from the third multivariate model: A restricted model of women who gave birth after 2003 (three years was run to investigate whether involvement with the justice system was associated with giving birth to children with FASD. 457 women (study and comparison group) gave birth to children after 2003, three years after justice system data became available. This smaller sample analysis generated a significant odds ratio of 6.61 (95% CI 1.45, 29.97), indicating women who gave birth to children with FASD were more likely to be involved with the justice system versus comparison group women. In this model, CFS involvement was removed due to collinearity between justice system involvement and CFS involvement. Maternal characteristics that were significant in the full model were also significant in this restricted model with the additional variables in it.

Table 4.7: Association between maternal demographic & socioeconomic risk factors and giving birth to children with FASD, restricting to children born in 1998 or later

Characteristic	Study group N = 327[1] (%)	Comparison group N = 962[1] (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Maternal age at birth of index child				
< 20 years	251 (76.76)	704 (73.18)	1.22 (0.9, 1.64)	2.88 (0.94, 4.65)
>= 20 years	76 (23.24)	258 (26.82)		REF
History of teen pregnancy				
Yes	142 (43.43)	129 (13.41)	**5.15 (3.77, 7.01)***	**3.91 (1.86, 8.25)***
No	185 (56.57)	833 (86.59)		REF
Married at the birth of index child				
Yes	25 (7.65)	666 (69.23)	**5.63 (3.63, 8.73)***	**4.70 (1.85, 11.94)***
No	302 (92.35)	296 (30.77)		REF
Gravidity				
0-3	163 (49.85)	917 (95.35)	**21.82 (13.69, 34.78)***	**7.40 (2.94, 18.73)***
=>4	164 (50.15)	45 (4.68)		REF
Parity				
0-3	239 (73.09)	955 (79.98)	**8.57 (3.88, 18.99)***	**9.58 (1.70, 54.09)***
=>4	88 (26.91)	7 (0.73)		REF
Diagnosis of psychiatric disorder three years before the birth of the child	269 (82.26)	259 (26.92)	**14.75 (9.95, 21.78)***	**9.64 (5.06, 18.48)***
Diagnosis of physical health disorder three years before the birth of the child	53 (16.21)	99 (10.29)	**1.69 (1.18, 2.43)***	**2.87 (1.10, 7.51)***
Inadequate or no prenatal care	124 (37.92)	155 (16.11)	**3.99 (2.88, 5.53)***	**3.08 (1.55, 6.12)***
Income assistance three years before the birth of the index child	61 (18.65)	91 (9.46)	**2.18 (1.53, 3.10)***	**2.56 (1.23, 5.33)***
Child and family services involvement three years before the birth of the index child	223 (68.20)	104 (31.08)	**17.90 (11.95, 26.81)***	**9.59 (4.78, 19.17)***
Antidepressants	37 (11.31)	21 (2.18)	**4.20 (2.97, 5.93)***	**2.54 (1.18, 5.43)***
Narcotic analgesic	63 (19.27)	42 (4.37)	**5.96 (3.78, 9.41)***	1.72 (0.615, 4.84)
NSAID prescriptions	48 (14.63)	27 (2.81)	**5.53 (3.40, 8.98)***	2.39 (0.77, 7.43)

Note: Child and family services, income assistance and prescription drug data are available after 1995; therefore the denominator was limited to women who had babies after 1998 to ensure three years of data were available before the birth of the child. All mothers with any missing data were removed form the cohort, as were their matches.

*p<0.05

Note: C statistic = 0.98

4.6   Discussion

Results from our large, population-based, Canadian sample demonstrate that mothers of children diagnosed with FASD have characteristics and health care service use that significantly differ from those of women in the general population who are similar in reproductive age and SES. Women who have given birth to children with FASD are more likely to have histories of teen pregnancy, be a lone parent at the time of giving birth to the child, have a history of income assistance, have given birth to more children and have had more pregnancies, have a history of psychiatric and/or physical illness before the birth of the child, and have prescriptions of antidepressants during pregnancy. These mothers are also more likely to have a history of involvement with child welfare services and the justice system before the birth of the child, as well as inadequate prenatal care during pregnancy.

Results of this study are comparable with international findings in populations of women who have given birth to children with FASD[5], suggesting there are universal maternal risk factors for giving birth to children with FASD, and for alcohol consumption during pregnancy. Although previously studied populations are very different from the one used in this study, the following maternal risk factors are common in with this study and studies from South Africa, the United States, and Italy: lower SES; high number of children and pregnancies; a higher presence of psychiatric symptoms (self reported or diagnosed); and indications of poor prenatal care[8,9,17,19-21,40,41].

The major contribution of this study to the existing body of literature is the addition of data from a large, population-based sample of women from a developed country with access to universal

health care. This population-based sample enhances the generalizability of results and increases the likelihood that maternal risk factors identified by this study are representative of the entire population of mothers of children with FASD. Using a matched comparison group, we are also better able to determine how these women differ from women in the general population who are similar in reproductive age and SES.

To the best of our knowledge, this is the first study to use linked administrative data to conduct a holistic investigation into the social determinants of health that may be risk factors for giving birth to children with FASD. We also investigated physical and mental health conditions and health care service utilization that may place women at increased risk. By utilizing validated physician, hospital and prescription drug claim data, this study demonstrated women who gave birth to children with FASD were more likely to have a diagnosis of a mental disorder three years before the birth of the index child and during the prenatal period. These data are validated for use in health services research and are not biased by limitations inherent in primary data collection, such as recall bias[25-32].

These data demonstrate a significant psychiatric burden exists for women giving birth to children with FASD, and that mental disorders may be a significant risk factor for giving birth to children with FASD. Moreover, these results provide context to possible underlying reasons why women drink during pregnancy, as these women may be self-medicating and using alcohol to cope with symptoms associated with mental disorders. These findings indicate that prevention of alcohol consumption during pregnancy should include a focus on improving the psychiatric health of women. Furthermore, not all children with FASD exhibit the same level of severity of

symptoms[2] and the presence of maternal mental disorders are known to have adverse effects on child outcomes. [42,43] Future work should investigate the extent to which FASD symptoms and outcomes for children are moderated by mental disorders.

The results of this study also demonstrated that women who give birth to children with FASD were also more likely to be prescribed antidepressants during pregnancy. There is conflicting evidence in the literature regarding the safety of antidepressant use during the prenatal period, with some studies demonstrating adverse effects in children including low birth weight, congenital malformations, and neurodevelopmental disorders [44]. It is important to investigate the effects of prenatal exposure to antidepressants in children diagnosed with FASD and how they may potentially moderate the relationship between prenatal alcohol and the manifestation of FASD symptoms. Antidepressants have also been shown to mitigate adverse effects in children exposed to maternal depression during pregnancy[44], and may play a role in decreasing primary or secondary symptoms present in children with FASD. Further research investigating the effects of antidepressants on children born with prenatal alcohol exposure should explore the potentially mediating or moderating effects of antidepressants on prenatal alcohol use and the manifestation of FASD symptoms.

In addition to mental disorders, this study also found mothers who gave birth to children with FASD were more likely to have a diagnosis of diabetes and/or respiratory disorder three years before the birth of their child. To the best of our knowledge this is the first study to report these results and further work should be done to investigate the association of these physical health disorders and the consumption of alcohol during pregnancy.

4.6.1 Strengths

This study was the first in this field to utilize a standardized, validated index to investigate the quality of prenatal care of women who gave birth to children with FASD. Results demonstrated women who gave birth to children with FASD were more likely to have inadequate prenatal care during the pregnancy of the index child, despite access to universal care. Results of this study were consistent with the few previous studies in the area that utilized smaller sample sizes and maternal self-report data[12,13,41,45]. These previous studies reported women who gave birth to children with FASD received less prenatal care and generally began care later into their pregnancies[12,13,41,45]. Further research should be done to determine barriers to obtaining adequate prenatal care for these women and for the development of effective outreach programs that facilitate prenatal care access for women at risk for alcohol use during pregnancy. Further research should also be conducted to investigate the role prenatal care may have in FASD prevention efforts, as a proportion of our study group were consuming alcohol during pregnancy while simultaneously accessing prenatal care.

The rich social data at our disposal allowed the investigation of characteristics that can be referred to as "social complexities", which are aspects in women's lives that may make them more susceptible to stress and risky alcohol use. This study found women who gave birth to children with FASD had higher involvement with child welfare services before the birth of the child, had substantial involvement with the justice system, and were more likely to be lone parents at the time of the birth of the index child or have a history of teen pregnancy as compared to women in our comparison group. These results are consistent with previous studies that demonstrate women who give birth to children with FASD have significant socioeconomic and

behavioural challenges[5,10]. Previous studies identified a history of substance use, trauma, and sexual and physical abuse, as well as having partners and family members with alcohol and/or drug abuse as maternal risk factors[5,10]. Due to the limitations in the data, this study could not investigate violence and trauma in the lives of the birth mothers included in this sample or other factors such as family history of alcohol use. However, this study adds findings that contribute to obtaining an in-depth and accurate depiction of the social complexities and adverse events in the lives of women who give birth to children with FASD. Furthermore, the identification of involvement with child welfare services as a maternal risk factor for giving birth to a child with FASD warrants further investigation, as this may be a barrier to obtaining treatment and support for alcohol use during pregnancy for women afraid of losing their children.

Women in our study who gave birth to children with FASD were of lower SES and more likely to have received income assistance before the birth of their child. While the association between poverty and FASD has been well documented in the examination of maternal risk factors for giving birth to children with FASD[5,7,10,46], limitations of previous studies have been the lack of population-based samples and bias of using only vulnerable and at risk populations. Due to the population-based nature of this study, these biases are unlikely in our findings and this study confirms that low SES and/or poverty is a reoccurring maternal risk factor in giving birth to children with FASD. All studies in this field have demonstrated that low SES and poverty increases maternal risk to give birth to children with FASD[5], indicating that the association between maternal poverty and risk for drinking during pregnancy and giving birth to children with FASD is an important global health issue.

Previous studies also identify older age at the time of the birth of the child[12,14,15,18,19,41,45,47],

however, this study did not find similar results, as we matched on the age of the birth of the

index child. This allowed us to produce a more similar comparison group of women to facilitate

the analysis of other less investigated outcomes, such as the investigation into co-morbidities and

prenatal care.

Using validated health and social data, the results of this study identify maternal risk factors that

can inform the development of evidence-based prevention interventions. Targeted prevention

efforts aimed at reducing or preventing alcohol exposure during pregnancy may have a

significant impact if they are integrated into existing systems serving this population,

specifically: mental health support, brief interventions in prenatal and primary health care

settings, justice system outreach, child welfare systems, and systems designed to alleviate

poverty such as income assistance programs. Moreover, the high proportion of mothers of

children with FASD with mental health issues in the years before the conception of their children

indicate that alcohol reduction counselling should be done in tandem with mental health support

of women in childbearing years that are at risk for alcohol consumption during pregnancy.

4.6.2   Limitations

The data used in this study allowed the investigation of many important maternal risk factors,

however the following potential risk factors could not be investigated due to the limitations in

our data: alcohol consumption patterns including quantity, frequency and timing; maternal body

size and BMI; maternal nutrition; genetic susceptibility; and trauma including history of physical

or sexual abuse. We also could not conduct investigation into risk factors associated with

severity of FASD in children due to limited data from the MB FASD Centre. Current work on improving data quality is being conducted at the MB FASD Centre, which may facilitate this important future work. Future research should also be conducted that investigates how these unexamined maternal risk factors mediate or moderate the effects of alcohol consumption during pregnancy.

The use of a clinically referred FASD sample may limit the generalizability of results, as women and children who were not referred to this clinic would be missing from our study. However, referrals to this clinic come from a wide variety of sources and from all regions in the province, strengthening the representativeness across populations. Furthermore, while we have taken great care in excluding all mothers with possible prenatal alcohol exposure and children with a diagnosis of FASD from our comparison group, we cannot be certain that there are no women who do not have un-reported prenatal alcohol use or children with undiagnosed FASD. However, this would serve to weaken rather than strengthen any of our findings. Finally, data on mental and physical health disorders are dependent on making contact with the health care system and are thus a report of treatment prevalence; women with undiagnosed disorders would not be counted in our analyses.

4.7   Conclusions

The prevention of FASD requires multiple intervention strategies and investments from health, justice, education, and social sectors. Identifying risk factors for giving birth to children with FASD is a key step to improving prevention and early intervention efforts. Identifying factors in the preconception period can lead to targeted prevention efforts that focus on contraception,

family planning, and education about the risks of alcohol consumption during pregnancy. The

identification of risk factors during pregnancy such as inadequate prenatal care and the presence

of mental illness can lead to targeted intervention programs or alcohol reduction programs. The

identification of mothers at high risk for giving birth to children with FASD can also facilitate

the early diagnosis of the child, which has been associated with a reduction of secondary

disabilities in children. Finally, identification of women at risk may also prevent future alcohol-

exposed pregnancies, ultimately decreasing the prevalence of FASD and bettering the lives of

these women and their children. This study makes an important contribution to global public

health in demonstrating that maternal risk factors for FASD are similar in Canada, a developed

country with universal access to health care, as in South Africa, and populations in the United

States, Italy, and Australia. Prevention strategies are needed that address these important and

universal risk factors for women who engage in alcohol consumption during pregnancy to

decrease the incidence of FASD.

Appendix Table 4.1: Definitions of possible maternal risk factors for giving birth to children with FASD

Outcome Measure	Definition
History of teen pregnancy	A woman was identified has having a history of teen pregnancy or birth if they had the following diagnostic codes from the ages 15-19: • live birth: ICD-9-CM code V27, ICD-10-CA code Z37 • missed abortion: ICD-9-CM code 632, ICD-10-CA code O02.1 • ectopic pregnancy: ICD-9-CM code 633, ICD-10-CA code O00 • abortion: ICD-9-CM codes 634-637 ICD-10-CA codes O03-O07 • intrauterine death: ICD-9-CM code 656.4, ICD-10-CA code O36.4 Or, a hospitalization with one of the following procedures: • surgical termination of pregnancy: ICD-9-CM codes 69.01, 69.51, 74.91; CCI codes 5.CA.89, 5.CA.90 • surgical removal of extrauterine (ectopic) pregnancy: ICD-9-CM codes 66.62, 74.3; CCI code 5.CA.93 • pharmacological termination of pregnancy: ICD-9-CM code 75.0; CCI code 5.CA.88 interventions during labour and delivery, CCI codes 5.MD.5, 5.MD.60
Low SES	Socioeconomic status was defined according to income quintiles and income assistance data. A woman was considered to have low SES if she was categorized as being in income quintile 1 or had a receipt of income assistance

Receipt of income assistance	A woman was identified as having received income assistance if she was coded as having received income assistance from the SAMIN database anytime during the period of five years before the birth of the child.
Involvement with justice system	A woman was considered to have involvement with the justice system if she had a record of an incident in the Prosecutions Information Management System. Involvement type was classified by the following categories: (1) Witness; (2) Victim; (3) Accused
Lone parent	Derived from the registry using the family registration number.
Mulitparous	Parity is defined as the number of births a mother has had after 20 weeks gestation. A multiple birth is counted as one and stillbirths are included. Parity was calculated using the hospital abstracts data and was categorized as: 0-3, 4-9, 10-14.
Multigravida	Gravidity is defined as the number of pregnancies, regardless of the duration, including the present pregnancy. Multiple fetuses (twins, triplets) count as one pregnancy. Gravidity was calculated using the hospital abstract data and was categorized as: 0-3 pregnancies, 4-9, 10-14.
Involvement with child and family services	A woman was defined as having any contact with Child and Family Services (CFS) 5 years prior to the birth of the index child if a record of any contact with CFS existed CFSIS, including: (1) Ever in Care – if a child was in care; (2) Ever received CFS Services – if there were no children in care but the family received protection or support services from CFS.
History of mental health disorder	**A woman was considered to have a history of a mental health disorder if in the 3 years prior to the birth of the child she had one or more of:** substance abuse, personality disorder, mood and anxiety disorder, pre- or postnatal psychological distress, schizophrenia, or antidepressant use.
Substance abuse	**A woman was considered to have a substance use disorder if in the 3 years prior to the birth of the child she had:** 1) one or more hospitalizations with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, or nondependent abuse of drugs (ICD-9-CM codes 291, 292, 303, 304, 305, ICD-10-CM codes: F10-F19 and F55) **OR** 2) one or more physician visits with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, or nondependent abuse of drugs using the same ICD-9-CM codes listed above.
Personality Disorder	**A woman was considered to have a personality disorders if in the 3 years prior to giving birth to the child she had the following:** 1) one or more hospitalizations with a diagnosis of personality disorder (ICD-9-CM code 301 or ICD-10- CA codes F34.0, F60, F61, F62, F68.1, F68.8, or F69) **OR** 2) one or more physician visits with a diagnosis of personality disorder: (ICD-9-CM code 301)
Mood & Anxiety Disorder	**A woman was considered to have mood or anxiety disorder if in the 3 years prior to giving birth to the child she had the following:** 1) one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction: ICD-9-CM codes 296.1-296.8, 300.4, 309 or 311; ICD-10-CA codes F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0 or with a diagnosis for an anxiety state, phobic disorders or obsessive-compulsive disorders: ICD-9-CM codes 300.0, 300.2, 300.3, 300.7; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42, F45.2; **OR** 2) one or more hospitalizations with a diagnosis for anxiety disorders: ICD-9-CM code 300; ICD-10-CA codes F32, F34.1, F40, F41, F42, F44, F45.0, F45.1, F45.2, F48, F68.0, or F99 AND one or more prescriptions for an antidepressant or mood stabilizer, including medications with the ATC codes N05AN01, N05BA, N06A; **OR** 3) one or more physician visits with a diagnosis for depressive disorder or affective psychoses: ICD-9-CM codes 296, 311; **OR** 4) one or more physician visits with a diagnosis for anxiety disorders: ICD-9-CM code 300 AND one or more prescriptions for an antidepressant or mood stabilizer,

	including medications with the ATC codes N05AN01, N05BA, N06A; **OR**
	5) three or more physician visits with a diagnosis for anxiety disorders or adjustment reaction: ICD-9-CM code 300, 309
Prenatal psychological distress	**A woman was considered to have prenatal psychological distress if in the eight months prior to giving birth she had:**
	1) one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296.2–296.8, 300.4, 309, 311; ICD–10–CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0); **OR**
	2) one or more physician visits with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296, 309 or 311); **OR**
	3) one or more hospitalizations with a diagnosis for anxiety disorders (ICD-9-CM code 300l ICD-10-CD codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99); **OR**
	4) one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
	5) one or more physician visits with a diagnosis of anxiety disorders one or more physician visits with a diagnosis for anxiety disorders (ICD–9–CM code 300) and one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
	6) one or more hospitalizations with a diagnosis for anxiety states, phobic disorders, or obsessive–compulsive disorders (ICD–9–CM codes 300.0, 300.2, 300.3; ICD–10–CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42); **OR**
	7) two or more physician visits with a diagnosis for anxiety disorders (ICD--CM code 300)
Postnatal psychological distress	**A woman was considered to have postnatal psychological distress if in the 12 months after giving birth she had:**
	1) one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296.2–296.8, 300.4, 309, 311; ICD–10–CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0); **OR**
	2) one or more physician visits with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296, 309 or 311); **OR**
	3) one or more hospitalizations with a diagnosis for anxiety disorders (ICD-9-CM code 300l ICD-10-CD codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99); **OR**
	4) one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
	5) one or more physician visits with a diagnosis of anxiety disorders one or more physician visits with a diagnosis for anxiety disorders (ICD–9–CM code 300) and one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
	6) one or more hospitalizations with a diagnosis for anxiety states, phobic disorders, or obsessive–compulsive disorders (ICD–9–CM codes 300.0, 300.2, 300.3; ICD–10–CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42); **OR**
	7) two or more physician visits with a diagnosis for anxiety disorders (ICD--CM code 300)
Schizophrenia	**A woman was considered to have schizophrenia if in the 3 years prior to giving birth to the child had the following:**
	1) one or more hospitalizations or physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295 or ICD-10-CA codes F20, F21, F23.2, F25; **OR**
	2) one or more physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295.
Antidepressant Use	**A woman was considered to have taken an antidepressant if there was one or more prescription identified by:** the Anatomical Therapeutic Chemical (ATC) drug

	classification codes: N06AA, N06AB, N06AF, N06AG, N06AX
History of a physical disorder	**A woman was considered to have a history of a physical disorder if 3 years prior to the birth of the child she had:** diabetes hypertension, ischemic heart disease, total respiratory morbidity.
Diabetes	**A woman was considered to have a history of diabetes if 3 years prior to the birth of the child she had:** 1) At least two physician visits or one hospitalization with a diagnosis of diabetes (ICD–9–CM code 250; ICD–10–CA codes E10–E14); **OR** 2) one or more prescriptions for medications to treat diabetes
Hypertension	**A woman was considered to have a history of hypertension if 3 years prior to the birth of the child she had:** 1) At least one physician visit or one hospitalization with an ICD–9–CM code of 401–405 (ICD–10–CA codes I10–I13, I15); **OR** 2) two or more prescriptions for hypertension drugs
Ischemic heart disease	**A woman was considered to have a history of total respiratory morbidity if 3 years prior to the birth of the child she had:** 1) at least two physician visits or one hospitalization for IHD (ICD–9–CM codes 410–414, ICD–10 codes I20–I22, I24, I25); **OR** 2) at least one physician visit with a code listed above and two or more prescriptions for IHD medications
Total respiratory morbidity	**A woman was considered to have a history of total respiratory morbidity if 3 years prior to the birth of the child she had:** 1) at least two physician visits or one hospitalization for IHD (ICD–9–CM codes 410–414, ICD–10 codes I20–I22, I24, I25); **OR** 2) at least one physician visit with a code listed above and two or more prescriptions for IHD medications
Adequate prenatal care	The adequacy of prenatal care was determined using the R-GINDEX (Revised-Graduated Prenatal Care Utilization Index). The following three variables were calculated using Hospital and Physician claims data: (1) gestational age of the newborn, (2) the trimester that prenatal care began; (3) the total number of prenatal visits during the pregnancy. The G-INDEX classifies prenatal care into the following categories: (1) Inadequate prenatal care; (2) Intermediate prenatal care; (3) Adequate prenatal care; (4) Intensive prenatal care; (5) No care; (6) Missing information

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Preface: Chapter 5

The complex, interconnected factors that place women at risk for alcohol use during pregnancy may also place women at higher risk for the development of psychiatric disorders. There is a dearth of research that investigates the psychiatric morbidity of women who give birth to children with FASD. The second research objective of this thesis was to investigate rates of psychiatric disorders of women who give birth to children with FASD relative to women who have not given birth to children with FASD including: rates of substance use disorder; personality disorder; mood and anxiety disorders; maternal psychological distress during pregnancy and postpartum; and antidepressant use before, during, and after pregnancy. This is the first population-based study that uses administrative data to investigate rates of psychiatric morbidity in this study population.

Publication details:

Singal D, Brownell M, Chateau D, Hanlon-Dearman A, Longstaffe S, Roos LL. The psychiatric morbidity of women who give birth to children with Fetal Alcohol Spectrum Disorder (FASD): Results of the Manitoba Mothers and FASD Study. *The Canadian Journal of Psychiatry* Jan 01 2017:706743717703646.

Chapter 5: The Psychiatric Morbidity of Women Who Give Birth to Children with Fetal Alcohol Spectrum Disorder (FASD): Results of the Manitoba Mothers and FASD Study

5.1   Abstract

Background: The complex, interconnected factors that place women at risk for alcohol use during pregnancy may also place women who give birth to children with FASD at higher risk for the development of psychiatric disorders. The objective of this study was to investigate differences in physician diagnosed psychiatric disorders between women who gave birth to children with an FASD diagnosis (study group) compared to women who gave birth to children without FASD (comparison group).

Methods: We linked population-level health and social services data to clinical data on FASD diagnoses to identify study group (n=702) and comparison group (n=2097) women matched 1:3 on date of birth of index child, region of residence and SES. Regression modeling produced relative rates (RRs) for outcomes.

Results: Mothers who gave birth to children with FASD had higher adjusted rates of substance use disorder (RR 12.65, 95% CI 8.99-17.80), personality disorder (RR 12.93, 95% CI 4.88-34.22), and mood and anxiety disorders (RR 1.75, 95% CI 1.49-2.07) before the pregnancy of the child. These mothers also had higher adjusted rates of maternal psychological distress during pregnancy (RR 5.35, 95% CI 4.58-6.35) and higher rates of postpartum psychological distress (RR 1.71, 95% CI 1.53 – 1.90). These women also had higher adjusted rates for antidepressant prescriptions before, during, and after the pregnancy.

Conclusions: A significant psychiatric burden exists for women giving birth to children with FASD. Clinicians should recognize the high rates of psychiatric concerns facing mothers who

give birth to children with FASD and should offer treatment and support to these women to improve their health and wellbeing and prevent further alcohol-exposed pregnancies.

5.2 Introduction

In Canada, over 10 percent of women report alcohol consumption during pregnancy[1] and in Manitoba, approximately 14% of women report prenatal alcohol use[2]. These statistics indicate alcohol use during pregnancy is a substantial provincial and national public health concern. Prenatal alcohol use places children at risk for Fetal Alcohol Spectrum Disorder (FASD), a diagnostic term including various symptoms and effects associate with prenatal alcohol exposure[3].

FASD has been recognized as the leading cause of intellectual disability in North America[4]. Patients with FASD experience myriad symptoms including sentinel facial features (smaller palpebral fissure, philtrum smoothness, and upper lip thinness) and neurodevelopmental abnormalities (motor skills, impaired cognition, language difficulties, academic challenges, memory impairment, and attention difficulties including impulse control and hyperactivity) as well as communication, behavioural, emotional, and social difficulties[3-6].

Over the past decade, international FASD prevalence estimates have ranged from 2% to 5%[7] in the general population and up to 23.3% in high-risk populations [8-17]. Among the general population of Canada, the pooled prevalence of Fetal Alcohol Syndrome was estimated to be approximately 1 per 1000 for FAS and 5 per 1000 for FASD[18]. The prevalence of FAS and FASD was estimated to be 38 and 16 times higher for First Nations populations, respectively[18].

Research has also demonstrated that the financial burden of FASD is significant. Popova et al[19]. utilized data from the Canadian Institute for Health Information and calculated direct health care

costs (acute care, psychiatric care, day surgery, emergency department use) from patients with

FASD in Canada at approximately $6.7 million[19]. Easton et al.[20] investigated the cost of lost

productivity due to FASD attributable morbidity and reported losses ranging from $418 million

to $1.08 billion annually[20]. This demonstrates the immense toll this disability has on patients,

families, and the health care system and highlights the need for prevention programs.

A crucial step in developing effective FASD prevention strategies is the early identification of

maternal and societal risk factors that are associated with giving birth to children with FASD.

It is important to acknowledge that women who drink during pregnancy are not doing so to

intentionally cause harm upon their children, but because of complex social, health and

economic factors. These factors include histories of violence, sexual abuse, poverty, low

socioeconomic status, social isolation, and living with partners with substance abuse issues[21-25].

The use of alcohol during pregnancy cannot be separated from these issues or from other

potentially harmful behaviours such as poor health practices, poor nutrition, and the use of other

harmful substances[21-25].

It is also important to note that historically women of disadvantaged backgrounds were

associated with a high risk of giving birth to children with FASD. However, there is an

increasing body of literature that is showing women of diverse backgrounds consume alcohol

during pregnancy[26] including women who are older, have high incomes and education, have

stressful jobs, are in abusive relationships, have partners who drink heavily, or are coping with

anxiety and depression[26].

The complex, interconnected factors that place women at risk for alcohol consumption during pregnancy also place women at higher risk for the development of psychiatric disorders [27-31]. The co-morbidity of psychiatric disorders and alcohol use and dependence has been widely reported in the literature[29,30,32-35]. Studies have also documented that almost two thirds of women with alcohol use issues may have a concurrent psychiatric diagnosis including anxiety and panic disorders, post-traumatic stress disorder, depression, eating disorders, as well as more severe psychiatric illness such as bipolar disorder and schizophrenia[36,37].

Furthermore, the increased frequency of alcohol use of these women also places them at high risk for psychiatric disorders [35], as alcohol can affect the central nervous system, and have detrimental effects on a person's family and interpersonal relationships, economic and employment circumstances, and possible involvement with the justice system[28].

There is currently a dearth of research that investigates the psychiatric morbidity of women who give birth to children with FASD. This is the first population-based study that utilizes administrative data to investigate the rates of psychiatric disorders of women who give birth to children with FASD compared to women with no reported pre-natal alcohol exposure. The occurrence of psychiatric disorders in women may increase the risk of developing alcohol use and dependence, as alcohol can be an agent for self-medication of symptoms associated with psychiatric disorders including depressive and anxious symptoms, hopelessness, paranoia, impulsivity, fear, and anger [27]. Investigating the psychiatric health of these women before, during, and after pregnancy can provide insight into why women may drink during pregnancy, as

well as identify critical time periods for targeted interventions to prevent subsequent alcohol exposed pregnancies. This will enable clinicians and policy makers to develop focused prevention strategies that promote the psychiatric wellbeing of women of childbearing age at risk for drinking during pregnancy.

The objectives of this study were to compare rates of physician diagnosed psychiatric disorders and antidepressant prescriptions during critical time periods in the lives of women who give birth to children with FASD, specifically:

(1) Compare rates of physician diagnosed psychiatric disorders among women whose children have FASD relative to women whose children do not have FASD three years before the pregnancy of the index child;

(2) Compare rates of physician diagnosed prenatal psychological distress (mood and/or anxiety disorder 8 months before the birth of the index child) and postpartum psychological distress (mood and/or anxiety disorder one year after the birth of the index child) among women whose children have FASD relative to women whose children do not have FASD;

(3) Compare rates of antidepressant prescriptions among women whose children have FASD relative to women whose children do not have FASD, 3 years before the pregnancy of the index child, during pregnancy, and one year after birth.

5.3   Methods

This study utilized the Manitoba Mothers and FASD Study (MB FASD Moms) cohort which is a retrospective cohort of mothers whose children were diagnosed with FASD in Manitoba and was

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generated to investigate risk factors, psychiatric, and physical health outcomes, as well as health and service utilization of these women. The details of this project's additional investigations are available elsewhere[38]. This chapter presents the psychiatric health results.

Data Sources: This study utilized de-identified administrative health, social, and education data from the Manitoba Population Research Data Repository (Repository) housed at the Manitoba Centre for Health Policy (MCHP) and clinical assessment data from the Manitoba FASD Centre, which is the only referral/diagnostic centre for FASD in the province. See Table 5.1 for a description of all databases used in this study.

Maternal diagnoses of psychiatric disorders were obtained from the hospital discharge abstracts, medical/physician reimbursement claims, and prescription claims data. Diagnostic codes follow the Canadian Coding Standards for the International Statistical Classification of Diseases and Related Health Problems 9th and 10th Revision. Data are de-identified and all files are linkable at the individual-level using an encrypted personal health number. The data in the Repository have been widely utilized for health research and the reliability and validity of the databases have been well established[39-46]. It is important to note that because this study utilizes administrative physician, hospital, and drug claims data, the rates of psychiatric disorders presented do not accurately represent the prevalence of psychiatric disorders in this population, but rates of physician health service use for psychiatric disorders. We may miss individuals who meet standard diagnostic criteria for a psychiatric disorder but did not receive a relevant diagnostic code, or those individuals who have not sought care from a physician.

