Epidemiology of Neurodevelopmental Disorders among Indigenous Children: from Global to Métis-specific Contexts

by

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Abstract

Neurodevelopmental disorders (NDDs) have been found to be more prevalent among Indigenous children. However, it is unclear whether this extends to all Indigenous children from countries with similar colonial histories. In this thesis, we conducted a systematic review to assess the evidence on the prevalence of NDDs among Indigenous children in Australia, Canada, New Zealand, and the USA and compared these estimates with those among non-Indigenous children. Limited evidence suggests a greater burden of Intellectual Disability affecting Indigenous children in Australia, New Zealand. This review also found a greater burden of Specific Learning Disorders affecting American Indian/Native American children compared to White children. There was inconclusive evidence or no evidence informing the prevalence of Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, Motor Disorder, and Communication Disorder in Indigenous children. This thesis also includes a population-based retrospective cohort study that evaluated the prevalence of neurodevelopmental disorders and disabilities (NDD/D) of all singleton Métis live births and a random sample of non-Métis live births in Alberta from 2006-2016. The study also compared maternal and neonatal characteristics of Métis and non-Métis children with NDD/D. This study found that the prevalence of NDD/D was similar between Métis and non-Métis children (adjusted odds ratio: 1.15; 95% confidence interval: 0.98, 1.34) adjusting for covariates. We found that compared to non-Métis children, Métis children with NDD/D in our cohort had a greater likelihood of being born to mothers who were younger than 20 years old, lived in rural locations, from the most materially deprived areas, and who smoked and used alcohol or drugs. These findings will be useful to inform strategies to improve the neurodevelopmental health of Indigenous children from countries with similar colonial histories and for Métis children in Alberta.

Preface

This thesis is an original work by Stuart Christian Lau. The thesis was written in accordance with the guidelines set by the Faculty of Graduate Studies and Research at the University of Alberta. Part of this thesis received research ethics approval from the University of Alberta Health Research Ethics Board – Health Panel (#Pro00098620).

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Chapter 1: Introduction

1.1 Literature Review

1.1.1 Neurodevelopmental Disorders

Neurodevelopmental Disorders (NDDs) is an umbrella term that classifies a group of diseases with onset during the development period and linked by a shared underlying problem with the development of the central nervous system (CNS). NDDs are characterized by cognitive, motor, sensory, behavioral, and/or psychologic function impairments. These impairments may range from specific limitations, such as learning difficulties, to global deficiencies, such as a lack of development in social and intellectual faculties.[1] Widely accepted classifications are from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organization's (WHO) International Classification of Diseases (ICD). While what was considered an NDD has differed between both systems, definitions of NDD have become more aligned in the most recent editions of the DSM (DSM-5) and ICD (ICD-11). Based on the DSM-5, NDDs include Intellectual Disability (ID), Autism Spectrum Disorders (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Motor Disorders (MD), Specific Learning Disorders (SLD), and Communication Disorders (speech or language; CD).[1, 2] Globally, 31 million people are affected by ASD, 73 million people have ADHD and 100 million individuals have an ID.[3]

In Canada, neurodevelopmental disorders and disabilities (NDD/D) is another classification that has begun to be operationalized in health research. NDD/D is a term that is used to describe a group of neurodevelopmental disorders and neuromuscular impairments that create functional limitations spanning the fundamental domains of child development, including movement, communication, cognition, social interactions, hearing and vision, behaviour, and emotion.[4] This non-categorical classification emphasizes functional difficulties that are common

to neurodevelopmental and neuromuscular impairments as opposed to specific diagnoses. This definition has been considered more useful for health services and policy planning. It groups diverse conditions based on similar consequences and assumes that individuals with NDD/D and families supporting individuals with NDD/D share similar experiences and needs.[5] NDD/D's emphasis on functional profiles of individuals also aligns with the WHO's contemporary definition of disability found in the International Classification of Functioning, Disability, and Health (ICF). The ICF conceptualizes functioning and disabilities based on the interaction between body function and structure impairment, activity limitation, and/or participation restriction in society. It emphasizes how contextual factors such as environmental and personal factors influence how an individual functions and experiences disability. Environmental factors describe the physical, social, and attitudinal environment that individuals live in, while personal factors include aspects that shape an individual (e.g., age, sex, gender, education).[6] Table 1 provides a list of diagnoses that have been classified under NDD/D Miller et al.'s seminal study on building this classification system. In Canada, NDD/D have been found to affect up to 5-8% of children.[4, 7]

For the rest of this chapter, when we use the term NDD, it will also consider conditions that fall under the NDD/D categorization. As well as impacting morbidity, NDDs have long-term negative consequences on health and well-being and present a significant financial burden to individuals and families affected by NDDs. Having an NDD is associated with decreased quality of life,[8, 9] employment opportunities,[10] and increased social and mental health problems.[11] In Canada, it has also been estimated that the median annual parental cost of caring for a child with a developmental disability is $44,570 and the median annual cost to society is $27,428.[12] As such, it is important to understand the factors that are associated with the development of NDDs.

1.1.3 Etiology of NDDs and NDD/D

Among NDDs, some conditions have a well-researched etiology. Down syndrome and muscular dystrophies have genetic predispositions,[13,14] and most cases of cerebral palsy are acquired upon on a brain injury during the first years of life.[15] However, for most other NDDs, the etiology is complex and heterogeneous. It is generally agreed upon that these disorders result from the interaction between genetics and a multitude of environmental factors. Mutations of genes related to molecular pathways involved in neurodevelopment, such as protein synthesis, synaptic signalling, and epigenetic regulation, have been identified as potential contributors to NDD phenotypes.[16] Some disorders, such as ASD and ADHD, have strong heritability.[17] However, biological marker studies have not provided sufficient evidence that genetics is directly associated with the development of NDDs. There is also strong genetic overlap across different NDDs.[18, 19] In addition to genetic influences on neurodevelopment, the impact of early-life exposures from pre-conception to early childhood have been associated with the development of NDDs in children.[20] It has been proposed that the effect of these risk factors interacts with genetic predispositions mediated by epigenetic changes during the development of the nervous system.[21, 22] Factors such as prematurity, fetal growth restriction, hypoxia, advanced parental age,[23] socioeconomic status,[24-26] and parental stress[27] are linked with atypical neurodevelopment. Extrinsic environmental factors such as maternal use of alcohol, drugs, or smoking are also associated with NDDs.[21] The complexity of the etiology of NDDs is further enhanced by the fact that NDDs frequently co-occur, which indicates the possibility of shared mechanisms among distinct conditions.[28] In summary, manifestation of many NDDs is multifactorial and likely results from complex interactions between genetic factors and early-life exposures that contribute to brain development.

1.1.4 Indigenous Children

The World Bank defines Indigenous peoples as "distinct social and cultural groups that share collective ancestral ties to the lands and natural resources where they live, occupy or from which they have been displaced." [29] It is widely recognized that Indigenous children around the world suffer from worse health outcomes compared to their non-Indigenous counterparts.[30] These health inequalities extends to Indigenous children living in developed countries such as Australia, Canada, New Zealand, and the United States (USA).[30] Many studies have identified that Indigenous children from these countries with similar colonial histories have a higher rate of disability (including NDDs) compared to non-Indigenous children.

1.1.5 Canadian Indigenous Children

Indigenous peoples of Canada refer to the original inhabitants of the land that is now known as Canada. There are three Indigenous groups legally recognized by the Canadian government, affirmed in Section 35(2) of the Constitution Act of 1982: First Nations, Inuit, and Métis.[31] Culturally, there are more than 50 Nations in Canada with unique cultures, traditions, languages, political structures, and histories.

In Canada, there are over 400,000 Indigenous children under 14 years old.[32] Indigenous children are a sacred part of many Indigenous communities.[33] Indigenous worldviews see children as the next generation of parents and leaders; therefore, the health of Indigenous children is vital to the health and well-being of future Nations.[33] However, First Nations, Inuit, and Métis children suffer from worse health outcomes than their non-Indigenous counterparts.[34] These health inequities are shaped by historical and contemporary effects of colonialism, which includes intergenerational trauma, loss of culture, identity and language, and destabilization of Indigenous

determinants of health.[30,34] These effects are further exacerbated by colonial policies and legislation which impact healthcare service access.[34]

Although there are three officially recognized Indigenous groups within Canada, the allocation of health resources is not equal for all Indigenous children. The Non-Insured Health Benefits (NHIB) program provides coverage for medically necessary goods and services for children less than 18 months whose parent are First Nations registered under the Indian Act, Inuk recognized by an Inuit land claim organization, or children older than 18 months who has Indian Status or recognition as Inuk by their Inuit land claim organization.[35] Jordan's Principle is a legal requirement which aims to provide all First Nations children living in Canada with access to all public services (health, social, and education).[36] Indigenous children such as Métis do not have the same access to health resources from these federal programs and principles.

1.1.6 Métis Children

Métis are distinct Indigenous people whose origins are from the marriage between First Nation women, such as Cree, Dene, Saulteaux, Anishinaabe, Assiniboine, and European (French, Scottish, English) fur-traders in the 18th century. The Métis historic homeland span the three prairie provinces (Alberta, Saskatchewan, and Manitoba), Northwest Territories, parts of British Columbia and Ontario, and Montana and North Dakota in the United States. Over generations, the intermingling of heritage led to the development of a distinct culture, language, and way of life.[37]

The Métis have had a contentious past with the government of Canada. While Métis communities were well-established within their Métis homelands, the government of Canada purchased lands from the Hudson's Bay Company during confederation without the consultation of the Métis, resulting in resistance from Métis communities and the Red River Rebellion. The dispute was resolved between the Métis and the Government of Canada through the Manitoba Act

in 1870, which included a provision for 1.4 million acres of land to be reserved for children of Métis households through the distribution of scrip. Métis scrip are certificates redeemable for land or money.[38] However, this distribution was delayed and never fully realized as recognized by the Supreme Court of Canada in 2013,[39] and many families were cheated out of resources guaranteed to them by the Government of Canada.[40] Furthermore, although the Canadian Constitutional Act of 1982 legally recognized the Métis as one of the Indigenous peoples in Canada, federal claim benefits that were granted to First Nations and Inuit through the Indian Act were not given to the Métis. It was not until a Federal Court Ruling in 2013 on the "Daniels v. Canada" court case that finally asserted that Métis people can claim the rights that were outline in Section 91(24) of the Constitution Act, 1867.[40] However, this case did not result in the federal government granting other claims in the court case which included the federal government assuming fiduciary duty and responsibility to the Métis. In 2016, an appeal of the decision led to the Daniel Decision, which clarifies that the federal government is responsible for Métis people living in Canada.[41]

Based on the 2016 Canadian Census, there are 587,545 self-identified Métis people living in Canada.[32] The Métis National Council is a national body that represents the Métis people in British Columbia, Alberta, Saskatchewan, Manitoba, and Ontario. Today, the Métis National Council defines Métis as "a person who self-identifies as Métis, is distinct from other Aboriginal Peoples, is of historic Métis Nation ancestry and who is accepted by the Métis Nation."[42]

In Alberta, there are 114,375 self-identified Métis people which is the largest Métis population in the Western provinces and the second largest Métis population in Canada, behind Ontario.[32] The Métis Nation of Alberta (MNA) is the representative voice for Métis people in Alberta. There are currently almost 50,000 registered members in the MNA. The purpose of the

MNA is to advance Métis governance and the socio-economic and cultural well-being of Métis people in Alberta.[43]

Although there are over 100,000 self-identified Métis children in Canada,[32] they are extremely underrepresented within health research.[42] Currently, Métis children do not receive the same healthcare infrastructure such as the NHIB and Jordan's principle that cover Inuit and First Nation children.[35, 36]

1.1.7 Understanding of Disability in Indigenous Communities

It is important to acknowledge that disability among Indigenous communities is often viewed differently compared to perspectives from dominant cultures. Western perspectives often define disabilities as impairments, limitations, and restrictions in relation to their environment.[45] Many Indigenous communities do not have words describing disability and have different interpretations for individuals experiencing what is medically considered a disability.[46-48] Some view children with disabilities as individuals with gifts and emphasize what they bring to the collective community.[46, 47] While we cannot generalize these views for all Indigenous groups, these views on disability must be taken into consideration to better understand and interpret the burden of disability and NDDs among Indigenous children.

1.1.8 NDDs among Indigenous Children

Currently, the evidence on the prevalence of NDD among Indigenous children compared to non-Indigenous children from countries with similar colonial histories is conflicting. Some jurisdictions have been found NDD to be more prevalent among Indigenous children,[49, 50] while others have found lower rates.[51] Among Indigenous children, colonialism is the most significant determinant of health. The effects of historical and contemporary colonialism, including dislocation from traditional lands, loss of culture and assimilation to Western culture, systemic

discrimination and racism, and political marginalization, directly contribute to Indigenous children's adverse health outcomes and disability.[30, 52, 53] Collating evidence on the prevalence of NDDs among Indigenous children compared to non-Indigenous children from countries of similar experiences of colonial histories could provide essential information on the burden of NDDs among Indigenous children. This information may be important to help guide policies and specific programming for Indigenous children to improve their neurodevelopmental health.

In Canada, there is limited health research on NDDs among Métis children and in Métis people in general. Previous evidence on the burden of NDDs among Métis individuals comes from the Statistics Canada Aboriginal Peoples Survey in 2017, which evaluated the burden of disabilities among Indigenous peoples aged 15 to 65 years. In this survey, the prevalence of learning disability (e.g., hyperactivity and attention problems) and developmental disability (e.g., autism) was greater in Métis individuals (6.6% and 1.5%, respectively) compared to non-Indigenous individuals (3.8% and 1.0%, respectively).[54] Other NDD research in Canada which included Métis children utilized a pan-Indigenous approach (aggregating First Nation, Métis, and Inuit children) which does not put into the context the unique historical experiences, perspectives, and ways of being of each Indigenous group.[51, 55] In that research, ADHD symptoms were more prevalent among Indigenous children while ASD rates were lower among Indigenous children compared to non-Indigenous children. Conducting a population-based study assessing the burden of NDDs among Métis is needed to help address the current knowledge gap.

This thesis aims to improve our understanding of the burden of NDDs among Indigenous children compared to non-Indigenous children. This purpose will be fulfilled through two separate studies. The first study is a systematic review which evaluates the current literature on the prevalence of NDDs among Indigenous and non-Indigenous children from countries with similar

histories of colonialism. As there currently are no studies evaluating the burden of NDDs among Métis compared to non-Métis children, we aim to fill that knowledge gap through a retrospective cohort study. The second study of the thesis is a population-based retrospective cohort study that will provide knowledge on the prevalence of NDD among Métis compared to non-Métis children in Alberta and assess the maternal and neonatal characteristics of Métis and non-Métis children with an NDD. This study aims to avoid a pan-Indigenous approach to study Indigenous health and will provide information that can be used by the MNA, policymakers, and clinicians who are involved in the development of health services for and care provision to Métis children and pregnant Métis women.

1.2 Research Objectives

1. To assess the evidence on the prevalence of NDDs among Indigenous children in Australia, Canada, New Zealand, and the USA
2. To evaluate and describe the epidemiology of NDDs in Métis children compared to non-Métis children in Alberta and compare maternal and neonatal characteristics of Métis and non-Métis children with NDDs

1.3 Organization of this Thesis

This thesis follows a paper-based thesis format.

Chapter 1 provides background information on NDDs, Indigenous peoples, Métis peoples, and gaps in knowledge regarding the neurodevelopmental health of Métis children.

Chapter 2 is a systematic review of scientific evidence on the prevalence of NDD among Indigenous children compared to non-Indigenous children in Australia, Canada, New Zealand, and the USA.

Chapter 3 is a retrospective cohort study that evaluates the prevalence of NDD/D among Métis children compared to non-Métis children and assesses maternal and neonatal characteristics of Métis and non-Métis children with NDD/D.

Chapter 4 discusses the study results from Chapter 2 and 3 and explores their implications for health care professionals and policymakers and future study directions.

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Table 1.1 List of NDD/D Identified in Miller et al.[4]

Domain		ICD-9	ICD-10
Motor	Infantile cerebral palsy	343	G80.9
	Spina bifida	741	Q05.9 (or Q05.*)
	Lack of coordination	781.3	R278 (or R27*)
	Muscular dystrophies and other myopathies	359	G71.0 (or G71*)
Speech-language communication	Other speech disturbance	784.5	R47.8*
	Aphasia	784.3	R47.01
	Developmental speech or language disorder	315.3	F80.*
	Problems with voice production	V41.4	R47.89
Learning-Cognition	Developmental disorder of scholastic skills	315.9	F81.9
	Mental and behavioral problems with learning	V40.0	F81.9
	Fetal alcohol syndrome / Newborn affected by maternal alcohol use	760.71	Q86.0 / P04.3
	Reading disorder	315.0	F81.0
	Other symbolic disfunction	784.6	R48.9
	Symptoms and signs involving cognitive functions and awareness / Attention and concentration deficit (ICD-10)	799.5	R41.8
	Hyperkinetic syndrome of childhood / attention-deficit hyperactivity disorder (ICD-10)	314.0	F90.*
	Unspecified intellectual disabilities ICD-10 (F79)	319.0	F79
	Down syndrome	758.0	Q90
Reciprocal social interaction	Pervasive developmental disorders (largely autism and its variants) Autistic disorder, Rett's syndrome, Asperger's syndrome, other childhood disintegrative disorder'	299.*	F84.*
Sensory	Deafness (conductive hearing loss)	389.0	H91.9
	Blindness and low vision	369.*	H54.0 / H54.7
	Problems with special senses and other special functions	V41	
Behavioral emotional psychological	Epilepsy and recurrent seizures	345.*	G40*
	Mental disorder ICD-10 (F99) or Unspecified intellectual disabilities ICD-10 (F79)	314.0	F90.*
	Other specified behavioral and emotional disorders	313.89	F98.8
	Tourette's disorder (combined vocal and multiple motor tic disorder [de la Tourette])	307.23	F95.2
	Anxiety disorder	300	F41.9
	Oppositional defiant disorder	313.81	F91.3
	Obsessive-compulsive disorder, unspecified	300.3	F42.9
	Major depressive disorder, single episode, unspecified	296.20	F32.9

Chapter 2: Prevalence of Neurodevelopmental Disorders among Indigenous Children: A Systematic Review

2.1 Background

Neurodevelopment is a complex and dynamic process that involves the organization and maturation of the central nervous system (CNS), which is crucial to proper sensory-motor, cognitive, and social-emotional development.[1, 2] Neurodevelopment initiates in utero, continuing into adulthood and can be influenced by biological, psychosocial, environmental, and sociocultural factors.[1, 3] Poor neurodevelopment may negatively influence children's health trajectories, such as missing typical developmental milestones, and manifest as neurodevelopmental disorders (NDDs).[1, 2] Neurodevelopmental Disorders (NDDs) is an umbrella term that describes "a group of conditions with onset in the developmental period" characterized by deficits that impair personal, social, academic, and occupational functioning.[4] The Diagnostic and Statistical Manual of Mental Disorders 5th Revision (DSM-5) classification of NDDs includes broad categories of intellectual disabilities (ID), autism spectrum disorders (ASD), attention-deficit/hyperactivity disorders (ADHD), communication disorders (CD), specific learning disorders (SLD), and motor disorders (MD).[4] Having a NDD is associated with negative consequences on long-term health and well-being, affecting quality of life, relationships, mental health, and earning capacity.[2, 5-7]

Estimates of NDD prevalence in children between 0 and 18 years old vary across different populations. In high-income countries such as the United States and Canada, it is estimated that NDDs affect 7-15% of children.[8, 9] A systematic review on the burden of NDDs in low- and middle-income countries estimates the prevalence in 7.6 per 1000 people.[10] One population that NDDs may disproportionately impact are Indigenous children due to major disparities in social determinants of health compared to non-Indigenous children.[11] A previous scoping review on ASD

among Australian Aboriginal children and adults found that prevalence rates were similar to those of non-Indigenous Australians.[12] Another review that landscaped research on ASD, cerebral palsy (CP), and fetal alcohol spectrum disorder (FASD) among Indigenous people in Canada found only evidence that examined FASD prevalence among Indigenous groups and did not compare it to non-Indigenous peoples.[13] In these reviews, other NDDs were not considered, nor did they focus on Indigenous children with similar experiences of colonialism.

For Indigenous children in countries with similar colonial histories (Australia, Canada, New Zealand, USA), intergenerational effects of colonialism prevail as one of the most important structural determinants of health, with devastating consequences on their health and well-being. The effects of historical and contemporary colonialism include the destabilization of Indigenous determinants of health and the perpetuation of dispossession, disempowerment, and racism that still contributes to Indigenous children's adverse health and increased disability. [11, 14, 15] The purpose of this systematic review was to assess the evidence on the prevalence of NDDs among Indigenous children in Australia (Aboriginal and Torres Strait Islander), Canada (First Nations, Inuit, and Métis), New Zealand (Māori), and the USA (Native Americans and Alaska Natives) and compare these estimates with those among non-Indigenous children. In this review, we use the term *Indigenous* to refer to all individuals of Indigenous ancestry.

2.2 Methods

The systematic review was planned, conducted, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16] A protocol for the systematic review was registered in the International Prospective Register of Systematic Reviews database (PROSPERO 2021, CRD42021238669).

2.2.1 Literature Search

Comprehensive literature searches were conducted in the following biomedical electronic databases to identify relevant studies: MEDLINE ALL (OVID Interface), EMBASE (OVID Interface), PsycInfo (OVID Interface), CINAHL Plus with Full text (EBSCOhost Interface), and Web of Science Core Collection. The search strategy was designed and executed by a medical research librarian (LD). The strategy included selected subject headings (e.g., MeSH terms) and free terms related to Indigenous peoples and NDDs. Additionally, grey literature was identified through Google Scholar and ProQuest Dissertation and Theses using selected keywords. The reference lists of potentially relevant studies were manually searched for additional articles. The search was limited to the period between 2005 and Feb 15, 2022 to reduce heterogeneity in the diagnostic case definitions of NDDs. No publication or language restrictions were applied. Full details of the search strategy can be found in Table S1.

2.2.2 Study Eligibility

Included were observational epidemiological studies (i.e., cohort and cross-sectional studies) that compared the prevalence of NDDs among Indigenous children aged 0-18 years in Australia, Canada, New Zealand, and the USA to non-Indigenous children. For this review, we defined Indigenous peoples as "distinct social and cultural groups that share collective ancestral ties to the lands and natural resources where they live, occupy or from which they have been displaced".[17] NDDs of interest were conditions defined by the DSM-5 including ID, CD, ASD, ASD, ADHD, SLD, and MD [4]. Non-primary research studies, letters to the editor, case reports, and case series were excluded from the review.