Table 5.1: Descriptions of datasets used for analysis

Name of Dataset	Description of Dataset	Years of Data Used	Information retrieved
Population Registry	A registry maintained by the provincial department of health of all Manitobans eligible to receive health services since 1970 and includes demographic information and 6-digit residential postal code[1].	1970/71 to June 2013	Demographic information: region of residence
Canada Census	Social data based on the Statistics Canada Population Census. These data were used to determine area-level income, with Manitoba population divided into income quintiles according to average household income, composed of five possible income groupings with Q1 being the lowest and Q5 being the highest income quintile[1].	1996, 2001, 2006, 2011	Socioeconomic status information
Employment and Income Assistance	Data maintained by Department of Families that provide information on Manitoba residents who receive provincial income assistance[1].	1995/96 to 2012/2013	Receipt of income assistance
Babies First/Families First Screening Program	Newborn risk screen data collected as part of a home visiting program conducted by Healthy Child Manitoba. The screen is filled out by Public Health Nurses on all families with newborns in Manitoba and captures data on biological, social and demographic risk factors and alcohol use during pregnancy[1].	2003 to 2013 = Families First 2000 to 2002 = Baby First	Alcohol and drug use during pregnancy, social isolation
InSight Program	Include data from an outreach program where mentors provide intensive support to women who are pregnant or have recently had a baby and use substances. This dataset includes information on women who have prenatal alcohol use[1].	1999 to 2012/2013	Alcohol and substance use during pregnancy
Hospital Discharge Abstracts	Health data maintained by Manitoba Health consisting of all hospitalizations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before April 1, 2004 and up to 25 ICD-10-CA diagnostic codes for discharges on or after April 1, 2004[1].	1981 to 2012/13	Physical and mental health diagnoses, antenatal hospitalizations, suicide attempts
Medical/Physician reimbursement claims	Health data maintained by Manitoba Health consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit[1].	1981 to 2012/13	Physical and mental health diagnoses, physician visits, prenatal care
Prescription claims: Drug Programs Information Network	Data maintained by Manitoba Health containing all prescription drug claims from the Drug Programs Information Network (DPIN, an electronic, on-line, point-of –sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba). Contains information on all prescription drugs dispensed in Manitoba[1].	1995/96 to 2012/13	Physical and mental health conditions
Manitoba FASD Centre	Includes clinical assessments and diagnoses received under the FASD umbrella for all children referred to the MB FASD Centre[1].	1999 to 2012/2013	FASD diagnosis, children diagnosed with FASD
Vital Statistics	A longitudinal population-based registry maintained by Manitoba's Vital Statistics Agency that includes all Manitobans who have died since January 1970 to	1970 to 2012/2013	Cause of premature death. suicide completion

	present and the cause of death[1].		
Education: Enrolment, Marks and Assessments	Education data maintained by the Department of Education and Training that provide information on enrolment, marks, and high school completion, and special funding. Special education funding is provided to children with severe to profound disabilities[1].	1995/96 to 2012/2013	High school completion, level of special education funding
Child and Family Services Information System (CFSIS)	A data management system that supports case tracking and reporting of services provided to children and families as they pass through the Manitoba Child and Family services (CFS) System. This database includes information on children in care as well as information of families receiving protective and support services[1].	1992/1993 to 2012/2013	Involvement with CFS

[1]http://umanitoba.ca/faculties/health_sciences/medicine/units/chs/departmental_units/mchp/resources/repository/datalist.html

5.3.1   Study Population

Women were drawn from the entire population of women whose child was born in Manitoba

between April 1, 1984 and March 31, 2012; two groups were generated (Figure 5.1):

Figure 5.1: Study Cohort Formation


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┌─────────────────────────────────────────────────────────────────────────────┐
│ Mothers of children born in Manitoba between April 1, 1984 and March 31, 2012│
│ who have postal code information and a mother-baby link  (229,340)            │
└─────────────────────────────────────────────────────────────────────────────┘
        │
        │       ┌─────────────────────────────────────────────────────────────┐
        │──────▶│ Mothers who had child(ren) in the MB FASD Dataset (1,935)     │
        │       └─────────────────────────────────────────────────────────────┘
        ▼
┌──────────────────────────────────┐   ┌──────────────────────────────────────┐
│ Mothers who did not have children │   │ Exclusion                            │
│ in the FASD dataset  (227,405)    │   │ • Child not diagnosed with FASD       │
└──────────────────────────────────┘   │   (1,216)                             │
        │                               │ • Mothers not covered by Manitoba     │
        │   ┌───────────────────────┐   │   Health three years prior to the    │
        │──▶│ Exclusion: prenatal   │   │   birth till the end of the study    │
        │   │ exposure to alcohol or│   │   period (17)                        │
        │   │ involvement in Insight│   └──────────────────────────────────────┘
        │   │ program (17,017       │
        │   │ children)             │   ┌──────────────────────────────────────┐
        │   └───────────────────────┘   │ Mothers of a child in the MB FASD     │
        ▼                               │ dataset who has received a clinical   │
┌──────────────────────────────────┐   │ diagnosis of FASD (702)               │
│ Mothers who have no record of     │   └──────────────────────────────────────┘
│ prenatal alcohol exposure (210,388)│              │
└──────────────────────────────────┘              ▼
        │                               ┌──────────────────────────────────────┐
        │   ┌───────────────────────┐   │ Study Group                          │
        │──▶│ Exclusion: mothers    │   │ n=702                                │
        │   │ with children with    │   └──────────────────────────────────────┘
        │   │ possible FASD         │
        │   │ diagnosis:            │
        │   │ • ADHD, FASD,         │
        │   │   pyscostimulant use, │
        │   │   or special needs    │
        │   │   funding (27,907)    │
        │   └───────────────────────┘
        ▼
┌──────────────────────────────────┐
│ Mothers who have no record of     │
│ giving birth to a child with a    │
│ possible FASD diagnosis (182,481) │
└──────────────────────────────────┘
        │   ┌───────────────────────┐
        │──▶│ Mothers not covered by│
        │   │ Manitoba Health three │
        │   │ years prior to the    │
        │   │ birth till the end of │
        │   │ study period (35,100) │
        │   └───────────────────────┘
        ▼
┌──────────────────────────────────┐
│ Mothers to chose matches from with│
│ no missing data or exclusion       │
│ (147,381)                         │
└──────────────────────────────────┘
        │   ┌───────────────────────┐
        │──▶│ Matching criteria     │
        │   │ • Maternal age of     │
        │   │   birth of index child│
        │   │ • Socioeconomic status│
        │   │ • Region of residence │
        │   └───────────────────────┘
        ▼
┌──────────────────────────────────┐
│ Up to a 3:1 match with study group│
│ (2,097)                           │
└──────────────────────────────────┘
        ▼
┌──────────────────────────────────┐
│ Comparison group                 │
│ n=2,097                          │
└──────────────────────────────────┘
```

Group 1: Study group: Mothers whose children received a clinical diagnosis of FASD:

Clinical data from the MB FASD Centre were used to ascertain all children and youth (birth to 21 years of age) in Manitoba who had been diagnosed with FASD between 1999 and 2012. This database was linked to administrative data from the MCHP Repository to identify these children's birth mothers. Only mothers who could be linked to their children, who had postal code information, and who were Manitoba residents registered

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to receive health care in the province and covered from the birth of their child until March 2013 were included.

Group 2: Comparison group: Mothers whose children did not received a clinical diagnosis of FASD: Women whose children did not receive an FASD diagnosis from the MB FASD Centre, with no known record of prenatal alcohol use, and whose children had no evidence of FASD from the Repository were matched to the study group of women on date of month of birth of the index child, socioeconomic status, and region of residence. Matching was done at a ratio of 3 women in our comparison group for each woman in our study group. To decrease the likelihood that the comparison women had children with undiagnosed FASD, the following exclusion criteria were used: (1) women with any children assessed at the Manitoba FASD Centre; (2) women with children who had a diagnosis of FASD as recorded in hospital or physician claims data using the following ICD codes: a hospital visit with International Classifcation of Diseses, 9[th] Revision, Clinical Modification (ICD-9-CM) code 760.71, ICD-10-CA code of 86.0 or a physician visit with any ICD 9 code 760; (3) women who had children prescribed psychostimulants or risperidone; (4) women with children diagnosed with ADHD (due to high comorbidity of FASD and ADHD diagnoses[47,48]; (5) women involved in the InSight Mentoring program (a program that provides support for women with alcohol and substance abuse issues); (6) women with a history of substance abuse disorder (including alcohol) during pregnancy as indicated by the physician and hospital claims; (7) women whose newborn risk screen indicated they had used alcohol during pregnancy; and, (8) women whose children received special education funding indicating they had severe to profound disabilities.

5.3.2 Outcome variables

For each mother in our study and comparison groups, we calculated the total number of

diagnoses of: mood and anxiety disorders; substance use disorders; schizophrenia, and

personality disorders 3 years before the pregnancy of the index child; prenatal psychological

distress (mood and/or anxiety disorder) 8 months before the birth of the index child; and

postpartum psychological distress (mood and/or anxiety disorder) 12 months after the birth of the

index child. Definitions for each outcome can be found in Table 5.2. We also calculated the total

number of women who had multiple diagnoses of psychiatric disorders (1 or 2 psychiatric

disorders, 3 disorders, or 4 or more disorders). Finally, we calculated the proportion of women

who had received at least one prescription for an antidepressant medication three years prior to

the birth of the index child, during the pregnancy of the index child, and one year after the birth

of the index child.

Table 5.2. Definitions of outcomes used to compare rates of mental disorders in women who gave birth to a child with FASD, and a matched sample of women who gave birth to a child without FASD

Outcome Measure	Definition
Substance abuse	**A woman was considered to have a substance use disorder if 3 years prior to the birth of the child she had:** 1) one or more hospitalizations with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, or nondependent abuse of drugs (ICD-9-CM codes 291, 292, 303, 304, 305, ICD-10-CM codes: F10-F19 and F55); **OR** 2) one or more physician visits with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, or nondependent abuse of drugs using the same ICD-9-CM codes listed above.
Personality Disorder	**A woman was considered to have a personality disorders if in the 3 years prior to giving birth to the child she had the following:** 1) one or more hospitalizations with a diagnosis of personality disorder (ICD-9-CM code 301 or ICD-10- CA codes F34.0, F60, F61, F62, F68.1, F68.8, or F69); **OR** 2) one or more physician visits with a diagnosis of personality disorder: (ICD-9-CM code 301)
Mood & Anxiety Disorder	**A woman was considered to have mood or anxiety disorder if in the 3 years prior to giving birth to the child she had the following:** 1) one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction: ICD-9-CM codes 296.1-296.8, 300.4, 309 or 311; ICD-10-CA codes F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1,

	F43.2, F43.8, F53.0, F93.0 or with a diagnosis for an anxiety state, phobic disorders or obsessive-compulsive disorders: ICD-9-CM codes 300.0, 300.2, 300.3, 300.7; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42, F45.2; **OR**
	2) one or more hospitalizations with a diagnosis for anxiety disorders: ICD-9-CM code 300; ICD-10-CA codes F32, F34.1, F40, F41, F42, F44, F45.0, F45.1, F45.2, F48, F68.0, or F99 AND one or more prescriptions for an antidepressant or mood stabilizer, including medications with the ATC codes N05AN01, N05BA, N06A; **OR**
	3) one or more physician visits with a diagnosis for depressive disorder or affective psychoses: ICD-9-CM codes 296, 311; **OR**
	4) one or more physician visits with a diagnosis for anxiety disorders: ICD-9-CM code 300 AND one or more prescriptions for an antidepressant or mood stabilizer, including medications with the ATC codes N05AN01, N05BA, N06A; **OR**
	5) three or more physician visits with a diagnosis for anxiety disorders or adjustment reaction: ICD-9-CM code 300, 309
Prenatal psychological distress	**A woman was considered to have prenatal psychological distress if in the eight months prior to giving birth she had:**
	1) one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296.2–296.8, 300.4, 309, 311; ICD–10–CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8,F53.0, F93.0); **OR**
	2) one or more physician visits with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296, 309 or 311); **OR**
	3) one or more hospitalizations with a diagnosis for anxiety disorders (ICD-9-CM code 300l ICD-10-CD codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99); **OR**
	4) one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
	5) one or more physician visits with a diagnosis of anxiety disorders one or more physician visits with a diagnosis for anxiety disorders (ICD–9–CM code 300) and one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
	6) one or more hospitalizations with a diagnosis for anxiety states, phobic disorders, or obsessive–compulsive disorders (ICD–9–CM codes 300.0, 300.2, 300.3; ICD–10–CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42); **OR**
	7) two or more physician visits with a diagnosis for anxiety disorders (ICD--CM code 300)
Postnatal psychological distress	**A woman was considered to have postnatal psychological distress if in the 12 months prior to giving birth she had:**
	1) one or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296.2–296.8, 300.4, 309, 311; ICD–10–CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8,F53.0, F93.0); **OR**
	2) one or more physician visits with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD–9–CM codes 296, 309 or 311); **OR**
	3) one or more hospitalizations with a diagnosis for anxiety disorders (ICD-9-CM code 300l ICD-10-CD codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99); **OR**
	4) one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
	5) one or more physician visits with a diagnosis of anxiety disorders one or more physician visits with a diagnosis for anxiety disorders (ICD–9–CM code 300) and one or more prescriptions for an antidepressant or mood stabilizer (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A); **OR**
	6) one or more hospitalizations with a diagnosis for anxiety states, phobic disorders, or obsessive–compulsive disorders (ICD–9–CM codes 300.0, 300.2, 300.3; ICD–10–CA codes

	F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42); **OR** 7) two or more physician visits with a diagnosis for anxiety disorders (ICD--CM code 300)
Schizophrenia	**A woman was considered to have schizophrenia if in the 3 years prior to giving birth to the child had the following:** 1) one or more hospitalizations or physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295 or ICD-10-CA codes F20, F21, F23.2, F25; **OR** one or more physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295.
Antidepressant Use	**A woman was considered to have taken an antidepressant if there was one or more prescription identified by:** the Anatomical Therapeutic Chemical (ATC) drug classification codes: N06AA, N06AB, N06AF, N06AG, N06AX

5.3.3 Data Analysis

Frequencies and percentages were used to describe the study population. Adjusted relative rates (aRRs) for the outcome variables were modeled using generalized linear models (GLM) with a Poisson distribution. A Negative Binomial distribution was used when data were over dispersed. Both models are suitable for non-normally distributed data such as counts. All analyses tested for differences between groups and adjusted for covariates.

Covariates: The following variables were included as potential covariates in each of the models: age of mother at birth of child (18 or under, 19 to 24, 25 to 34, 35 and higher) and socioeconomic status (SES). SES was defined using area level data from census information. Area-level income quintiles were ranked from 1 (low) to 5 (high) on the basis of ranges of mean household income, and grouped into five categories, with approximately 20% of the population assigned to each quintile[49].

A summary dataset for the total number of events (e.g. total number of mothers with mood and anxiety disorders) was produced to model the rate of events comparing women with children with FASD and those with children without FASD. For each outcome of interest, we ran a model to test for statistical differences between our study and comparison groups.

5.4   Results

5.4.1   Descriptive statistics

Our study groups consisted of women born from 1946 to 1992 with ages ranging from 14 to 46 years (Table 5-3). Most women were from an urban location. Study group women were more likely to be lone parents, younger age at first birth, and tended to have lower SES, higher gravidity, and higher parity (Table 5.3).

5.4.2   Rates of physician diagnosed psychiatric disorders

Women in the study group had a higher number of unique psychiatric diagnoses (including prenatal and postnatal psychological distress, personality disorder, substance use disorder, mood and anxiety disorders, and schizophrenia) compared to the comparison group (mean number of psychiatric disorders = 2.13 versus 0.79, respectively). Eighty percent of women in the study group had a diagnosis of a psychiatric disorder either before the birth of their child, during their pregnancy, or during the postpartum period, compared to 27% of the comparison group. Almost 30% of women in the study group had 3 or more psychiatric disorders versus 6% of the comparison group (Figure 5.2).

Table 5.3: Characteristics of women whose children are diagnosed with FASD and a matched sample of women whose children do not have FASD

Characteristic	Study Group N = 702 (%)	Comparison Group N = 2097 (%)
Maternal age at birth of index child		
Mean year, (SD)	24.59 (6.15)	29.24 (5.69)
Range	14 - 43	14 - 46
Maternal age at birth of index child		
< 18 years	72 (10.26)	231 (11.02)
18-24 years	333 (47.44)	831 (39.63)
25- 29 years	146 (20.80)	525 (25.04)
30-34 years	96 (13.68)	367 (17.50)
35 + and missing[1]	55 (7.83)	143 (6.82)
Missing	< s[2]	0
Maternal Age at first birth		
< 18 years	266 (37.89)	246 (11.73)
18-24 years	340 (48.43)	854 (43.06)
25- 29 years	54 (7.69)	530 (25.27)
30-34 years	29 (4.13)	306 (14.59)
35 + and missing[1]	13 (1.85)	112 (5.34)
Missing	< s[2]	0
History of teen pregnancy	266 (37.89)	246 (11.73)
Region of residence		
Rural	251 (35.75)	764 (36.43)
Urban	451 (64.24)	1333 (63.57)
Mean household income		
Q1	466 (64.38)	1398 (66.67)
Q2	104 (14.81)	312 (14.88)
Q3	57 (8.12)	171 (8.15)
Q4	36 (5.13)	108 (5.15)
Q5	26 (3.70)	78 (3.72)
Missing	13 (1.85)	30 (1.43)
Receipt of Income assistance three years before birth of the index child	N=345[3] 63 (18.26)	N=1026[3] 174 (8.30)
SES		
Low (Q1)	466 (66.38)	1398 (66.67)
Middle (Q2 & Q3)	161 (22.93)	483 (23.03)
High (Q4 & Q5)	62 (8.83)	186 (8.87)
Missing	13 (1.85)	30 (1.43)
Married at the birth of child	66 (9.40)	773 (36.86)
Gravidity		
0-3	357 (50.85)	1966 (93.75)
=>4	306 (43.59)	113 (5.39)
Missing	39 (5.56	18 (0.86)
Parity		
0-3	524 (74.64)	2063 (98.38)
=>4	139 (19.80)	16 (0.76)
Missing	39 (5.56)	18 (0.86)
Diagnosis of psychiatric disorder three years before the birth of the child[4]	580 (82.62)	566 (26.99)

[1] Number of missing women was < 6, therefore the number of missing women was combined with the "over 35 age group" to ensure privacy rules of MCHP data were adhered to.

Figure 5.2: Number of mental disorder diagnoses of women who gave birth to a child with FASD, and a matched sample of women who gave birth to a child without FASD
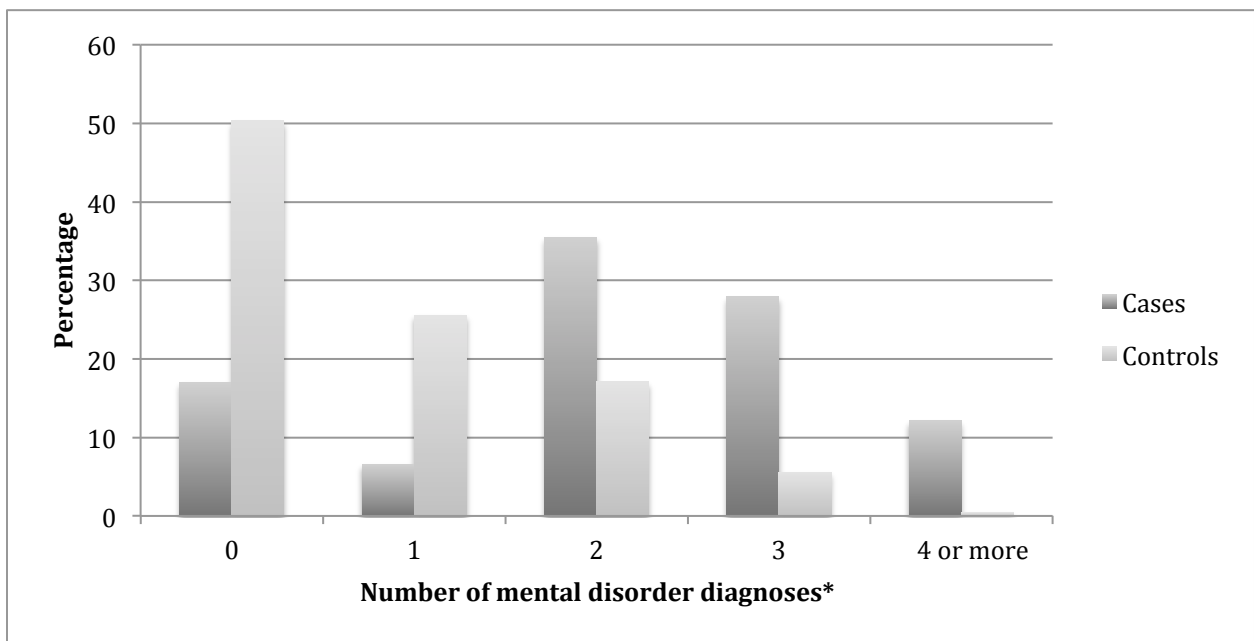
* Includes: substance abuse, personality disorder, mood and anxiety disorder, prenatal psychological distress, postnatal psychological distress, schizophrenia

(1) **Rates of physician diagnosed psychiatric disorders before pregnancy (the preconception period):** Women in the study group had higher adjusted rates of substance use disorder (aRR 12.65, 95% CI 8.99-17.80), personality disorder (aRR 12.93, 95% CI 4.88,34.22), and mood and anxiety disorders (aRR 1.75, 95% CI 1.49-2.07) three years before the pregnancy of their child compared to the comparison group (Table 5-4). There were few women diagnosed with schizophrenia in both groups, therefore regression analyses was not conducted.

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(2) **During pregnancy (the prenatal period):** Women in the study group had a higher rate of prenatal psychological distress (aRR 5.35, 95% CI 4.58-6.35) (Table 5-4).

(3) **After pregnancy (the postnatal period)**: Women in the study group had a higher rate of postpartum psychological distress (RR 1.71, 95% CI 1.53 – 1.90), compared to the comparison group (Table 5.4).

(4) **Rates of Prescribed Antidepressants:** Women in the study group had significantly higher rates of antidepressant prescriptions before pregnancy (RR 3.37, 95% CI 2.47-4.58), during pregnancy (RR 4.88, 95% CI 3.00-7.97), and after pregnancy (RR 3.48, CI 2.47-4.90) compared to the comparison group (Table 5.5).

Table 5.4: Rates of mental disorders of women who gave birth to a child with FASD, and a matched sample of women who gave birth to a child without FASD

	Study Cohort Crude Rate (%)		Effect Estimate Adjusted RR** (95% CI)
Outcome	**Study group N = 702**	**Comparison group N = 2097**	**Study versus comparison group**
Substance abuse[1]	179 (25.50)	41 (1.96)	**12.65 (8.99-17.80)**
Personality Disorder[1]	22 (3.13)	6 (0.29)	**12.93 (4.88-34.22)**
Mood & Anxiety Disorder[1]	237 (33.76)	397 (19.93)	**1.75 (1.49-2.07)**
Prenatal psychological distress[2]	529 (75.36)	293 (13.97)	**5.35 (4.58-6.25)**
Postnatal psychological distress[3]	528 (75.21)	923 (44.02)	**1.71 (1.53-1.90)**
Schizophrenia[1]	< 6[4]	7 (0.33)	NA[5]

Note: Adjusted for age at birth of index child, socioeconomic status. Bolded RRs are statistically significant.

** RR = Relative Rate CI = Confidence Interval

[1] Diagnosis 3 years before the pregnancy of the child

[2] Diagnosis 8 months before the birth of the child

[3] Diagnosis 12 months after the birth of the child

[4] Crude rate suppressed if n <6

[5] Regression analysis not appropriate due to small number of outcome events in study groups

Table 5.5: Use of antidepressant medications by women who gave birth to a child with FASD, and a matched sample of women who gave birth to a child without FASD

Outcome	Study Cohort Crude Rate (%)		Effect Estimate Adjusted RR** (95% CI)
	Study group N = 702	Comparison group N = 2097	Study versus comparison group
Antidepressant medication use three years before pregnancy	109 (15.53%)	98 (4.67%)	**3.37** (2.47-4.58)
Antidepressant medication use during prenatal period	48 (6.84%)	29 (1.38%)	**4.88 (3.00-7.97)**
Antidepressant medication use one year after pregnancy	85 (12.11%)	76 (3.62%)	**3.48** (2.47-4.90)

Note: Adjusted for age at birth of index child, socioeconomic status. Antidepressant medication use refers to at least one prescription during the specified time period. Bolded RRs are statistically significant.

** RR = Relative Rate CI = Confidence Interval

5.5   Discussion

Among women whose children had an FASD diagnosis, 80% had at least one psychiatric disorder before the birth of their child, 75% had a diagnosis of prenatal psychological distress, and 75% had a diagnosis of postpartum psychological distress, indicating a substantial burden of psychiatric illness exists in this population. The results of this paper identify multiple points where targeted psychiatric interventions can be implemented among women who are at risk for alcohol use during pregnancy, specifically: (1) before, (2) during and (3) after pregnancy.

(1) **Before pregnancy:** The significantly increased risk of having a psychiatric disorder including substance use disorder, personality disorder, and mood and anxiety disorders 3 years prior to pregnancy among our study group indicates that the presence of psychiatric illness during the preconception and pregnancy period may be a risk factor for drinking during pregnancy. These results provide context to possible underlying reasons why women drink during pregnancy, as these women may be self-medicating and using

alcohol to cope with symptoms associated with psychiatric disorders that exist before they conceive.

These results identify the importance of targeted psychiatric interventions that help women who are at risk for alcohol consumption during pregnancy manage their psychiatric illness during the preconception period. Clinicians providing psychiatric treatment to women in childbearing years who consume alcohol should be aware of the increased risk these women have of not being able to stop alcohol consumption during pregnancy; therefore, targeted preconception counselling that integrates psychiatric treatment as well as alcohol reduction strategies should be used in this population. Since many pregnancies are unplanned, this counselling can also include birth control and family planning strategies that will help reduce the incidence of future alcohol-exposed pregnancies.

Research has demonstrated the identification of substance abuse and maternal risk factors during the preconception period provides opportunities for health care professionals to assist women in reducing major health risks[50]. Preconception counselling can lead to reductions in alcohol consumption, especially during the first trimester. Our study results demonstrate the need for clinicians providing care to integrate psychiatric counselling and alcohol reduction counselling for women who present with risk factors to give birth to children with FASD.

(2) **During pregnancy (the prenatal period):** A substantial number of women in our study group have a high burden of psychiatric illness during their pregnancies, during which

they consumed alcohol. Evidence demonstrates that psychiatric disorders, specifically prenatal psychological distress (including anxiety and depression), can have adverse side effects on mothers and children, including preterm birth and low birth weight[51], developmental delay in children[52,53], impaired mother and child bonding[54], and attention deficit hyperactivity disorder in children[55]. This study provides evidence that alcohol consumption during pregnancy may be an additional adverse side effect of prenatal psychological stress in women of childbearing years.

The significantly higher risk of prenatal psychological distress in women who give birth to children with FASD demonstrates that FASD prevention should include increased accessible, affordable, and non-judgmental resources to improve the psychiatric health of women of child bearing years with psychiatric concerns. Moreover, not all children with FASD exhibit the same level of severity of symptoms[4] and as stated above the presence of psychiatric disorders are known to have adverse effects on child outcomes[52,53]. Future work should investigate the extent to which FASD symptoms and outcomes for children are moderated by maternal psychiatric disorders.

Furthermore, a significantly higher rate of women who gave birth to children with FASD compared to our comparison group took antidepressants during pregnancy. There is conflicting evidence in the literature regarding the safety of antidepressant use during the perinatal period, with some studies demonstrating adverse effects in children including low birth weight, congenital malformations, and persistent pulmonary hypertension in infants[56]. Antidepressants have also been shown to mitigate adverse effects in children

exposed to maternal depression during pregnancy[56], and may play a role in decreasing primary or secondary symptoms present in children with FASD. Further research investigating the effects of antidepressants on children born with prenatal alcohol exposure should explore the potentially mediating or moderating effects of antidepressants on prenatal alcohol use and the manifestation of FASD symptoms.

(3) **After pregnancy (the postnatal period):** The significantly higher rates of post-partum depression in women who give birth to children with FASD indicate the need for targeted and specific support resources after the birth of a child exposed in-utero to alcohol. Studies have demonstrated that early interventions that improve maternal psychiatric health in pregnancy and the postpartum period can improve infant, child, and maternal outcomes[57-59]. Targeted interventions to improve the psychiatric health of women at risk for alcohol abuse during childbearing years and pregnancy may not only improve both maternal and child outcomes but also potentially decrease the risk for subsequent children born with FASD through alcohol reduction and cessation strategies.

The results of this study are consistent with the few published studies in this area. A study by Astley et al, (2000) surveyed 80 birth mothers of children with Fetal Alcohol Syndrome to generate a profile of these women[21]. They reported that 96% of women had one to ten psychiatric disorders[21]. A more recent study investigated the psychological distress among Northern Plains Indian mothers with children referred to screening for FASD using maternal interview data and reported that 19% of women had psychological distress, including symptoms of depression and anxiety[60]. However, both studies utilized

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survey data, which is limited by selection bias, as women seeking psychiatric health services may be more likely to participate in surveys. Women participating in surveys may also exhibit recall bias[61]. Women may have been pregnant several years in the past compared to when the surveys were administered, thus decreasing accuracy of their ability to recall diagnosis received around that time period.

To our knowledge, the rates of prenatal psychological distress have only been reported in a report investigating the perinatal health of women in Manitoba and this definition has not been used in any other population-based maternity studies in Canada[62]. Our rates are much higher compared to rates of prenatal and postpartum psychological distress reported for women in the general population in Manitoba, which were 7.5% and 13.8%, respectively[62]. While definitions of psychological distress and psychiatric disorders vary widely in the literature, general population rates of psychiatric disorders among the Canadian population are reported at approximately 13%[63], and rates of postpartum depression have been reported to be approximately 7% in Canada[64]. Our rates were much higher which may be attributed to differences in definition, or because women in both of our study groups are of lower SES and may be a higher risk group for psychiatric illness[62].

5.5.1 Strengths & Limitations

Administrative data eliminate selection and recall bias, thus offering more valid information when investigating health services utilization[40,45,46]. The use of administrative data in the present study also provides the largest sample size of women who have given birth to children with

FASD to date in Canada, and enhances the accuracy of psychiatric disorder diagnoses compared to studies utilizing primary data collection. Furthermore, the use of pharmaceutical data in investigating the use of antidepressants before, during, and after pregnancy confirms the substantial rates of psychiatric disorders observed in our study population and identifies areas for future research.

A limitation of this study is the use of a clinically referred FASD sample, limiting the generalizability of the findings. However, the use of this clinically based sample is also a strength, as the children in this study have undergone an accurate and comprehensive multidisciplinary assessment in a central tertiary-level provincial diagnostic clinic which follows the updated Canadian guidelines for the diagnosis of FASD[3,4]. While mothers of children with FASD who are not referred to the clinic for assessment were not included in our study, this is the largest sample size of women who have given birth to a child with a confirmed clinical diagnosis of FASD in Canada. Due to the changes in FASD diagnostic guidelines over the course of the study period (e.g. example the change in growth restriction not being a requirement for a diagnosis), we may be missing children who did not meet one set of guidelines as compared to another, and thus the number of women included in our study may be under representing women who have children with FASD in Manitoba; future work should be done validating both sets of diagnostic criteria in identifying birth mothers of children with FASD.

While we have taken great care in excluding all mothers with possible prenatal alcohol exposure and children with a diagnosis of FASD, we cannot be certain that there are no women in our

comparison group that do not have un-reported prenatal alcohol use or children with

undiagnosed FASD. However, this would serve to weaken rather than strengthen our findings.

In addition, as in all studies using administrative databases, this study is reliant on the accuracy

of physician coding; however, as previously stated, MCHP data have been extensively validated

for conducting this type of research[40,42-46].

Finally, this study is dependent on women making contact with the health care system and

excluded women with undiagnosed psychiatric disorders, women who have not been assigned

relevant diagnostic codes, or mothers of children with undiagnosed FASD. Women who have

only sought non-pharmacological care from a psychologist or support group would also be

excluded. Thus, as previously stated, this study does not report prevalence rates of psychiatric

disorders in our cohort, but the prevalence of physician health service use for psychiatric illness.

Therefore, the burden of psychiatric illness in this group may be underestimated.

5.6   Conclusions

This study presents novel data regarding the complex psychiatric issues faced by women who

have given birth to children with FASD. Our findings indicate that the prevention of alcohol

consumption in pregnancy should include a focus on improving the psychiatric health of women.

Support programs and interventions that improve the psychiatric health of women at risk for

alcohol consumption during pregnancy should be an integral part of policies targeted at

decreasing alcohol use during pregnancy. Women with psychiatric disorders who use alcohol

should be provided education about the risks of using alcohol when pregnant, and compassionate

evidence-based support for the cessation of alcohol consumption during pregnancy. The significantly higher rates of post-partum psychological distress observed in women who have given birth to children with FASD also indicate the need for increasing treatment resources that focus on improving psychiatric health for these women. Furthermore, services to improve post-partum psychiatric health in this group of women may also prevent subsequent alcohol exposed pregnancies, thereby preventing further FASD births.

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Preface: Chapter 6

Women who give birth to children with Fetal Alcohol Spectrum Disorder (FASD) may be at increased risk of suicide, as there is a strong association between alcohol dependence and suicide. Moreover, women who give birth to children with FASD also have complex histories that may place them at risk for suicide including: abuse; poverty; substance use disorders; intergenerational trauma; and high rates of psychiatric disorders. To date there is no Canadian population-based data that quantifies the burden of suicide in this population. The objective of this study is to compare rates of suicide among women who have given birth to children with FASD relative to women who have not given birth to children with FASD during critical time periods in their lives, including: before pregnancy, during pregnancy, during the postpartum period (maternal death) and until the end of the study period (April 1, 1979 to November 11, 2013). The identification of suicide risk in critical time periods in these women's lives aids to the development of targeted prevention and support programs.

> *It is important to note that we are not drawing associations between the diagnosis of FASD in a child and maternal suicide, as children may be diagnosed years prior to the suicide attempt. We are using the FASD diagnosis in children to identify a potentially vulnerable group of women with alcohol use issues who may require targeted, multifactorial interventions to decrease suicide risk in this population*

Publishing details:

Chapter 6: Suicide and suicide attempts among women in the Manitoba Mothers FASD Cohort: A retrospective cohort analysis utilizing linked administrative data

6.1   Abstract

Background: Women who give birth to children with FASD may be at increased risk for suicide, however there are little data in this area. Linked administrative data were used to investigate risk of suicide attempt and completion rates among mothers who gave birth to a child with an FASD diagnosis.

Methods: We conducted a retrospective cohort analysis of all children born in Manitoba between April 1, 1984 and March 31, 2012 who had an FASD diagnosis from April 1, 1999 to March 31, 2012, with follow-up till December 1, 2013 (study group; n=702). We generated a comparison group of women (n=2097) matched 1:3 on date of birth of index child, region of residence, and SES. Regression modeling produced relative rates adjusted for SES, maternal age at birth, and previous suicide attempts.

Results: A total of 2,799 women produced 40,390.21 person years by the end of the study period. Rates were higher among the study group for suicide completion (adjusted RR 6.20, 95% confidence interval (CI) 2.36-16.31), number of women attempting suicide (adjusted RR 4.62, 95% CI 2.53-8.43), and number of attempts after the birth of the child until the end of the study period (adjusted RR 3.92, 95% CI 2.30-6.09).

Conclusion: This study identifies a group of women with increased rates of social complexities, mental disorders, and alcohol use that places them at risk for suicide and highlights the need for mental health supports.

6.2   Background

Suicide is also the most common cause of maternal death in developed countries[1]. Maternal deaths are defined as deaths occurring from direct (obstetric complications) and indirect (conditions not directly related to obstetric) causes between 42 and 356 days postpartum[1,2]. Few Canadian studies have examined the rates of maternal death due to suicide, and there is no individual level investigation of maternal deaths to identify contributing factors[3]. Identifying groups of vulnerable women who are at risk for suicidal behaviour is crucial for the development of effective prevention strategies.

Women who give birth to children with Fetal Alcohol Spectrum Disorder (FASD) may be at increased risk of suicide. These women have histories of frequent and heavy alcohol use, and there is a strong association between alcohol dependence and suicide[4-10]. They also have complex histories that may place them at risk for suicide including: abuse; poverty; substance use disorders; intergenerational trauma [11-16]; and high rates of psychiatric disorders[17-20]. These women often experience stigma and are afraid of losing their children to child welfare systems[13,21-23] which can lead to hopelessness and helplessness, strong risk factors for suicidal behaviour[10,24]. To date there is no Canadian population-based data that quantifies the burden of suicide in this population.

The objective of this study is to compare rates of suicide among women who have given birth to children with FASD relative to women who have not given birth to children with FASD during critical time periods in their lives, including: before pregnancy; during pregnancy; during the postpartum period (maternal death) and till the end of the study period (December 1, 2013). The

identification of suicide risk during critical time periods in these women's lives aids to the development of targeted prevention and support programs. It is important to note that we are not drawing associations between the diagnosis of FASD in a child and maternal suicide, as children may be diagnosed years prior to the suicide attempt. We are using the FASD diagnosis in children to identify a potentially vulnerable group of women with alcohol use issues who may require targeted, multifactorial interventions to decrease suicide risk in this population.

6.3 Methods

6.3.1 Study Setting & Design

This is a retrospective analysis of the Manitoba Mothers and FASD (MB FASD Moms) cohort, which consists of mothers of children born in Manitoba between April 1, 1984 and March 31, 2012 who had an FASD diagnosis between April 1, 1999 to March 31, 2012, with follow-up until December 1, 2013. The year 1999 was chosen as the first year to ascertain FASD diagnosis as this is when accurate FASD diagnosis data was attainable. Suicide attempts were investigated five years before and one year after the birth of the child, until the end of the study period, resulting in a total study period of April 1, 1979 to November 11, 2013. Ethical approval was received from the University of Manitoba's Health Research Ethics Board.

6.3.2 Data Sources

De-identified administrative data from the Manitoba Population Health Research Data Repository (Repository) housed at the Manitoba Centre for Health Policy (MCHP) and clinical assessment data from the Manitoba FASD Centre, which is a referral/diagnostic centre for FASD in the province were used as the primary data sources. Data on suicide attempts and completions,

as well as all-cause mortality, were obtained from: Vital Certificates of mortality (include cause of death); physician reimbursement claims; and hospital discharge abstracts (Table 6.1). De-identified health records are transferred to MCHP from the government department that administers the universal health insurance programme for the province and contain scrambled identifiers that allow for linkages across multiple databases and years of data. Linkages are performed using de-identified, unique personal health identification numbers. The linkage of these databases has very high accuracy and data in the Repository have been widely utilized for health research. The reliability of the databases have been well established[25-32]. See the study protocol paper for additional details [33].

Table 6.1: Description of datasets used for analysis

Name of Dataset	Description of Dataset	Years of Data Used	Information retrieved
Population Registry	A registry maintained by Manitoba Health of all Manitobans eligible to receive health services since 1970 and includes demographic information and 6-digit residential postal code[1].	1970/71 to June 2013	Demographic information: region of residence
Canada Census Information	Social data based on the Statistics Canada Population Census. These data were used to determine area-level income, with Manitoba population divided into income quintiles according to average-level household income, composed of five possible income groupings with Q1 being the lowest and Q5 being the highest income quintile[1].	1996, 2001, 2006, 2013	Socioeconomic status information
Employment and Income Assistance Data	Data maintained by Department of Families that provide information on Manitoba residents who receive provincial employment and income Assistance[1].	1995/96 to 2012/2013	Receipt of income assistance
Babies First/Families First Screening Program data	Newborn risk screen data collected as part of a home visiting program conducted by Healthy Child Manitoba. The screen is filled out by Public Health Nurses on all families with newborns in Manitoba and captures data on biological, social and demographic risk factors and alcohol use during pregnancy[1].	2003 to 2013 = Families First 2000 to 2002 = Baby First	Alcohol and drug use during pregnancy Social isolation
Insight Program data	Includes data from an outreach program where mentors provide intensive support to women who are pregnant or have recently had a baby and use substances. This dataset includes information on women who have prenatal alcohol use[1].	1999 to 2012/2013	Alcohol and substance use during pregnancy

Hospital Abstracts	Health data maintained by Manitoba Health consisting of all hospitalizations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before April 1, 2004 and up to 25 ICD-10-CM diagnostic codes for discharges on or after April 1, 2004[1].	1981 to 2012/13	Physical and mental health diagnoses Antenatal hospitalizations Suicide attempts
Medical/Physician reimbursement claims	Health data maintained by Manitoba Health consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit[1].	1981 to 2012/13	Physical and mental health diagnoses Physician visits Prenatal care
Prescription claims data: Drug Programs Information Network	Data maintained by Manitoba Health containing all prescription drug claims from the Drug Programs Information Network (DPIN, an electronic, on-line, point-of –sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba). Contains information on all prescription drugs dispensed in Manitoba[1].	1995/96 to 2012/13	Physical and mental health conditions
Manitoba FASD Centre data	Include clinical assessments and diagnoses received under the FASD umbrella for all children referred to the MB FASD Centre[1].	1999 to 2012/2013	FASD diagnosis Children diagnosed with FASD
Vital Statistics data	A longitudinal population-based registry maintained by Manitoba's Vital Statistics Agency that includes all Manitobans who have died since January 1970 to present and the cause of death[1].	1970 to 2012/2013	Cause of premature death Suicide completion
Education data: Enrolment, Marks and Assessments	Education data maintained by the Department of Education and Training that provide information on enrolment, marks, and high school completion, and special funding. Special education funding is provided to children with severe to profound disabilities[1].	1995/96 to 2012/2013	High school completion, level of special education funding
Child and Family Services Information System (CFSIS)	A data management system that supports case tracking and reporting of services provided to children and families as they pass through the Manitoba Child and Family services (CFS) System. This database includes information on children in care as well as information of families receiving protective and support services[1].	1992/1993 to 2012/2013	Involvement with child and family services

[1]http://umanitoba.ca/faculties/health_sciences/medicine/units/chs/departmental_units/mchp/resources/repository/datalist.html

6.3.3 Cohort formulation

Women were drawn from the entire population of women whose child was born in Manitoba between April 1, 1984 and March 31, 2012; two groups were generated (Figure 6.1):

Group 1: Study Group: Women who gave birth to a child with FASD: Clinical data from the MB FASD Centre were used to ascertain all children and youth (birth to 21 years of age) diagnosed with FASD between 1999 and 2012. This database was linked to administrative data from the MCHP Repository to identify these children's birth mothers.

Only mothers who could be linked to their children, who had postal code information, and who were Manitoba residents registered to receive health care in the province and covered from the birth of their child until November 2013 were included. The mean age of the child's FASD diagnosis was 8.2 years (SD 4.89, range: birth to 26.43 years)

Group 2: Comparison group: Women whose children did not receive an FASD diagnosis from the MB FASD Centre, with no record of prenatal alcohol use, whose children had no evidence of FASD from the Repository were matched up to 3 to 1 with women in the study group on: date of month of birth of the index child, socioeconomic status, and region of residence. Comparison group women were identified from the MCHP Data Repository. To decrease the likelihood that the comparison women had children with undiagnosed FASD, the following exclusion criteria were used: (1) women with any children assessed at the Manitoba FASD Centre; (2) women with children who had a diagnosis of FASD as recorded in hospital or physician claims data using the following ICD codes: a hospital visit with ICD 9CM code 760.71, ICD 10CCA code of 86.0 or a physician visit with any ICD 9 code 760; (3) women who had children who had prescriptions for psychostimulants or risperidone; (4) women with children diagnosed with ADHD (due to high comorbidity of FASD and ADHD diagnoses[34,35]; (5) women involved in the InSight Mentoring program (a program that provides support for women with alcohol and substance abuse issues); (6) women with a history of substance abuse disorder (including alcohol) during pregnancy as indicated by the physician and hospital claims; (7) women whose newborn risk screen indicated they had used alcohol during pregnancy; and, (8) women whose children received special education funding indicating they had severe to profound disabilities.