Two reviewers (SL and NC) screened all titles and abstracts generated from the literature searches to identify potentially relevant articles. Full text of articles deemed relevant and studies

whose title and abstract provided insufficient information were retrieved and evaluated independently by two reviewers (SL and NC) for eligibility in the review. Disagreements about study selection were resolved through discussion between the two reviewers until consensus was reached.

2.2.3 Risk of Bias Assessment

Two independent reviewers (SL and NC) assessed the risk of bias (RoB) of all included studies. Disagreements about RoB were resolved through discussion until consensus was reached. Cohort studies were assessed using the Newcastle-Ottawa Quality (NOS) Assessment Scale for cohort studies.[18] The NOS evaluates RoB based on the following criteria: selection of study participants, comparability among study groups, ascertainment of exposures, outcome assessment, and adequacy of follow-up of the cohorts. Scores in the NOS scale are based on the allocation of stars within each category. RoB were graded as either low (selection 3-4 stars, comparability 2 stars, outcome 3 stars), moderate (selection 2 stars, comparability 1 star, outcome 2 stars), or high (selection 0-1 stars, comparability 0 stars, outcome 0-1 star). Cross-sectional studies were assessed using a 9-item scale developed by Hoy et al. [19] This scale assesses the RoB of prevalence studies in categories of sample selection, non-response bias, data collection, measurement reliability and validity. Hoy score for studies ranges from 0-9, where a score of 0-3 in any category was classified to have low RoB, 4-6 as unclear RoB, and 7-9 for high RoB.[19] Plots of domain-level judgements for individual studies and weighted bar plots of the distribution of RoB judgements within each bias domain were generated using the Risk-of-bias VISualization tool (robvis).[20]

2.2.4 Data Extraction and Synthesis

A standardized data collection form was used to collect information from included studies. All study data were extracted by one reviewer (SL) and verified for accuracy by a second reviewer

(NC). The following information about study characteristics, populations, and comparison groups were extracted from the individual studies: country, publication year, study design, study setting, Indigenous population and comparison group, sample source, sex distribution, and age range of the study populations. This review used White children as the comparison group in all analyses. In studies where White children were not separately identified, groups identified as "non-Indigenous children" were used for comparisons. Outcomes data collected included the type of NDD, diagnostic criteria used in the study, and proportions and/or prevalence estimates (i.e., prevalence rates, prevalence rate ratios, prevalence odds ratios [POR], where possible) with 95% confidence intervals (CI) when raw data could not be obtained. The prevalence of each NDD was calculated using the number of events as the numerator and group size as denominators. In studies where NDD prevalence was studied over time, endpoint data for period prevalence was taken for this review. When studies presented prevalence data through graphs instead of numerical values, the WebPlotDigitizer program[21] was used to extract data from the plot. Evidence tables were used to summarize the characteristics and results of individual studies categorized by type of NDD and Indigenous group. A narrative synthesis of study results was completed following the Synthesis Without Meta-analysis (SWiM) guidelines to present information about study characteristics, populations, and outcomes using evidence direction plots.[22] For NDDs including more than two studies of similar study design and conducted in the same Indigenous groups, a Mantel-Haenszel random-effects meta-analysis was used to calculate POR with 95% CI to compare NDD prevalence between Indigenous and white or non-Indigenous children. Statistical heterogeneity across studies was assessed using the I^2 statistics and characterized as small (I^2 less than 25%), moderate (I^2 between 26 and 74%), and high (I^2 greater than 75%).[23] Heterogeneity was also

investigated qualitatively by looking at methodological differences across individual studies. Statistical analyses were performed on Review Manager (RevMan) software version 5.3.[24]

2.3 Results

2.3.1 Search Results

A total of 1,468 references were identified through the electronic literature searches. Grey literature searches and reference lists review identified 29 additional titles and abstracts. After duplicates were removed, screening of 898 titles and abstracts resulted in 96 articles selected as potentially relevant. After full-text examination of these potentially relevant articles, 27 studies met the inclusion criteria for the review. Of these, 12 references were multiple publications of three studies[25-27] and therefore excluded from this review (Table S2). This review synthesizes data from 12 unique studies. Details of study selection are outlined in Figure 1.

2.3.2 Characteristics of Included Studies

Twelve studies provided data on the prevalence of NDDs in Indigenous children. Table 1 summarizes the key characteristics of these 12 studies. There were six retrospective cohort studies,[25, 28-32] one prospective cohort study,[27] four cross-sectional studies,[33-36] and one ecological study.[26] Two studies were conducted in Australia,[26, 27] one study in Canada,[29] four in New Zealand,[28, 31, 33, 34] and five in the USA.[26, 30, 32, 35, 36] Five studies evaluated ADHD prevalence,[30, 31, 34-36] seven studies for ASD,[25-29, 32, 34] three for ID,[25, 26, 33] and one for SLD.[26]

The Indigenous children populations in studies conducted in Australia were identified as Aboriginal Australian children.[25, 27] The Indigenous children group in the Canadian study[29] were identified as "Aboriginal". Māori children made up the Indigenous groups in all four New Zealand studies.[28, 31, 33, 34] Studies conducted in the USA included children of American Indian and Alaskan Native (AI/AN) [26, 30, 32, 36] or Native American ancestry.[35] Comparison groups used in Australian

studies were referenced as non-Indigenous Children.[25, 27] In the Canadian study, Indigenous children were compared to a group designated as non-Indigenous children.[29] The comparison groups in studies from New Zealand were non-Māori Children,[32] European, Pacific Islander, or children of other ethnicities.[28, 31, 34] All studies from the USA included children of White, Black, Hispanic, and Asian backgrounds in their comparison groups. In addition to these categories, some studies included children of Native Hawaiian and Pacific Islander background,[30] children of Pacific Islander background,[26] children identified as belonging to two or more ethnic groups,[26] children of unknown ethnicity,[35] or children of other ethnic groups[30, 35] as a comparison.

Most studies ascertained Indigenous ancestry through information provided in administrative databases and health records. Other studies determined Indigeneity through personal/parent/primary caregiver interviews,[27, 34, 36] census data,[33, 36] and computer-assisted personal interviews.[33]

For outcome assessment, studies in Australia used regional-level data sources[24] or parent/teacher interviews.[37] The Canadian study used a provincial-level perinatal health database to assess outcomes.[29] Studies in New Zealand used national health databases[28, 31] and census data.[33, 34] American studies used national-level education databases,[26] census data,[36] regional/state-level health datasets,[30] state-level education and health data,[32] and clinical data.[35]

NDD categories were created in the studies using different case definitions. In ADHD studies, diagnoses were based on the International Classification of Diseases (ICD) 9 diagnostic codes,[30, 35] ICD-10 diagnostic codes,[30, 31] children who received two or more prescription drugs of ADHD drugs,[31] or collected from a census questionnaire.[34, 36] Studies for ASD defined cases using diagnostic codes from the DSM-IV,[28] ICD- 9,[29, 32] ICD-10,[28, 32] or Socrates health database (New Zealand national database for disability support);[28] census questionnaires;[34] or through teacher

and/or parent interview.[27] Two studies on ASD did not report the diagnostic criteria.[25, 26] In ID studies, primary caregiver interviews,[33] or diagnostic criteria of having an IQ <70[25] were used to determine ID cases. One study did not provide ID case definitions.[26] In the study on SLD, no diagnostic criteria were reported.[26]

2.3.3 Risk of Bias Assessment

Overall, cohort studies were assessed as having a high RoB. In cohort studies, one study had a low RoB,[25] one had a moderate RoB,[29] and five had a high RoB.[26-28, 30, 31] These studies were effective in aspects related to the selection of exposed and unexposed cohorts, exposure ascertainment, outcome assessment, and length and adequacy of follow-up of cohorts. However, many studies failed to provide sufficient information on the comparability of the exposed and unexposed cohorts or whether NDDs were present at the beginning of the studies. Figure 2 summarizes the RoB of cohort and ecological studies based on the NOS.

All cross-sectional studies were rated as having a low risk of bias.[32-36] One aspect where cross-sectional studies performed poorly was related to the samples lack of representativeness of the study population and whether data was collected directly from the study subjects. Figure 3 summarizes the RoB assessment of cross-sectional studies.

2.3.4 Data Synthesis

Figure 4 and Table 2 provide summaries of the POR and 95%CI for the NDD outcomes from all studies included in the review. Meta-analysis of prevalence data was only complete for some Indigenous groups and NDDs due to a limited number of studies. The rest of the results were synthesized narratively.

2.3.5 ADHD Prevalence

Five studies (two conducted in New Zealand[31, 34] and three in the USA[30, 35, 36]) reported the prevalence of ADHD between Indigenous and non-Indigenous children. In the two studies comparing the prevalence of ADHD between Māori and non-Māori children, one retrospective cohort study[31] estimated a lower ADHD prevalence among Māori children compared to their non-Māori counterparts (POR: 0.46; 95%CI: 0.49, 0.54), while the cross-sectional study[34] found no differences in prevalence between the two groups (POR: 1.34; 95%CI: 0.71, 2.51). A meta-analysis of two-cross sectional studies completed in the USA showed no differences in the prevalence of ADHD between AI/AN children and non-Indigenous children (pooled POR: 1.02, 95%CI: 0.79, 1.33) (Figure 5). Statistical heterogeneity was low between the studies (I^2: 0%, p = 0.68). One study[29] from the USA reported a higher prevalence in White children compared to AI/AN children (3.94 per 100 in AI/AN children; 5.64 per 100 in White children) (Table 1), but the lack of raw data for calculations precluded the calculation of a POR. None of the studies evaluated the prevalence of ADHD among Indigenous children in Australia or Canada (Table 3).

2.3.6 ASD Prevalence

Seven studies (two from Australia,[25, 27] one from Canada,[29] two from New Zealand,[28, 34] and two from the USA[26, 32]) compared the prevalence of ASD between Indigenous and non-Indigenous children. A meta-analysis of two cohort studies[25, 27] did not show differences in the prevalence of ASD between children of Australian Aboriginal ancestry and non-Aboriginal children (pooled POR: 0.43; 95%CI: 0.11, 1.58) (Figure 3). There was high heterogeneity between the two studies (I^2: 88%, p=0.003). In Canada, one study[29] identified that the odds of ASD were greater in non-Indigenous children compared to their non-Indigenous counterparts (POR: 0.43; 95%CI: 0.30, 0.60). Studies comparing ASD prevalence between Māori and non-Māori children

yielded inconsistent results. While one study[28] identified a higher prevalence of ASD among non-Māori children (POR: 0.71; 95%CI: 0.68, 0.75), the other study[34] found no difference in ASD prevalence between the two groups (POR: 1.52; 95%CI: 0.80, 2.89) (Figure 2). The two studies conducted in the USA yielded substantially different estimates. An ecological study[26] found greater ASD among White children compared to AI/AN children (POR: 0.75; 95%CI: 0.73, 0.77), but no difference was observed in a cross-sectional study (POR: 1.37; 95%CI: 0.99, 1.89).[32]

We explored various study characteristics as potential sources of high heterogeneity in the meta-analysis of ASD prevalence among Australian Aboriginal children. The two studies included in the meta-analysis used different methods to identify ASD cases.[25, 27] One study relied on administrative health data, while the other used teacher/parental reports. The variation in case ascertainment likely contributed to differences in prevalence estimates.