6.3.4   Outcome: Suicidal Behaviour

Attempts: The total number of women who attempted suicide at least once in both study groups during the following time periods (defined as any hospital admission with any diagnosis of a suicide attempt, including accidental and self-inflicted poisoning, poisoning with undetermined intent, and self-inflicted injuries) (Table 7.2 for ICD codes) was calculated: (1) five years before the pregnancy of the index child; (2) during pregnancy (date of conception to date of birth); (3) postpartum (birth to one year after birth); (4) from one year after birth to the end of the study period.

Completions: The number of suicide completions (see Table 6.2) during the postpartum period (maternal death due to suicide) and after the birth of the child until the end of the study period were analyzed.
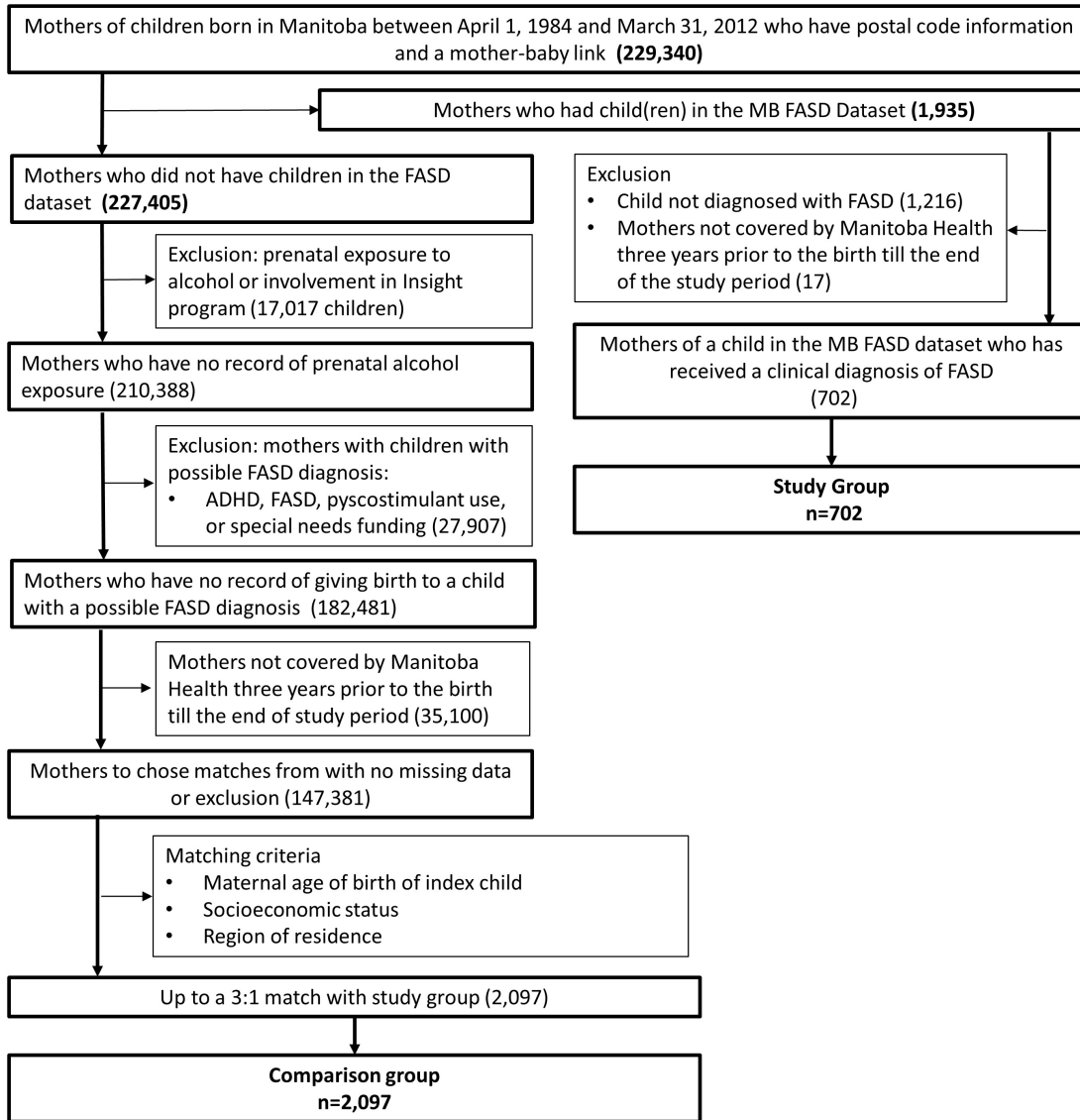
Figure 6.1: Study Cohort Formation


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┌─────────────────────────────────────────────────────────────────────────────┐
│ Mothers of children born in Manitoba between April 1, 1984 and March 31, 2012 │
│ who have postal code information and a mother-baby link  (229,340)            │
└─────────────────────────────────────────────────────────────────────────────┘
        │
        │              ┌──────────────────────────────────────────────────────┐
        │─────────────▶│ Mothers who had child(ren) in the MB FASD Dataset (1,935) │
        │              └──────────────────────────────────────────────────────┘
        ▼                                        │
┌───────────────────────────────┐    ┌────────────────────────────────────────┐
│ Mothers who did not have       │    │ Exclusion                              │
│ children in the FASD           │    │ • Child not diagnosed with FASD (1,216)│
│ dataset (227,405)              │    │ • Mothers not covered by Manitoba Health│
└───────────────────────────────┘    │   three years prior to the birth till  │
        │                             │   the end of the study period (17)     │
        │   ┌──────────────────────┐  └────────────────────────────────────────┘
        │──▶│ Exclusion: prenatal   │                   │
        │   │ exposure to alcohol or│                   ▼
        │   │ involvement in Insight│  ┌────────────────────────────────────────┐
        │   │ program (17,017 child)│  │ Mothers of a child in the MB FASD       │
        ▼   └──────────────────────┘  │ dataset who has received a clinical     │
┌───────────────────────────────┐    │ diagnosis of FASD (702)                 │
│ Mothers who have no record of  │    └────────────────────────────────────────┘
│ prenatal alcohol exposure      │                   │
│ (210,388)                      │                   ▼
└───────────────────────────────┘    ┌────────────────────────────────────────┐
        │   ┌──────────────────────┐  │ Study Group                             │
        │──▶│ Exclusion: mothers    │  │ n=702                                   │
        │   │ with children with    │  └────────────────────────────────────────┘
        │   │ possible FASD diagnosis:│
        │   │ • ADHD, FASD,         │
        │   │   pyscostimulant use, │
        │   │   or special needs    │
        │   │   funding (27,907)    │
        ▼   └──────────────────────┘
┌───────────────────────────────┐
│ Mothers who have no record of  │
│ giving birth to a child with a │
│ possible FASD diagnosis (182,481)│
└───────────────────────────────┘
        │   ┌──────────────────────┐
        │──▶│ Mothers not covered by│
        │   │ Manitoba Health three │
        │   │ years prior to the    │
        │   │ birth till the end of │
        │   │ study period (35,100) │
        ▼   └──────────────────────┘
┌───────────────────────────────┐
│ Mothers to chose matches from  │
│ with no missing data or        │
│ exclusion (147,381)            │
└───────────────────────────────┘
        │   ┌──────────────────────┐
        │──▶│ Matching criteria     │
        │   │ • Maternal age of birth│
        │   │   of index child      │
        │   │ • Socioeconomic status│
        │   │ • Region of residence │
        ▼   └──────────────────────┘
┌───────────────────────────────┐
│ Up to a 3:1 match with study   │
│ group (2,097)                  │
└───────────────────────────────┘
        ▼
┌───────────────────────────────┐
│ Comparison group               │
│ n=2,097                        │
└───────────────────────────────┘
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Table 6.2: Definitions of outcome variables

Outcome	Definition
Suicide	**A woman was considered to have completed suicide if the following ICD codes were used in the "cause of death" field in the Vital Statistics Mortality Data (our definition includes accidental poisonings):** 1) accidental poisoning: ICD-9 codes E850-E854, E858, E862, E868; 2) ICD-10 codes X40-X42, X46, X47; **OR** 2) poisoning with undetermined intent: ICD-10 codes Y10-Y12, Y16, Y17 OR 3) self-inflicted poisoning: ICD-9 codes E950-E952, ICD-10 codes X60-X69; **OR** *4)* self-inflicted injury by hanging, strangulation and suffocation: ICD-9 code E953, ICD-10 code X70; **OR** *5)* self-inflicted injury by drowning: ICD-9 code E954, ICD-10 code X71; **OR** *6)* self-inflicted injury by firearms and explosives: ICD-9 code E955, ICD-10 codes X72-X75; **OR** *7)* self-inflicted injury by smoke, fire, flames, steam, hot vapours and hot objects: ICD-9 codes E958.1, E958.2; ICD-10 codes X76, X77; **OR** *8)* self-inflicted injury by cutting and piecing instruments: ICD-9 code E956; ICD-10 codes X78, X79; **OR** *9)* self-inflicted injury by jumping from high places: ICD-9 code E957, ICD-10 code X80; **OR** *10)* self-inflicted injury by jumping or lying before a moving object: ICD-9 code E958.0, ICD-10 code X81; **OR** *11)* self-inflicted injury by crashing of motor vehicle: ICD-9 code E958.5, ICD-10-CA code X82; **OR** *12)* self-inflicted injury by other and unspecified means: ICD-9 codes E958.3, E958.4, E958.6-E958.9; ICD-10 codes X83, X84; **OR** *13)* late effects of self-inflicted injury: ICD-9 code E959
Suicide attempts	**A woman was considered to have attempted suicide if in the 5 years prior to the birth of the child she had:** 1) one hospitalization with a diagnosis for suicide and self-inflicted injury: ICD-9-CM codes E950-E959, ICD-10-CA codes X60-X84; **OR** 2) one hospitalization with a diagnosis code for accidental poisoning: ICD-9-CM codes 965, 967, 969, 977.9, 986, E850-E854, E858, E862, E868; ICD-10-CA codes T39, T40,T42.3, T42.4, T42.7,T43, T50.9, T58, X40-X42, X44, X46, X47, Y10-Y12, Y16, Y17, only if there is a physician visit with a diagnosis code for accidental poisoning and a psychiatric tariff code either during the hospital stay or within 30 days post-discharge. Psychiatric tariff codes are as follows: From the **psychiatric schedule:** 8444 Psychotherapy - group of two to four patients 8446 Psychotherapy - group of five or more patients 8472 Child and Youth Management Conference 8475 Psychiatry - Patient Care Family Conference 8476 Psychiatric Social Interview 8503 Complete history and psychiatric examination - adult 8504 Complete history and psychiatric examination - child 8553 Psychiatry Consultation - adult 8554 Psychiatry Consultation - child 8581 Psychotherapy - individual 8584 Psychiatric care - individual 8588 Electroshock therapy 8596 Consultation - Unassigned patient – child From the **general schedule:**

	8580 Psychotherapy - individual
	8587 Electroshock therapy
	8589 Psychotherapy - group

6.4   Data Analysis

Adjusted relative rates (aRRs) for the outcome variables were modeled using generalized linear models (GLM) with a Poisson or Negative Binomial distribution. All analyses tested for differences between groups and adjusted for covariates. To model the rate of events for our two groups, a summary dataset for the total number of suicide events, including attempts and completions for unique strata, and the total number of person-years at risk for the strata was created. To ensure an analysis of rates of events versus one of counts was being conducted, the log of the total number of person-years was used as an offset in the model.

6.5   Covariates

The following variables were included as potential covariates in each of the models generating rates of suicide attempts and completions: age of mother at birth of child, and SES at the time of the birth of the index child. SES was defined according to area level data from census information. Area-level income quintiles were ranked from 1 (low) to 5 (high) on the basis of ranges of mean household income from census information, and grouped into five categories, with approximately 20% of the population assigned to each quintile[36]. For models investigating rates of women who attempted or completed suicide after the birth of the child, adjustment for suicide attempts five years before the birth of the index child to account for pre-existing mental health issues was done.

6.6   Results

Our study groups consisted of women born from 1946 to 1992 with ages at the time of the birth of the index child ranging from 14 to 46 years (Table 6.3). Study group women were more likely to be lone parents, be younger at first birth, and tended to have lower SES, higher gravidity and higher parity and higher proportion of mental disorders versus women in our comparison group (Table 6.3). Among the course of our study period a total of 101 women died by any cause (as defined in the vital statistics database); 75% of these women were from our study group. The most common cause of death among this group of women was intentional self-poisoning/harm.

Attempts: There were a total of 10103.40 person years for our study group, and 29331.55 person years for the comparison group when examining suicide attempts until the end of the study period. The study group had significantly higher adjusted rates of women who attempted suicide (adjusted relative rate (RR) 5.23, 95% confidence interval (CI) 2.63-10.42) and adjusted RR after the birth of the child (adjusted RR 4.62, 95% CI 2.53-8.43) (Table 6.4). Less than 6 women in both groups attempted suicide during the pregnancy or during the postpartum period.

Completions: There were a total of 10694.56 person years for our study group, and 29695.65 person years for the comparison group when examining suicide completions till the end of the study period. Study group women had significantly higher adjusted rates of women who completed suicide after the post-partum period (adjusted RR 6.20, 95% CI 2.36-16.09). Study group women had a higher mean age of suicide, 37.46 (SD 6.13, range 29.00-51.49) versus 25.75 (SD 5.96, rage 20.85, 34.55), and the mean number of years after the birth of the child for the suicide was 12 years (SD 5.13, range 4.07-20.19).

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Table 6.3: Characteristics of women whose children are diagnosed with FASD and a matched sample of women whose children do not have FASD

Characteristic	Study Group (N = 702)	Comparison Group (N = 2,097)
Maternal age at birth of index child		
Mean year, (SD)	24.43 (6.14)	29.24 (5.69)
Range	14 - 43	14 - 46
Maternal age at birth of index child		
< 18 years	72 (10.26)	231 (11.02)
18-24 years	333 (47.44)	831 (39.63)
25- 29 years	146 (20.80)	525 (25.04)
30-34 years	96 (13.68)	367 (17.50)
35 + and missing[1]	55 (7.83)	143 (6.82)
Missing	< s[1]	0
Maternal Age at first birth		
< 18 years	266 (37.89)	246 (11.73)
18-24 years	340 (48.43)	854 (43.06)
25- 29 years	54 (7.69)	530 (25.27)
30-34 years	29 (4.13)	306 (14.59)
35 + and missing[1]	13 (1.85)	112 (5.34)
Missing	< s[1]	0
History of teen pregnancy	266 (37.89)	246 (11.73)
Region of residence		
Rural	251 (35.75)	764 (36.43)
Urban	451 (64.24)	1333 (63.57)
Mean household income		
Q1 (lowest)	466 (64.38)	1398 (66.67)
Q2	104 (14.81)	312 (14.88)
Q3	57 (8.12)	171 (8.15)
Q4	36 (5.13)	108 (5.15)
Q5 (highest)	26 (3.70)	78 (3.72)
Missing	13 (1.85)	30 (1.43)
Receipt of Income assistance 3 years before birth of the index child[2]	N = 345[2]	N=1026[2]
	63 (18.26)	98 (9.55)
SES		
Low (Q1)	466 (66.38)	1398 (66.67)
Middle (Q2 & Q3)	161 (22.93)	483 (23.03)
High (Q4 & Q5)	62 (8.83)	186 (8.87)
Missing	13 (1.85)	30 (1.43)
Married at the birth of child	66 (9.40)	773 (36.86)
Gravidity		
0-3	357 (50.85)	1966 (93.75)
=>4	306 (43.59)	113 (5.39)
Missing	39 (5.56	18 (0.86)
Parity		
0-3	524 (74.64)	2063 (98.38)
=>4	139 (19.80)	16 (0.76)
Missing	39 (5.56)	18 (0.86)
Involvement with child and family services 3 years before the birth of the child[3]	N=345[4]	N=1026[4]
	228 (66.09)	136 (13.26)
Diagnosis of psychiatric disorder three years	580 (82.62)	566 (26.99)

before the birth of the child[5]		
Substance abuse[6]	179 (25.49)	49 (2.32)
Personality Disorder[6]	22 (3.13)	6 (0.29)
Mood & Anxiety Disorder[6]	237 (33.76)	397 (18.93)
Schizophrenia[6]	< s[1]	7 (0.33)
Prenatal psychological distress[7]	529 (75.36)	293 (13.97)
Postnatal psychological distress[8]	528 (75.21)	923 (44.01)

[1] Number of missing women was < 6, therefore the number of missing women was combined with the "over 35 age group" to ensure privacy rules of MCHP data were adhered to.

[2] Income data is available after 1995, therefore the denominator was limited to women who had babies after 1998 to ensure three years of data were available before the birth of the child to evaluate the number of women who had income assistance three years before the birth of their children; 345 women in the study group and 1026 women in the comparison group had babies after 1998

[3] Includes voluntary or involuntary involvement with child and family services of any children of the mother or the mother herself (if she was under the age of 18 at the time), including any support services or out of home placements.

[4] CFS data is available after 1995, therefore, the denominator was limited to women who had babies after 1998 to ensure three years of data were available before the birth of the child; 345 women in the study group and 1026 women in the control group had babies after 1998

[5] Includes diagnosis of: substance abuse, personality disorder, mood and anxiety disorder, schizophrenia, prenatal psychological distress

[6] Diagnosis three years before the birth of the child

[7] Diagnosis 8 months before the birth of the child

[8] Diagnosis 12 months after the birth of the child

Table 6.4: Rates of suicide attempts and completions of women who have given birth to children diagnosed with FASD and a matched sample of women who have not give birth to children diagnosed with FASD

	Study Cohort; no. of cohort (Crude rate per 1000 person years)		
Outcome	**Study Group N = 702**	**Comparison Group N = 2097**	**aRR (95% CI)**
Suicide attempts five years before the birth of the index child			
Number of women who attempted suicide	47 (13.97)	34 (3.27)	5.23 (2.63-10.42)[1]
Number of attempts	71 (20.76)	48 (4.61)	7.05 (3.23-5.40)[1]
Suicide attempts during pregnancy			
Number of women who attempted suicide	S[2]	S[2]	N/A
Number of attempts	S[2]	S[2]	N/A
Suicide attempts during the postpartum period			
Number of women who attempted suicide	S[2]	S[2]	N/A
Number of attempts	S[2]	14	N/A
Suicide attempts after the postpartum period till the end of study period			
Number of women who attempted suicide	64 (6.33)	39 (1.32)	**4.62 (2.53-8.43)[4]**
Number of attempts	102 (10.10)	104 (3.55)	**3.92 (2.30-6.09)[4]**
Suicide completion			
Number of women who committed suicide[3]	14 (1.39)	6 (0.20)	**6.20 (2.36,16.31)[4]**

Note: CI = 95% confidence interval, RR = relative rate

[1] Adjusted for age at birth of index child and socioeconomic status (SES)

[2] Suppressed: events less than 6 must be suppressed to adhere to MCHP privacy policies

[3] From entire study period i.e. five years before the birth of the child till December 1st, 2013

[4] Adjusted for age at birth of index child, SES and suicide attempts in the 5 years before the birth of the index child

6.7   Discussion

The results of our study indicate women who give birth to children with FASD have increased social complexities including low SES, lone parents, and higher gravidity and parity, and higher rates of mental health disorders that may place them at higher risk for suicide attempts and completions later in life. These women also have higher rates of all-cause mortality, highlighting the overall high-risk nature of this cohort.

Among the study group, rates of completed and attempted suicide after the postpartum period were greater than our comparison group, even when controlling for previous suicide attempts before the birth of the child, a marker for pre-existing health indications. These results indicate these women are at risk for suicide in the years after the birth of their child. Women in the study group did not have an increased risk for maternal death due to suicide during the postpartum period, however they did have higher rates of prenatal and postpartum psychological distress than the comparison group. Furthermore, women in the study group had a higher proportion of mental disorders, and prenatal and postpartum psychological distress compared to women in our comparison group (Table 6.3). These results emphasize the complex relationship between mental health disorders, high levels of alcohol consumption, and suicide.

Our results are consistent with a previous study of women giving birth to children with FASD conducted in a Northern Plains Indians population that reported a 40% rate of attempted suicides and high rates of intentional and accidental injuries[22]. Our research enhances the sparse knowledge base in this area by reinforcing that women who give birth to children with FASD are at increased risk for suicide attempts and completions using the largest sample size to date which

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enhances the internal validity of our results. Previous studies have utilized survey and interview data, which are limited by recall bias[22].

A limitation of this study is the use of a clinically referred sample, limiting the generalizability of the findings. However, this sample is also a strength, as confirmation of prenatal alcohol use at a level associated with teratogenicity (ie. a diagnosis of FASD) is required as part of the clinical assessment. However, the study group does not include women with alcohol use disorders who do not have children referred for FASD assessment. Moreover, although we have taken great care in excluding all mothers with possible prenatal alcohol exposure (see figure 6.1), we cannot be certain that there were no women in our comparison group who do not have un-reported prenatal alcohol use. However, this would serve to weaken rather than strengthen our findings.

Suicide attempts are often under-coded in administrative databases as physicians may list underlying mental illness as the diagnosis or not accurately chart the occurrence of suicidal behaviour[37]. There is low sensitivity in the use of these data to track the prevalence of suicide outcomes; findings of a validation study comparing emergency department and patient coding for suicide and self-harm attempts versus clinical assessment data suggest using hospital and physician claims to identify suicidal outcomes in patients miss up to one half to two thirds of outcomes[37]. Furthermore, only women who received medical care for a suicide attempt or whose death was classified as a suicide would be included in this study. These data also do not capture suicidal ideations, further underestimating the burden of suicidal behaviour in this population. Moreover, we are not reporting the true prevalence of psychiatric disorders in our cohort, but the prevalence of physician health service use for psychiatric illnesses; as MCHP data depend on

women making contact with the health care system. Therefore, this study excludes women with undiagnosed psychiatric disorders and women who have not been assigned relevant diagnostic codes. Mental disorders among women who only sought care from a psychologist or support group would not be captured.

These data are not collected for research purposes; there may be unmeasured risk factors that develop or change in the time to suicide that our analysis could not account for. Future research exploring factors placing women at higher risk for suicide that could not be investigated using administrative data should be conducted. We also could not identify what proportions of women from our study population were from Indigenous communities. Because suicide is a significant issue in these communities,[38,39] it would be important to describe the burden of suicide among women who give birth to children with FASD who are Indigenous.

Finally, contrary to our hypothesis, the study results indicate that women with a child with FASD are not at higher risk for maternal death due to suicide. Further analysis using a larger sample size should be conducted to confirm this finding, as suicide attempts are difficult to study in shorter time periods. This finding may also depend on the increased social support women in Manitoba receive during the first year after the birth of a child as there are universal support programs available to all women and families in Manitoba at high risk for adverse outcomes. Further investigation exploring the reasons behind this encouraging finding should be conducted.

6.8   Conclusions

Women who give birth to children with FASD are at an increased risk of suicide attempts and completions later in life; this probably reflects the social complexities faced by this group of women, as well as the high rates of mental disorders and the high levels of alcohol consumption in this cohort. Interventions are needed that: (1) screen for suicidal behaviour in women at high risk to consume alcohol during pregnancy and are diagnosed with mental disorders; and (2) provide mental health support for women who have alcohol exposed pregnancies to help prevent suicide later in life.

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Preface: Chapter 7

While researchers and policy makers acknowledge the importance of alcohol screening and brief interventions in prenatal care (PNC) settings to prevent Fetal Alcohol Spectrum Disorder (FASD), few studies have investigated the actual rates of PNC utilization in women who have given birth to children with FASD**.** Documenting whether women who give birth to children with FASD access PNC and receive adequate PNC is the first step in investigating the potential role PNC settings can play in reducing prenatal alcohol use and ultimately the incidence of FASD. This knowledge is imperative to the success of screening programs implemented in PNC settings to ensure women targeted by these programs are actually utilizing the health care service. The objective of this chapter is to investigate the quality of prenatal care of women who give birth to children with FASD relative to women who have not given birth to children with FASD utilizing the revised Gradated Index of Prenatal Care Utilization. To the best of our knowledge, this is the first study to utilize a population-based sample from a country with a universal health care system to compare rates of PNC utilization among women whose child(ren) have FASD relative to women whose children do not have FASD.

Publishing details:

Chapter 7: Prenatal care of women who give birth to Children with Fetal Alcohol Spectrum Disorder in a universal health care system: A population-based retrospective cohort study utilizing linkable administrative data

7.1 Abstract

Background: While researcher and policy makers acknowledge the importance of alcohol screening and brief interventions in prenatal care (PNC) settings to prevent Fetal Alcohol Spectrum Disorder (FASD), few studies have investigated the actual rates of PNC utilization in women giving birth to children with FASD**.** This study investigates rates of PNC utilization of women who have given birth to children with FASD compared to women who have given birth to children without FASD.

Methods: This study utilized linked population-based administrative data housed in, Winnipeg, Manitoba, including women who gave birth to a child between April 1, 1984 and March 31, 2012, with follow-up from to 2013. A study group of women who gave birth to a child(ren) diagnosed with FASD from a provincially centralised FASD assessment clinic from March 31, 1999 to April 1, 2012 (study group) (n= 702) was generated. A comparison group of women from the general population whose children who did not have an FASD diagnosis (n=2097) were matched on region of residence, date of birth of child with FASD, and socioeconomic status. Adequacy of prenatal care utilization was defined using the revised Graduated Index of Prenatal Care Utilization.

Results: Rates of inadequate PNC were higher among the study group (adjusted relative rate (RR) 2.47, 95% Confidence interval (CI) 2.08 to 2.94), as well as no PNC (adjusted RR 3.55,

95% CI 2.42 to 5.22). Among the study group 63% accessed PNC, with 59% receiving

intermediate, adequate, or intensive PNC.

Conclusion Despite higher rates of women in our study group not receiving adequate PNC, a

substantial proportion of women did access adequate PNC and gave birth to children with FASD.

Results represent an important opportunity for screening and brief intervention programs to be

delivered in prenatal health care settings.

7.2   Background

Almost ten percent of women across the world consume alcohol during pregnancy, which can lead to Fetal Alcohol Spectrum Disorder (FASD) in children[1]. FASD is a diagnostic term encompassing the range of effects associated with prenatal alcohol exposure[2] including: facial dysmorphology; growth restriction; neurodevelopmental abnormalities; as well as behavioural, emotional, and social difficulties that persist throughout the lifespan[2-4]. FASD affects millions of individuals throughout the world[1]; the global incidence of FASD has been approximated at one in every 100 live births[5], and significantly higher in vulnerable populations[6-8]. These high rates of FASD worldwide make the prevention of this disorder a global public health concern and a significant clinical and policy challenge.

Physicians delivering prenatal health care (PNC) services to women are in a unique position to help prevent or reduce the amount of alcohol consumption during pregnancies, and can play an integral role in decreasing FASD prevalence. PNC is often the first point of access to care for many women of childbearing age and a frequently used preventative health care service in countries with access to universal health care. PNC reduces the incidence of perinatal morbidity by identifying potential risks, treating physical and mental health conditions, and helps women to address social and behavioural factors that contribute to poor outcomes for both the mother and infant[9,10]. Physicians delivering PNC should routinely screen for alcohol use in pregnancy, and when identified, refer patients to treatment and support programs, and link women to community resources. PNC can also potentially help mitigate the damaging effects of alcohol consumption during pregnancy by treating co-morbid health and mental disorders in women and educating women about proper nutrition and prenatal health. PNC has been shown to be more effective if it

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begins in the first trimester of pregnancy and regular visits are continued throughout pregnancy[11].

The International Charter on Prevention of FASD[12] recognizes the importance of screening for at-risk alcohol use in women of childbearing age in primary care settings. Recommendations by professional societies such as the American Congress of Obstetrics state screening, brief intervention (BI) and referral to treatment (SBIFT) should be implemented in general primary care and obstetric settings to reduce alcohol use during pregnancy. Brief intervention programs applied in primary care settings have been effective in reducing risky alcohol use[13]. These interventions could help reduce the incidence of prenatal alcohol exposure and ultimately FASD. Interventions to reduce prenatal alcohol exposure in prenatal care settings are particularly relevant to countries having universal health care, specifically free access to regular PNC, as cost can be a significant barrier to seeking care.

While researcher and policy makers acknowledge the importance of alcohol screening and brief interventions in PNC settings to prevent FASD, few studies have investigated the actual rates of PNC utilization in women who have given birth to children with FASD. Research has documented barriers that may impede women at risk for an alcohol exposed pregnancy to not access PNC during pregnancy, including feeling stigmatized by drug and alcohol use and dependence[14,15], depression and mental disorders[15], having negative attitudes towards PNC[14,16], or believing it unnecessary[14,16]. Further barriers include lack of a regular health care provider before pregnancy, and negative attitudes of health care providers[16]. Patients also identify lack of

childcare, lengthy weight times, and issues obtaining transportation to get to appointments as barriers to care[15-18].

Documenting whether women who give birth to children with FASD access PNC and receive adequate PNC is the first step in investigating the potential role PNC settings can play in reducing prenatal alcohol use and ultimately the incidence of FASD. This knowledge is imperative to the success of screening programs implemented in PNC settings to ensure women who these programs target are utilizing the health care service.

To the best of our knowledge, this is the first study to utilize a population-based sample from a country with a universal health care system to compare rates of PNC utilization among women whose child(ren) have FASD relative to women whose children do not have FASD.

7.3   Methods

7.3.1   Setting

This study utilized the Manitoba Mothers and FASD Study (MB FASD Moms) cohort which is a large, population-based retrospective cohort of women whose child(ren) were diagnosed with FASD in Manitoba, Canada[19]. Manitoba is a central Canadian province with approximately 1.2 million residents who all receive universal healthcare coverage.

7.3.2   Data Sources

This study utilized administrative health, social and educational data from the Manitoba Population Research Data Repository (Repository) housed at the Manitoba Centre for Health

Policy (MCHP) and clinical assessment data from the Manitoba FASD Centre, which is the only

referral/diagnostic centre for FASD in the province. Table 7.1 provides a description of all

databases used in this study. Rates of PNC utilization were obtained from the Hospital Discharge

Abstracts, and medical/physician reimbursement claims. Data are de-identified and all databases

are linkable at the person-level through a scrambled personal health identification number.

Table 7.1: Description of datasets used for analysis

Name of Dataset	Description of Dataset	Years of Data Used	Information retrieved
Population Registry	A registry maintained by the provincial department of health of all Manitobans eligible to receive health services since 1970. Includes demographic information and 6-digit residential postal code[1].	1970/71 to June 2013	Demographic information: region of residence
Canada Census	Social data based on the Statistics Canada Population Census. These data were used to indicate area-level income, with Manitoba population divided into income quintiles according to average household income, composed of five possible income groupings with Q1 being the lowest and Q5 being the highest income quintile[1].	1996, 2001, 2006, 2011	Socioeconomic status information
Employment and Income Assistance	Data maintained by Department of Families that provide information on Manitoba residents who receive provincial income assistance[1].	1995/96 to 2012/2013	Receipt of income assistance
Babies First/Families First Screening Program	Newborn risk screen data collected as part of a home visiting program conducted by Healthy Child Manitoba. The screen is filled out by Public Health Nurses on all families with newborns in Manitoba and captures data on biological, social and demographic risk factors and alcohol use during pregnancy[1].	2003 to 2013 = Families First 2000 to 2002 = Baby First	Alcohol and drug use during pregnancy, social isolation
InSight Program	Data from an outreach program where mentors provide support to women who use substances and are pregnant or have recently had a baby[1]. This dataset includes information on women who have prenatal alcohol use.	1999 to 2012/2013	Alcohol and substance use during pregnancy
Hospital Discharge Abstracts	Health data maintained by Manitoba Health consisting of all hospitalizations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before April 1, 2004 and up to 25 ICD-10-CA diagnostic codes for discharges on or after April 1, 2004[1].	1981 to 2012/13	Physical and mental health diagnoses, antenatal hospitalizations, suicide attempts
Medical/Physician reimbursement claims	Health data maintained by Manitoba Health consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit[1].	1981 to 2012/13	Physical and mental health diagnoses, physician visits, prenatal care

Prescription claims: Drug Programs Information Network	Drug claim data maintained by Manitoba Health containing all prescription drug claims from the Drug Programs Information Network (DPIN, an electronic, on-line, point-of –sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba)[1]. Contains information on all prescription drugs dispensed in Manitoba.	1995/96 to 2012/13	Physical and mental health conditions
Manitoba FASD Centre	Include clinical assessments and diagnoses received under the FASD umbrella for all children referred to the MB FASD Centre[1]	1999 to 2012/2013	FASD diagnosis, children diagnosed with FASD
Vital Statistics	A longitudinal population-based registry maintained by Manitoba's Vital Statistics Agency that includes all Manitobans who have died since January 1970 to present and the cause of death[1].	1970 to 2012/2013	Cause of premature death. suicide completion
Education: Enrolment, Marks and Assessments	Education data maintained by the Department of Education and Training that provide information on enrolment, marks, and high school completion, and special funding. Special education funding is provided to children with severe to profound disabilities[1].	1995/96 to 2012/2013	High school completion, level of special education funding

[1]http://umanitoba.ca/faculties/health_sciences/medicine/units/chs/departmental_units/mchp/resources/repository/datalist.html

7.3.3   Study Cohort

Women included in this study were drawn from the entire Manitoba population of women who had a live birth in Manitoba between April 1, 1999 and March 31, 2012, and continued living in Manitoba until November 31, 2013. This population generated two groups (Figure 7.1):

Group1: Study Group: Mothers whose children received a clinical diagnosis of FASD:
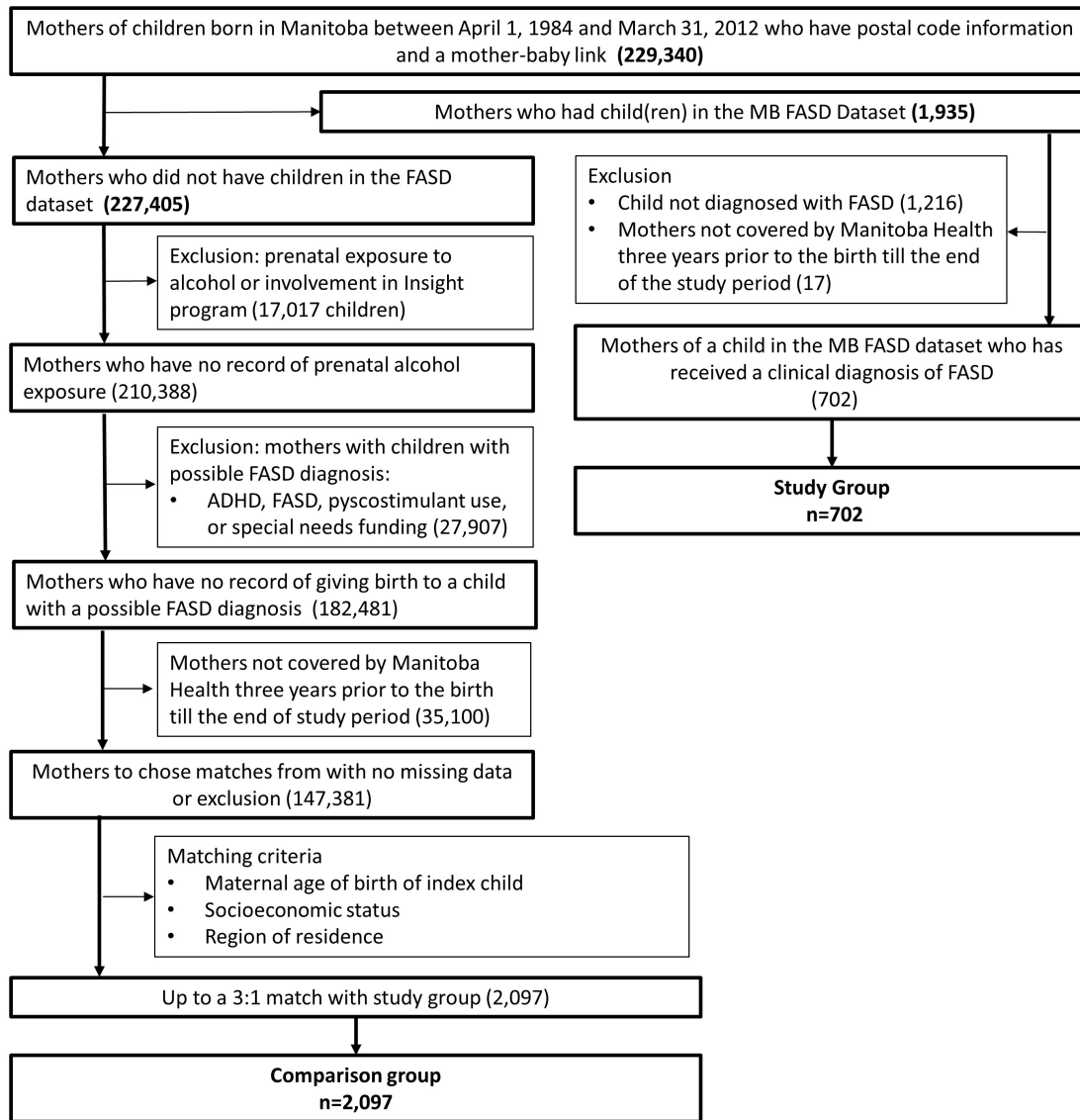
Clinical data from the MB FASD Centre was used to ascertain all children and youth (birth to 21 years of age) in Manitoba who had been diagnosed with FASD between 1999 and 2012. This database was linked to administrative data from the Repository to identify these children's birth mothers. Only mothers who could be linked to their children, who had postal code information, and who were Manitoba residents registered to receive health care in the province and covered from three years before the birth of their child until March 2013 were included.

Group 2: Comparison Group: Mothers whose children did not receive a diagnosis of

FASD: Women whose children did not receive an FASD diagnosis from the MB FASD

Centre, with no record of prenatal alcohol, whose children had no evidence of FASD from the Repository were matched to the study group of women on month of birth of the index child, socioeconomic status, and region of residence. Matching was done at a ratio of 3 comparison women for 1 woman in our study group. To decrease the likelihood that the comparison women had children with undiagnosed FASD the following exclusion criteria were used: (1) women with any children assessed at the Manitoba FASD Centre; (2) women with children who had a diagnosis of FASD recorded in hospital or physician claims data using the following ICD codes: a hospital visit with ICD-9CM code 760.71, ICD 10CCA code of 86.0 or a physician visit with any ICD 9 code 760; (3) women who had children prescribed psychostimulants or risperidone; (4) women with children diagnosed with ADHD (due to high comorbidity of FASD and ADHD diagnoses [20,21]; (5) women involved in the InSight Mentoring program (a program that provides support for women with alcohol and substance abuse issues); (6) women with a history of substance abuse disorder (including alcohol) during pregnancy as indicated by the physician and hospital claims; (7) women whose newborn risk screen indicated they had used alcohol during pregnancy and; (8) women whose children received special education funding indicating they had severe to profound disabilities.

Figure 7.1: Study Cohort Formation

Mothers of children born in Manitoba between April 1, 1984 and March 31, 2012 who have postal code information and a mother-baby link **(229,340)**

Mothers who had child(ren) in the MB FASD Dataset **(1,935)**

Mothers who did not have children in the FASD dataset **(227,405)**

Exclusion
- Child not diagnosed with FASD (1,216)
- Mothers not covered by Manitoba Health three years prior to the birth till the end of the study period (17)

Exclusion: prenatal exposure to alcohol or involvement in Insight program (17,017 children)

Mothers who have no record of prenatal alcohol exposure (210,388)

Mothers of a child in the MB FASD dataset who has received a clinical diagnosis of FASD (702)

Exclusion: mothers with children with possible FASD diagnosis:
- ADHD, FASD, pyscostimulant use, or special needs funding (27,907)

Study Group
n=702

Mothers who have no record of giving birth to a child with a possible FASD diagnosis (182,481)

Mothers not covered by Manitoba Health three years prior to the birth till the end of study period (35,100)

Mothers to chose matches from with no missing data or exclusion (147,381)

Matching criteria
- Maternal age of birth of index child
- Socioeconomic status
- Region of residence

Up to a 3:1 match with study group (2,097)

Comparison group
n=2,097

7.3.4 Variables

Outcome: Hospital discharge abstracts and physician claims files were used to assess the number and timing of PNC visits. Gestational age of the baby was obtained from the hospital birth record, and physician claims files were used to identify number and initiation of PNC visits. Pregnancy trimesters were defined as: first - date of conception to 91 days; second - 92-189 days, and; third - 190 days to date of birth. The date of conception was calculated by subtracting the gestational age from the birthdate of the child. The following outcomes were calculated to investigate PNC utilization: (1) no care; (2) late initiation of PNC; (3) care initialized in 1st trimester; (4) care initialized in 2nd trimester; (5) care initialized in 3rd trimester; (6) low number of prenatal visits; (7) adequacy of PNC. See Table 7.2 for definitions of all outcomes.

Adequacy of PNC was evaluated using the Revised Graduated Index of Prenatal Care Utilization (R-GINDEX), a validated and commonly used index to measure utilization of PNC[22]. The following three variables were required to utilize this index and were obtained from hospital and physician records: (1) gestational age of newborn; (2) trimester that PNC began; (3) total number of prenatal visits during pregnancy. The R-GINDEX has six categories of care including: "no care"; "inadequate care"; "intermediate care"; "adequate care"; "intensive care"; and "missing". This index is based on the full American College of Obstetricians and Gynaecologist's guidelines and has been utilized by various studies to evaluate PNC throughout North America[9,10,22,23].

Table 7.2: Definitions of outcomes used to compare prenatal health care (PNC) utilization among women whose child(ren) have a diagnosis of FASD and women whose child(ren) do not have FASD

Outcome Measure	Definition
Late initiation of PNC	A woman was considered to have late initiation of prenatal care if her prenatal care began after the first trimester (date of conception to 91 days).
No care	A woman was considered to have no prenatal care if no prenatal care was initiated in the first, second, or third trimester.
Care initialized in first trimester	A woman was considered to have care initialized in the first trimester if her first prenatal visits was in the first trimester (date of conception to 91 days).
Care initialized in 2nd trimester	A woman was considered to have care initialized in the 2nd trimester if her first prenatal visits was in the second trimester (92-189 days).
Care initialized in 3rd trimester	A woman was considered to have care initialized in the 3rd trimester if her first prenatal visits was in the third trimester (190 days to date of birth).
Low number of prenatal visits	A woman was considered to have a low number of prenatal visits if she had less than five prenatal care visits prior to delivery.
Inadequate or no PNC	The proportion of women with no or inadequate prenatal care was determined using the R-GINDEX.
Quality of pre-natal care by the R-GINDEX	The Revised-Graduated Prenatal Care Utilization Index is a measure of the adequacy of prenatal care by a health care provider which identified six major categories of prenatal care: inadequate prenatal care, intermediate prenatal care, adequate prenatal care, intensive care, no care and missing information[10]. Knowledge of three birth-related outcomes are required to calculate R-GINDEX: 1) the gestational age of the infant (date of pregnancy and birth) as calculated from the hospital abstract[10]; 2) the trimester during which prenatal care began, using hospital abstracts and physician claims data. The ICD-9-CM tariffs that were included are: 8400, 8401, 8501, 8507, 8509, 8529, 8540, 8550[10]; 3) the total number of prenatal visits during pregnancy as calculated from the hospital abstract and physician claims[10].
Inadequate PNC	The proportion of women with inadequate prenatal care was determined using the R-GINDEX.
Intermediate PNC	The proportion of women with intermediate prenatal care was determined using the R-GINDEX.
Adequate PNC	The proportion of women with adequate prenatal care was determined using the R-GINDEX.
Intensive PNC	The proportion of women with inadequate prenatal care was determined using the R-GINDEX. Women whose number of visits is approximately one standard deviation about the mean number of visits for each trimester of initiation and the gestational age at delivery were labelled as intensive care users[10]. "These women have an unexpectedly large number of PNC visits, which may indicate potential morbidity or complications"[10].
No care	The proportion of women with no prenatal care was determined using the R-GINDEX. care initiated in any trimester
Missing information	The proportion of women with inadequate prenatal care was determined using the R-GINDEX. gest < 24 weeks and care began in trimester three Gest age <11 and care began in trimester 2 And no care initiated in any trimester – no visits If gestation age missing

7.3.5 Covariates

The following covariates were selected based on clinical relevance and were adjusted for in each of the outcome models: age of mother at birth of child, region of residence, and SES. SES was defined using area-level (available at the dissemination area level which is approximately 400-700 individuals[36]) mean household income from census information, and grouped into quintiles ranked from 1 (low) to 5 (high) with approximately 20% of the population assigned to each quintile[24].

7.3.6 Analysis

A summary dataset for the total number of events (e.g. total number of mothers with inadequate PNC) was produced to model the rate of PNC utilization comparing the study and comparison groups. Adjusted relative rates (aRRs) of PNC utilization were modeled using generalized linear models (GLM) with a Poisson or negative binomial distribution, which are suitable for non-normally distributed data such as counts. All analysis tested for differences between groups and adjusted for covariates. The log of the population was included as an offset in the model so that a relative rate versus a relative count of events was modeled. Administrative data are not collected for research purposes; therefore, we could not include various confounding variables present in the literature known to impact women accessing health care services, including limited transportation and feelings of stigma or fear. To address this limitation, a gamma sensitivity analysis was conducted to measure how strong an unmeasured confounder would have to be to nullify statistically significant results.

7.4   Results

Our study population consisted of women who were born from 1946 to 1992 with ages ranging

from 14 to 46 years (Table 7.3). Most women from both groups were from an urban location and

had a wide variety of social and health complexities (Table 7.3). Women in our study groups had

low SES; 19% had a history of receiving income assistance before the birth of the child,

indicating the considerable level of poverty present in this cohort. Women in the study group

were also more likely to be lone parents, have higher gravidity and parity, and have more mental

disorders.

Table 7.3: Characteristics of women whose children are diagnosed with FASD and a matched sample of women whose children do not have FASD

Characteristic	Exposed Cases (N = 702)	Comparison Group (N = 2,097)
Maternal age at birth of index child		
Mean year, (SD)	24.43 (6.14)	29.24 (5.69)
Range	14 - 43	14 - 46
Maternal age at birth of index child		
< 18 years	72 (10.26)	231 (11.02)
18-24 years	333 (47.44)	831 (39.63)
25- 29 years	146 (20.80)	525 (25.04)
30-34 years	96 (13.68)	367 (17.50)
35 + and missing[1]	55 (7.83)	143 (6.82)
Missing	< s[2]	0
Maternal Age at first birth		
< 18 years	266 (37.89)	246 (11.73)
18-24 years	340 (48.43)	854 (43.06)
25- 29 years	54 (7.69)	530 (25.27)
30-34 years	29 (4.13)	306 (14.59)
35 + and missing[1]	13 (1.85)	112 (5.34)
Missing	< s[2]	0
History of teen pregnancy	266 (37.89)	246 (11.73)
Region of residence		
Rural	251 (35.75)	764 (36.43)
Urban	451 (64.24)	1333 (63.57)
Mean household income		
Q1 (lowest)	466 (64.38)	1398 (66.67)
Q2	104 (14.81)	312 (14.88)
Q3	57 (8.12)	171 (8.15)
Q4	36 (5.13)	108 (5.15)
Q5 (highest)	26 (3.70)	78 (3.72)
Missing	13 (1.85)	30 (1.43)

Receipt of Income assistance 3 years before birth of the index child[3]	N = 345[3]	N=1026[3]
	63 (18.26)	98 (9.55)
SES		
Low (Q1)	466 (66.38)	1398 (66.67)
Middle (Q2 & Q3)	161 (22.93)	483 (23.03)
High (Q4 & Q5)	62 (8.83)	186 (8.87)
Missing	13 (1.85)	30 (1.43)
Married at the birth of child	66 (9.40)	773 (36.86)
Gravidity		
0-3	357 (50.85)	1966 (93.75)
=>4	306 (43.59)	113 (5.39)
Missing	39 (5.56	18 (0.86)
Parity		
0-3	524 (74.64)	2063 (98.38)
=>4	139 (19.80)	16 (0.76)
Missing	39 (5.56)	18 (0.86)
Involvement with child and family services 3 years before the birth of the child[4]	N=345[4]	N=1026[4]
	228 (66.09)	136 (13.26)
Diagnosis of psychiatric disorder three years before the birth of the child[5]	580 (82.62)	566 (26.99)
Substance abuse[6]	179 (25.49)	41 (1.96)
Personality Disorder[6]	22 (3.13)	6 (0.29)
Mood & Anxiety Disorder[6]	237 (33.76)	397 (18.93)
Schizophrenia[6]	< s[1]	7 (0.33)
Prenatal psychological distress[7]	529 (75.36)	293 (13.97)
Postnatal psychological distress[8]	528 (75.21)	923 (44.01)

[1] Number of missing women was < 6, therefore the number of missing women was combined with the "over 35 age group" to ensure privacy rules of MCHP data were adhered to.

[2] Crude rate suppressed if n<6

[3] Income data is available after 1995, therefore the denominator was limited to women who had babies after 1998 to ensure three years of data were available before the birth of the child to evaluate the number of women who had income assistance three years before the birth of their children; 345 women in the study group and 1026 women in the comparison group had babies after 1998

[4] CFS data is available after 1995, therefore, the denominator was limited to women who had babies after 1998 to ensure three years of data were available before the birth of the child; 345 women in the study group and 1026 women in the control group had babies after 1998

[5] Includes: substance abuse, personality disorder, mood and anxiety disorder, prenatal psychological distress, postnatal psychological distress, schizophrenia

[6] Diagnosis three years before the birth of the index child

[7] Diagnosis 8 months before the birth of the index child

[8] Diagnosis 12 months after the birth of the index child

7.4.1 Prenatal Care Utilization

Thirty-three percent of the study group had inadequate PNC, and 8.12% had no PNC versus 14%

and 2% of our comparison group, respectively (Table 7.4). When adjusting for maternal age,

region of residence, and SES, our study group had over two times the rate of inadequate PNC

(adjusted relative rate (RR) 2.47, 95% Confidence interval (CI) 2.08 to 2.94), and over 3 times

the rate of no PNC versus our comparison group (adjusted RR 3.55, 95% CI 2.42 to 5.22).

Women in the study group also had higher rates of: PNC that was initiated in the 2nd trimester

(adjusted RR 1.69, CI 1.35 to 2.13); late/no initiation of care (adjusted RR 1.69, 95% CI 1.39,

2.04); low number of prenatal visits (adjusted RR 3.15, 95% CI 2.59, 3.83); intermediate PNC

(adjusted RR 1.62, 95% CI 1.34, 1.94); and inadequate/no PNC (adjusted RR 2.63, 95% CI 2.25

to 3.08). Despite the high rates of inadequate or no prenatal care, 59% of women in the study

group did receive intermediate, adequate, or intensive PNC.

7.4.2   Gamma Sensitivity Analysis

Sensitivity analyses found that all the models generating rates of quality and frequency of

prenatal care were robust to unmeasured confounding (Table 7.4), including late or no initiation

of care and all levels of quality of PNC measured by the R-GINDEX. Hence, the likelihood of

confounders existing, after adjusting for covariates included in the models, that would nullify the

direction and significance of our results is small. The findings regarding care initiated in first

trimester may be more sensitive to unmeasured confounding and could potentially become non-

significant if there were very strong unmeasured confounders that we were unable to account for.

The findings regarding care initiated in the third trimester was quite sensitive to unmeasured

confounding. However, neither of these would weaken the overall findings from these analyses.

Table 7.4: Prenatal care of women who have given birth to a child with FASD compared to women who have not given birth to a child with FASD

Outcome	Study Cohort Crude Rate (%)		Adjusted RR (95% CI)	Sensitivity to unmeasured confounding[1]
	Women who gave birth to a child with FASD (N = 702)	Women who did not give birth to a child with FASD (N = 2097)	'Women who gave birth to a child with FASD' vs 'Women who did not give birth to a child with FASD' (Reference)	
Trimester care was initiated				
1st trimester	536 (76.35)	1798 (85.74)	0.88 (0.81, 0.97)	17.9
2nd trimester	116 (16.52)	209 (9.97)	1.69 (1.35, 2.13)	56.9
3rd trimester	33 (4.70)	65 (3.10)	1.54 (1.02, 2.35)	4.1
Late or no initiation of PNC	166 (23.65)	299 (14.26)	1.69 (1.39, 2.04)	63.8
Low number of PNC	209 (29.77)	200 (9.54)	3.15 (2.59, 3.83)	83.1
Quality of PNC care by the R-GINDEX				
Inadequate PNC	234 (33.33)	287 (13.69)	2.47 (2.08, 2.94)	80.9
Intermediate PNC	175 (24.93)	327 (15.59)	1.62 (1.34, 1.94)	61.8
Adequate PNC	113 (16.10)	399 (19.03)	0.84 (0.68, 1.04)	NS
Intensive PNC	123 (17.52)	1036 (49.40)	0.35 (0.29, 0.43)	82.0
No care[2]	57 (8.12)	48 (2.20)	3.55 (2.42, 5.22)	69.7
Inadequate or no PNC[2]	291 (41.45)	335 (15.98)	2.63 (2.25, 3.08)	87.3

Note: Adjusted for: region of residence, age at birth of index child, SES

[1]Analyzed by using γ sensitivity test; γ sensitivity analysis was not calculated for those findings that were not statistically significant (NS).

7.5   Discussion

A substantial portion of women who give birth to children with FASD receive inadequate PNC. Over a third (41%) of women in the study group received inadequate or no PNC, compared to just over 15% of women in the comparison group. Differences between women who gave birth to a child with FASD compared to those who did not remained even after adjusting for factors that could contribute to use of PNC. These results suggest that screening and intervention programs implemented in PNC settings may miss an extremely high risk population for alcohol use during pregnancy. Outreach efforts developed to reduce the inequities in access to and use of prenatal care of women who may be harder to reach may also be useful to implement within FASD prevention strategies focusing on prenatal care of women. An example of such a program

is the Partners in Inner-city Integrated Prenatal Care (PIIPC) that aims to reduce inequity in the use of prenatal care in the Winnipeg Health Region by helping women overcome barriers to care[25]. Results demonstrate that the PIIPC project has decreased barriers to care and increased collaboration between providers across the city; these improvements have led to increased use of PNC by women in the inner-city[25].

Despite the high proportion of inadequate PNC in the study group, 59% of women who have given birth to a child with FASD received adequate, intensive, or intermediate PNC and consumed alcohol throughout their pregnancy. Results of this study therefore also demonstrate that a significant proportion of women who give birth to children with FASD do access regular PNC, and identify an important target for alcohol prevention and reduction interventions.

These results are consistent with the few previous studies in this area[26-29]. All previous studies reported that women who give birth to children with FASD receive less PNC than women in comparison groups, and generally begin PNC later in their pregnancies[26-29]. While these studies laid the groundwork for this type of investigation, previous research utilized small sample sizes generated from high risk populations, and were not conducted in countries with universal access to health care. The model of health care delivery is important when investigating health care utilization, as lack of health care insurance or inability to pay for health services are significant barriers to accessing regular care. Moreover, cultural differences between women in high-risk conditions, may preclude the generalization of results to women in general populations. Furthermore, measures used to assess the frequency of PNC visits in previous studies were not

standardized, potentially resulting in biases when calculating the frequency of care received by women.

This study adds to the international literature by contributing data from a large North American sample of women who have access to universal PNC, and novel analysis that utilizes a standardized index to evaluate PNC utilization and quality. Using this index, we can assess the varying degrees of PNC quality and utilization among our study sample, and not only assess if women received inadequate care, but also what proportions received adequate PNC and continued to drink during pregnancy. This is also the first study to use administrative data claims in investigating PNC utilization of women who give birth to children with FASD. These data are ideal to investigate health care utilization of populations and have been extensively validated for conducting this type of research[10,30-35]. These data also eliminate important biases inherent in previous studies utilizing primary data collection methods including non-response, recall and interviewer bias. Furthermore, by utilizing clinical data from the Manitoba FASD Centre we have ensured that our study group comprises women whose children have undergone a comprehensive multidisciplinary assessment in a central tertiary-level provincial diagnostic clinic which follows the Canadian guidelines for the diagnosis of FASD[2].

However, the use of this sample is also a limitation; the use of a clinically referred FASD sample limits generalizability of findings, as women whose children are not referred to the clinic for assessment will be excluded from the study group and potentially included in the comparison group. While we have taken great care in excluding all mothers with possible prenatal alcohol exposure and children with a diagnosis of FASD, we cannot be certain that there are no women

in our comparison group that do not have un-reported prenatal alcohol use or undiagnosed children with FASD. However, this would serve to weaken rather than strengthen our findings. Additionally, the number and time within the pregnancy of PNC visits was estimated from administrative claims and these estimates rely on the accuracy of physician coding. There may be missing PNC records in hospital or physician charts and healthcare providers who do not submit claims for PNC may be missed. However, as previously stated, MCHP data have been extensively validated for conducting this type of research[10,30-35].

This study cannot determine if physicians have screened patients for alcohol use during pregnancy or counselled these women about the importance of refraining from alcohol use during pregnancy. Although universal screening for substance use during pregnancy is recommended, women are not all screened during their PNC visits as physicians may be inadequately trained to screen for prenatal alcohol use and may question the likelihood that women will reduce their alcohol use. Physicians also may be unaware of how to help patients or connect them with resources if women do admit to alcohol use. Pregnant women may also be reluctant to disclose alcohol use during pregnancy due to fear, stigma, and judgement. Further investigation is warranted that evaluates existing approaches and knowledge of PNC physicians regarding screening, identifying, and treating women at risk for alcohol consumption during pregnancy. Study results also indicate the need for further work that uncovers barriers and facilitators to accessing PNC for women with alcohol use and dependence issues, and the development of effective outreach programs that make it easier for women at high risk for alcohol use during pregnancy to access PNC and provide programs and supports for abstaining from alcohol during pregnancy.

7.6   Conclusion

Women who give birth to children with FASD have higher rates of inadequate PNC. The implementation of effective outreach programs may facilitate access to PNC for harder to reach groups of women. Results of this study also demonstrated that a substantial percentage of these women did receive adequate PNC and consumed enough alcohol during pregnancy to affect the fetus, highlighting an important target for the use of screening and brief intervention programs to be implemented in primary care settings delivering PNC. Future work should be done examining the role of PNC physicians in the prevention of alcohol-exposed pregnancies and ultimately the reduction of FASD.

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Preface: Chapter 8

Canada is a global leader in advocacy for and the development of FASD prevention strategies; as a result, public knowledge of FASD is much higher in Canada versus worldwide. However, reducing the number of alcohol-exposed pregnancies in this country and throughout the world remains challenging. The goal of the Manitoba Mothers and FASD (MB FASD Moms) study was to continue the novel work done by Canadians and international experts in this field and contribute high quality, robust evidence supporting a woman-centered approach to the prevention of FASD in Canada. The goal of this work is to provide policy makers and health care professionals responsible for developing FASD preventions strategies with results from the first population-based Canadian study on women who give birth to children with FASD. This final chapter summarizes key findings from each of the empirical studies included in this dissertation (Chapters 4-7). To facilitate knowledge translation to key areas of prevention identified by experts in FASD prevention in the Canadian policy sector, this chapter incorporates policy implications of this body of work into the Canadian FASD Prevention Framework. This chapter also discusses how to incorporate the results of this work into clinical practice, specifically implications for addressing the social determinants of health associated with giving birth to children with FASD. This chapter concludes with a summary of the strengths and limitations of this work as well as directions for future research.

The goal of this research was to generate results that contribute to the understanding of the life circumstances of women giving birth to children with FASD in Canada, and provide an informed picture of the social determinants of health that place women at increased risk for giving birth to

a child with FASD. To achieve this goal, large, population-based administrative databases were linked together to facilitate five related research papers. The first paper was a study protocol that described the development of the MB FASD Moms study and included an overview of: study objectives, description of data sources, data linkage, study design, analysis plan, and strengths and limitations of the databases (Chapter 3). The second paper investigated various social determinants of health that were potential maternal risk factors associated with FASD (Chapter 4). The third paper investigated rates of psychiatric morbidity among women who gave birth to children with FASD compared to women from the general population who did not give birth to children with FASD (Chapter 5). The fourth paper examined rates of suicide and suicide attempts during critical time periods in these study groups (Chapter 6). The fifth paper analyzed quality of prenatal care among the study groups (Chapter 7). This final chapter summarized key findings from each of the empirical studies (Chapters 4-7) and concludes with clinical and policy implications of these findings and directions for future research.

Chapter 8: Conclusions and Policy Implications

8.1 Summary of findings

Through linking physician, hospital, drug, social system, vital statistics, FASD clinic, and census data this thesis adds to the existing evidence base and facilitates FASD prevention efforts by: (1) identifying women living in conditions of high risk who should be targeted for prevention and intervention, but may be difficult to identify using other methods of data collection; (2) identifying areas in health and social services that can be targeted for FASD prevention and support programmes to enhance service delivery to this population. This research is important for informing effective targeting and development of policy resources that can help women cope with the challenges and stresses in their lives to decrease prenatal alcohol consumption and ultimately prevent FASD.

The major contribution of this study to the existing body of literature is the addition of data from a large, population-based sample of women from a developed country with access to a universal health care system. This population-based sample enhances the generalizability of results and increases the likelihood that maternal risk factors identified by this study are representative of the entire population of mothers of children with FASD. Using matched comparison groups, we were also better able to determine how the study group differed from women in the general population who are similar in reproductive age and socioeconomic status. This research complements evidence on maternal risk factors associated with giving birth to children with FASD obtained from survey and interview methods from high risk populations across the world. In addition, this work contributes significantly to the existing evidence base by providing robust

and accurate data that document high rates of psychiatric morbidity and suicide attempts and completions among women who give birth to children with FASD from a generalizable sample. Finally, this study provides insight into the quality of prenatal care received by these women. These outcomes are difficult to capture using primary data collection.

Chapter 4 identifies maternal characteristics associated with giving birth to children with FASD, including: history of teen pregnancy, lone parenthood, higher gravidity and parity, having a diagnosis of a psychiatric disorder and/or physical health disorder up to three years before the birth of the child, taking antidepressants during pregnancy, and having inadequate prenatal care. Women who gave birth to children with FASD were also more likely to be involved with the child welfare and justice systems and be receiving income assistance. These findings suggest Canadian women who give birth to children with FASD are at increased risk for several social complexities, as well as mental and physical illness before and during their pregnancies. FASD prevention strategies are needed that address these maternal risk factors to help reduce the incidence of FASD. The results of this paper are consistent with international literature in this field[1,2], suggesting there are certain universal maternal risk factors, such as low SES and poverty, for giving birth to children with FASD. Moreover, our results reiterated that the most vulnerable women in society are at greatest risk for consuming the amount and frequency of alcohol during pregnancy that results in children being born with FASD.

Chapter 5 contributes comprehensive and robust evidence documenting the significant psychiatric burden faced by women who have given birth to children with FASD during critical time periods, including: 3 years before the pregnancy of the index child; during the pregnancy;

and during the postpartum period (1 year after birth of index child). While it is widely accepted that mental health disorders co-occur with alcohol use issues[3-5], no studies have used validated health services data to investigate specific rates of diagnosed psychiatric morbidity in this population. Findings from this research indicate that the prevention of alcohol consumption in pregnancy should include a focus on improving the psychiatric health of women of childbearing age with alcohol use issues during the preconception period, during pregnancy, and during the postpartum period to prevent the possibility of subsequent alcohol-exposed pregnancies. Support programs and interventions that improve the psychiatric health of women at risk for alcohol consumption during pregnancy should be an integral part of policies targeted at decreasing alcohol use during pregnancy. Women with psychiatric disorders who use alcohol should be provided with education about risks of drinking when pregnant, and compassionate evidence-based support for the cessation of alcohol consumption during pregnancy should be developed for women of childbearing age with psychiatric disorders. The significantly higher rates of postpartum psychological distress observed in women who have given birth to children with FASD also indicate the need for increasing treatment resources that focus on improving psychiatric health for these women prior to the birth of their children. Services to improve postpartum psychiatric health in this group of women may also prevent subsequent alcohol exposed pregnancies, thereby preventing further FASD births. Services should also be provided to support the family and child during the postpartum period.

Chapter 6 expands the investigation into the burden of psychiatric morbidity in this study population by documenting the significantly higher rates of suicide attempts and completions among mothers who gave birth to a child with FASD. The increased rates of suicide are likely a

reflection of the intersection of the social complexities faced by this group of women, as well as the high rates of mental disorders and high levels of alcohol consumption in this cohort. Interventions are needed that: (1) screen for suicidal behaviour in women who are at high risk to consume alcohol during pregnancy and are diagnosed with mental health disorders; (2) provide mental health support for women who have alcohol exposed pregnancies to help prevent suicide later in life.

Chapter 7 provides robust evidence from data validated for the investigation of health services use among large populations that complements previous findings of studies utilizing primary data collection methods[6-8], which indicate that women who give birth to children with FASD have poor prenatal care. Previous studies did not use standardized measures to assess the frequency or quality of prenatal care; using a validated index, this study assessed the varying degrees of quality and utilization of prenatal care among study groups. Results of this study demonstrate that over 40% of women who gave birth to children with FASD received inadequate prenatal care. These results suggest screening programs implemented in prenatal care settings may miss an extremely high risk population for alcohol use during pregnancy, and that these women are not receiving important prenatal care that monitors their own health and the health of their fetus. Women with alcohol use issues should be educated about the importance of prenatal care, and outreach programs should be developed that target women at risk for alcohol use during pregnancy and facilitate the access of prenatal care for this population.

Despite the high proportion of inadequate prenatal care in the study group, 59% of women who gave birth to a child with FASD did receive adequate prenatal care. Results of this study also

demonstrate that a significant proportion of women who give birth to children with FASD do access regular prenatal care and identify an important target for prevention and reduction interventions. Future investigation is warranted that evaluates existing approaches and knowledge of physicians providing prenatal care regarding the screening, identification and treatment of women at risk for alcohol consumption during pregnancy. There is a need for work that uncovers barriers and facilitators to accessing prenatal care for women with alcohol use and dependence issues to assess the role that physicians delivering prenatal care can play in the prevention of FASD.

Taken together, the findings of this dissertation suggest mothers who give birth to children with FASD in a Canadian population have a host of social complexities, high rates of psychiatric morbidity, and are at increased risk of suicide completions and attempts at critical time periods of their lives. These women also obtain lower quality of prenatal care than women in the general population of similar SES and reproductive age. The intention of this work was not to permit causal interpretations regarding the causes of drinking during pregnancy, but rather to produce work that is hypothesis-generating and highlights the need for targeted preventions and supports in specific areas, including:

(1) addressing the social determinants of health for women of childbearing age or those considering pregnancy who are at risk for prenatal alcohol consumption during the preconception period and throughout pregnancy;

(2) providing mental health support to women at risk for prenatal alcohol consumption during preconception, pregnancy, and the postpartum period; and

(3) improving prenatal care and access to prenatal care for women at risk for prenatal alcohol consumption.

8.2   Policy Implications: Providing Evidence to the CanFASD FASD Prevention Framework

Over a million infants a year are born with FASD, a disorder with a known and preventable cause[9]. Hence, the prevention of FASD is an important public health and social issue. Although the direct cause of FASD is maternal alcohol consumption during pregnancy, prevention efforts focused solely on educational campaigns to refrain from alcohol consumption during pregnancy have proven to be less effective with women at high risk to give birth to children with FASD[10,11].

Results of this dissertation report potential underlying causes for drinking during pregnancy in a Canadian population-based sample, such as stressful life events including the involvement of child welfare and justice systems, mental health disorders, and poverty. These results reinforce that FASD prevention needs to incorporate not only individual responsibility of mothers-to-be but also systemic responsibility for the societal supports and systems involved in women's lives.

Results of this research suggest targeted prevention efforts aimed at reducing or preventing alcohol exposure during pregnancy may have an impact if integrated into existing systems serving this population, specifically: mental health support, brief interventions in prenatal and primary health care settings, justice system outreach, child welfare systems, and systems designed to alleviate poverty such as income assistance programs. Study results support The International Charter on the Prevention of FASD, which states "broad-based policy initiatives

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and actions at different levels of every society are urgently needed to encourage abstinence from alcohol during pregnancy and to prevent fetal alcohol spectrum disorder"[9]. Knowledge generated by this study can inform policy makers and health care professionals in their efforts to develop more effective and targeted prevention, early intervention and treatment programs, and enhance the policy and service delivery for this vulnerable population of women in Manitoba.

The objectives and results of the MB FASD Moms study are aligned with national prevention efforts in Canada that advocate "multi-sectoral approaches tailored to the level of women's risk" to consume alcohol during pregnancy[11]. Results from the MB FASD Moms study can provide evidence for the *Canada FASD Research Network Four Part Model of FASD Prevention*. In 2008 the Public Health Agency of Canada developed a multi-level model for the prevention of FASD[12]. This model was updated in 2013 by members of the Canada FASD Research Network's Action Team on FASD Prevention from a Woman's Health Determinants Perspective[13]. This framework identifies "four mutually reinforcing prevention approaches as effective in delivering FASD prevention that are linked to overall alcohol strategies"[13]. The four levels consist of practices, polices and programs that aid women in improving their own health and the health of their children with support from family, support networks, services, and community[13].

The four levels of FASD prevention include:

Level 1: Raising awareness Broad awareness building and health promotion efforts and community development. This level emphasizes the importance of raising public awareness through universal campaigns, public policy initiatives, and health promotion activities[13].

Level 2: Brief counselling with girls and women of childbearing age. This level of

prevention focuses on encouraging open dialogue and discussion of alcohol use with all

women of childbearing years and their support networks. Discussions should include

strategies to cope without alcohol, engagment in prenatal support, and family and

pregnancy planning[13].

Level 3: Specialized prenatal support. This level of prevention attempts to reach and assist

women who are consuming alcohol during pregnancy and have social, economic and

health complexities[13]. This level of prevention consists of targeted, holistic support of

women who are pregnant and have issues with alcohol and substances (e.g. outreach and

mentoring programs)[13]**.**

Level 4: Postpartum support for new mothers with alcohol use problems. This level of

prevention includes supporting new mothers to make progress and healthy challenges

regarding their alcohol and substance use post-pregnancy[13]. This includes continuing to

provide holistic and non-judgmental health care, and social support beyond pregnancy[13].

The results of the MB FASD Moms study provide Canadian policy experts and health care

professionals who have the responsibility of developing effective FASD prevention strategies

with robust empirical evidence regarding maternal risk factors for giving birth to children with

FASD as well as insight into birth mothers' physical and mental health and prenatal care

utilization. This evidence can be used to obtain resources and funding to develop effective and

targeted FASD prevention strategies in each level of the framework, as well as inform the

development of targeted and effective prevention programs at the policy and clinical level. See

Table 8.1 for how results of this work can be integrated into each part of the prevention

framework.

Table 8.1: Integrating evidence from the Manitoba Mothers and FASD Study into the CanFASD FASD Prevention Framework

Level of Prevention	Objective	Evidence from the Manitoba Mothers and FASD Study to support prevention efforts
Level 1: Raising awareness[13]	Broad-based awareness and health promotion[13]	• Results from chapter 4 support the creation of respectful, non-stigmatizing messaging that fosters awareness of the social complexities and mental and physical health issues facing Canadian women at risk for giving birth to children with FASD. • Results from chapter 4 support the facilitation of multiple sectors of society to be involved in FASD prevention including the justice system, child welfare system, health care system, and systems designed to alleviate poverty such as income and social assistance. • Results from chapter 5 support the creation of messaging that encourages friends and family to provide needed mental health support for women of childbearing age, or during pregnancy for women who have mental health issues and are at risk for prenatal alcohol consumption. • Results from chapter 6 support the creation of suicide prevention campaigns for women who have given birth to children with FASD. • Results of chapter 7 support the creation of awareness campaigns that encourage women with alcohol use issues to seek proper prenatal care; for providers to deliver consistent messaging about the detrimental effects of alcohol consumption during pregnancy and refer women to support programs addressing alcohol use and other challenges in their lives; and the importance of incorporating FASD prevention strategies into practices delivering prenatal care.
Level 2: Brief counselling with girls and women of childbearing age[13]	Discussion of alcohol use and related risks with all women of childbearing years and their support networks[13]	• Results of chapter 4 support involving discussion of alcohol use and related risks in the systems where women at high risk to drink during pregnancy are already engaged, including: justice system, child welfare systems, health care system, systems designed to alleviate poverty. • Results of chapters 5, 6 and 7 support the training of clinicians providing psychiatric care to provide screening and brief intervention strategies dealing with alcohol cessation and reduction. • Results of chapter 7 support the need for training of primary health care providers of prenatal care to effectively and sensitively discuss alcohol and substance use issues with women of childbearing age and pregnant women. • Results of chapter 7 support the need for consistent screening of alcohol use during pregnancy during prenatal care appointments.
Level 3: Specialized prenatal support[13]	Reaching and assisting girls and women at highest risk, who are using alcohol during pregnancy and	• Results of chapter 4 indicate that a significant proportion of women who give birth to children with FASD are involved with child welfare services; these results support the need for sensitive interventions that address the fear women have of their children being taken away from them, and for the integration of FASD prevention into support services from child welfare systems • Results of chapter 4 support resources for networked providers who are

	have related health, social and financial concerns[13]	• specialized in women's health, prenatal and maternity care, and for substance use, mental wellness, and trauma-informed practice to be integrated into FASD prevention. • Results of chapters 4, 5, and 6 highlight the need for specialized mentoring programs that can address the above-mentioned needs. • Results of chapters 4, 5, and 6 highlight the need for the integration of support and treatment of mental disorders into alcohol prevention strategies.
Level 4: Postpartum and new mother support[13]	Support for new mothers with alcohol problems[13]	• Results from chapters 4, 5, and 6 highlight the need for long term support services that extend past pregnancy, particularly for the treatment of mental health issues and substance use issues that do not generally go away after pregnancy. • Results from chapter 5 highlight the increased rates of postpartum psychological distress among women who give birth to children with FASD, underscoring the need for mental health and other ongoing supports after the birth of the child to improve maternal and child health, and to prevent subsequent alcohol exposed pregnancies. • Results from chapter 6 highlight the increased rates of suicide and suicide attempts after the birth of children among women who have given birth to children with FASD; these results support the integration of suicide prevention for families affected by FASD.

Finally, study results highlight that low SES and /or poverty are maternal risk factors for giving birth to children with FASD. These results are consistent with the existing body of literature indicating low SES and poverty are universal maternal risk factors for giving birth to children with FASD[2,14,15]. It is widely accepted that poverty plays an important role in the health and wellbeing of women of childbearing age[16,17]; women living in poverty are at greater risk for exposure to high levels of stress, may have inadequate nutritional intake, have substance abuse/use issues during pregnancy, and are more likely to have mental health issues[16,17]. Poverty during the prenatal period also affects the health of offspring; research has demonstrated that women living in poverty are more likely to give birth to preterm or low birth weight infants[16,17].

While the role of poverty is widely accepted in determining the health of a society, challenges remain in the development and support of national anti-poverty strategies and for the implementation of specific strategies targeted to reduce inequity throughout populations in

Canada. The results of this study can be used for the integration of anti-poverty policies in the field of FASD prevention, as well as the advocacy of national and provincial policies that reduce poverty among women of childbearing age, including the need for income support during the prenatal period. A study conducted by Brownell et al. (2016) found the receipt of an unconditional income supplement by low income women during pregnancy was associated with positive outcomes for newborns including and reductions in low birth weight and preterm birth.[18] Women also had increased rates of breastfeeding initiation compared to women with low income who did not receive the supplement[18]. Women at risk to give birth to children with FASD who are among the lowest SES could benefit from these types of prenatal income supplement programs to obtain better nutrition, pay bills, and alleviate stresses associated with living in poverty, potentially resulting in better health outcomes for their infants.

8.3   Clinical Implications: Addressing the social determinants of health associated with giving birth to children with FASD in clinical practice

While the prevention of FASD should undoubtedly take a multi-sectored approach, and involve policy makers, community, and public health professionals, the role of physicians is often overlooked and their impact may be underestimated. Effective prevention of FASD centers around the social determinants of health, and historically, the role of physicians addressing the social determinants of health in clinical practice was not routine[19]. In recent years, physicians have recognized that addressing the social determinants of health does influence the health of their patients in a positive manner; however, they may lack the skills and knowledge of how to incorporate these complex needs into their practices[20]. Moreover, there is disparity among physicians in regards to knowledge, attitudes and practices regarding FASD and alcohol use

during pregnancy, and knowledge about the link between the social determinants of health and the prevention of FASD[21]. Physicians may not receive training in how to address issues of alcohol use and abuse, not have time to address issues of alcohol use and social complexities during appointments with patients, not be connected to community support resources or treatment options for women with alcohol use issues, or not fully understand the detrimental effects of alcohol on fetal development[21,22].

An important finding from this dissertation is that many of the women who gave birth to children with FASD in Manitoba were indeed accessing the health care system during the preconception period, as well as during pregnancy, for treatments for mental health disorders, physical health disorders and prenatal psychological distress. Thus, these women are known to the health care system and are seeking care from physicians in hospitals or as outpatients during critical time periods where alcohol screening and prevention efforts could be implemented. Physicians delivering primary care/prenatal care services to women are in a unique position to help prevent or reduce the amount of alcohol consumption during pregnancy, and can play an integral role in FASD prevention efforts, as primary care is often the first point of access for many women of childbearing age. Prenatal care reduces the incidence of prenatal morbidity by identifying potential risks, treating health conditions and helping women address social and behavioural factors that contrite to poor outcomes for mothers and infants[23,24]. As such, physicians delivering prenatal care should routinely screen for alcohol use in pregnancy, and when identified, refer patients to treatment and support programs and link women to community resources, as recommended by the Canadian guidelines for diagnosis of FASD[25,26].

In addition to screening for alcohol use during pregnancy, FASD prevention within clinical practice should address social determinants of health and barriers and facilitators for access to prenatal care in women of childbearing age, particularly those at high risk for alcohol use during pregnancy. Based on the results of this dissertation, the following are specific actions physicians delivering prenatal care can use to help address the social determinants of health within their own practices, as well as suggestions on how to increase alcohol screening during pregnancy. These suggestions are based upon a recent paper published in the Canadian Medical Association Journal that identifies actions clinicians can use to help address social determinants of health as part of their clinical practices [19], as well as a separate expert consensus on the recognition, screening and documentation of alcohol use during pregnancy[27].

(1) **Identify social challenges for women of childbearing age:** This study adds to the growing evidence base suggesting that interventions designed to increase social support for pregnant women by addressing the social determinants of women's health may create better health outcomes for both mothers and children[10,28-30]. Providing interventions and supports that increase social support may also aid in the prevention of future alcohol-exposed pregnancies[10,28-30]. Strategies that focus only on reducing or ceasing alcohol use may miss opportunities for addressing important socioeconomic, health and economic factors that could place women at risk for alcohol use issues in the first place[10,28-30]. These factors include those identified in this study: mental disorders, physical disorders, low SES, stressful life circumstances such as involvement with the child welfare and justice systems, and being a lone parent, as well as additional factors identified in other studies including lack of support from families or partners, physical and sexual abuse, and trauma[1]. The framework for taking action on the social determinants of health in clinical

practice published in the Canadian Medical Association Journal highlighted the importance of clinicians to identify hidden social challenges in the lives of their patients[19]. These recommendations are particularly applicable to helping reduce alcohol use among women who are at risk to give birth to children with FASD due to the complex life issues they may be facing and the possibility of self-medication with alcohol[11,30]. Research demonstrates that "failure to identify hidden social challenges in patients' lives can lead to misdiagnosis and inappropriate interventions"[19], for example, failing to ask about the role of violence in a patient with pelvic fracture[31]. Recent clinical guidelines recommend practitioners to pick up on "clinical flags" and "patient cues" to investigate a patient's social history in diagnostic workups[19]. The first step in providing holistic, women-centered care that addresses the social determinants of health in clinical practice is to identify social challenges among women of childbearing age, especially those that may be at high risk to consume alcohol during pregnancy. Physicians should inquire about social issues in women's lives in a culturally sensitive and empathic way[19]. Clinical tools that guide physicians on how to begin dialogue with patents regarding social challenges in an sensitive and appropriate way are readily available[19]. These tools can offer guidance to address issues of lack of employment, food insecurity, trauma, physical and sexual abuse, and fears regarding access health care or social services[19,20]. By addressing these social complexities physicians could play a role in reducing the factors that place women at risk to give birth to children with FASD and ultimately reduce the incidence of FASD.

(2) **Connecting patients to support services and community support programs:** Once social complexity issues have been identified, physicians should connect patients with