2.3.7 ID Prevalence

Three studies (one study from Australia,[25] New Zealand,[33] and the USA[26] each) compared ID prevalence in Indigenous and non-Indigenous children. In all three studies, the prevalence of having an ID was greater among Indigenous children (Aboriginal Australian, Māori, AI/AN) than non-Indigenous children (Table 2). The POR among these studies ranged from 1.31 (95%CI: 1.27, 1.35) to 2.84 (95%CI:2.67, 3.02) (Figure 2). This review did not identify studies estimating the prevalence of ID among Indigenous children in Canada (Table 3).

2.3.8 MD Prevalence

There were no studies that examined the prevalence of MDs in Indigenous children in Australia, Canada, New Zealand, and the USA (Table 3).

2.3.9 CD Prevalence

This review did not identify studies that examined the prevalence of CDs in Indigenous children in Australia, Canada, New Zealand, and the USA (Table 3).

2.3.10 SLD Prevalence

One study comparing SLD prevalence between AI/AN and White children in the USA[26] found a higher prevalence among AI/AN children than White children (POR: 1.66; 95%CI: 1.64, 1.68) (Figure 2). No studies on SLD prevalence among Indigenous and non-Indigenous children were identified in Australia, Canada, or New Zealand.

2.4 Discussion

This systematic review provides a comprehensive assessment of 12 studies that evaluated the prevalence of NDDs in Indigenous children from Australia, Canada, New Zealand, and the USA. There is evidence that Australian Aboriginal children have a greater prevalence of ID while no differences between Australian Aboriginal children and non-Aboriginal children were found in the meta-analysis for ASD prevalence. One Canadian study provided evidence of a higher prevalence of ASD among non-Indigenous children. For Māori children, ID prevalence was higher compared to non-Māori children, while evidence was unclear for ADHD and ASD. Limited evidence suggested that AI/AN children in the USA had higher ID and SLD prevalence than White children, while there was a lack of consensus among studies estimating the prevalence of ASD and ADHD among AI/AN children. These results must be interpreted in view of the dearth of evidence for each Indigenous group and NDD identified in this review (Table 2).

This review also identified a substantial knowledge gap regarding the prevalence of some NDDs across the Indigenous groups evaluated. Specifically, there were no studies on ADHD, MD, SLD, and CD among Australian Aboriginal children. Only ASD prevalence has been compared

between Indigenous and non-Indigenous children in Canada. In New Zealand, we found no epidemiological data comparing MD, SLD, and CD among Māori and non-Māori children. In the USA, epidemiological data on the prevalence of all NDDs except for MD and CD have been published for AI/AN children. Knowledge gaps found in this study are consistent with other reviews on Indigenous children and NDDs,[12, 13, 38] and well-designed observational studies are needed to address the lack of data on under-studied NDDs among Indigenous groups (Table 3).

Overall, this review found inconclusive evidence to inform differences in the prevalence of ADHD between Māori and non-Māori children and between AI/AN and White children (Table 2). To our knowledge, this is the first review to collate evidence on ADHD prevalence among Māori and AI/AN children. Inconsistent results between studies may be explained by differences study setting and the definition used to diagnose ADHD across the individual studies.[30, 31, 34-36] Alternatively, it is possible that ADHD diagnoses are underreported among these Māori and AI/AN children. It has been previously reported that Māori children with ADHD are less likely to access mental health services which may contribute to inaccuracies in the number of diagnoses.[39] Additionally, stereotyping and racial biases during clinical decision-making may contribute to children in minority groups from the USA being less likely to be diagnosed with ADHD compared to White children.[40, 41] Although we did not identify any studies comparing ADHD prevalence between Aboriginal Australian children and Indigenous children from Canada with their respective non-Indigenous counterparts, previous reports have described an increased prevalence of ADHD symptomology among Indigenous children from these two countries.[42, 43] However, inequities related to ADHD should not be generalized across different Indigenous children as they all have distinct experiences accessing health care of within their respective countries. Future research

should focus on ways to better identify Māori and AI/AN children with ADHD to further understand the relationship between Indigeneity and ADHD in these two groups.

The greatest body of evidence identified in this review was related to evaluating ASD prevalence among Indigenous and non-Indigenous children. Crude prevalence estimates across seven studies showed ASD prevalence was similar between Indigenous and non-Indigenous children or higher among non-Indigenous children across all the Indigenous groups considered in the review (Table 2). These findings are consistent with results from a previous scoping review assessing the prevalence of ASD among Australian Aboriginal people.[12] Similar to problems related to ADHD diagnoses, ASD underdiagnosis has often been identified as an important challenge in epidemiological studies evaluating ASD among Indigenous people. A previously published literature review assessing the under-detection of ASD among Indigenous populations suggested that ASD is underdiagnosed within Indigenous communities because of disadvantaged geographic locations (e.g., living in remote areas) that act as barriers to accessing diagnostic services and ethnic biases in the diagnostic process.[44] Additionally, ASD and FASD exhibit overlapping impairment characteristics (e.g., cognitive, sensory, and social difficulties)[45] and racial biases during assessments of Indigenous children may result in preferences in diagnosing FASD over ASD. The prevalence of ASD among Indigenous children is likely greater than the rates we found in this review.

This review found that Aboriginal Australian, Māori, and AI/AN children have a higher prevalence of ID than non-Indigenous children (Table 2). A higher prevalence of SLD was also found among AI/AN children compared to White children. The higher prevalence of ID among Aboriginal Australian children correlated with smoking rates during pregnancy, [25] which has been found to be a risk factor that affects brain development.[45] However, these findings are based on a

single study for each Indigenous group and warrant further investigation to strengthen the evidence base for these conditions.

While the prevalence estimates of some NDDs (ID and SLD) were consistent with reports of health disparities between Indigenous and their non-Indigenous counterparts,[11] findings regarding Indigenous children having lower prevalence or no differences in ADHD and ASD compared to non-Indigenous children do not reflect these inequalities. In addition to the problem of underdiagnoses of these disorders mentioned previously, this discrepancy may potentially be attributable to Indigenous peoples' experiences of colonialism. Indigenous families often avoid health care due to the fear of discrimination, racism, stigma, and the lack of culturally sensitive care which decreases access to diagnostic services.[47-49] Avoidance of health care is further amplified by exposure to determinants of health (e.g., income, employment, education) among Indigenous peoples that are a product of historical and contemporary colonialism.[14] Additionally, it is also possible that differences between Indigenous and Western conceptions of disability contribute to these discrepancies in the results. Some Indigenous communities are more accepting of individuals with a disability and embrace uniqueness and diversity which contrasts the widely understood views on disability that focus on impairment and limitations.[50-53] This cultural difference can alter Indigenous people's engagement with 'disability' healthcare services as culturally appropriate services may not be provided. These barriers to healthcare are likely contributors to the increased burden of disability among Indigenous children compared to non-Indigenous children as adequate management of NDDs is not received, although current epidemiological data may not suggest it. It is important to recognize the distinct experiences Indigenous children face to design solutions to accurately describe prevalence among Indigenous children and provide quality care through Indigenous perspectives.

Future research should expand the current knowledge base on the prevalence of NDDs among Indigenous children, particularly in underrepresented NDDs. Research on solutions to improve diagnostic accuracy that integrates the diverse context Indigenous children live in should also be completed in partnership with Indigenous communities.

2.4.1 Strengths and Limitations of the Systematic Review

To our knowledge, this is the first comprehensive systematic review that consolidates current epidemiological evidence on NDDs among Indigenous children of countries with similar histories of colonization. Strengths of this study include using a rigorous methodology to identify relevant studies and independent screening of studies by two reviewers to decrease selection bias. Dual independent assessment of quality and data extraction was performed to minimize potential assessor biases.

Findings in this review are potentially limited by methodological heterogeneity and moderate quality of included studies. Studies included in this review had different study design characteristics that may sample populations differently leading to imbalances between the populations being compared. There were also methodological differences in how Indigeneity and NDDs were defined. Studies in this review relied on parent and/or teacher interviews and administrative health and education databases to identify Indigenous populations. Different NDD case definitions were used in individual studies, such as relying on interviews versus diagnostic codes, which further influenced the validity of prevalence estimates. Furthermore, the wide spectrum of age of populations across the included studies makes obtaining precise prevalence estimates difficult as proper diagnoses of NDDs may not be possible until a child is older due to psychometric limitations of developmental assessments.[1] Finally, most of the cohort studies were at a high risk of bias because comparability between the cohort of Indigenous and non-Indigenous

children was not reached due to the lack of match and adjustment for confounders between the two groups.

Additionally, the small number of studies available and methodological heterogeneity made data synthesis challenging and limited our ability to make conclusions on the comparison of some NDD prevalence between Indigenous and non-Indigenous children. The small number of studies available may also hinder the precision of our effect estimates in the meta-analysis.[53]

2.5 Conclusion

Limited evidence suggests a greater burden of ID affecting Indigenous children in Australia, New Zealand, and the USA. This review also found a greater burden of SLD affecting AI/AN children compared to White children. There is inconclusive evidence or no evidence informing the prevalence of other NDDs in Indigenous children. In addition to the need to address the knowledge gap for some NDDs across Indigenous groups, future research on NDDs among Indigenous children should identify strategies to estimate the prevalence of NDDs among Indigenous groups accurately and incorporate Indigenous worldviews on disability.

2.6 References

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Table 2.1 Characteristics of Included Studies

Study	Country	Study Design	Setting	Population Characteristics	Source for Cases Used	Diagnostic Criteria	Prevalence Estimates and Prevalence Odds/Rate/Risk Ratio with 95% Confidence Interval (CI)
Attention Deficit/Hyperactivity Disorder							
Chung 2019[29]	USA	Retrospective Cohort	Regional	N= 867,453 Age Range = 5-11 yr. Female % = not reported Indigenous group: • AI/AN Comparison group: • White	Electronic medical records	ICD-9 (314.x) ICD-10 (F90.x)	*No raw data reported Prevalence per 100 (2016 Data): • AI/AN: 3.94 • White: 5.64
Donovan 2019[30]	New Zealand	Retrospective Cohort	National	N= 49,923 Age Range = 0-18 yr. Female % = 48.50% Indigenous group: • Māori (n= 14,149) Comparison groups: • Non-Māori (European, Pacific, MELAA, Asian, Other) (n=35,807)	Government Research Database (Integrated Data Infrastructure)	ICD-10 or a child received two or more prescriptions of ADHD drugs	*No raw data reported Prevalence Odds Ratio (ref. European): • 0.456 (95%CI: 0.387-0.537)
Wong 2021[35]	USA	Cross-Sectional	National	N= 120,129 Age Range = 8 yr. Female % = 49.00% Indigenous group: • AI/AN	National Health Interview Survey	Survey question	*No raw data reported Prevalence per 100: • AI/AN: 11.93 (95%CI: 9.42–15.00) • White: 11.32 (95%CI: 11.02-11.62) Prevalence Risk Ratio (ref. White):

<table>
<tr><td></td><td></td><td></td><td></td><td>Comparison groups:

• White, Black, Asian, Other, Hispanic</td><td></td><td></td><td>• 1.03 (95%CI: 0.79 – 1.34) (adjusted for sex and survey year)</td></tr>
<tr><td>Ministry of Health 2021[33]</td><td>New Zealand</td><td>Cross-Sectional</td><td>National</td><td>N= 2,954

Age range = 0-14 yr.