support resources in the health care system and outside the health care sector, including community support and mentoring programs [19,20].

(3) Implementing routine screening for prenatal alcohol use during the preconception period and during pregnancy: Canadian guidelines for diagnosis of FASD recommend screening of all pregnant women for alcohol use[25,26], however, some physicians report feeling uncomfortable inquiring about alcohol use or feel that screening and dealing with alcohol use is beyond the scope of their practice[27]. Results of the present study indicate that women who give birth to children with FASD do access treatment for health care disorders, particularly for mental health disorders and for prenatal care. Clinicians providing treatment for mental disorders for women of childbearing age should screen for alcohol use during pregnancy. Moreover, primary care settings delivering prenatal care should follow guidelines and screen for prenatal alcohol use using interview methods, motivational interviewing, supportive dialogue techniques, or structural questionnaire (examples include: T-ACE screening questionnaire for at risk drinking for pregnant women, and the TWEAK 5-item screening tool) in cases where drinking and/or alcohol use is confirmed[27]. A safe, supportive environment should be created during this screening process[27].

(4) Implementing FASD prevention through brief interventions in prenatal care delivery: As stated above, results of this study demonstrate a proportion of women giving birth to children with FASD are obtaining prenatal care, which identifies an important service that can be targeted for prevention and alcohol reduction interventions. Research demonstrates that brief intervention counselling is a cost-effective, timely and effective intervention that can be implemented in various clinical settings and is useful in

helping pregnant women who drink moderate amounts of alcohol to reduce alcohol use during pregnancy[22,27,32]. Brief intervention strategies include: (1) assessment and feedback after assessment; (2) goal setting through contracts; (3) positive reinforcement; and (4) education through information pamphlets/booklets and handouts[33].

(5) Implementing outreach programs to facilitate prenatal care in difficult to reach groups of women: Results of the current study demonstrate that over 40% of women who gave birth to children with FASD received inadequate prenatal care. These results suggest screening programs implemented in prenatal care settings may miss a population at high risk for alcohol use during pregnancy, and that these women are not receiving important prenatal care that monitors their own health and the health of their fetus. Women with alcohol use issues who access other services should be educated about the importance of prenatal care. Outreach programs developed to reduce the inequities in access to and use of prenatal care for women who may be harder to reach may also be useful to implement within FASD prevention strategies. An example of such a program is the Partners in Inner-city Integrated Prenatal Care (PIIPC) that aims to reduce inequities in the use of prenatal care in the Winnipeg Health Region by helping women overcome barriers to care[34]. Results demonstrate that the PIIPC project has reduced barriers to care and facilitated communication between programs across the city, resulting in increased use of PNC by inner-city women[34].

The results of this dissertation indicate that there is an important role for clinicians in preventing FASD by addressing the social determinants of health of women at risk for consuming alcohol during pregnancy. There should be widespread support of integrating physicians – in primary

care, prenatal health care, and psychiatric service settings – as significant players in FASD

prevention.

Table 8.2: Recommendations for health care providers to influence the social determinants of health that place women at risk for giving birth to children with FASD during the preconception period, during pregnancy, and during the postpartum period

	At the patient level	At the practice level
Preconception period	• Birth control and family planning counseling for women who are at high risk to give birth to children with FASD. • Implementing preconception counseling • Making "social diagnoses" that incorporate the social determinants of health such as poverty, low education, unemployment, violence, trauma, stressful circumstances including involvement of child and family services, involvement in the justice system. • Referring patients to support resources beyond the health care system. • Implementing routine screening for prenatal alcohol use. • Implementing outreach programs to facilitate prenatal care in harder to reach groups of women. • Screening for mental disorders • Addressing alcohol use in a sensitive and caring way. • Implementing brief interventions regarding alcohol use. • Providing mental health supports. • Providing alcohol use disorder support.	• Develop partnerships with community groups and public health interventions designed to treat and support women with substance use issues. • Improve access to preconception care and prenatal care for hard to reach patient groups • Integrate outreach programs for hard to reach women who may be at high risk for alcohol use during pregnancy • Integrate patients' social support facilitators into primary care or prenatal care team • Engage in partnerships with local community support groups and public health programs • Engage with mentoring programs designed to prevent and reduce alcohol during pregnancy. • Engage with systems beyond the health care system that women at risk to give birth to children with FASD are involved with such as Justice System and Child Welfare System
Pregnancy	• Making "social diagnoses" that incorporate the social determinants of health such as poverty, low education, unemployment, violence, trauma, stressful circumstances including involvement of child and family services, involvement in the justice system. • Referring patients to support resources beyond the health care system. • Implementing routine screening for prenatal alcohol use. • Implementing outreach programs to facilitate prenatal care in harder to reach groups of women. • Screening for mental disorders • Addressing alcohol use in a sensitive and caring way. • Implementing brief interventions regarding alcohol use. • Providing mental health supports. • Providing alcohol use disorder support.	
Postpartum period	• Connecting women to support services for new mothers. • Connecting women to specialized post-partum supports. • Connecting women to alcohol reduction programming.	

8.4   Strengths and Limitations

Detailed discussion of the strengths and limitations of this work have been presented in the methods chapter of this paper, as well each of the individual papers presenting empirical results. Table 8.3 summarizes the primary strengths and limitations of this work in the context of common biases inherent in observational and descriptive studies[35].

Table 8.3: Strengths and Limitations of the Manitoba Mothers and FASD Study

Bias/Challenge	Strengths	Limitations
Generalizability	• Population-based data available for hard to reach populations i.e. mothers who give birth to children with FASD. • Largest Canadian sample of women who have given birth to children with FASD to date, enhances generalizability of results. • The Manitoba FASD Centre offers a valid and reliable clinical diagnosis of FASD; thus, women in this sample have been clinically confirmed to have given birth to children with FASD.	• There are no validated algorithms to define FASD diagnosis in the MCHP Data Repository; therefore clinical data was required to link mothers to children. • The use of a clinically referred FASD sample may limit the generalizability of results, as women and children who are not referred to this clinic would be missing. However, referrals to the clinic come from a wide variety of sources and from all regions in the province, strengthening the generalizability across populations.
Attrition bias	• Difficult to follow large groups of women who have given birth to children with FASD using primary data collection due to the length of time needed to obtain longer-term outcomes. The use of population-based linkable administrative data decreases this bias and allows the study of longitudinal outcomes.	• Women who moved out of the province were removed from the study; however this was a very small percentage of women.
Selection bias	• Built on a registry of an entire population, limits selection bias.	• Only women who sought treatment for health services were included in rates for outcome measures, thus, women not treated by a physician or who did not seek care were not captured in outcome measures. This may result in an underestimation of outcomes, such as an underestimation of mental disorders among study groups.
Obtaining an accurate comparison group	• The MCHP Repository provides access to information from the whole population of Manitoba and thus facilitates the creation of clinically relevant comparison groups and accurate comparative analysis. • Using the multiple available datasets,	• Cannot be certain that there are no women in our comparison group who do not have un-reported prenatal alcohol exposure or children with undiagnosed FASD; however this would serve to weaken rather than

	comparison groups can be created using a host of matched characteristics (age, sex, location disease specific cohorts).	strengthen any of the findings.
Recall bias	• Administrative data eliminate recall bias.	
Valid and reliable definition of FASD	• The Manitoba FASD Centre offers a valid and reliable clinical diagnosis of FASD, thus it is certain that women in this study group have indeed given birth to children with FASD.	• Children with undiagnosed FASD, or who are not referred to the MB clinic will be missed.
Validated outcomes and definitions	• Administrative data used in analysis have been validated for health services research[35-38]. • Administrative data in the Repository allow for analysis in various domains that influence health outcomes.	• Only women who sought treatment for health services were included in rates for outcome measures, thus, women not treated by a physician or did not seek care, or who were mis-diagnosed were not captured in outcome measures. This may result in an underestimation of outcomes, such as an underestimation of mental disorders among study groups.
Data collection	• Administrative data facilitate timely and cost-effective studies. • Access to a wide range of outcomes and variables which facilitate holistic, longitudinal investigation into social determinants of health and maternal risk.	• Data are not collected for research purposes; therefore this study cannot assess risk factors outside the scope of these data, including information on interpersonal relationships, violence and abuse, psychological trauma, or patient insight. • Data regarding patterns of alcohol use during pregnancy were not usable for data analysis.

8.5 Future Research

The Manitoba Mothers and FASD study examined several maternal factors associated with

giving birth to children with FASD in Manitoba. Over the course of this study questions were

raised beyond the scope of this dissertation, which warrant further investigation. The following

are areas of future research:

(1) **Investigating alcohol use patterns and linking with specific maternal risk factors:** It

was the original intention of this dissertation to investigate alcohol use patterns including

frequency, duration, and quantity of alcohol consumed and their association with

maternal risk factors. However, descriptive analysis and data cleaning demonstrated that

data on alcohol consumption patterns were not consistent or complete enough for further analysis. This is one of the limitations of using administrative data for research, as these data are not collected for research purposes. Future work should be done in collaboration with the Manitoba FASD Centre to introduce data quality measures to capture these data to expand this work and facilitate this type of inquiry.

(2) **Linking maternal risk factors with severity of FASD symptoms and diagnoses in children:** It was also the original intention of this dissertation to investigate the association between maternal risk factors and the severity of FASD symptoms. However, preliminary data analysis and data cleaning demonstrated that the data on FASD symptoms of children were not consistent or complete enough further analysis. As stated above, this is one of the limitations with using administrative data, as data are not collected for research purposes. Future work should be done in collaboration with the Manitoba FASD Centre to introduce data quality measures to ensure the rich clinical information collected regarding symptoms is recorded in the data system.

(3) **Identifying paternal risk factors:** There is a paucity of data investigating the role paternal factors play in the development of FASD in children. Research demonstrates that women with alcohol use/substance use issues are more likely to use substances if they have partners who also have substance and alcohol use issues[39]. Future work linking fathers to children and women to the MB FASD Moms study should be done to determine if this type of inquiry is possible using MCHP administrative data.

(4) **Investigating the role of the primary care provider in the screening of alcohol use during pregnancy and in the prevention of FASD in Manitoba:** Future investigation is warranted that evaluates existing approaches and knowledge of physicians providing

prenatal care regarding screening, identification, and treatment of women at risk for

alcohol consumption during pregnancy. There is a need for work that uncovers barriers

and facilitators to accessing prenatal care for women with alcohol use and dependence

issues to assess the role prenatal care physicians can play in the prevention of FASD.

(5) **The modification of risk of the development of FASD in children and the interplay**

of maternal risk factors should be investigated when richer clinical data are available on

symptom severity in the Manitoba FASD dataset. For example, the presence of maternal

morbidity such as mental and/or physical illness, and exposure to antidepressants during

pregnancy could be mediating or moderating factors in the development of FASD in

offspring. There is also a paucity of this type of data in the current literature base in this

field.

8.6   Conclusion

The goal of the MB FASD Moms study was to continue the novel work done by Canadians and

international experts in this field and contribute high quality, robust evidence that supports a

woman-centered approach to the prevention of FASD in Canada. Using a large, population-based

sample and comprehensive, multi-sector linked administrative data, this study has generated a

considerable amount of data that are being disseminated in quality peer-reviewed journals, policy

meetings, academic conferences, and through knowledge translation channels such as the

Evidence Network (www.evidencenetwork.ca). It is our hope that policy makers, FASD

prevention experts, and health care professionals will have new evidence that equips them with

reliable findings that accurately identify maternal risk factors for giving birth to children with

FASD. This information can provide new opportunities for prevention, with specific targeted

focus on women with mental health issues, and can facilitate the access of timely,

compassionate, and effective prenatal care to ultimately reduce the incidence of FASD.

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BMJ Open

Manitoba mothers and fetal alcohol spectrum disorders study (MBMomsFASD): protocol for a population-based cohort study using linked administrative data

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ABSTRACT

Introduction: Fetal alcohol spectrum disorder (FASD) is a significant public health concern. To prevent FASD, factors that place women at risk for giving birth to children with FASD must be investigated; however, there are little data in this area. This paper describes the development of the Manitoba mothers and FASD study, a retrospective cohort of mothers whose children were diagnosed with FASD, generated to investigate: (1) risk factors associated with giving birth to children with FASD; (2) maternal physical and health outcomes, as well as the usage of health and social services.

Methods: The study population will be identified by linking children diagnosed with FASD from a provincially centralised FASD assessment clinic (from 31 March 1999 to 31 March 2012) to their birth mothers using de-identified administrative health data housed at the Manitoba Centre for Health Policy. Preliminary analysis has identified over 700 mothers, which is the largest sample size in this field to date. A comparison cohort of women with children who did not have an FASD diagnosis matched on the region of residence, date of birth of child with FASD and socioeconomic status will be generated to compare exposures and outcomes. Potential demographic, socioeconomic, family history, and physical and mental health risk factors will be investigated by linking a range of health and social databases, furthering insight into the root causes of drinking during pregnancy. The longitudinal data will allow us to document the usage patterns of healthcare and social services throughout significant periods in these women's lives to identify opportunities for prevention.

Ethics and dissemination: Ethical approval has been obtained by the University of Manitoba's Health Research Ethics Board and the Manitoba Health Information Privacy Committee. Dissemination of study results will include engagement of stakeholders and policymakers through presentations and reports for policymakers, in parallel with scientific papers.

Strengths and limitations of this study

- Through the use of linked clinical and administrative data, the Manitoba Centre for Healthy Policy Data Repository allows the generation of the largest population-based sample of all women whose children were diagnosed with fetal alcohol spectrum disorder (FASD).
- The Manitoba FASD Centre offers a valid and reliable clinical diagnosis of FASD, and by linking these records to the birth mothers, we can be certain that women in this sample have given birth to children with FASD.
- Administrative data eliminate re-call bias and offer accurate information that can be isolated in critical periods of time throughout a study participant's lifespan.
- The study is subject to the limitations of administrative data and is reliant on the accuracy of data submitted by the organisations that deliver services.
- While we have taken great care in excluding all mothers with possible prenatal alcohol exposure and children with a diagnosis of FASD, we cannot be certain that there are no women in our comparison group who do not have un-reported prenatal alcohol use or children with undiagnosed FASD.

BACKGROUND

The prevention of fetal alcohol disorder (FASD) is a significant public health concern. In North America, over 10% of women report alcohol consumption during pregnancy.[1] Prenatal alcohol use places infants at risk for FASD, an umbrella term comprising a range of effects associated with prenatal alcohol exposure.[2] FASD has been recognised as the leading preventable cause of mental retardation in North America, highlighting FASD and prenatal alcohol consumption as

substantial public health issues.[2] Individuals with FASD experience myriad symptoms, including facial dysmorphology, growth restriction, central nervous system and neurodevelopmental abnormalities, as well as behavioural, emotional and social difficulties.[2][3] Over the past decade, international FASD prevalence estimates have ranged from 2% to 5%[4] in the general population and up to 23.3% in high-risk populations.[5–14]

FASD has been referred to as the world's only entirely preventable birth defect. Since the identification of fetal alcohol syndrome (FAS) in the 1970s, women who drink during pregnancy have been stigmatised and held responsible for causing this 'preventable' condition.[15] The notion that this disorder can be prevented is rooted in the theory that the exposure can be easily eliminated.[15] However, this response does not account for the many complex factors that influence women to engage in prenatal alcohol consumption, such as poverty, poor housing, trauma, physical and sexual abuse, mental disorders, lack of education and substance dependence.[16][17] The use of alcohol during pregnancy cannot be separated from these issues in the lives of women, and from other potentially harmful behaviours such as poor health practices, poor nutrition and the use of other harmful substances.[16][17] Only through identifying the demographic, social and economic factors that place women at risk for alcohol consumption during pregnancy can we obtain insight into the root causes of this behaviour and identify target points for prevention and support.

What is known about women whose children are diagnosed with FASD?

The WHO's global strategy to reduce the harmful use of alcohol highlights the importance of identification and prevention of the use of alcohol among pregnant women.[18] Although a growing body of literature investigating prenatal alcohol use exists, there are limited data focusing on the birth mothers of children who are diagnosed with FASD.

A systematic literature review conducted in 2013 summarised studies that identified maternal factors associated with the development of FASD.[19] The review identified 15 studies that were conducted throughout the world, including the USA, South Africa and New Zealand.[9][20–29] The included studies summarised demographic factors, family and social factors, psychiatric and neuropsychological factors, and patterns of alcohol consumption, and identified the following maternal factors associated with the development of FASD: older age, lower educational level, lower socioeconomic status (SES), unemployment during pregnancy, rural residence, higher parity and gravidity, family relatives with alcohol abuse issues, mental disorders, psychological distress, physical and sexual abuse, use of tobacco and illicit drugs during pregnancy, and a more severe pattern of alcohol consumption in general and in pregnancy, including more binge drinking.[19]

What are the evidence gaps in the current literature?

While these studies have laid the groundwork for investigating factors associated with giving birth to children with FASD, they have several important limitations that may preclude them from informing FASD prevention strategies in North America:

1. *Limited generalisability*: first, there are no Canadian studies and few studies from the USA that were conducted at a population level. The majority of studies are from South Africa and Italy, and many focus on women who are from high-risk populations, such as indigenous populations.[7][23][24][30] Owing to differences in population demographics and cultural norms, caution should be taken when extrapolating these results to the general North American population.

2. *Small sample sizes*: previous studies have utilised small samples that range from 8 to 250 birth mothers.[20][22–25][30] These small sample sizes may be a function of the complexity of diagnosing children with FASD, particularly because alcohol consumption during pregnancy is underreported.[4][10] However, these sample sizes limit the generalisability of results, have limited power to detect significant differences among comparison groups and limit the ability to conduct powerful multivariate analyses.

3. *Recall bias*: the majority of studies in this area are also limited by recall bias from self-report survey and interview data.[11][20][31–33] There are many factors that affect the validity of self-report data in alcohol use during pregnancy, including severity of alcohol use disorder, issues of confidentiality, stigmatisation, fear of disclosure, fear of involvement of child welfare services, mental disorders and denial of alcohol use as a problem.[25][32] Moreover, the accuracy of the information provided by self-reports is questionable, especially during periods of high alcohol consumption, which affects memory and judgement.[34]

4. *Limited data on diagnosed physical and mental health disorders*: no previous studies have documented clinically diagnosed physical and mental health disorders in women who give birth to children with FASD using reliable and validated clinical data, highlighting an important gap in the literature. There is a strong association with mental health disorders and alcohol consumption[35–40] and investigating this relationship in women who give birth to children with FASD is extremely important for the advocacy of effective support and prevention strategies.

5. *Limited data on service utilisation*: a few studies have investigated prenatal care in this population through self-report data and have found that these women receive fewer prenatal visits compared to women in the general population, and generally begin prenatal care later in their pregnancies.[23][24][30][41] However, these results are limited by recall bias and do not report any other health or social services use.

How can administrative health and social data help address evidence gaps?

The Manitoba mothers and FASD study (MBMomsFASD) is a data linkage project that will generate a retrospective cohort of all mothers who gave birth to children diagnosed with FASD in Manitoba, Canada. In partnership with the Manitoba FASD Centre (a provincially centralised FASD assessment and diagnostic clinic) and the Manitoba Centre for Healthy Policy (MCHP) (a population health research unit within the University of Manitoba, Canada), we will analyse explanatory variables associated with giving birth to children with FASD by analysing potential risk factors that are present *before* giving birth to a child with FASD (eg, SES, marital status, prenatal psychological distress, inadequate prenatal care), as well as maternal outcomes *after* the child with FASD is born (eg, postpartum psychological distress, suicide attempts and completion).

This study will make important contributions to the literature by filling existing gaps and addressing key methodological limitations identified in previous studies by using linked administrative health, social and education data housed at the MCHP. The MCHP Data Repository (herein referred to as the 'Repository') is one of the world's most comprehensive collections of population-based administrative databases. These data are a powerful tool to investigate factors that promote the health of populations, as well as to understand the usage of health-care services and social programmes of populations and specific groups.[42] The Repository consists of population-wide administrative data from health and social service agencies, education institutions and Canadian Census,[42–44] which allow the investigation of outcomes from multiple domains in a cohort of individuals.[42–44] This approach allows for an enhanced assessment of overall well-being and the impact of the multiple social determinants of health. This type of holistic investigation is particularly relevant to women who give birth to children with FASD. Women who drink during pregnancy often have histories that are rooted in abuse, poverty, other substance abuse and mental and/or physical illness.[17 45 46] Owing to the wealth of social and health data within the Repository, these data are an ideal source to investigate potential factors associated with prenatal alcohol consumption that results in the birth of a child with FASD. Administrative data are also ideal to investigate the usage of health and social systems among a population for any length of time or specified years.[42–44 47 48] We will document the usage of health and social systems among women whose children have been diagnosed with FASD to provide insight into how they navigate the health, social and education systems.

Research questions

1. What are the differences in: (a) demographic characteristics; (b) socioeconomic characteristics; (c) family characteristics; (d) psychiatric morbidity; (e) suicide behaviour; (f) physical morbidities, and (g) use of health

and social services among women whose children have a clinical diagnosis of FASD compared to women whose children do not have a diagnosis of FASD?

2. What demographic, socioeconomic, family, mental and physical health characteristics are associated/predictive with giving birth to children with FASD compared to not giving birth to children with FASD?

METHODS AND ANALYSIS
Description of data sources

Records from the following data sources will be requested and linked together for analyses:

1. *Manitoba FASD Centre*: This data set includes information on all children assessed at the clinic from 31 March 1999 to 31 March 2012 and consists of children who have received a diagnosis of FASD, children who have been assessed but do not meet the criteria for FASD and those who have received a deferred status, meaning that they will be assessed at a later time (eg, when children are older, symptoms are more apparent). The clinic uses the Canadian diagnostic guidelines developed by Chudley *et al*,[2] and the updated guidelines published by Cook *et al*.[49] These guidelines include all alcohol-related disabilities that are included under the FASD definition: alcohol-related neurodevelopmental disorder (ARND), alcohol-related birth defects, FAS and partial FAS (pFAS). Diagnosis of FASD is conducted by a multidisciplinary team and FASD diagnosis typically includes screening and referral; physical examination and differential diagnosis; neurobehavioral assessment; and treatment and follow-up.[2]

2. *MCHP Repository*: The following databases will be utilised in this study:
   A. *The population registry*: a registry maintained by the provincial department of health of all Manitobans eligible to receive health services since 1970 (updated semiannually) and includes demographic information and 6-digit residential postal code;
   B. *Canada census information*: social data based on the Statistics Canada Population Census. These data were used to determine area-level income, with the Manitoba population divided into quintiles according to average area-level household income, composed of five income groupings with Q1 being the lowest and Q5 being the highest income quintile;
   C. *Employment and income assistance*: data from the Social Assistance Management Information Network that provide information on Manitoba residents who receive provincial employment and income assistance, a programme that provides financial assistance for meeting the basic needs of living.
   D. *Education data*: education data maintained by the provincial department of education that provides information on enrolment, marks, and high

school completion, and special funding. Special education funding is provided to children with severe to profound disabilities.

E. *Babies first/families first screening programme data*: data collected as part of a universal screening programme conducted by Healthy Child Manitoba. The screen is filled out by Public Health Nurses on all families with newborns in Manitoba and captures data on biological, social and demographic risk factors, including alcohol use during pregnancy.

F. *Healthy baby prenatal benefit*: data from the Healthy Baby programme, which provides an income supplement to help women meet nutritional needs during pregnancy and connects women to programmes and resources in their area;

G. *InSight program data*: data from an outreach program where mentors provide intensive support to substance-using women who are pregnant or have recently had a baby. This data set includes information on women who have prenatal alcohol use;

H. *Justice system data*: an incident tracking system maintained by the provincial department of justice. These data include information on incidents, charges and involvements (eg, witness, accused, victim) in the justice system in Manitoba;

I. *Hospital discharge abstracts*: consisting of all hospitalisations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before 1 April 2004 and up to 25 ICD-10-CM diagnostic codes for discharges on or after 1 April 2004.

J. *Medical/physician reimbursement claims*: consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit;

K. *Pharmaceutical drug claims*: containing all prescription drug claims from the Drug Program Information Network (DPIN, an electronic, online, point-of-sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba). Contains information on all prescription drugs dispensed in Manitoba;

L. *Manitoba vital certificates mortality data*: a longitudinal population-based registry maintained by Manitoba's Vital Statistical Agency that includes all Manitobans who have died since January 1970 to present and the cause of death;

M. *Child and family services data*: a data management system that supports case tracking and reporting of services provided to children and families as they are served through the Manitoba Child and Family services (CFS) System. This database includes information on children in care as well as information of families receiving protection and support services.

See table 1 for descriptions and years of data sets used for analysis.

Data linkage

De-identified health records are transferred to MCHP from Manitoba Health, Seniors and Active Living (MHSAL, government department that administers the universal health insurance programme for the province) and contain scrambled identifiers that allow for linkages across multiple databases and years of data. MHSAL acts as a third party for other non-health data providers to develop cross-walk files allowing individual-level linkages across different data sectors. Linkages are performed using de-identified personal health identification numbers, which are unique nine-digit numeric identifiers assigned by Manitoba Health to every person registered for health insurance in Manitoba.

The main sources of data for this work will be the MB FASD database and the databases identified above from the Repository. This linkage produces a powerful tool for studying children and families with FASD that combines the comprehensive health, social and education administrative data with detailed clinical information. For this study the first linkage will identify the study population through linking children identified as having a clinical diagnosis of FASD to their birth mothers. Children diagnosed with FASD through the MB FASD Centre will be linked to their mothers using the 'Hospital Newborn to Mother Linkage' which is a Registry file in the Repository. This file contains basic demographic and hospital data on newborns born in a hospital in Manitoba from 1984/1985 onward and their mothers. This file includes all live and stillbirths to Manitoba residents, and babies born in out of province hospitals to Manitoba residents, if reported to MHSAL. Babies not included are those: born out of hospital, born in Manitoba hospitals to out-of-province residents, those born out of province to Manitoba residents who are not reported to MHSAL. A baby's birth record is matched to the mother's obstetrical delivery record using PHINs. The next linkage involves linking the study population to several other Repository data sets (hospital, physician, drug and the social and educational databases specified above) through one-to-one links between PHINs and data records. For example a woman in the Repository identified as having given birth to a child diagnosed with FASD from the MB FASD data set will be linked to her individual hospital abstract records, physician claims records and prescription data records. No identifying information is used to merge these files as linkage is conducted through using encrypted PHINs in order to ensure the utmost privacy and confidentiality of the data of Manitobans.

Study Population: Two groups of women will be generated to address research questions.

Group 1 (Cases/Exposed): Mothers whose children have received a clinical diagnosis of FASD: Clinical data from the MB FASD Centre will be used to ascertain all children and youth (birth to 21 years of age) in Manitoba who have been diagnosed with FASD between 1999 and 2012. This database will be linked to administrative data from the

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Table 1 Description of data sets used for analysis and types of information retrieved

Name of data set	Description of data set	Years of data used	Information retrieved
Population Registry	A registry maintained by Manitoba Health of all Manitobans eligible to receive health services since 1970 and includes demographic information and 6-digit residential postal code	1970/1971 to June 2013	Demographic information: region of residence
Canada Census Information	Social data based on the Statistics Canada Population Census. These data were used to determine area-level income, with Manitoba population divided into income quintiles according to average area-level household income, composed of five possible income groupings with Q1 being the lowest and Q5 being the highest income quintile	1996, 2001, 2006, 2013	SES information
Employment and Income Assistance Data	Data maintained by Manitoba Jobs and the Economy that provide information on Manitoba residences who receive provincial employment and income assistance	1995/1996 to 2012/2013	SES information
Education data: Enrolment, Marks and Assessments	Education data maintained by Manitoba Education and Advanced Learning that provides information on enrolment, marks and high school completion, and special funding. Special education funding is provided to children with severe to profound disabilities	1995/1996 to 2012/2013	High school completion, level of special education funding
Baby First/Families First Screening Program data	Data collected as part of a universal screening programme conducted by Healthy Child Manitoba. The screen is filled out by Public Health Nurses on all families with newborns in Manitoba and captures data on biological, social and demographic risk factors, including alcohol use during pregnancy	2003 to 2013=Families First 2000 to 2002=Baby First	Alcohol and drug use during pregnancy Maternal education Social isolation
Healthy Baby Prenatal Benefit and Healthy Baby Community Support Program	Data from the Healthy Baby programs (administered by Healthy Child Manitoba), which provide financial benefits to help women meet nutritional needs during pregnancy and connects women to programs and resources in their area	2001 to 2011/2012	Demographic and SES information Program participation
InSight Program data	Includes data from an outreach program where mentors provide intensive support to women who are pregnant or have recently had a baby and use substances. This data set includes information on women who have prenatal alcohol use	1999 to 2012/2013	Alcohol and substance use during pregnancy
Hospital Abstracts	Health data maintained by Manitoba Health consisting of all hospitalisations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before 1 April 2004 and up to 25 ICD-10-CM diagnostic codes for discharges on or after 1 April 2004	1984 to 2012/2013	Physical and mental health diagnoses Antenatal hospitalisations Suicide attempts
Medical/Physician reimbursement claims	Health data maintained by Manitoba Health consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit	1984 to 2012/2013	Physical and mental health diagnoses Physician visits Prenatal care

Continued

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Table 1 Continued

Name of data set	Description of data set	Years of data used	Information retrieved
Prescription claims data: Drug Program Information Network	Data maintained by Manitoba Health containing all prescription drug claims from the DPIN (an electronic, online, point-of-sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba). Contains information on all prescription drugs dispensed in Manitoba	1995/1996 to 2012/2013	Physical and mental health diagnoses
Manitoba FASD Centre data	Includes clinical assessments and diagnoses received under the FASD umbrella for all children referred to the MB FASD Centre	1999 to 2012/2013	FASD diagnosis Children diagnosed with FASD
Vital statistics data	A longitudinal population-based registry maintained by Manitoba's Vital Statistics Agency that includes all Manitobans who have died since January 1970 to present and the cause of death	1970 to 2012/2013	Cause of premature death Suicide completion
Justice System: The Prosecutions Information Management System	An incident tracking system maintained by Manitoba Justice. These data include information on incidents, charges and involvements (eg, witness, accused, victim) in the justice system in Manitoba	2002 to 2011/2012	Justice system involvement
Child and Family Services Information System	A data management system that supports case tracking and reporting of services provided to children and families as they pass through the CFS system. This database includes information on children in care as well as information of families receiving protective and support services	1992/1993 to 2012/2013	Involvement with CFS

CFS, Manitoba Child and Family services; DPIN, Drug Program Information Network; FASD, Fetal alcohol spectrum disorder; SES, socioeconomic status.

MCHP Repository to identify these children's birth mothers. Only mothers who can be linked to their children (who had a baby–mother linkage), who have postal code information and who were Manitoba residents registered to receive healthcare in the province and covered from their birth until March 2012 will be included. If a mother has multiple children diagnosed with FASD, we will use the first child diagnosed with FASD as the index child.

Group 2 (Comparison group/unexposed): mothers whose children have not received a clinical diagnosis of FASD: Women whose children have never received an FASD diagnosis from the MB FASD Centre, with no known record of prenatal alcohol use in the databases available, and whose children have no evidence of FASD from the Repository will be matched to the exposed group of women on the date of month of birth of the index child, SES and region of residence. Matching will be performed without replacement, at a ratio of three controls for each case. To decrease the likelihood that the comparison women have children with undiagnosed FASD, the following exclusion criteria will be used: (1) women with any children assessed at the Manitoba FASD Centre; (2) women with children who had a diagnosis of FASD as recorded in hospital or physician claims data using the following ICD codes: a hospital visit with ICD 9CM code 760.71, ICD 10CCA code of 86.0 or a physician visit with any ICD 9 code 760; (3) women who had children who had prescriptions for psychostimulants or risperidone; (4) women with children diagnosed with ADHD (due to high comorbidity with a diagnosis of FASD and ADHD;[50 51] (5) women involved in the InSight Mentoring programme (a programme that provides support for women with alcohol and substance abuse issues); (6) women with a history of substance abuse disorder (including alcohol) during pregnancy as indicated by the physician and hospital claims; (7) women whose newborn risk screen indicates they had used alcohol during pregnancy; and (8) women whose children received special education funding indicating they had severe to profound disabilities.

Study design

Two study designs will be used based on the two different research questions being addressed.
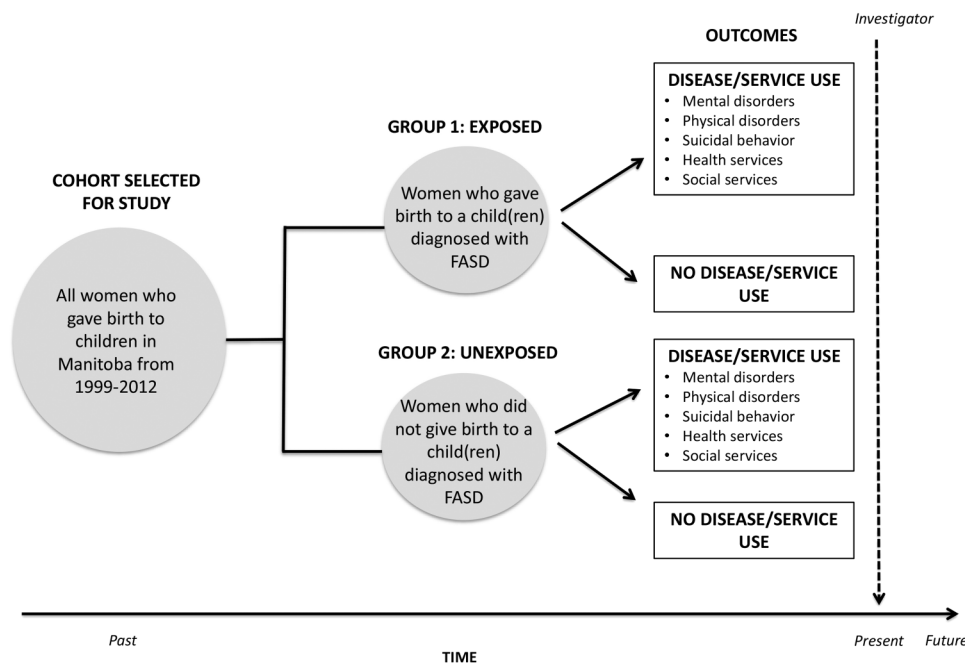
Research question 1

A *retrospective matched cohort study* design will be used to investigate differences in rates of psychiatric morbidity, suicide attempts and completion, physical health disorders and usage of health and social services (outcome

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variables) (see figure 1) between our exposed group (group 1) and our unexposed group (group 2) before and after the birth of the index child.

Research question 2

A *retrospective matched case–control* design will be used to investigate potential risk factors (exposure variables)

associated with giving birth to a child with FASD (outcome) (see figure 2). Our case group (group 3) will be compared to our comparison group (group 4) to investigate whether they had the following risk factors *before* the birth of the child and whether these factors were associated with giving birth to children with FASD: demographic and socioeconomic factors, family history,

Figure 1 A retrospective matched cohort study design to investigate differences in rates of psychiatric morbidity, suicide attempts and completion, physical health disorders and health and social services utilisation between the exposed unexposed group before and after the birth of the index child.
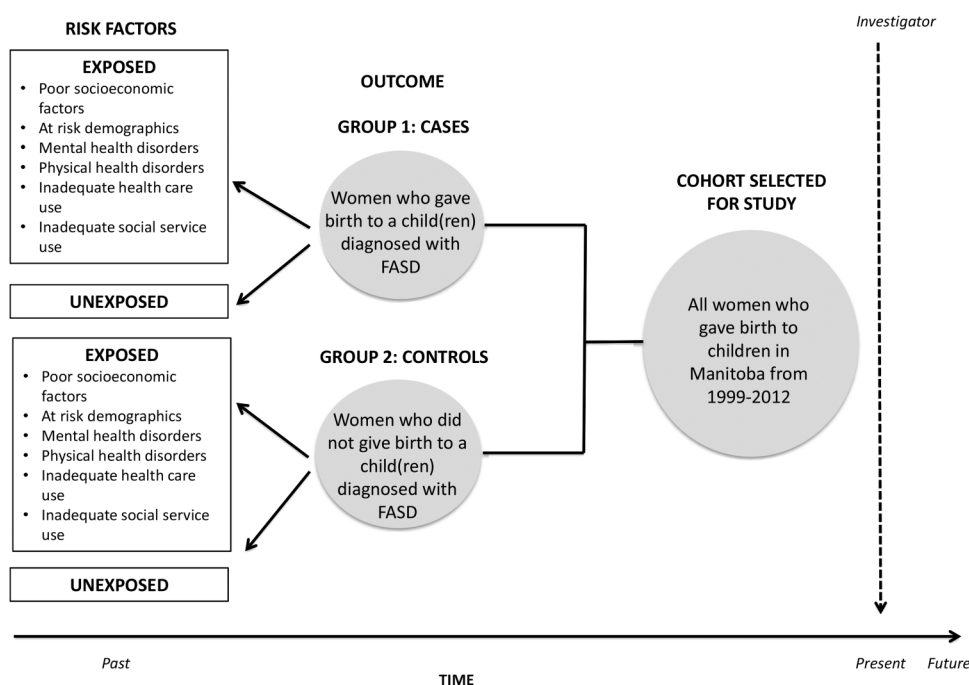
Figure 2 A retrospective matched case–control design to investigate potential risk factors associated with giving birth to a child with fetal alcohol spectrum disorder.

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mental disorder diagnoses, physical health diagnosis, use of healthcare and social services.

Analysis plan: research question 1

Outcomes

To investigate health outcomes and use of services among our exposed and unexposed groups, the following outcomes will be investigated:

A. Psychiatric morbidity: diagnosis of substance abuse disorder, personality disorder, mood and anxiety disorder, and schizophrenia 3 years prior to the birth of the index child. Prenatal psychological distress (8 months prior to the birth of the index child) and postnatal psychological distress (from birth to 12 months prior to the birth of the index child) (see table 2 for definitions)