Female % = 47.30%

Indigenous group:

• Māori (n= 1,034 children)

Comparison groups:

• European/Other, Pacific, Asian (n=1,920; European/Other only n= 1,998)</td><td>New Zealand Health Survey</td><td>Survey question</td><td>*No data on number of cases

Prevalence per 100:

• Māori: 3.1 (95%CI: 1.7-5.1)
• European/Other: 2.5 95%CI: (1.7 - 3.4)

Prevalence Rate Ratio (ref. non-Māori):

• 1.34 (95%CI: 0.71-2.51) (adjusted for age and gender)</td></tr>
<tr><td>Reyes 2012[34]</td><td>USA</td><td>Cross-sectional</td><td>Clinical</td><td>N= 7,954

Age Range = 5-17 yr.

Female = 50.90%

Indigenous group:

• Native American (n=37)

Comparison groups:

• White, Black, Hispanic, Asian, Other, Unknown (n=7,917; White only n = 6,231)</td><td>Obtained from electronic medical records</td><td>ICD-9 (314.0 - 314.9)</td><td><table><tr><td></td><td>ADHD</td><td>No ADHD</td><td>Total</td></tr><tr><td>Native American</td><td>1</td><td>36</td><td>37</td></tr><tr><td>White</td><td>247</td><td>5,984</td><td>6,231</td></tr></table>
Prevalence:

• Native American: 2.70%
• White: 3.90%

Prevalence Odds Ratio (ref. White):

• 0.67 (95%CI: 0.09 – 4.93)</td></tr>
</table>

<table>
<tr><th colspan="7">Autism Spectrum Disorder</th></tr>
<tr>
<td>Abdullahi 2019[24]</td>
<td>Australia</td>
<td>Retrospective Cohort</td>
<td>Regional</td>
<td>N= 764,749

Age range = not reported

Female % = 48.70%

Indigenous group:

• Australian-born mothers of Indigenous background (n=44,184)

Comparison group:

• Non-Indigenous (n=720,565)</td>
<td>Western Australia Data Linkage System</td>
<td>Not Reported</td>
<td>
<table>
<tr><th></th><th>ASD</th><th>No ASD</th><th>Total</th></tr>
<tr><td>Indigenous</td><td>31</td><td>44,153</td><td>44,184</td></tr>
<tr><td>Non-Indigenous</td><td>2,203</td><td>718,362</td><td>720,565</td></tr>
</table>
Prevalence:

• Indigenous: 0.070%
• Non-Indigenous Background: 0.31%

Prevalence Odds Ratio (ref. non-Indigenous):

• 0.23 (95%CI: 0.16 – 0.33)
</td>
</tr>
<tr>
<td>Bowden 2020[27]</td>
<td>New Zealand</td>
<td>Retrospective Cohort</td>
<td>National</td>
<td>N= 1,560,297

Age Range = 0-24 yr.

Female % = 48.30%

Indigenous group:

• Māori (n=385,728)

Comparison groups:

• New Zealand Europeans, Pasifika, Asian, MELAA, Other (n=1,174,569; European only n=1,028,182)</td>
<td>Programme for the Integration of Mental Health Data; The National Minimum Dataset; Socrates</td>
<td>DSM IV, ICD-10-AM; Socrates Case Identification Codes</td>
<td>
<table>
<tr><th></th><th>ASD</th><th>No ASD</th><th>Total</th></tr>
<tr><td>Māori</td><td>1,980</td><td>383,748</td><td>385,728</td></tr>
<tr><td>European</td><td>7,401</td><td>1,020,771</td><td>1,028,172</td></tr>
</table>
Prevalence:

• Māori: 0.51%
• European: 0.72%

Prevalence Odds Ratio (ref. Europeans):

• 0.71 (95%CI: 0.68 – 0.75)
</td>
</tr>
<tr>
<td>Burstyn 2010[28]</td>
<td>Canada</td>
<td>Retrospective Cohort</td>
<td>Regional</td>
<td>N= 218,890

Age Range = 4-10 yr.

Female % = 48.90%

Indigenous group:</td>
<td>Physician billing records for ASD</td>
<td>ICD-9 (299.0, 299.8)</td>
<td>
<table>
<tr><th></th><th>ASD</th><th>No ASD</th><th>Total</th></tr>
<tr><td>Aboriginal</td><td>34</td><td>14,452</td><td>14,486</td></tr>
<tr><td>Non-Aboriginal</td><td>899</td><td>164,041</td><td>164,940</td></tr>
</table>
Prevalence:
</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>• Aboriginal Group (n=14,486)

Comparison group:

• Non-Indigenous (n=164,940)</td><td></td><td></td><td>• Aboriginal: 0.23%
• Non-Aboriginal: 0.55%

Prevalence Odds Ratio (ref. non-Aboriginal):

• 0.43 (95%CI: 0.30 – 0.60)</td></tr>
<tr><td>de Brey 2021[25]</td><td>USA</td><td>Ecological</td><td>Education</td><td>N= 50,693,775

Age range = 3-21 yr.

Female % = not reported

Indigenous group:

• AI/AN (n= 490,000)

Comparison groups:

• White, Black, Hispanic, Asian, Pacific Islander, Two or more Race (n= 50,203,775; White only n= 23,845,000)</td><td>Obtained from the Intellectual Disability Exploring Answers Database</td><td>Not reported</td><td><table><tr><td></td><td>ASD</td><td>No ASD</td><td>Total</td></tr><tr><td>AI/AN</td><td>5,990</td><td>484,010</td><td>490,000</td></tr><tr><td>White</td><td>385,867</td><td>23,459,133</td><td>23,845,000</td></tr></table>
Prevalence:

• AI/AN: 1.20%
• White: 1.62%

Prevalence Odds Ratio (ref. White):

• 0.75 (95%CI: 0.73 – 0.77)</td></tr>
<tr><td>Ministry of Health 2021[33]</td><td>New Zealand</td><td>Cross-Sectional</td><td>National</td><td>N= 2,954

Age range = 0-14 yr.

Female % = 47.30%

Indigenous group:

• Māori (n= 1,034 children)

Comparison groups:

• European/Other, Pacific, Asian (n=1,920;</td><td>New Zealand Health Survey</td><td>Collected from the New Zealand Health Survey</td><td>*No data of number of cases

Prevalence per 100:

• Māori: 3.1 (95%CI: 1.7 - 5.1)
• European/Other: 2.5 (95%CI: 1.7 - 3.4)
• Pacific: 3.2 (95%CI: 1.6 – 5.6)
• Asian: 1.9 (95%CI: 0.7-3.8)

Prevalence Rate Ratio (ref. non-Māori):

• 1.52 (95%CI: 0.80-2.87) (Adjusted Ratio for Age and Gender)</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>European/Other only n= 1,998)</td><td></td><td></td><td></td></tr>
<tr><td>Maenner 2021[31]</td><td>United States</td><td>Cross-sectional</td><td>Regional</td><td>N=220,281

Age range = 8 yr.

Female % = 48.90%

Indigenous group:

• AI/AN (n=approx. 13,216)

Comparison groups:

• White, Black, Hispanic, Asian/Pacific Islander (n= approx. 218,959; White only n= approx. 113,664)</td><td>The Autism and Developmental Disabilities Monitoring</td><td>ICD-9/ICD-10 Code (299.00-299.99/F84 expect F84.2)</td><td>*No raw data reported; estimates from percentages published

<table><tr><td></td><td>ASD</td><td>No ASD</td><td>Total</td></tr><tr><td>AI/AN</td><td>38</td><td>1,284</td><td>1322</td></tr><tr><td>White</td><td>2,410</td><td>111,254</td><td>113,664</td></tr></table>
Prevalence per 100:

• AI/AN: 2.90 (95%CI: 2.13-3.94)
• White: 2.12 (95%CI: 2.03-2.20)

Prevalence Odds Ratio (ref. White):

• 1.37 (95%CI: 0.99 – 1.89)</td></tr>
<tr><td>May 2020[26]</td><td>Australia</td><td>Prospective Cohort</td><td>Regional</td><td>N= 7,213

Age range = 12-13 yr.

Female % = 49.80%

Indigenous group:

• Indigenous (n= 201)

Comparison group:

• Non-Indigenous (n= 7,012)</td><td>Teacher-/Parent Report</td><td>Teacher/Parent Interview</td><td><table><tr><td></td><td>ASD</td><td>No ASD</td><td>Total</td></tr><tr><td>Indigenous</td><td>6</td><td>195</td><td>201</td></tr><tr><td>Non-Indigenous</td><td>237</td><td>6,775</td><td>7,012</td></tr></table>
Prevalence:

• Indigenous: 3.0%
• Non-Indigenous: 3.3%

Prevalence Odds Ratio (ref. Non-Indigenous):

• 0.88 (95%CI: 0.39 - 2.00)</td></tr>
<tr><td colspan="8">Intellectual Disability</td></tr>
<tr><td>Abdullahi 2019[24]</td><td>Australia</td><td>Retrospective Cohort</td><td>Regional</td><td>N= 764,749

Age range = not reported

Female % = 48.70%

Indigenous group:</td><td>Western Australia Data Linkage System</td><td>IQ < 70</td><td><table><tr><td></td><td>ID</td><td>No ID</td><td>Total</td></tr><tr><td>Indigenous</td><td>1,207</td><td>42,977</td><td>44,184</td></tr><tr><td>Non-Indigenous</td><td>7,066</td><td>713,499</td><td>720,565</td></tr></table>
Prevalence:</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td>• Australian-born mothers of Indigenous background (n=44,184)

Comparison group:

• Non-Indigenous (n=720,565)</td><td></td><td></td><td>• Indigenous: 2.7%
• Non-Indigenous Background: 0.98%

Prevalence Odds Ratio (ref. non-Indigenous):

• 2.84 (95%CI:2.67 – 3.02)</td></tr>
<tr><td>de Brey 2021[25]</td><td>USA</td><td>Ecological</td><td>Education</td><td>N= 50,693,775

Age range = 3-21 yr.

Female % = not reported

Indigenous group:

• AI/AN (n=490,000)

Comparison groups:

• White, Black, Hispanic, Asian, Pacific Islander, Two or more Race (n=50,203,775; White only n= 23,845,000)</td><td>Obtained from the Intellectual Disability Exploring Answers Database</td><td>Not reported</td><td><table><tr><td></td><td>ID</td><td>No ID</td><td>Total</td></tr><tr><td>AI/AN</td><td>5,325</td><td>484,010</td><td>490,000</td></tr><tr><td>White</td><td>177,840</td><td>23,459,133</td><td>23,845,000</td></tr></table>
Prevalence:

• AI/AN: 1.09%
• White: 0.75%

Prevalence Odds Ratio (ref. White):
• 1.46 (95%CI: 1.42 – 1.50)</td></tr>
<tr><td>Himona 2019[32]</td><td>New Zealand</td><td>Cross-Sectional</td><td>National</td><td>N= 23,000 (14,900 Adults; 8,100 Children)

Age Range = 0-14 yr.

Female % = not reported

Indigenous Group:

• Māori

Comparison Group:

• Non-Māori</td><td>Survey/ Computer Assisted Telephone Interview/ Computer Assisted Personal Interview</td><td>The parent or caregiver was asked whether a child (5–14 years old) has a recognized intellectual disability</td><td>*Authors applied cross-sectional data onto population data

<table><tr><td></td><td>ID</td><td>No ID</td><td>Total</td></tr><tr><td>Māori</td><td>7,000</td><td>484,010</td><td>235,000</td></tr><tr><td>Non-Māori</td><td>15,000</td><td>23,459,133</td><td>654,000</td></tr></table>
Prevalence:

• Māori: 2.98%
• Non-Māori: 2.30%

Prevalence Odds Ratio (ref. non-Māori):</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>• 1.31 (95%CI: 1.27 – 1.35)</td></tr>
<tr><td colspan="8">Specific Learning Disorders</td></tr>
<tr><td>de Brey 2021[25]</td><td>USA</td><td>Ecological</td><td>Education</td><td>N= 50,693,775

Age range = 3-21 yr.
Female % = not reported

Indigenous Group:

• AI/AN (n=490,000)

Comparison Groups:

• White, Black, Hispanic, Asian, Pacific Islander, Two or more Race (n=50,203,775; White only n = 23,845,000)</td><td>Obtained from the Intellectual Disability Exploring Answers Database</td><td>Not reported</td><td><table><tr><td></td><td>SLD</td><td>No SLD</td><td>Total</td></tr><tr><td>AI/AN</td><td>33,618</td><td>484,010</td><td>490,000</td></tr><tr><td>White</td><td>1,014,426</td><td>23,459,133</td><td>23,845,000</td></tr></table>Prevalence:

• AI/AN: 6.86%
• White: 4.25%

Prevalence Odd Ratio (ref. White):

• 1.66 (95%CI: 1.64 – 1.68)</td></tr>
</table>

ADHD= Attention Deficit/Hyperactivity Disorder; AI/AN = American Indian and Alaska Natives; ASD = Autism Spectrum Disorder; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases; ID = Intellectual Disability; IQ = Intellectual Quotient; MD = Motor Disorders; MELAA = Middle Eastern Latin American and African; SLD = Specific Learning Disorders; USA = United States of America

Table 2.2 Effect Direction Plot for Prevalence Odds Ratios of NDDs among Indigenous children compared to Non-Indigenous Children

Study	Design	Country	Indigenous Group	Comparison Group	NDD Outcome[a]			
					ADHD	ASD	ID	SLD
Abdullahi 2019[24]	RCS	AUS	Aboriginal	Non-Aboriginal	-			-
May 2020[26]	PCS	AUS	Aboriginal	Non-Aboriginal	-		-	-
Burstyn 2010[28]	RCS	CAN	Aboriginal	Rest of cohort	-		-	-
Bowden 2020[27]	RCS	NZ	Māori	European	-		-	-
Donovan 2019[30]	RCS	NZ	Māori	Non-Māori		-	-	-
Himona 2019[32]	CS	NZ	Māori	Non-Māori	-	-		-
Ministry of Health 2021[33]	CS	NZ	Māori	European			-	-
Chung 2019[29]	RCS	USA	AI/AN	White	 *	-	-	-
de Brey 2021[25]	E	USA	AI/AN	White	-			
Maenner 2021[31]	CS	USA	AI/AN	White	-		-	-
Reyes 2012[34]	CS	USA	AI/AN	White		-	-	-
Wong 2021[35]	CS	USA	AI/AN	White		-	-	-

[a]Effect direction:  = Higher in Indigenous group,  = Higher in comparison group,  = No difference, - = not applicable;

*Chung 2019 did not provide raw data and effect direction was determined using the authors' figure. ADHD= Attention Deficit/Hyperactivity Disorder; AI/AN = American Indian and Alaska Natives; ASD = Autism Spectrum Disorder; AUS = Australia; CAN = Canada; CS = Cross-Sectional Study; E = Ecological Study; ID = Intellectual Disability; MD = Motor Disorders; PCS = Prospective Cohort Study; RCS = Retrospective Cohort Study; SLD = Specific Learning Disorders; NZ = New Zealand; USA = United States of America.

Table 2.3 Evidence Gaps in NDD Research among Indigenous Children

Indigenous Group	NDD Outcome					
	ADHD	ASD	ID	MD	CD	SLD
Australian Aboriginal	✗	✓	✓	✗	✗	✗
Indigenous Children in Canada	✗	✓	✗	✗	✗	✗
Māori Children	✓	✓	✓	✗	✗	✗
AI/AN	✓	✓	✓	✗	✗	✓

✓ – Epidemiological study comparing NDD prevalence among Indigenous and non-Indigenous exists; ✗ - Epidemiological study comparing NDD prevalence among Indigenous and non-Indigenous do not exist

Figure 2.1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram for Study Selection