B. Suicidal behaviour: suicide attempts (3 years before the birth of the index child, during pregnancy, during the postpartum period, until the end of the study period) and completion (from birth to the end of the study period) (table 3).

C. Physical health disorders: diabetes, hypertension, ischaemic heart disease, total respiratory morbidity (3 years prior to the birth of the index child) (see table 4 for definitions).

D. Use of healthcare service: average number of physician/ambulatory visits 1 year before the pregnancy with the index child, average number of physician/ambulatory visits during the pregnancy with the index child, average number of all hospitalisations 3 years before the birth of the child, average number of antenatal hospitalisations 3 years before the birth of the index child, late initiation of prenatal care, no prenatal care, low number of prenatal visits, inadequate prenatal care (see table 5)

E. Use of social services: receipt of healthy baby prenatal benefit (1 year prior to the birth of the child), participation in healthy baby support program (1 year prior to the birth of the child), participation in InSight Mentoring programme (1 year prior to the birth of the child), record of a Family First/Baby First Screen (after the birth of the index child) (see table 6).

Statistical analysis: Univariate statistics, including proportions and means, will be calculated for all outcome variables (ie, events). Adjusted relative rates for all outcomes will be calculated using generalised estimating equations with a Poisson distribution. A negative binomial distribution will be used if data are overdispersed. Both models are suitable for non-normally distributed data such as counts. All analyses will test for differences between study groups and will adjust for the following covariates: receipt of income assistance, SES (low, middle, high), age of mother at birth of child (18 or under, 19 to 24, 25 to 34, 35 and over).

To model the rates of events for our two groups, we will create a summary data set for the total number of events (eg, total number of mothers with mood and anxiety disorder) for unique strata and the total number of per-person years at risk for the strata. We will include the log of the total number of person-years as an offset in the model to produce an analysis of rates of events, rather than simple counts, and to generate estimates of adjusted RRs of events. This procedure will ensure that any variation in follow-up times for women in the study groups will be accounted for.

Analysis plan: research question 2

To investigate potential risk factors associated with giving birth to a child with FASD, the following exposure variables will be investigated 5 years prior to the birth of the index child for our case and comparison group:

A. Demographic and socioeconomic factors: maternal age at birth of index child, maternal age at first birth, history of teen pregnancy, region of residence, mean household income, SES, receipt of income assistance, high school completion, involvement with the justice system (see table 7 for definitions);

B. Family history: marital status, gravidity, parity, birth order of the index child (first, middle, last), involvement with CFS, type of FASD diagnosis of child (see table 8 for definitions);

C. Diagnosis of a mental disorder: substance abuse disorder, personality disorder, mood and anxiety disorder, schizophrenia, prenatal psychological distress, suicide attempts (table 2);

D. Diagnosis of a physical health disorder: diabetes, hypertension, ischaemic heart disease, total respiratory morbidity (table 4);

E. Quality of prenatal care: late initiation of prenatal care, no prenatal care, low number of prenatal visits, inadequate prenatal care (table 5).

Statistical analysis: research question 2: univariate statistics will be used to describe all potential risk factors for cases and comparison women. Bivariate associations between each independent variable and outcome (having a child with FASD) will be conducted as a preliminary investigation of the relationship between the outcome and risk factor. Associations between groups will be tested using t-tests for continuous variables and Pearson's χ^2 tests for categorical variables. Variables with a p value of ≤ 0.2 in the bivariate analysis will be included in a multivariate regression analysis using conditional logistic regression, which is appropriate for studies using a matched case–control design, and accounts for observations that are correlated. Goodness-of-fit tests will be run to test the fit of the model and diagnostics will be run to assess collinearity between independent variables.

DISCUSSION

The MBMomsFASD is the largest, most comprehensive, in-depth investigation into the characteristics, health and mental health, and use of services among women whose children have been diagnosed with FASD. This study offers numerous methodological advantages over

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Table 2 Definitions of mental disorders exposure/outcome variables

Variable	Time frame	Database	Operation definition/ICD codes
Diagnosis of a psychiatric disorder	3 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	A woman was considered to have a psychiatric disorder if she had one of the following (see specific definitions below): substance abuse disorder, personality disorder, mood and anxiety disorder, schizophrenia or prenatal psychological distress
Substance abuse disorder	3 years prior to the birth of the index child	Physician claims Hospital Abstracts Prescription claims	A woman was considered to have a substance use disorder if 5 years prior to the birth of the child she had: 1. One or more hospitalisations with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, or non-dependent abuse of drugs (ICD-9-CM codes 291, 292, 303, 304, 305, ICD-10-CM codes: F10-F19 and F55) OR 2. One or more physician visits with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, or non-dependent abuse of drugs using the same ICD-9-CM codes listed above
Personality disorder	3 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	A women was considered to have a personality disorders if in the 5 years prior to giving birth to the child she had the following: 1. One or more hospitalisations with a diagnosis of personality disorder (ICD-9-CM code 301 or ICD-10- CA codes F34.0, F60, F61, F62, F68.1, F68.8, or F69) OR 2. One or more physician visits with a diagnosis of personality disorder: (ICD-9-CM code 301)
Mood and anxiety disorder	3 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	A women was considered to have mood or anxiety disorder if in the 5 years prior to giving birth to the child she had the following: 1. One or more hospitalisations with a diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction: ICD-9-CM codes 296.1-296.8, 300.4, 309 or 311; ICD-10-CA codes F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, F93.0 or with a diagnosis for an anxiety state, phobic disorders or obsessive–compulsive disorders: ICD-9-CM codes 300.0, 300.2, 300.3, 300.7; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42, F45.2; OR 2. F48, F68.0, or F99 AND one or more prescriptions for an antidepressant or mood stabiliser, including medications with the ATC codes N05AN01, N05BA, N06A; OR 3. One or more physician visits with a diagnosis for depressive disorder or affective psychoses: ICD-9-CM codes 296, 311; OR 4. One or more physician visits with a diagnosis for anxiety disorders: ICD-9-CM code 300 AND one or more prescriptions for an antidepressant or mood stabiliser, including medications with the ATC codes N05AN01, N05BA, N06A; OR 5. Three or more physician visits with a diagnosis for anxiety disorders or adjustment reaction: ICD-9-CM code 300, 309
Schizophrenia	3 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	A women was considered to have schizophrenia if in the 5 years prior to giving birth to the child had the following: 1. One or more hospitalisations or physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295 or ICD-10-CA codes F20, F21, F23.2, F25; OR 2. One or more physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295.

Continued

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Table 2 Continued

Variable	Time frame	Database	Operation definition/ICD codes
Prenatal psychological distress	8 months prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	A woman was considered to have prenatal psychological distress if in the 8 months prior to giving birth she had: 1. One or more hospitalisations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD-9-CM codes 296.2–296.8, 300.4, 309, 311; ICD–10–CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8,F53.0, F93.0) OR 2. One or more physician visits with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD-9-CM codes 296, 309 or 311) OR 3. One or more hospitalisations with a diagnosis for anxiety disorders (ICD-9-CM code 300l ICD-10-CD codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99) OR 4. One or more prescriptions for an antidepressant or mood stabiliser (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A) OR 5. One or more physician visits with a diagnosis of anxiety disorders one or more physician visits with a diagnosis for anxiety disorders (ICD-9-CM code 300) and one or more prescriptions for an antidepressant or mood stabiliser (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A) OR 6. One or more hospitalisations with a diagnosis for anxiety states, phobic disorders, or obsessive–compulsive disorders (ICD-9-CM codes 300.0, 300.2, 300.3; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42) OR 7. Two or more physician visits with a diagnosis for anxiety disorders (ICD—CM code 300)
Postnatal psychological distress	12 months after the the birth of the index child	Physician claims Hospital abstracts Prescription claims	A woman was considered to have postnatal psychological distress if in the 12 months prior to giving birth she had: 1. One or more hospitalisations with a diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction (ICD-9-CM codes 296.2–296.8, 300.4, 309, 311; ICD-10-CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8,F53.0, F93.0) OR 2. One or more physician visits with a diagnosis for depressive disorder, affective psychoses, neurotic depression or adjustment reaction (ICD-9-CM codes 296, 309 or 311) OR 3. One or more hospitalisations with a diagnosis for anxiety disorders (ICD-9-CM code 300l ICD-10-CD codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, F99) OR 4. One or more prescriptions for an antidepressant or mood stabiliser (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A) OR 5. One or more physician visits with a diagnosis of anxiety disorders one or more physician visits with a diagnosis for anxiety disorders (ICD-9-CM code 300) and one or more prescriptions for an antidepressant or mood stabiliser (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, N06A) OR 6. One or more hospitalisations with a diagnosis for anxiety states, phobic disorders, or obsessive–compulsive disorders (ICD-9-CM codes 300.0, 300.2, 300.3; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42) OR 7. Two or more physician visits with a diagnosis for anxiety disorders (ICD—CM code 300)

Table 3 Definitions of suicide behaviour exposure/outcome variables

Variable	Time frame	Database	Operation definition/ICD codes
Suicide attempts	5 years prior to the birth of the index child During pregnancy During the postpartum period From 1 year after the birth of the child until the end of the study period	Physician claims Hospital abstracts	A women was considered to have attempted suicide if 5 years prior to the birth of the child she had: 1. One hospitalisation with a diagnosis for suicide and self-inflicted injury: ICD-9-CM codes E950-E959, ICD-10-CA codes X60-X84; OR 2. One hospitalisation with a diagnosis code for accidental poisoning: 3. ICD-9-CM codes 965, 967, 969, 977.9, 986, E850-E854, E858, E862, 4. E868; ICD-10-CA codes T39, T40,T42.3, T42.4, T42.7,T43, T50.9, 5. T58, X40-X42, X44, X46, X47, Y10-Y12, Y16, Y17, only if there is a 6. Physician visit with a diagnosis code for accidental poisoning and a 7. Psychiatric tariff code either during the hospital stay or within 30 days 8. Postdischarge. Psychiatric tariff codes are as follows: 9. From the psychiatric schedule: ▶ 8444 Psychotherapy—group of two to four patients ▶ 8446 Psychotherapy—group of five or more patients ▶ 8472 Child and Youth Management Conference ▶ 8475 Psychiatry—Patient Care Family Conference ▶ 8476 Psychiatric Social Interview ▶ 8503 Complete history and psychiatric examination—adult ▶ 8504 Complete history and psychiatric examination—child ▶ 8553 Psychiatry Consultation—adult ▶ 8554 Psychiatry Consultation—child ▶ 8581 Psychotherapy—individual ▶ 8584 Psychiatric care—individual ▶ 8588 Electroshock therapy ▶ 8596 Consultation—Unassigned patient—child From the general schedule: ▶ 8580 Psychotherapy—individual ▶ 8587 Electroshock therapy ▶ 8589 Psychotherapy—group
Suicide completion	From birth until the end of the study period	Vital Statistics Mortality Data	A women was considered to have completed suicide if the following ICD codes were used in the 'cause of death' field in the Vital Statistics Mortality Data (our definition including accidental poisonings): 1. Accidental poisoning: ICD-9 codes E850-E854, E858, E862, E868; 2. ICD-10 codes X40-X42, X46, X47 OR poisoning with undetermined intent: ICD-10 codes Y10-Y12, Y16, Y17 OR 3. Self-inflicted poisoning: ICD-9 codes E950-E952, ICD-10 codes X60-X69 OR 4. Self-inflicted injury by hanging, strangulation and suffocation: ICD-9 code E953, ICD-10 code X70 OR 5. Self-inflicted injury by drowning: ICD-9 code E954, ICD-10 code X71 OR 6. Self-inflicted injury by firearms and explosives: ICD-9 code E955, ICD-10 codes X72-X75 OR

Continued

Table 3 Continued

Variable	Time frame	Database	Operation definition/ICD codes
			7. Self-inflicted injury by smoke, fire, flames, steam, hot vapours and hot objects: ICD-9 codes E958.1, E958.2; ICD-10 codes X76, X77 OR
			8. Self-inflicted injury by cutting and piecing instruments: ICD-9 code E956; ICD-10 codes X78, X79 OR
			9. Self-inflicted injury by jumping from high places: ICD-9 code E957, ICD-10 code X80 OR
			10. Self-inflicted injury by jumping or lying before a moving object: ICD-9 code E958.0, ICD-10 code X81 OR
			11. Self-inflicted injury by crashing of motor vehicle: ICD-9 code E958.5, ICD-10-CA code X82 OR
			12. Self-inflicted injury by other and unspecified means: ICD-9 codes E958.3, E958.4, E958.6-E958.9; ICD-10 codes X83, X84 ORlate effects of self-inflicted injury: ICD-9 code E959

Table 4 Definitions of physical health disorders exposure/outcome variables

Variable	Time frame	Database	Operation definition/ICD codes
Hypertension	5 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	A woman was considered to have a history of hypertension if 5 years prior to the birth of the child she had: 10. At least one physician visit or one hospitalisation with an ICD-9-CM code of 401–405 (ICD-10-CA codes I10–I13, I15), OR 11. two or more prescriptions for hypertension drugs
Total respiratory morbidity	5 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	A woman was considered to have a history of total respiratory morbidity if 5 years prior to the birth of the child she had: One physician visit or hospitalisation in 1 year with: asthma, acute bronchitis, chronic bronchitis, bronchitis not specified as acute or chronic, emphysema or chronic airway obstruction (ICD-9-CM codes 466, 490, 491, 492, 493, 496; ICD-10 codes J20, J21, J40–J45).
Diabetes	5 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	A woman was considered to have a history of diabetes if 5 years prior to the birth of the child she had: 1. At least two physician visits or one hospitalisation with a diagnosis of diabetes (ICD-9-CM code 250; ICD-10-CA codes E10–E14), OR 2. One or more prescriptions for medications to treat diabetes
Ischaemic heart disease	5 years prior to the birth of the index child	Physician claims Hospital abstracts Prescription claims	A woman was considered to have a history of total respiratory morbidity if 5 years prior to the birth of the child she had: 1. At least two physician visits or one hospitalisation for IHD (ICD-9-CM codes 410–414, ICD-10 codes I20–I22, I24, I25), OR 2. At least one physician visit with a code listed above and two or more prescriptions for IHD medications

studies using primary data collection. First, the use of linked clinical and administrative data is the study's greatest strength. It is difficult to ascertain and follow large groups of women whose children have a clinical diagnosis of FASD using primary data collection, due to challenges of attrition and length of follow-up time needed to obtain longer term outcomes of mothers (eg, suicide). In our study we identify mothers through children who are diagnosed at the Manitoba FASD Centre, which is one of the first and only provincially centralised FASD diagnostic clinics in Canada and as a result, one of the largest. Through the use of linked

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Table 5 Definitions of health services exposure/outcome variables

Variable	Time frame	Database	Operation definition/ICD codes
Physician visits			
Ambulatory care visits	1 year prior to birth of index child	Physician claims	Ambulatory visits are defined as all contacts with physicians (family practitioner and specialists) that do not include hospitalisations. These visits include office visits, walk-in clinics, home visits, personal or home/nursing home visits and outpatient department's visits. They do not include emergency department visits. The type of visit is determined by a tariff code in the physician claims data
Hospital visits			
Hospitalisations	3 years before the birth of the child	Hospital Abstracts	A woman was considered to have a hospitalisation if a billing claim was submitted to the provincial government for services a hospital had provided in order to receive reimbursement for care. These services include physician visits, laboratory/pathology, X-ray/radiology, surgical services, anaesthesia, postoperative care
Antenatal hospitalisations	During the pregnancy of the index child	Hospital Abstracts	An antenatal hospitalisation is a hospitalisation in which a woman was pregnant but did not deliver during the hospitalisation of the index child. Reasons include threatened preterm labour, haemorrhage, diabetes, hypertensive disorders, abdominal pain etc. A woman was considered to have an antenatal hospitalisation if there was a record of hospitalisation not resulting in delivery in the hospital abstracts database
Prenatal care			
Prenatal care visit	During the pregnancy of the index child	Physician claims	A prenatal care visit was defined as the following physician tariff codes from the physician claims data: 8400 (complete prenatal assessment), 8401 (prenatal visits subsequent), 8501 (office visits, regional history and examination), 8507, 8509 (office visits), 8529 (regional intermediate visit or well baby care), 8540 (office visits complete history and physician examination, new patient), 8550 (consultation)
Late initiation of prenatal care	During the pregnancy of the index child	Physician claims	A woman was considered as having late initiation of prenatal care if she began care after the first trimester of pregnancy (date of conception—91 days). This was determined by assessing when the first prenatal care tariff date was
No care	During the pregnancy of the index child	Physician claims	A woman was considered as having no prenatal care if she had no visits with a prenatal care tariff during her pregnancy
Care initialised in first trimester	During the pregnancy of the index child	Physician claims	A woman was considered as having care initialised in the first trimester if her first prenatal visit was between the date of conception to 91 days
Care initialised in second trimester	During the pregnancy of the index child	Physician claims	A woman was considered as having care initialised in the second trimester if her first prenatal visit was between 92 to 189 days
Care initialised in third trimester	During the pregnancy of the index child	Physician claims	A woman was considered as having care initialised in the third trimester if her first prenatal visit was between 189 days to the birth of the child
Low number of prenatal visits	During the pregnancy of the index child	Physician claims	A woman was considered to have a low number of prenatal visits if she had less than five prenatal care visits as determined by counting the number of prenatal care tariffs she had during the pregnancy of the index child.
Quality of prenatal care by the R-GINDEX	During the pregnancy of the index child	Physician claims Hospital Abstracts	The adequacy of prenatal care was determined using the R-GINDEX (Revised-Graduated Prenatal Care Utilisation Index). The following three variables were calculated using hospital and physician claims data: (1) gestational age of the newborn, (2) the trimester that prenatal care began; (3) the total number of prenatal visits during the pregnancy.

Continued

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Table 5   Continued

Variable	Time frame	Database	Operation definition/ICD codes
			The G-INDEX classifies prenatal care into the following categories: 1. Inadequate prenatal care 2. Intermediate prenatal care 3. Adequate prenatal care 4. Intensive prenatal care 5. No care 6. Missing information

Table 6   Definitions of social services exposure/outcome variables

Variable	Time frame	Database	Operation definition/ICD codes
Healthy baby program services			
Receipt of healthy baby prenatal benefit	1 year prior to the birth of the child	Healthy Baby Community Support Programme data set	The Healthy Baby Prenatal Benefit is income supplement for pregnant women who live in Manitoba and have a net family income of less than $32,000. A woman was considered to have received the prenatal benefit if at any time during the eligibility period of the benefit (14 weeks, until delivery) she received the benefit as coded in the Healthy Baby Prenatal Benefit Data set
Participation in healthy baby support programme	1 year prior to the birth of the child	Healthy Baby Community Support Programme data set	The Healthy Baby Programme is a support programme delivered by the province of Manitoba to offer social support and learning opportunities that encourage prenatal care and promote healthy infant development. A woman was considered to have participated in this programme if she had a file in the Healthy Baby Community Support Programme data set
InSight Mentoring Program Participation	1 year prior to the birth of the child	Healthy Child Manitoba Data	The InSight programme is an outreach programme where mentors provide intensive support to women who are pregnant or have recently had a baby and use substances. A woman was considered to have participated in this programme if she had a file in the Insight Program Database
Babies First/Families First Screen	After the birth of the index child	Healthy Child Manitoba	Public health nurses in Manitoba attempt to assess all families with newborns (using a validated screen) within a week of discharge from the hospitals. Families are asked about support and challenges, including parents' alcohol and drug use, mental health, education etc. Three or more risk factors indicate that a family may require additional supports such as intensive home visiting, financial supports, support programs etc. Before 2003, this programme was known as the Babies First home visiting programme
Record of a Families First screen for the index child	After the birth of the index child	Healthy Child Manitoba Data	A woman was identified as having a Families Frist Screen if she had a record of a screen after the birth of the index child in the Families First Data set
Record of a Baby First Screen for the index child	After the birth of the index child	Healthy Child Manitoba Data	A woman was identified as having a Babies Frist Screen if she had a record of a screen after the birth of the index child in the Families First Data set

Table 7 Definitions of demographic and socioeconomic exposure/outcome variables

Variable	Time frame	Database	Operation definition/ICD codes
Mother's age at birth of index child	Year of birth of index child	Registry	A woman's age at birth of index child was determined by subtracting the date of conception of the index child by the birth date of the mother
History of a teen birth or pregnancy	15 years prior to the birth of the index child	Hospital Abstracts	A woman was identified has having a history of teen pregnancy or birth if they had the following diagnostic codes from the ages 15–19: ▶ Live birth: ICD-9-CM code V27, ICD-10-CA code Z37 ▶ Missed abortion: ICD-9-CM code 632, ICD-10-CA code O02.1 ▶ Ectopic pregnancy: ICD-9-CM code 633, ICD-10-CA code O00 ▶ Abortion: ICD-9-CM codes 634-637 ICD-10-CA codes O03-O07 ▶ Intrauterine death: ICD-9-CM code 656.4, ICD-10-CA code O36.4 Or, a hospitalisation with one of the following procedures: ▶ Surgical termination of pregnancy: ICD-9-CM codes 69.01, 69.51, 74.91; CCI codes 5.CA.89, 5.CA.90 ▶ Surgical removal of extrauterine (ectopic) pregnancy: ICD-9-CM codes 66.62, 74.3; CCI code 5.CA.93 ▶ Pharmacological termination of pregnancy: ICD-9-CM code 75.0; CCI code 5.CA.88 ▶ Interventions during labour and delivery, CCI codes 5.MD.5, 5.MD.60
Region of residence—urban/rural	Year of birth of index child	Registry	Region of residence is categorised as being rural or urban as determined by the postal code registered with Manitoba Health. Those who are registered to Winnipeg (population=xxx) or Brandon (population=yyy) are categorised as urban, while the rest of Manitoba is considered to be rural
Region of residence—RHA	Year of birth of index child	Registry	In Manitoba, an RHA is a regional governance structure set up by the provincial government to be responsible for the delivery and administration of health services in a specified geographic area. From July 2002 to 2 June 2012 Manitoba consisted for the following RHAs: Winnipeg, Brandon, South Eastman, Assiniboine, Central, Parkland, North Eastman, Interlake, Burntwood, NOR-MAN, and Churchill. On 1 June 2012 these existing 11 RHAs were amalgamated into five larger regions. The new RHAs are listed below, with the old RHAs listed in brackets: 1. Winnipeg (Winnipeg, Churchill); 2. Interlake-Eastern (Interake, North Eastman); 3. Prairie Mountain (Assiniboine, Brandon, Parkland); 4. Southern (Central, South Eastman); 5. Northern (Burntwood, NOR-MAN)
Income Quintiles	Five years prior to the birth of the index child	Registry: Census Data	Income quintile is an aggregate, area-level measure of the average household income of residents in small areas, ranking them from poorest to wealthiest, and then grouping the population into five equal categories (1 being the poorest and 5 being the wealthiest). Each quintile contains ~20%

Continued

Table 7 Continued

Variable	Time frame	Database	Operation definition/ICD codes
			of the population. The income quintile measure is derived from the 2006 Statistics Canada Census data by aggregating household income to the dissemination area and then ranking neighbourhoods by income. Income quintiles are produced separately for urban and rural populations and are used as a proxy measure of individual SES. If the postal code is missing for a study participant, income quintiles cannot be calculated
Receipt of income assistance	5 years prior to the birth of the index child	Registry: Social Assistance	A woman was identified as having received income assistance if she was coded as having received income assistance from the social assistance management information database anytime during the period of 5 years before the birth of the child
SES	Year of birth of index child	Registry: Census Data	SES was defined according to income quintiles and income assistance data. A woman was considered to have: ▶ Low SES if she was categorised as being in income quintile 1 or had a receipt of income assistance ▶ Middle SES if she was categorised as being in income quintile 2 or 3 ▶ High SES if she was categorised as being in income quintile 4 or 5
Maternal education level—high school completion		Education: enrolment, marks and assessment data	A woman was considered to have completed high school if she graduated within 6 years of starting grade nine. Criteria to assess if she graduated includes: 1. A Graduation Flag—a dichotomous variable derived from the 'Year End Status' variable on the student's high school marks data. If this variable indicated that the student graduated, then the student would be identified as a 4-year, 5-year or 6-year high school graduate—depending on which year (4th, 5th or 6th) of being in high school did this 'Year End Status' first appear on the student's record. If the yearend status variable is missing, two other measures are used to determine high school graduation/completion: 2. If the student earned 28–30 or more high school credits 3. If the student earned 6 or more grade 12 credits regardless of how many credits in the total the student had earned
Involvement with the Justice System	During the entire study period	Manitoba Justice	A woman was considered to have involvement with the justices system if she had a record of an incident in the Prosecutions Information Management System. Involvement type was classified by the following categories: (1) witness; (2) victim; (3) accused

RHA, Regional Health Authority; SES, socioeconomic status.

clinical and administrative data, the MCHP Repository allows the generation of a large population-based group of all women whose children were diagnosed with FASD in Manitoba since 1999 (preliminary n over 700 cases), which is the largest sample size in this field to date, enhancing the generalisability of our study results.

Second, the Manitoba FASD Centre offers a valid and reliable clinical diagnosis of FASD, and as a result we can be certain that women in this sample have given

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Table 8 Definitions of family history exposure/outcome variables

Variable	Time frame	Database	Operation definition/ICD codes
Marital status	Time of birth of index child	Registry	A woman was considered to be married if her marital status variable in the Registry was indicated as 'married' or if she could be linked to a spouse through family linkages developed at MCHP
Gravidity	Entire study period	Hospital abstracts	Gravidity is defined as the number of pregnancies, regardless of the duration, including the present pregnancy. Multiple fetuses (twins, triplets) count as one pregnancy. Gravidity was calculated using the hospital abstract data and was categorised as: 0–3 pregnancies, 4–9, 10–14
Parity	Entire study period	Hospital abstracts	Parity is defined as the number of births a mother has had after 20 weeks gestation. A multiple birth is counted as one and stillbirths are included. Parity was calculated using the hospital abstracts data and was categorised as: 0–3, 4–9, 10–14.
Birth order of the child	Time of birth of the index child	Registry	Birth order of the child was defined by the variable 'Birth Order' in the Registry Centre data and was categorised as: first, middle or last
Any CFS involvement	5 years prior to the birth of the index child	Child and Family Services Information System	A woman was defined as having any contact with CFS 5 years prior to the birth of the index child if a record of any contact with CFS existed in the Child and Family Services Information System, this includes: (1) ever in care—if a child was in care; (2) ever received CFS services—if there were no children in care but the family received protection or support services from CFS
Children in care	5 years prior to the birth of the index child	Child and Family Services Information System	A woman was defined as having children in care if she had a child who had been removed from the home due to a situation where authorities deemed their family unable or unfit to look after them properly. In some cases, children are voluntarily placed into care by their parents, or they come into care for a variety of reasons, including abuse and neglect, illness, death of a parent, addiction issues or conflict in the family or disabilities
Children receiving CFS	5 years prior to the birth of the index child	Child and Family Services Information System	A woman was defined as having received protection or support services from CFS 5 years prior to the birth of the index child. Will investigate both involvement of children of the mother with CFS, as well as her own involvement as a minor with CFS
FASD diagnosis of index child	Entire study period	FASD Centre data	The type of FASD diagnosis of the index child was determined by the diagnosis variable in the FASD Centre data and was categorised as the following: (1) alcohol-ARND, (2) FAS or (3) pFAS
Other FASD affected children	At time of birth of index child	FASD Centre	A mother was identified as having other children affected by FASD by a variable in the FASD Centre data set 'other affected children'

ARND, alcohol-related neurodevelopmental disorder; CFS, Manitoba Child and Family services; FAS, fetal alcohol spectrum; FASD, fetal alcohol spectrum disorder; MCHP, Manitoba Centre for Healthy Policy and pFAS, partial FAS.

birth to children with FASD. Previous studies investigating characteristics of women who have consumed alcohol during pregnancy cannot confirm a clinically corroborated diagnosis of FASD in children. Therefore, these women may have different characteristics, use of healthcare and social services from those women whose children developed FASD.

Third, through the Repository, we have access to information on the whole population of Manitoba. These data facilitate the creation of clinically relevant comparison groups and accurate comparative analysis. Using the multiple available databases, comparison groups can be created using a host of matched characteristics, including age, sex, SES, geographic location and disease specific cohorts.[42] These comparative analyses are difficult to perform using primary data recruitment methods as controls and cases can be difficult to identify, can take years to recruit and are subject to attrition.[48] Moreover,

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through the use of hospital, physician, educational and social administrative data to develop exclusion criteria, the likelihood that women in the comparison group had children with undiagnosed FASD can be decreased. This is potentially a major limitation in previous studies as FASD is an extremely underdiagnosed condition.

Fourth, through leveraging the comprehensive, longitudinal databases available at MCHP, we can investigate novel health outcomes not yet studied. Specifically we can document the mental health diagnoses of women who give birth to children with FASD and determine rates of prenatal and postnatal anxiety and depression, as well as suicide attempts and completions. Women with alcohol substance use issues are at higher risk for prenatal and postpartum depression,[52–54] investigating these outcomes specifically in mothers who give birth to children with FASD can provide evidence to policymakers responsible for optimising FASD prevention and support resources. Furthermore, maternal suicide is an increasing public health issue[55] and investigating whether women who give birth to children with FASD are at increased risk for suicide is also important to optimise support resources and that these women do not slip through the cracks. Furthermore, due to the longitudinal nature of the data, an analysis of system usage of women before, during and after pregnancy can be conducted and compared to women in the general population whose children have not been diagnosed with FASD. This analysis is important to identify points for prevention, early intervention and treatment and effective resource allocation, as well as supporting the health and well-being of women who give birth to children with FASD. The Repository is ideal for these analyses, as the data accurately calculate the usage of healthcare services and have been validated for research purposes.[42–44 47 48 56 57] MCHP data have been used to calculate the usage of the healthcare services among related populations in the past; for example, Brownell et al[58] used MCHP data to document the usage of health and social systems among children with FASD.

Finally, administrative data eliminate re-call bias and offer accurate information that can be isolated in critical periods of time throughout a study participant's lifespan. It is difficult to conduct studies on mothers with children with FASD due to stigmatisation and attrition of study participants. Furthermore, studies using primary data collection may be conducted after a significant time period has passed because of these women's pregnancies. This makes the recall of specific diagnoses, events and use of health services during the pregnancy difficult and increases the likelihood of inaccuracy. The use of our data is an important opportunity to ascertain accurate, unbiased information on these mothers and their use of health and social services and comorbid diagnoses before and during pregnancy and the postpartum period.

While the use of routinely collected population data has numerous advantages, there are a few limitations that warrant discussion. First, the use of a clinically referred FASD sample may limit the generalisability of findings, as we may be missing women and children who are not referred to this clinic. Owing to the complex nature of FASD, the multiple comorbidities associated with the disorder, underreporting, coding patterns of physicians and the complex multidisciplinary teams required to diagnose FASD, there is no algorithm that has been developed to identify children with FASD in the MCHP Repository using other data sources. Therefore, record linkage with the Manitoba FASD Centre is necessary to confirm a clinical diagnosis of FASD in children in Manitoba. However, the referrals to the clinic come from a wide variety of sources and from all regions in the province, strengthening the representativeness across populations. Second, while we have taken great care in excluding all mothers with possible prenatal alcohol exposure and children with a diagnosis of FASD, we cannot be certain that there are no women in our comparison group who do not have un-reported prenatal alcohol use or children with undiagnosed FASD. However, this would serve to weaken rather than strengthen any of our findings. Furthermore, as in all studies using administrative databases, this study is reliant on the accuracy of data submitted by the organisations that deliver services, and may have variations in data collection methods and compliance rates in the recording of information that may result in data errors.[42] However, as previously stated, MCHP data have been extensively validated for conducting this type of research. Furthermore, outcome data are dependent on the individual making contact with the healthcare system and are, therefore, a report of treatment prevalence; thus, this study would exclude women with undiagnosed physical health or mental health disorders. Furthermore, the Repository does not capture information on interpersonal relationships, violence and abuse, psychological trauma or patient insight, which is important for the understanding of underlying causes of the drinking during pregnancy and would provide context to results of larger quantitative studies. However, data collection methods are often resource and time intensive and studies with patient insight often have small sample sizes, limiting generalisability. Although these types of data are not readily available in the Repository, the results of this study have the potential to lay the groundwork for the development of future work in this area. Finally, due to the exploratory nature of this study, there are multiple comparisons being performed and we acknowledge the potential for an inflated type 1 error, which is a limitation of this work. Future research should be conducted that corroborates the results from this proposed study.

DISSEMINATION
This study will be conducted at MCHP, which is a secure computing environment. Strict security measures are in place to protect the data files and to restrict access. The

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data in the Repository contain no identifiable personal information and are used only for research purposes. Data will be presented in a summary form, ensuring that identification of individuals is not possible.

To ensure the translation of the project's findings to policymakers, government stakeholders and community organisations, a study advisory group comprising physicians specialising in FASD, members of Healthy Child Manitoba (a provincial governmental organisation that works with the community to improve the well-being of Manitoba's children and youth) and FASD researchers has been established. During the final stages of the project, we will hold a forum to discuss policy implications arising from the project. Outputs from the project will include peer-reviewed papers, summary reports in formats intended for policy and community organisations and presentations at academic conferences and government meetings.

CONCLUSION AND POLICY IMPLICATIONS

The databases brought together for this study and the results produced will generate a significant amount of longitudinal outcome data and contribute to our understanding of the life circumstances of mothers who give birth to children with FASD. The study results will provide an informed picture of the determinants of health that place women at increased risk of alcohol consumption during pregnancy, and giving birth to children with FASD. Moreover, the study results will offer insight into how women whose children have been diagnosed with FASD navigate health and social service systems during the perinatal and postnatal periods. These results will add to the evidence base and facilitate FASD prevention efforts through identifying: (1) high-risk women who should be targeted for prevention and intervention, (2) areas in health and social services that can be targeted for FASD prevention and support programmes to enhance service delivery to this population. Research providing insight into the factors that place women at risk for having children with FASD is vital for effective targeting and developing of policy resources that can help women cope with the influences and stresses in their lives in order to decrease prenatal alcohol consumption and ultimately prevent FASD.

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The Psychiatric Morbidity of Women Who Give Birth to Children with Fetal Alcohol Spectrum Disorder (FASD): Results of the Manitoba Mothers and FASD Study

La morbidité psychiatrique des femmes qui accouchent d'enfants souffrant d'un trouble du spectre de l'alcoolisation fœtale (TSAF): résultats de l'étude sur les mères manitobaines et le TSAF

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Abstract

Objective: To investigate differences in physician-diagnosed psychiatric disorders between women who gave birth to children with a fetal alcohol spectrum disorder (FASD) diagnosis (study group) compared to women who gave birth to children without FASD (comparison group).

Methods: We linked population-level health and social services data to clinical data on FASD diagnoses to identify study group ($n = 702$) and comparison group ($n = 2097$) women matched 1:3 on date of birth of index child, region of residence, and socioeconomic status. Regression modeling produced relative rates (RRs) for outcomes.

Results: Mothers who gave birth to children with FASD had higher adjusted rates of substance use disorder (RR, 12.65; 95% confidence interval [CI], 8.99-17.80), personality disorder (RR, 12.93; 95% CI, 4.88-34.22), and mood and anxiety disorders (RR, 1.75; 95% CI, 1.49-2.07) before the pregnancy of the child. These mothers also had higher adjusted rates of maternal psychological distress during pregnancy (RR, 5.35; 95% CI, 4.58-6.35) and higher rates of postpartum psychological distress (RR, 1.71; 95% CI, 1.53-1.90). These women also had higher adjusted rates for antidepressant prescriptions before, during, and after the pregnancy.

Conclusions: A significant psychiatric burden exists for women giving birth to children with FASD. Clinicians should recognise the high rates of psychiatric concerns facing mothers who give birth to children with FASD and should offer treatment and support to these women to improve their health and well-being and prevent further alcohol-exposed pregnancies.

Résumé

Objectif : Rechercher les différences des troubles psychiatriques diagnostiqués par un médecin entre les femmes qui ont accouché d'enfants ayant un diagnostic de TSAF (groupe d'étude) et les femmes qui ont accouché d'enfants sans TSAF (groupe témoin).

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Méthodes : Nous avons lié les données de la santé et des services sociaux dans la population aux données cliniques sur les diagnostics de TSAF afin d'identifier les femmes du groupe d'étude (n = 702) et du groupe témoin (n = 2097) appariées 1:3 selon la date de naissance de l'enfant de référence, la région de résidence et le statut socio-économique. Le modèle de régression a produit des taux relatifs (TR) pour les résultats.

Résultats : Les femmes qui ont accouché d'enfants ayant un TSAF avaient des taux ajustés plus élevés de trouble lié à l'utilisation d'une substance (TR 12,65; IC à 95% 8,99 à 17,80), de trouble de la personnalité (TR 12,93; IC à 95% 4,88 à 34,22), et de troubles de l'humeur et anxieux (TR 1,75; IC à 95% 1,49 à 2,07) avant d'être enceintes de l'enfant. Ces mères avaient aussi des taux ajustés plus élevés de détresse maternelle psychologique durant la grossesse (TR 5,35; IC à 95% 4,58 à 6,35) et des taux plus élevés de détresse psychologique du post-partum (TR 1,71; IC à 95% 1,53 à 1,90). Ces femmes avaient aussi des taux ajustés plus élevés d'ordonnances d'antidépresseurs avant, pendant et après la grossesse.

Conclusions : Un fardeau psychiatrique significatif existe pour les femmes qui accouchent d'enfants ayant un TSAF. Les cliniciens devraient reconnaître les taux élevés des problèmes psychiatriques auxquels font face les mères qui accouchent d'enfants ayant un TSAF et offrir traitement et soutien à ces femmes pour améliorer leur santé et leur bien-être, et prévenir d'autres grossesses exposées à l'alcool.

In Canada, over 10% of women report alcohol consumption during pregnancy,[1] and in Manitoba, approximately 14% of women report prenatal alcohol use.[2] These statistics indicate alcohol use during pregnancy is a substantial provincial and national public health concern. Prenatal alcohol use places children at risk for fetal alcohol spectrum disorder (FASD), a diagnostic term comprising a range of effects associated with prenatal alcohol exposure.[3]

FASD has been recognised as the leading cause of intellectual disability in North America.[4] Patients with FASD experience a myriad of symptoms, including sentinel facial features (smaller palpebral fissure, philtrum smoothness, and upper lip thinness) and neurodevelopmental abnormalities (motor skills, impaired cognition, language difficulties, academic challenges, memory impairment, and attention difficulties, including impulse control and hyperactivity) as well as communication, behavioural, emotional, and social difficulties.[3-6]

Over the past decade, international FASD prevalence estimates have ranged from 2% to 5%[7] in the general population and up to 23.3% in high-risk populations.[8-17] Among the general population of Canada, the pooled prevalence of fetal alcohol syndrome (FAS) was estimated to be approximately 1 per 1000 for FAS and 5 per 1000 for FASD.[18] The prevalence of FAS and FASD was estimated to be 38 and 16 times higher for First Nations populations, respectively.[18]

Research has also demonstrated that the financial burden of FASD is significant. Popova et al.[19] used data from the Canadian Institute for Health Information and calculated direct health care costs (acute care, psychiatric care, day surgery, emergency department use) from patients with FASD in Canada at approximately $6.7 million. Easton et al.[20] investigated the cost of lost productivity due to FASD-attributable morbidity and reported losses ranging from $418 million to $1.08 billion annually. This demonstrates the immense toll this disability has on patients, families, and the health care system and highlights the need for prevention programs.

A crucial step in developing effective FASD prevention strategies is the early identification of maternal and societal risk factors that are associated with giving birth to children with FASD.

It is important to acknowledge that women who drink during pregnancy are not doing so to intentionally cause harm upon their children but because of complex social, health, and economic factors. These factors include histories of violence, sexual abuse, poverty, low socioeconomic status, social isolation, and living with partners with substance abuse issues.[21-25] The use of alcohol during pregnancy cannot be separated from these issues and from other potentially harmful behaviours such as poor health practices, poor nutrition, and the use of other harmful substances.[21-25]

It is also important to note that historically, women of disadvantaged backgrounds were associated with a high risk of giving birth to children with FASD, but there is an increasing body of literature that is showing women of diverse backgrounds consume alcohol during pregnancy,[26] including women who are older, have high incomes and education, have stressful jobs, are in abusive relationships, have partners who drink heavily, or are coping with anxiety and depression.[26]

The complex, interconnected factors that place women at risk for alcohol consumption during pregnancy also place

women at higher risk for the development of psychiatric disorders.[27-31] The comorbidity of psychiatric disorders and alcohol use and dependence has been widely reported in the literature.[29,30,32-35] Studies have also documented that almost two-thirds of women with alcohol use issues may have a concurrent psychiatric diagnosis, including anxiety and panic disorders, posttraumatic stress disorder, depression, eating disorders, and more severe psychiatric illness such as bipolar disorder and schizophrenia.[36,37]

Furthermore, the increased frequency of alcohol use of these women also places them at high risk for psychiatric disorders,[35] as alcohol can affect the central nervous system and have detrimental effects on a person's family and interpersonal relationships, economic and employment circumstances, and possible involvement with the justice system.[28]

There is currently a dearth of research that investigates the psychiatric morbidity of women who give birth to children with FASD. This is the first population-based study that uses administrative data to investigate the rates of psychiatric disorders of women who give birth to children with FASD compared to women with no reported prenatal alcohol exposure. The occurrence of psychiatric disorders in women may increase the risk of developing alcohol use and dependence, as alcohol can be an agent for self-medication of symptoms associated with psychiatric disorders, including depressive and anxious symptoms, hopelessness, paranoia, impulsivity, fear, and anger.[27] Investigating the psychiatric health of these women before, during, and after pregnancy can provide insight into why women may drink during pregnancy, as well as identify critical time periods for targeted interventions to prevent subsequent alcohol-exposed pregnancies. This will enable clinicians and policy makers to develop focused prevention strategies that promote the psychiatric well-being of women of childbearing age at risk for drinking during pregnancy.

The objectives of this study were to compare rates of physician-diagnosed psychiatric disorders and antidepressant prescriptions during critical time periods in the lives of women who give birth to children with FASD, specifically:

1. Compare rates of physician-diagnosed psychiatric disorders among women whose children have FASD relative to women whose children do not have FASD 3 years before the pregnancy of the index child
2. Compare rates of physician-diagnosed prenatal psychological distress (mood and/or anxiety disorder 8 months before the birth of the index child) and postpartum psychological distress (mood and/or anxiety disorder 1 year after the birth of the index child) among women whose children have FASD relative to women whose children do not have FASD
3. Compare rates of antidepressant prescriptions among women whose children have FASD relative to women whose children do not have FASD 3 years before the pregnancy of the index child, during pregnancy, and 1 year after birth

Methods

This study used the Manitoba Mothers and FASD Study (MBMomsFASD) cohort, which is a retrospective cohort of mothers whose children were diagnosed with FASD in Manitoba and was generated to investigate risk factors, psychiatric and physical health outcomes, and health and service utilisation of these women. The details of this project's additional investigations are available elsewhere.[38] This article presents the psychiatric health results.

Data Sources

This study used de-identified administrative health, social, and education data from the Population Research Data Repository housed at the Manitoba Centre for Health Policy (MCHP) and clinical assessment data from the Manitoba FASD Centre, which is the only referral/diagnostic centre for FASD in the province. See Table 1 for a description of all databases used in this study.

Maternal diagnoses of psychiatric disorders were obtained from the hospital discharge abstracts, medical/physician reimbursement claims, and prescription claims data. Diagnostic codes follow the Canadian Coding Standards for the International Statistical Classification of Diseases and Related Health Problems (ICD), Ninth Revision (ICD-9-CA) and Tenth Revision (ICD-10-CA). Data are de-identified and all files are linkable at the person level through the use of an encrypted personal health number. The data in the repository have been widely used for health research, and the reliability and validity of the databases have been well established.[39-46] It is important to note that because this study uses administrative physician, hospital, and drug claims data, the rates of psychiatric disorders presented do not accurately represent the prevalence of psychiatric disorders in this population but rates of physician health service use for psychiatric disorders. We may miss individuals who meet standard diagnostic criteria for a psychiatric disorder but did not receive a relevant diagnostic code or those individuals who have not sought care from a physician.

Study population

Group 1 (study group): mothers whose children received a clinical diagnosis of FASD. Clinical data from the Manitoba FASD Centre were used to ascertain all children and youth (birth to 21 years of age) in Manitoba who had been diagnosed with FASD between 1999 and 2012. This database was linked to administrative data from the MCHP repository to identify these children's birth mothers. Only mothers who could be linked to their children, who had postal code information, and who were Manitoba residents registered to receive health care in the province and covered from the birth of their child until March 2013 were included.

Group 2 (comparison group): mothers whose children did not received a clinical diagnosis of FASD. Women whose children did not receive an FASD diagnosis from the Manitoba FASD

Table 1. Description of Data Sets Used for Analysis.

Name of Data Set	Description of Data Set	Years of Data Used	**Information Retrieved**
Population Registry	A registry maintained by Manitoba Health of all Manitobans eligible to receive health services since 1970 and includes demographic information and 6-digit residential postal code.	1970/1971 to June 2013	Demographic information: region of residence
Canada Census information	Social data based on the Statistics Canada Population Census. These data were used to determine area-level income, with Manitoba population divided into income quintiles according to average-level household income, composed of 5 possible income groupings, with Q1 being the lowest and Q5 being the highest income quintile.	1996, 2001, 2006, 2013	Socioeconomic status information
Employment and Income Assistance data	Data maintained by Department of Families that provide information on Manitoba residences who receive provincial employment and income assistance.	1995/1996 to 2012/2013	Receipt of income assistance
Babies First/Families First Screening Program data	Newborn risk screen data collected as part of a home visiting program conducted by Healthy Child Manitoba. The screen is filled out by public health nurses on all families with newborns in Manitoba and captures data on biological, social, and demographic risk factors and alcohol use during pregnancy.	2003 to 2013 = Families First 2000 to 2002 = Baby First	Alcohol and drug use during pregnancy Social isolation
Insight Program data	Includes data from an outreach program where mentors provide intensive support to women who are pregnant or have recently had a baby and use substances. This data set includes information on women who have prenatal alcohol use.	1999 to 2012/2013	Alcohol and substance use during pregnancy
Hospital abstracts	Health data maintained by Manitoba Health consisting of all hospitalisations in Manitoba, including up to 16 ICD-9-CM diagnostic codes for discharges before April 1, 2004, and up to 25 ICD-10-CM diagnostic codes for discharges on or after April 1, 2004.	1984 to 2012/2013	Physical and mental health diagnoses Antenatal hospitalisations Suicide attempts
Medical/physician reimbursement claims	Health data maintained by Manitoba Health consisting of all ambulatory physician visits in Manitoba and include a single ICD-9 diagnostic code associated with each visit, coded to the third digit.	1984 to 2012/2013	Physical and mental health diagnoses Physician visits Prenatal care
Prescription claims data: Drug Programs Information Network	Data maintained by Manitoba Health containing all prescription drug claims from the Drug Programs Information Network (DPIN, an electronic, online, point-of-sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba). Contains information on all prescription drugs dispensed in Manitoba.	1995/1996 to 2012/13	Physical and mental health conditions
Manitoba FASD Centre data	Includes clinical assessments and diagnoses received under the FASD umbrella for all children referred to the Manitoba FASD Centre	1999 to 2012/2013	FASD diagnosis Children diagnosed with FASD
Vital Statistics data	A longitudinal population-based registry maintained by Manitoba's Vital Statistics Agency that includes all Manitobans who have died since January 1970 to present and the cause of death.	1970 to 2012/2013	Cause of premature death Suicide completion
Education data: Enrolment, Marks and Assessments	Education data maintained by the Department of Education and Training that provides information on enrolment, marks, and high school completion, as well as special funding. Special education funding is provided to children with severe to profound disabilities.	1995/1996 to 2012/2013	High school completion, level of special education funding
Child and Family Services Information System (CFSIS)	A data management system that supports case tracking and reporting of services provided to children and families as they pass through the Manitoba Child and Family Services (CFS) System. This database includes information on children in care as well as information of families receiving protective and support services.	1992/1993 to 2012/2013	Involvement with child and family services

FASD, fetal alcohol spectrum disorder; ICD-9-CM, International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, Clinical Modification; ICD-10-CM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification.

Centre, with no known record of prenatal alcohol use, and whose children had no evidence of FASD from the repository were matched to the study group of women on date of month of birth of the index child, socioeconomic status, and region of residence. Matching was done at a ratio of 3 women in our comparison group for each woman in our study group. To decrease the likelihood that the comparison women had children with undiagnosed FASD, the following exclusion criteria were used: 1) women with any children assessed at the Manitoba FASD Centre; 2) women with children who had a diagnosis of FASD as recorded in hospital or physician claims data using the following ICD codes: a hospital visit with International Classification of Diseases, 9[th] Revision, Clinical Modification (ICD-9-CM) code 760.71, ICD-10-CA code of 86.0, or a physician visit with any ICD-9 code 760; 3) women with children who had prescriptions for psychostimulants or risperidone; 4) women with children diagnosed with attention-deficit hyperactivity disorder (ADHD) (due to high comorbidity of FASD and ADHD diagnoses[47,48]; 5) women involved in the InSight Mentoring program (a program that provides support for women with alcohol and substance abuse issues); 6) women with a history of substance abuse disorder (including alcohol) during pregnancy as indicated by the physician and hospital claims; 7) women whose newborn risk screen indicated they had used alcohol during pregnancy; and 8) women whose children received special education funding indicating they had severe to profound disabilities.

Outcome Variables

For each mother in our study and comparison groups, we calculated the total number of diagnoses of mood and anxiety disorders, substance use disorders, schizophrenia, and personality disorders 3 years before the pregnancy of the index child, prenatal psychological distress (mood and/or anxiety disorder) 8 months before the birth of the index child, and postpartum psychological distress (mood and/or anxiety disorder) 12 months after the birth of the index child. Definitions for each outcome can be found in Table 2. We also calculated the total number of women who had multiple diagnoses of psychiatric disorders (1 or 2 psychiatric disorders, 3 disorders, or 4 or more disorders). Finally, we calculated the proportion of women who had received at least 1 prescription for an antidepressant medication 3 years prior to the birth of the index child, during the pregnancy of the index child, and 1 year after the birth of the index child.

Data Analysis

Frequencies and percentages were used to describe the study population. Adjusted relative rates (aRRs) for the outcome variables were modeled using generalised linear models (GLMs) with a Poisson distribution. A negative binomial distribution was used when data were overdispersed. Both models are suitable for nonnormally distributed data such as

counts. All analyses tested for differences between groups and adjusted for covariates. Decisions regarding which covariates to exclude from the models were determined by frequency distributions and tests of significance.

The following variables were included as potential covariates in each of the models: age of mother at birth of child (18 or younger, 19 to 24, 25 to 34, 35 and higher) and socioeconomic status (SES). SES was defined using area-level data from census information. Area-level income quintiles were ranked from 1 (low) to 5 (high) on the basis of ranges of mean household income and grouped into 5 categories, with approximately 20% of the population assigned to each quintile.[49]

A summary data set for the total number of events (e.g., total number of mothers with mood and anxiety disorders) was produced to model the rate of events comparing women with children with FASD and those with children without FASD. For each outcome of interest, we ran a model to test for statistical differences between our study and comparison groups.

Results

Descriptive Statistics

Our study groups consisted of women born from 1946 to 1992 with ages ranging from 14 to 46 years (Table 3). The majority of women were from an urban location. Study group women were more likely to be lone parents, were younger age at first birth, and tended to have lower SES, higher gravidity, and higher parity (Table 3).

Rates of Physician-Diagnosed Psychiatric Disorders

Women in the study group had a higher number of unique psychiatric diagnoses (including prenatal and postnatal psychological distress, personality disorder, substance use disorder, mood and anxiety disorders, and schizophrenia) compared to the comparison group (mean number of psychiatric disorders = 2.13 versus 0.79, respectively). Eighty percent of women in the study group had a diagnosis of a psychiatric disorder before the birth of their child, during their pregnancy, or during the postpartum period compared to 27% of the comparison group. Almost 30% of women in the study group had 3 or more psychiatric disorders versus 6% of the comparison group (Figure 1).

1. **Rates of physician-diagnosed psychiatric disorders before pregnancy (the preconception period):** Women in the study group had higher adjusted rates of substance use disorder (aRR, 12.65; 95% CI, 8.99-17.80), personality disorder (aRR, 12.93; 95% CI, 4.88-34.22), and mood and anxiety disorder (aRR, 1.75; 95% CI, 1.49-2.07) 3 years before the pregnancy of their child compared to the comparison group (Table 4). There were few women diagnosed with schizophrenia in both groups,

Table 2. Definitions of Outcomes Used to Compare Rates of Mental Disorders in Women Who Gave Birth to a Child with FASD and a Matched Sample of Women Who Gave Birth to a Child without FASD.

Outcome Measure	Definition
Substance abuse	**A woman was considered to have a substance use disorder if 5 years prior to the birth of the child, she had the following:** 1) 1 or more hospitalisations with a diagnosis of alcohol or drug psychoses, alcohol or drug dependence, or nondependent abuse of drugs (ICD-9-CM codes 291, 292, 303, 304, 305, ICD-10-CM codes: F10-F19 and F55) **OR** 2) 1 or more physician visits with a diagnosis of alcohol or drug psychoses, alcohol or drug dependence, or nondependent abuse of drugs using the same ICD-9-CM codes listed above.
Personality disorder	**A women was considered to have a personality disorders if in the 5 years prior to giving birth to the child, she had the following:** 1) 1 or more hospitalisations with a diagnosis of personality disorder (ICD-9-CM code 301 or ICD-10-CA codes F34.0, F60, F61, F62, F68.1, F68.8, and F69) **OR** 2) 1 or more physician visits with a diagnosis of personality disorder (ICD-9-CM code 301)
Mood and anxiety disorder	**A women was considered to have mood or anxiety disorder if in the 5 years prior to giving birth to the child, she had the following:** 1) 1 or more hospitalisations with a diagnosis of depressive disorder, affective psychoses, neurotic depression, or adjustment reaction: ICD-9-CM codes 296.1-296.8, 300.4, 309, and 311; ICD-10-CA codes F31, F32, F33, F34.1, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, and F93.0 or with a diagnosis of an anxiety state, phobic disorders, or obsessive-compulsive disorders: ICD-9-CM codes 300.0, 300.2, 300.3, and 300.7; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, F42, and F45.2 **OR** 2) 1 or more hospitalisations with a diagnosis of anxiety disorders: ICD-9-CM code 300; ICD-10-CA codes F32, F34.1, F40, F41, F42, F44, F45.0, F45.1, F45.2, F48, F68.0, and F99 AND 1 or more prescriptions for an antidepressant or mood stabiliser, including medications with the ATC codes N05AN01, N05BA, and N06A **OR** 3) 1 or more physician visits with a diagnosis of depressive disorder or affective psychoses: ICD-9-CM codes 296 and 311 **OR** 4) 1 or more physician visits with a diagnosis of anxiety disorders: ICD-9-CM code 300 AND 1 or more prescriptions for an antidepressant or mood stabiliser, including medications with the ATC codes N05AN01, N05BA, and N06A **OR** 5) 3 or more physician visits with a diagnosis of anxiety disorders or adjustment reaction: ICD-9-CM code 300 and 309
Prenatal psychological distress	**A woman was considered to have prenatal psychological distress if in the 8 months prior to giving birth, she had the following:** 1) 1 or more hospitalisations with a diagnosis of depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD-9-CM codes 296.2-296.8, 300.4, 309, and 311; ICD-10-CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, and F93.0) **OR** 2) 1 or more physician visits with a diagnosis of depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD-9-CM codes 296, 309, and 311) **OR** 3) 1 or more hospitalisations with a diagnosis of anxiety disorders (ICD-9-CM code 300; ICD-10-CA codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, and F99) **OR** 4) 1 or more prescriptions for an antidepressant or mood stabiliser (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, and N06A) **OR** 5) 1 or more physician visits with a diagnosis of anxiety disorders (ICD-9-CM code 300) and 1 or more prescriptions for an antidepressant or mood stabiliser (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, and N06A) **OR** 6) 1 or more hospitalisations with a diagnosis of anxiety states, phobic disorders, or obsessive-compulsive disorders (ICD-9-CM codes 300.0, 300.2, and 300.3; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, and F42) **OR** 7) 2 or more physician visits with a diagnosis of anxiety disorders (ICD-9-CM code 300)
Postnatal psychological distress	**A woman was considered to have postnatal psychological distress if in the 12 months prior to giving birth, she had the following:** 1) 1 or more hospitalisations with a diagnosis of depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD-9-CM codes 296.2-296.8, 300.4, 309, and 311; ICD-10-CA codes F31, F32, F33, F341, F38.0, F38.1, F41.2, F43.1, F43.2, F43.8, F53.0, and F93.0) **OR** 2) 1 or more physician visits with a diagnosis of depressive disorder, affective psychoses, neurotic depression, or adjustment reaction (ICD-9-CM codes 296, 309, and 311) **OR** 3) 1 or more hospitalisations with a diagnosis of anxiety disorders (ICD-9-CM code 300; ICD-10-CA codes F32.0, F34.1, F40, F41, F42, F44, F45.0, F451, F452, F48, F68.0, and F99) **OR**

(continued)

Table 2. (continued)

Outcome Measure	Definition
	4) 1 or more prescriptions for an antidepressant or mood stabiliser (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, and N06A) **OR**
	5) 1 or more physician visits with a diagnosis of anxiety disorders (ICD-9-CM code 300) and 1 or more prescriptions for an antidepressant or mood stabiliser (ATC codes N03AB02, N03AB52, N03AF01, N05AN01, and N06A) **OR**
	6) 1 or more hospitalisations with a diagnosis of anxiety states, phobic disorders, or obsessive-compulsive disorders (ICD-9-CM codes 300.0, 300.2, and 300.3; ICD-10-CA codes F40, F41.0, F41.1, F41.3, F41.8, F41.9, and F42) **OR**
	7) 2 or more physician visits with a diagnosis of anxiety disorders (ICD-9-CM code 300)
Schizophrenia	**A women was considered to have schizophrenia if in the 5 years prior to giving birth, she had the following:**
	1) 1 or more hospitalisations or physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295 or ICD-10-CA codes F20, F21, F23.2, and F25 **OR**
	2) 1 or more physician visits with a diagnosis of schizophrenia: ICD-9-CM code 295
Antidepressant use	**A women was considered to have taken an antidepressant if there was 1 or more prescriptions identified by:** ATC drug classification codes: N06AA, N06AB, N06AF, N06AG, and N06AX

ATC, Anatomical Therapeutic Chemical; FASD, fetal alcohol spectrum disorder; ICD-9-CM, International Statistical Classification of Diseases and Related Health Problems, Ninth Revision, Clinical Modification; ICD-10-CA, Canadian Coding Standards for the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; ICD-10-CM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Clinical Modification.

and therefore regression analyses were not conducted.

2. **During pregnancy (the prenatal period):** Women in the study group had a higher rate of prenatal psychological distress (aRR, 5.35; 95% CI, 4.58-6.35) (Table 4).

3. **After pregnancy (the postnatal period):** Women in the study group had a higher rate of postpartum psychological distress (RR, 1.71; 95% CI, 1.53-1.90) compared to the comparison group (Table 4).

4. **Rates of prescribed antidepressants:** Women in the study group had significantly higher rates of antidepressant prescriptions before pregnancy (RR, 3.37; 95% CI, 2.47-4.58), during pregnancy (RR, 4.88; 95% CI, 3.00-7.97), and after pregnancy (RR, 3.48, CI 2.47-4.90) compared to the comparison group (Table 5).

Discussion

Among women whose children had an FASD diagnosis, 80% had at least 1 psychiatric disorder before the birth of their child, 75% had a diagnosis of prenatal psychological distress, and 75% had a diagnosis of postpartum psychological distress, indicating a substantial burden of psychiatric illness exists in this population. The results of this article identify multiple points where targeted psychiatric interventions can be implemented among women who are at risk for alcohol use during pregnancy, specifically before, during, and after pregnancy.

1. **Before pregnancy (the preconception period):** The significantly increased risk of having a psychiatric

disorder, including substance use disorder, personality disorder, and mood and anxiety disorders, 3 years prior to pregnancy among our study group indicates that the presence of psychiatric illness during the preconception period may be a risk factor for drinking during pregnancy. These results provide context to possible underlying reasons why women drink during pregnancy, as these women may be self-medicating and using alcohol to cope with symptoms associated with psychiatric disorders that exist before they conceive.

These results identify the importance of targeted psychiatric interventions that help women who are at risk for alcohol consumption during pregnancy manage their psychiatric illness during the preconception period. Clinicians providing psychiatric treatment to women in childbearing years who consume alcohol should be aware of the increased risk these women have of not being able to stop alcohol consumption during pregnancy; therefore, targeted preconception counselling that integrates psychiatric treatment as well as alcohol reduction strategies should be used in this population. Since a large number of pregnancies are unplanned, this counselling can also include birth control and family planning strategies that will help reduce the incidence of future alcohol-exposed pregnancies.

Research has demonstrated that the identification of substance abuse and maternal risk factors during the preconception period provides opportunities for health care professionals to assist women in reducing major health risks.[50] Research has also demonstrated that preconception counselling can lead to reductions in alcohol consumption, especially during the first trimester. Our study results

Table 3. Characteristics of Women Whose Children are Diagnosed with FASD and a Matched Sample of Women Whose Children Do Not Have FASD.

Characteristic	Exposed Cases (n = 702)	Comparison Group (n = 2097)
Maternal age at birth of index child		
Mean (SD), y	24.59 (6.15)	29.24 (5.69)
Range	14-43	14-46
Maternal age at birth of index child, n (%)		
<18 years	72 (10.26)	231 (11.02)
18-24 years	333 (47.44)	831 (39.63)
25-29 years	146 (20.80)	525 (25.04)
30-34 years	96 (13.68)	367 (17.50)
35+ and missing[a]	55 (7.83)	143 (6.82)
Missing	s[b]	0
Maternal age at first birth, n (%)		
<18 years	266 (37.89)	246 (11.73)
18-24 years	340 (48.43)	854 (43.06)
25-29 years	54 (7.69)	530 (25.27)
30-34 years	29 (4.13)	306 (14.59)
35+ and missing[a]	13 (1.85)	112 (5.34)
Missing	s[b]	0
History of teen pregnancy, n (%)	266 (37.89)	246 (11.73)
Region of residence, n (%)		
Rural	251 (35.75)	764 (36.43)
Urban	451 (64.24)	1333 (63.57)
Mean household income, n (%)		
Q1	466 (64.38)	1398 (66.67)
Q2	104 (14.81)	312 (14.88)
Q3	57 (8.12)	171 (8.15)
Q4	36 (5.13)	108 (5.15)
Q5	26 (3.70)	30 (1.43)
Missing	13 (1.85)	78 (3.72)
Socioeconomic status, n (%)		
Low (Q1)	466 (66.38)	1398 (66.67)
Middle (Q2 and Q3)	161 (22.93)	483 (23.03)
High (Q4 and Q5)	62 (8.83)	186 (8.87)
Missing	13 (1.85)	30 (1.43)
Married at the birth of child, n (%)	66 (9.40)	773 (36.86)
Gravidity, n (%)		
0-3	357 (50.85)	1966 (93.75)
≥4	306 (43.59)	113 (5.39)
Missing	39 (5.56)	18 (0.86)
Parity, n (%)		
0-3	524 (74.64)	2063 (98.38)
≥4	139 (19.80)	16 (0.76)
Missing	39 (5.56)	18 (0.86)
Diagnosis of psychiatric disorder 3 years before the birth of the child, n (%)[d]	580 (82.62)	566 (26.99)
Receipt of income assistance 3 years before birth of the index child	N = 345[c]	N=1026[c]
	63 (18.26)	98 (9.55)

[a]Number of missing women was <6; therefore, the number of missing women was combined with the "over 35 age group" to ensure privacy rules of Manitoba Centre for Health Policy data were adhered to.
[b]Crude rate suppressed if n < 6.
[c]Income assistance data is available after 1995, we limited the denominator to women who had babies after 1998 to ensure three years of data were available before the birth of the child to evaluate the number of women who had income assistance three years before the birth of their children; 345 women in our study group and 1026 women in our control group had babies after 1998.
[d]Includes substance abuse, personality disorder, mood and anxiety disorder, prenatal psychological distress, postnatal psychological distress, and schizophrenia.
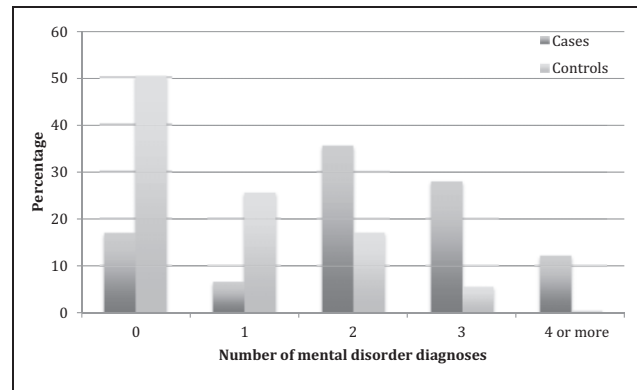
Figure 1. Number of mental disorder diagnoses of women who gave birth to a child with fetal alcohol spectrum disorder (FASD) and a matched sample of women who gave birth to a child without FASD. Includes substance abuse, personality disorder, mood and anxiety disorder, prenatal psychological distress, postnatal psychological distress, and schizophrenia.

Table 4. Rates of Mental Disorders of Women Who Gave Birth to a Child with FASD and a Matched Sample of Women Who Gave Birth to a Child without FASD.

Outcome	Study Cohort: Crude Rate (%)		Effect Estimate: Adjusted RR (95% CI)
	Study Group (n = 702)	Comparison Group (n = 2097)	Study vs. Comparison Group
Substance abuse[a]	179 (25.50)	41 (1.96)	**12.65 (8.99,17.80)**
Personality disorder[a]	22 (3.13)	6 (0.29)	**12.93 (4.88-34.22)**
Mood and anxiety disorder[a]	237 (33.76)	397 (19.93)	**1.75 (1.49-2.07)**
Prenatal psychological distress[b]	529 (75.36)	293 (13.97)	**5.35 (4.58-6.25)**
Postnatal psychological distress[c]	528 (75.21)	923 (44.02)	**1.71 (1.53-1.90)**
Schizophrenia[a]	<6[d]	7 (0.33)	NA

Note: Adjusted for age at birth of index child, socioeconomic and status. Bolded RRs are statistically significant. CI, confidence interval; FASD, fetal alcohol spectrum disorder; NA, regression analysis not appropriate due to small number of outcome events in both study groups; RR, relative rate.
[a]Diagnosis 3 years before the pregnancy of the child.
[b]Diagnosis 8 months before the birth of the child.
[c]Diagnosis 12 months after the birth of the child.
[d]Crude rate suppressed if n < 6.

demonstrate the need for clinicians providing care to integrate psychiatric counselling and alcohol reduction counselling for women who present with risk factors to give birth to children with FASD.

2. **During pregnancy (the prenatal period):** A substantial number of women in our study group had a

Table 5. Use of Antidepressant Medications by Women Who Gave Birth to a Child with FASD and a Matched Sample of Women Who Gave Birth to a Child without FASD.

Outcome	Study Cohort: Crude Rate (%)		Effect Estimate: Adjusted RR (95% CI)
	Exposed (n = 702)	Unexposed (n = 2097)	Exposed vs. Unexposed
Antidepressant medication use 3 years before pregnancy	109 (15.53)	98 (4.67)	**3.37 (2.47-4.58)**
Antidepressant medication use during prenatal period	48 (6.84)	29 (1.38)	**4.88 (3.00-7.97)**
Antidepressant medication use 1 year after pregnancy	85 (12.11)	76 (3.62)	**3.48 (2.47-4.90)**

Note: Adjusted for age at birth of index child and socioeconomic status. Antidepressant medication use refers to at least 1 prescription during the specified time period. Bolded RRs are statistically significant. CI, confidence interval; FASD, fetal alcohol spectrum disorder; RR, relative rate.

high burden of psychiatric illness during their pregnancies, during which they consumed alcohol. Evidence demonstrates that psychiatric disorders, specifically prenatal psychological distress (including anxiety and depression), can have adverse side effects on mothers and children, including preterm birth and low birth weight,[51] developmental delay in children,[52,53] impaired mother and child bonding,[54] and ADHD in children.[55] This study provides evidence that alcohol consumption during pregnancy may be an additional adverse side effect of prenatal psychological stress in women of childbearing years.

The significantly higher risk of prenatal psychological distress in women who give birth to children with FASD demonstrates that FASD prevention should include increased accessible, affordable, and nonjudgemental resources to improve the psychiatric health of women of childbearing years with psychiatric concerns. Moreover, not all children with FASD exhibit the same level of severity of symptoms,[4] and as stated above, the presence of psychiatric disorders is known to have adverse effects on child outcomes.[52,53] Future work should investigate the extent to which FASD symptoms and outcomes for children are moderated by maternal psychiatric disorders.

Furthermore, a significantly higher rate of women who gave birth to children with FASD compared to our comparison group took antidepressants during pregnancy. There is conflicting evidence in the literature regarding the safety of antidepressant use during the perinatal period, with some studies demonstrating adverse effects in children, including

low birth weight, congenital malformations, and persistent pulmonary hypertension in infants.[56] Antidepressants have also been shown to mitigate adverse effects in children exposed to maternal depression during pregnancy[56] and may play a role in decreasing primary or secondary symptoms present in children with FASD. Further research investigating the effects of antidepressants on children born with prenatal alcohol exposure should explore the potentially mediating or moderating effects of antidepressants on prenatal alcohol use and the manifestation of FASD symptoms.

3. **After pregnancy (the postnatal period):** The significantly higher rates of postpartum depression in women who give birth to children with FASD indicate the need for targeted and specific support resources after the birth of a child exposed in utero to alcohol. Studies have demonstrated that early interventions that improve maternal psychiatric health in pregnancy and the postpartum period can improve infant, child, and maternal outcomes.[57-59] Targeted interventions to improve the psychiatric health of women at risk for alcohol abuse during childbearing years and pregnancy may not only improve both maternal and child outcomes but also potentially decrease the risk for subsequent children born with FASD through alcohol reduction and cessation strategies.

The results of this study are consistent with the few published studies in this area. A study by Astley et al[21] surveyed 80 birth mothers of children with fetal alcohol syndrome to generate a profile of these women. They reported that 96% of women had 1 to 10 psychiatric disorders.[21] A more recent study investigated the psychological distress among Plains Indian mothers with children referred to screening for FASD using maternal interview data and reported that 19% of women had psychological distress, including symptoms of depression and anxiety.[60] However, both of these studies used survey data, which are limited by selection bias, as women seeking psychiatric health services may be more likely to participate in surveys. Women participating in surveys may also exhibit recall bias.[61] Women may have been pregnant several years in the past compared to when the surveys were administered, thus decreasing accuracy of their ability to recall diagnosis received around that time period.

To our knowledge, the rates of prenatal psychological distress have only been reported in a report investigating the perinatal health of women in Manitoba, and this definition has not been used in any other population-based maternity studies in Canada.[62] Our rates are much higher compared to rates of prenatal and postpartum psychological distress reported for women in the general population in Manitoba, which were 7.5% and 13.8%, respectively.[62] While definitions of psychological distress and psychiatric disorders vary widely in the literature, general population rates of psychiatric disorders among the Canadian population are reported at approximately 13%,[63] and rates of postpartum depression

have been reported to be approximately 7% in Canada.[64] Our rates were much higher, which may be attributed to differences in definition or because women in both of our study groups are of lower SES and may be a higher risk group for psychiatric illness.[62]

Strengths and Limitations

Administrative data eliminate selection and recall bias, thus offering more valid information when investigating health services utilisation.[40,45,46] The use of administrative data in the present study also provides the largest sample size of women who have given birth to children with FASD to date in Canada and enhances the accuracy of psychiatric disorder diagnoses compared to studies using primary data collection. Furthermore, the use of pharmaceutical data in investigating the use of antidepressants before, during, and after pregnancy confirms the substantial rates of psychiatric disorders observed in our study population and identifies areas for future research.

A limitation of this study is the use of a clinically referred FASD sample, as opposed to a population-based sample, limiting the generalisability of the findings. However, the use of this clinically based sample is also a strength, as the children in this study have undergone an accurate and comprehensive multidisciplinary assessment in a central tertiary-level provincial diagnostic clinic that follows the Canadian guidelines and updated guidelines for the diagnosis of FASD.[3,4] While mothers of children with FASD who are not referred to the clinic for assessment were not included in our study, this is the largest sample size of women who have given birth to a child with a confirmed clinical diagnosis of FASD in Canada. Due to the changes in FASD diagnostic guidelines over the course of the study period (e.g., the change in growth restriction not being a requirement for a diagnosis), we may be missing children who did not meet one set of guidelines as compared to another, and thus the number of women included in our study may be underrepresenting women who have children with FASD in Manitoba; future work should be done validating both sets of diagnostic criteria in identifying birth mothers of children with FASD.

While we have taken great care in excluding all mothers with possible prenatal alcohol exposure and children with a diagnosis of FASD, we cannot be certain that there are no women in our comparison group who do not have unreported prenatal alcohol use or children with undiagnosed FASD. However, this would serve to weaken rather than strengthen our findings.

In addition, as in all studies using administrative databases, this study is reliant on the accuracy of physician coding; however, as previously stated, MCHP data have been extensively validated for conducting this type of research.[40,42-46]

Finally, this study is dependent on women making contact with the health care system and would exclude women with undiagnosed psychiatric disorders, women who have not been assigned with relevant diagnostic codes, or mothers of children with undiagnosed FASD. Women who have only sought nonpharmacological care from a psychologist or support group would also be excluded. Thus, as previously stated, this study does not report prevalence rates of psychiatric disorders in our cohort but the prevalence of physician health service use for psychiatric illness. Therefore, the burden of psychiatric illness in this group may be underestimated.

Conclusions

This study presents novel data regarding the complex psychiatric issues faced by women who have given birth to children with FASD. Our findings indicate that the prevention of alcohol consumption in pregnancy should include a focus on improving the psychiatric health of women. Support programs and interventions that improve the psychiatric health of women at risk for alcohol consumption during pregnancy should be an integral part of policies targeted at decreasing alcohol use during pregnancy. Women with psychiatric disorders who use alcohol should be provided education about the risks of using alcohol when pregnant and compassionate, evidence-based support for the cessation of alcohol consumption during pregnancy. The significantly higher rates of postpartum psychological distress observed in women who have given birth to children with FASD also indicate the need for increasing treatment resources that focus on improving psychiatric health for these women. Furthermore, services to improve postpartum psychiatric health in this group of women may also prevent subsequent alcohol exposed pregnancies, thereby preventing further FASD births.

Services Research from the Manitoba Centre for Health Policy and from the Canadian Foundation for Fetal Alcohol Research.

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UNIVERSITY | BANNATYNE CAMPUS
OF MANITOBA | Research Ethics Boards

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Ms. D. Singal	UofM/Community Health Sciences	H2013:221

APPROVAL DATE:	EXPIRY DATE:
July 3, 2013	July 3, 2014

STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):
Dr. M. Brownell

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE;
NA	Investigating the Characteristics and Health Care Utilization of Women Who Give Birth to Children with Fetal Alcohol Spectrum Disorder

SPONSORING AGENCIES AND/OR COORDINATING GROUPS:
MHRC/Graduate Students Award

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
May 5, 2013 and June 19, 2013	May 9, 2013 and June 19, 2013

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date

Protocol:
Protocol   May 5, 2013
Consent and Assent Form(s):

Other:
Data Fields   May 13, 2013

CERTIFICATION
The above named research study/project has been reviewed in a *delegated manner* by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

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The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. *For logistics of performing the study, approval must be sought from the relevant institution(s).*
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval.** **A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

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Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone:** (204) 789-3255/ **Fax:** (204) 789-3414

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