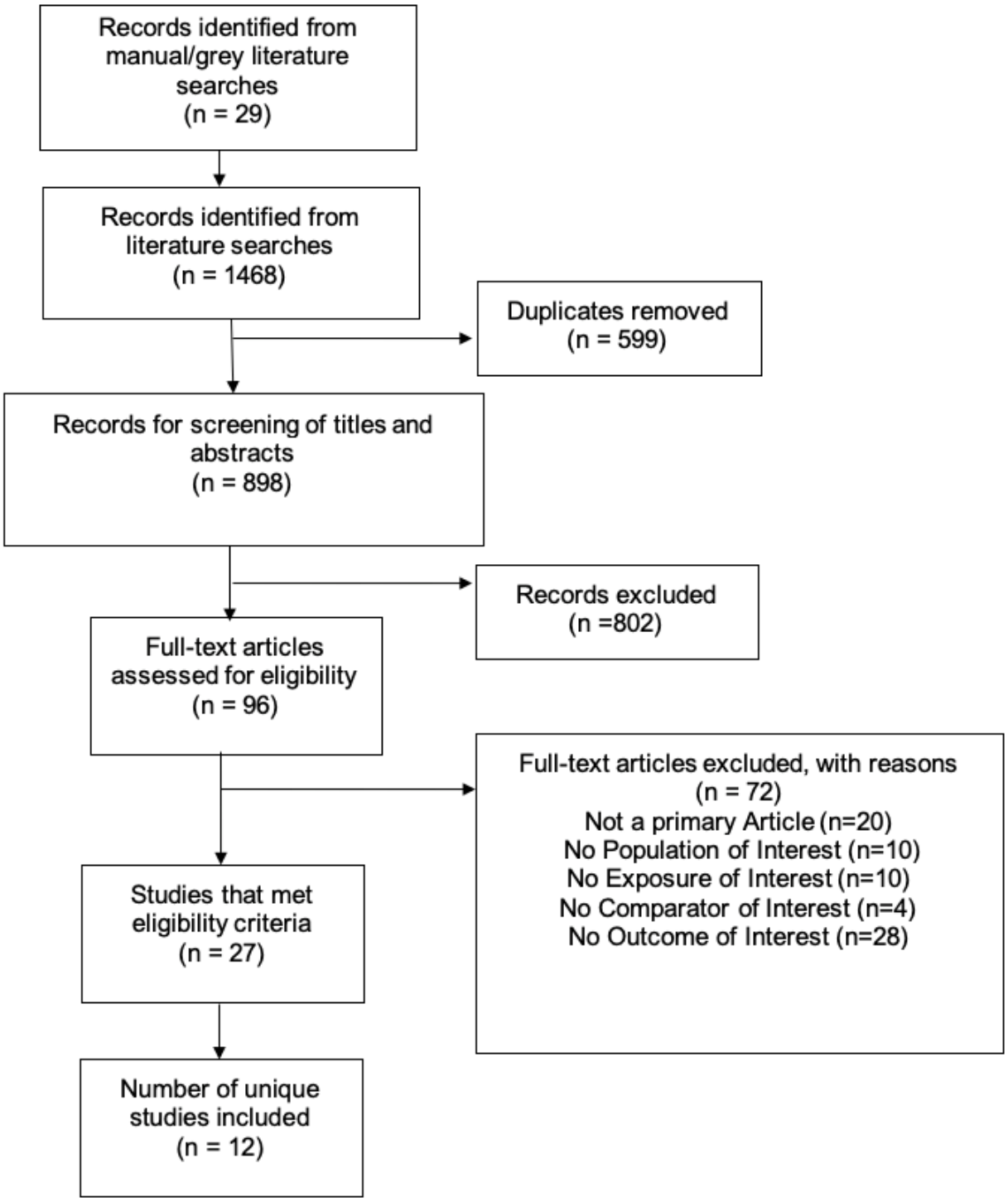


Figure 2.2 Risk of Bias Summary for Cohort and Ecological Studies

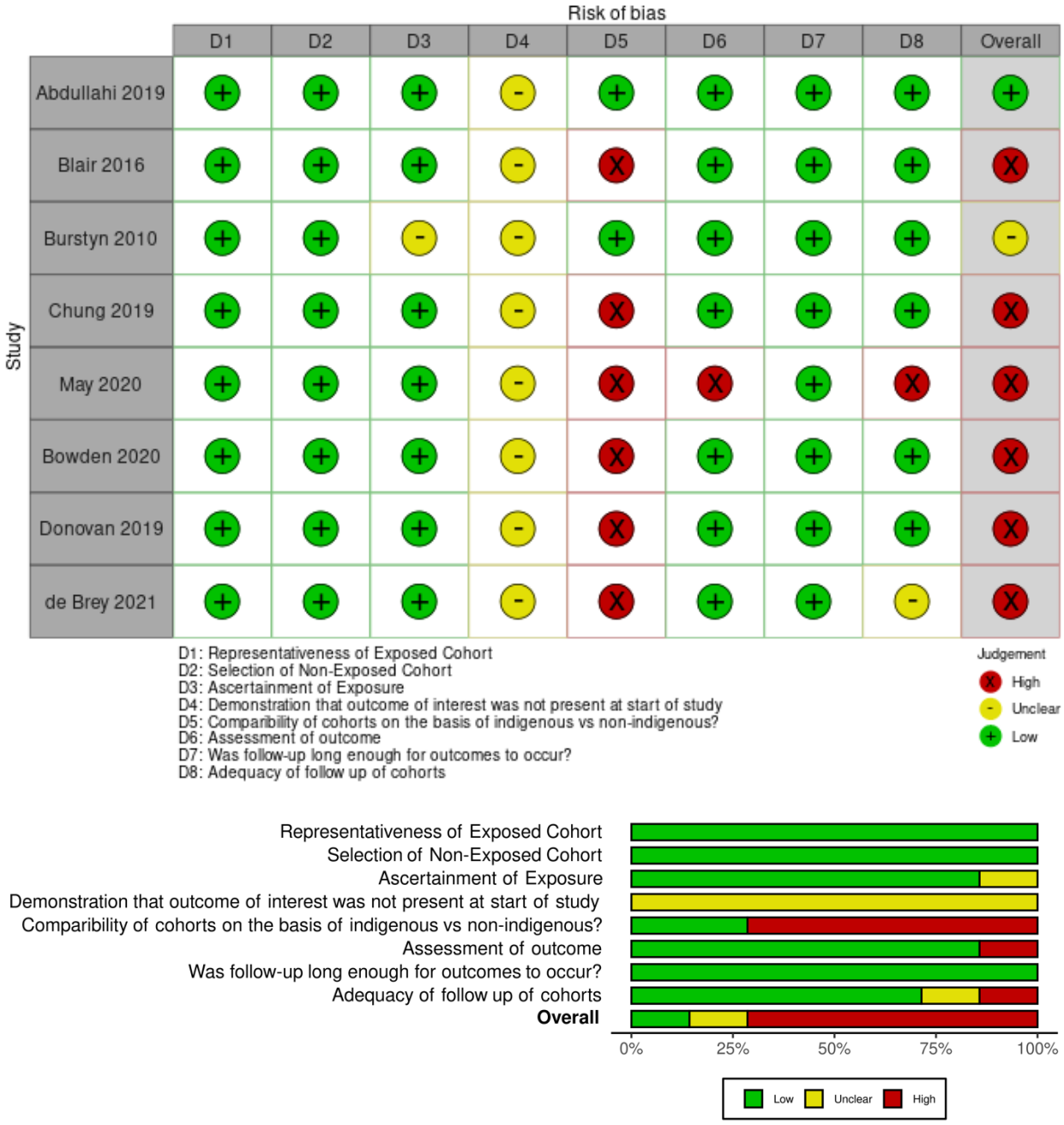
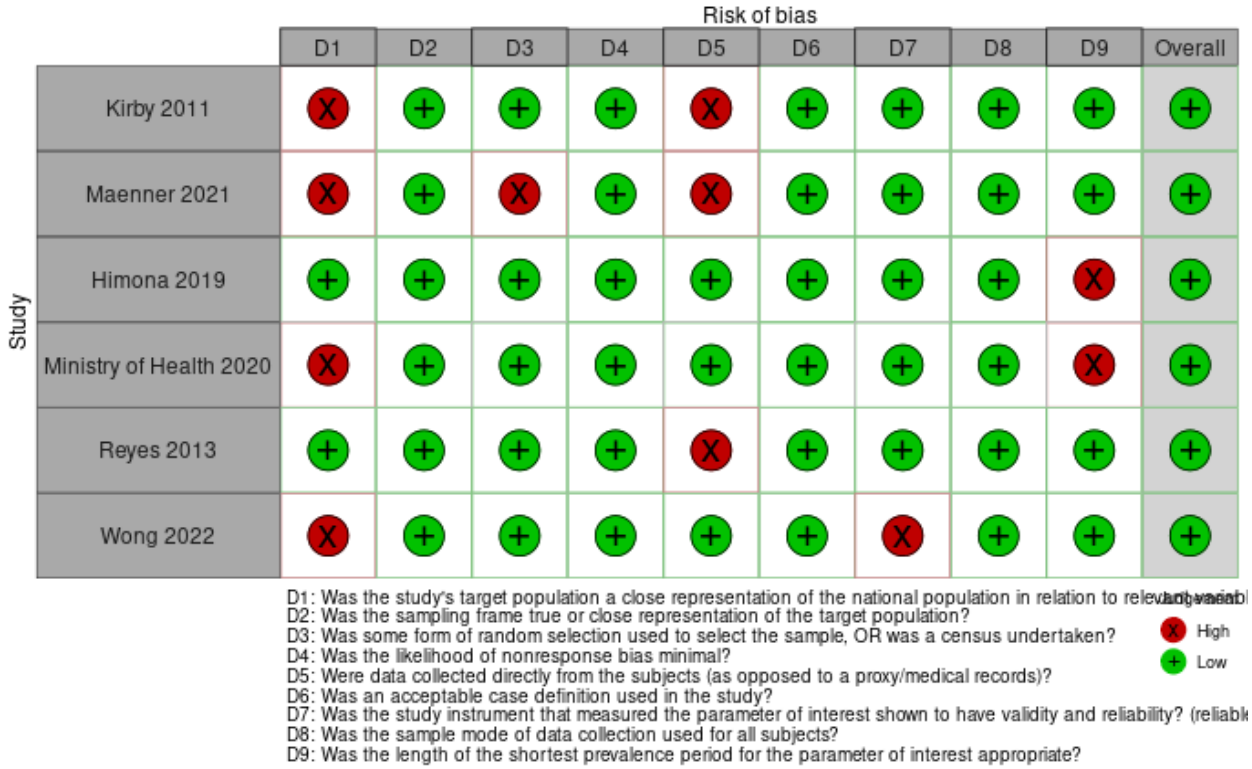


Figure 2.3. Risk of Bias Summary for Cross-Sectional Studies



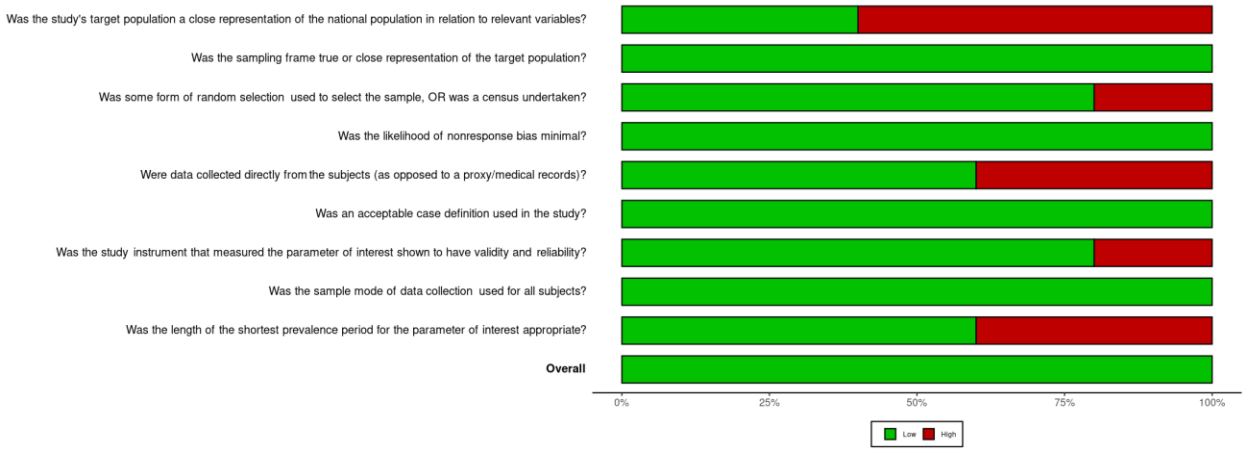


Figure 2.4 NDD Prevalence Estimates between Indigenous and non-Indigenous Children from Included Studies

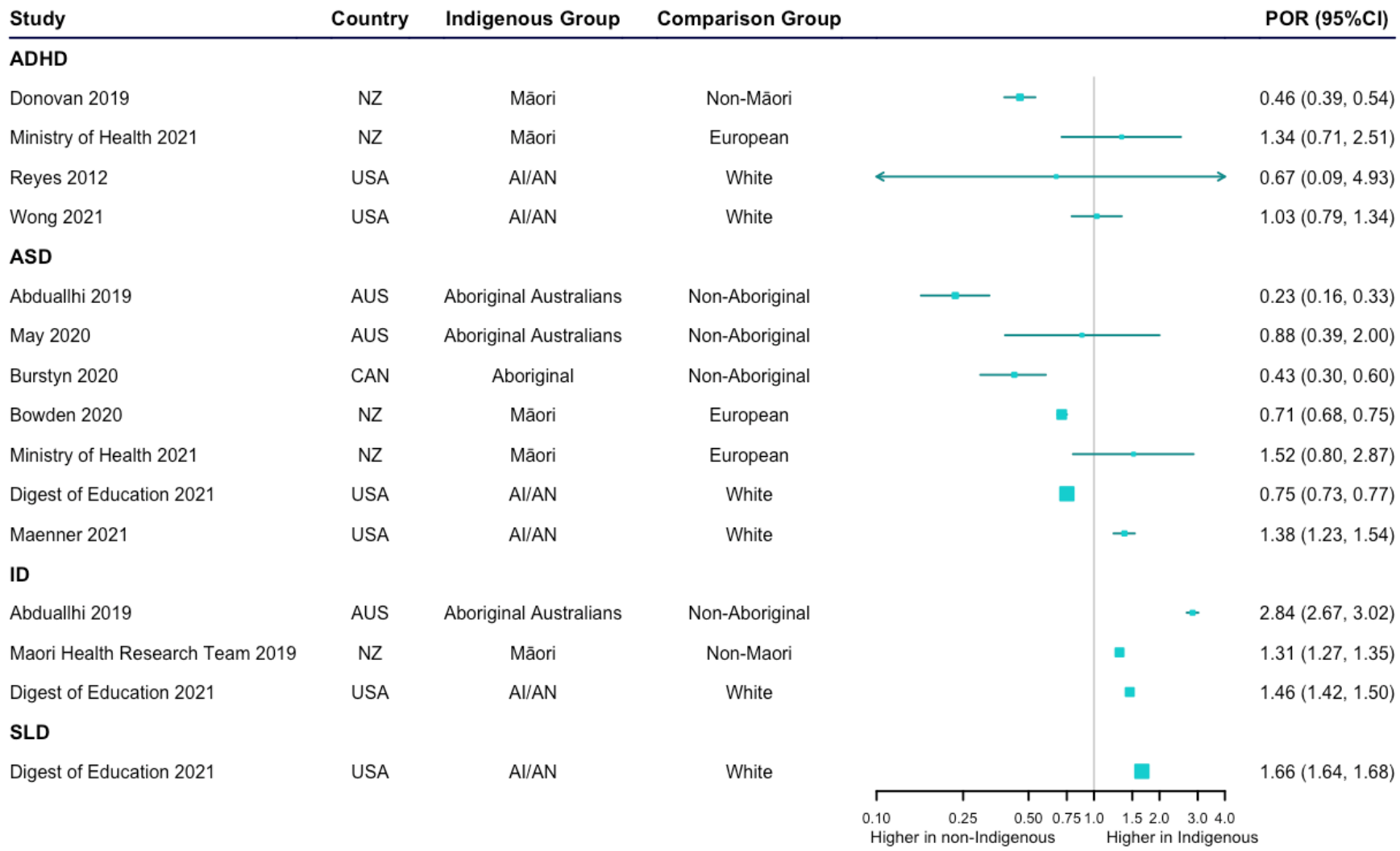


Figure 2.5 Meta-analysis of ADHD Prevalence between AI/AN vs White Children

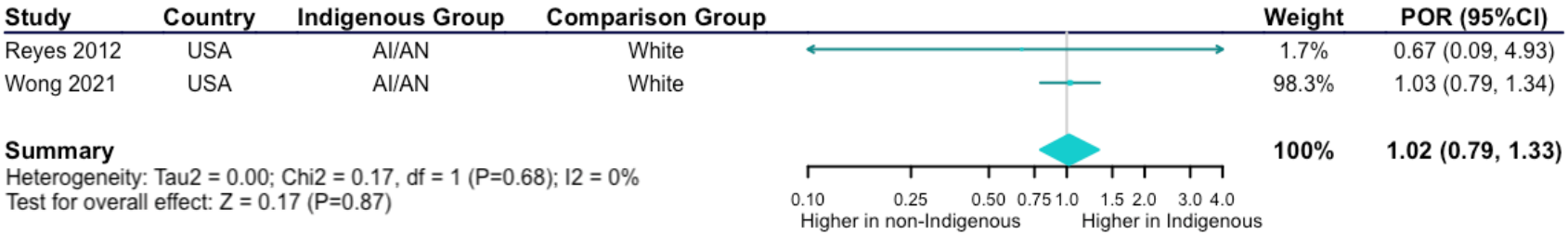
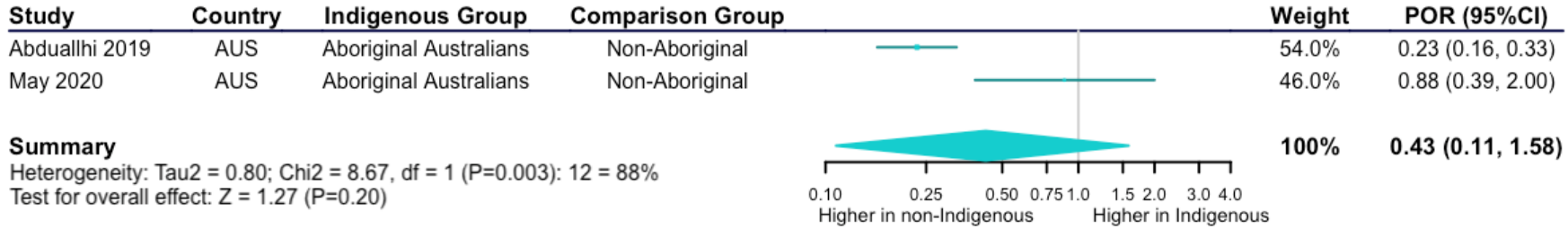


Figure 2.6 Meta-analysis of ASD Prevalence between Aboriginal Australian and non-Aboriginal Children



Chapter 3: Neurodevelopmental Disorders among Métis Children in Alberta

3.1 Introduction

Métis are a distinct group of Indigenous people in Canada. They are one of three Indigenous groups officially recognized by the Canadian Constitution Act, 1982, Section 35.[1] Their origins trace back to the union between European fur traders and First Nation women in the 17th century. Today, the term Métis describes a group of people descendants of Indigenous and European ancestry with a distinct combination of culture, language and identity.[2] In Canada, there are over 100,000 children who are identified as Métis, with Alberta having the second largest population of Métis people in Canada and the largest amongst the Western Provinces.[3] In Alberta, the Métis Nation of Alberta is the provincial representative voice for almost 50,000 Métis in Alberta and recognize a Métis person as one "who self-identifies as a Métis, is distinct from other Indigenous peoples, is part of historic Métis Nation ancestry, and is accepted by the Métis Nation.[4]

Neurodevelopmental disorders and disabilities (NDD/D) is a term previously used by Miller et al. to describe a group of neurological conditions associated with functional limitations within the fundamental domains of child development (motor, speech, learning-cognition, social, sensory, and neuropsychological). Some diagnoses under NDD/D include autism spectrum disorder (ASD), attention deficit-hyperactivity disorder (ADHD), specific learning disabilities, cerebral palsy (CP), and fetal alcohol syndromes (FAS).[5] The NDD/D term was used by the researchers to emphasize the functional profiles of individuals rather than specific diagnoses to align with the International Classification of Functioning, Disability, and Health (ICF) that conceptualizes functioning and disability as the complex relationship between environmental and personal factors with an individual's health condition. Based on the ICF, disability can be determined based on impairment of body function and structure, activity limitation, and/or

participation restriction as a member of society.[6] Categorization based on consequences of conditions is useful for policy, program, and intervention planning.[7] NDD/D categorization was applied previously within a Canadian provincial administrative health database to identify children with NDD/D.[8]

In Canada, of the 5% of children affected by disabilities, 74% are diagnosed with NDD/D.[5] These neurological conditions can be lifelong and are associated with social and mental health problems and future employment and earning opportunities.[9, 10] Previous research assessing NDD/Ds among Indigenous children has taken pan-Indigenous approaches (aggregating data from First Nations, Métis, and Inuit children), evaluated only First Nations children, or focused on prevalence among older age groups including older children and adults (15 years and older).[3, 11-14] In these studies, developmental and learning disabilities and ADHD symptomology were more prevalent among Indigenous children than non-Indigenous children,[3,11] while ASD was less prevalent among Indigenous children.[12] It was also found that Indigenous children with CP had worse health outcomes than non-Indigenous children, including injury and other impairments.[13] Health disparities between Indigenous children and non-Indigenous children have been recognized to be shaped by the effects of historical and contemporary effects of colonialism, including systemic racism, discrimination, and intergenerational trauma. The effects of colonialism on health outcomes may operate through increased exposure to social determinants of health.[15] However, critical knowledge gaps remain about the neurodevelopmental health of Métis children and research specific to their neurodevelopmental health is needed to address the needs and experiences of Métis people.

In Canada, the burden of NDD/D among Métis children aged 0-10 years old compared to non-Métis children has not yet been studied. To address this knowledge gap, this study evaluates

the prevalence and assess maternal and neonatal characteristics of NDD/D among Métis children compared to non-Métis children in Alberta.

3.2 Methods

3.2.1 Study Design

A retrospective birth cohort study of all singleton live births of Métis women and a random sample of children born to non-Métis mothers in Alberta from 2006 to 2016 with longitudinal follow-up data until 2019 was conducted. This study follows the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines for observational epidemiological studies.[16] The University of Alberta Health Research Ethics Board – Health Panel approved this study (#Pro00098620).

3.2.2 Data Sources

This study used linked data from a previous project, *Ehawawisit,*[17] which evaluated maternal sociodemographic characteristics, pregnancy, and perinatal outcomes of all live births from Métis and non-Métis women in Alberta between 2006 and 2016. *Ehawawisit* previously identified a cohort of singleton births from Métis and non-Métis mothers by linking data from the Métis Nation of Alberta (MNA) Identification Registry (MNAIR) and the Alberta Perinatal Health Program (APHP), which make up the cohort used in this study. The APHP is a validated perinatal clinical registry which contains maternal and perinatal data for all deliveries occurring in a hospital or attended by a registered midwife at home in Alberta. Maternal and child personal health numbers are captured in the same record which facilitates longitudinal follow-up of children's outcomes after birth. The MNAIR is a dataset managed by the MNA that contains demographic information on approximately 43,000 Métis people in Alberta. New longitudinal health data for each child in the cohort collected between April 1, 2006, to March 31, 2019, from the

administrative health databases were linked with data from the *Ehawawisit* study. Sociodemographic characteristics were collected through the Alberta Health Care Insurance Plan (AHCIP), a population registry covering all Alberta residents. Data on NDD/D diagnoses were captured from the Discharge Abstract Database (DAD), the Alberta Physician Claim Assessment (APCA) dataset, and the National Ambulatory Care Reporting System (NARCS). The DAD provided diagnostic and intervention information on all hospitalizations using the International Classification of Diseases (ICD), 10th Revision, enhanced Canadian Version (ICD-10-CA) diagnostic codes for each episode of care and Canadian Classification of Health Intervention (CCI) procedural codes for interventions received. The APCA contains physician billing claims data, including information on all services (medical, surgical, obstetrical, anaesthesia, and diagnostic) provided by fee-for-service physicians in Alberta using ICD, 9th Revision (ICD-9) and CCI procedure codes. The NACRS collects information on all emergency presentations and services delivered within acute care institutions in Alberta using ICD-10-CA codes for each episode of care and CCI for procedures.

3.2.3 Study Population

All singleton births between 2006 and 2016 from Métis mothers and a random sample of non-Métis mothers from the *Ehawawisit* study make up the birth cohort of this study.[17]

3.2.4 Study Procedure

A cohort of Métis and non-Métis live births were previously identified in the *Ehawawisit*.[17] In that study, probabilistic linkage between the MNAIR and the APHP identified a cohort of Métis women who gave birth while the cohort of non-Métis mothers who gave birth were identified in the APHP. In this study, we included all Métis children from *Ehawawisit*[17] and randomly sampled a ratio of 1:4 children born to non-Métis mothers to make up the non-Métis children cohort. The

Alberta Health Analytic and Performance Reporting Branch, the Strategy for Patient Oriented Research and the APHP facilitated linkage between *Ehawawisit* study data and new longitudinal child administrative health data. For each child, longitudinal data on sociodemographic characteristics and neurodevelopmental outcomes were collected from administrative health databases. The follow-up period of each child ran from their date of birth (between April 1, 2006, and March 31, 2016) until they turned ten years old, or the end of the study period (March 31, 2019), when they died, or moved out of the province. The study flow process is summarized in Figure 1.

3.2.5 Definition of Child Neurodevelopmental Disorders

The primary outcome was the prevalence of NDD/D during the first ten years of life. NDD/D were defined following an approach previously adopted by Arim et al.[8] In this approach, ICD-9/ICD-10 diagnostic codes for Canada's most common NDD/D based on the Participation and Activity Limitation Survey (PALS) were categorized into six functional limitation domains: motor, speech/communication, learning-cognition, social, sensory, and neuropsychological. A full list of the diagnostic codes used in this study and their corresponding domains can be found in the Appendix. Children with ≥2 medical encounters or one hospitalization for a specific condition/diagnostic code during the follow-up period (2006-2019) were identified to have an NDD/D as previously ascertained in the Arim et al.[8] study.

3.2.6 Study Covariates

Maternal factors: We collected data on variables previously found to be statistically different between Métis and non-Métis mothers from *Ehawawisit*,[17] and those of theoretical importance to NDD/D and Indigeneity. They included maternal age at delivery, health behaviours during pregnancy (smoking, alcohol, and drug use), area of residence (urban/rural), mode of

delivery (vaginal or caesarean), and area-level material and social deprivation. Material and social deprivation were used as proxy measures of socioeconomic status (SES). These measures were calculated using the Pampalon Material and Social Deprivation Index. The Pampalon Index uses information from the Canadian census by dissemination area to create an area-level composite measure of material and social deprivation. The material deprivation component integrates data on education, employment, and income, while the social deprivation component is composed of information on marital status, one-person household, and single-parent families. Material and social deprivation are both reported in quintiles, where quintile 1 (Q1) represents the least deprived group and Q5 represents the most deprived group. The Pampalon Index has been used previously in Canadian studies as a valid measure of area-level SES.[18] Maternal postal code at the time of delivery was used to assign an area of residency and geographically linked to dissemination areas to determine quintiles of deprivation.

Neonatal factors: We collected data on the infant's sex, birth weight, gestational age at delivery (classified as preterm for <37 weeks and term for children born >37 weeks gestation), small for gestational (birth weight for gestational age < 10^{th} percentile), and Apgar scores at 5-minutes.

3.2.7 Statistical Analysis

Sociodemographic characteristics and information about Métis and non-Métis children were described using frequencies and percentages for categorical data and means with standard deviations (SD) for continuous variables. Fisher's exact or Chi-square ($\chi 2$) test for categorical variables and t-test for continuous variables were conducted to determine whether covariate sampling distribution differed between the cohorts of Métis and non-Métis children. A p-value of <0.05 was considered statistically significant. Period prevalence estimates were calculated for the

proportion of Métis and non-Métis children affected by NDD/D during the study period. The numerator for the prevalence estimates was the number of individuals who met the NDD/D criteria (time at the second medical encounter with diagnostic code or first hospitalization, whichever occurred first), and the denominator was the total number of Métis or non-Métis children.

Logistic regression was used to determine the crude prevalence odds ratio (OR) with 95% confidence intervals (CI) comparing NDD/D prevalence among Métis and non-Métis children. Adjusted odds ratios (aOR) with 95%CI were calculated comparing NDD/D prevalence among Métis and non-Métis children after adjusting for covariates which were statistically different between the two cohorts, theoretically significant predictors,[19-23] and potential sources of confounding identified in the Directed Acyclic Graph (DAG) (Figure 2). The creation of the DAG followed Shrier and Platt's recommendations for their use in epidemiological studies.[24] Briefly, DAGs are visual representations created to highlight relationships and assumptions between variables and identify potential biasing pathways. The DAG informed the development of the final adjustment set for the logistic regression model. The final logistic regression model adjusted for: maternal age at delivery, area of residency, maternal smoking, maternal substance use, material and social deprivation, child's sex, preterm birth, caesarean section, and 5-minute Apgar Score. Finally, for Métis and non-Métis children with NDD/D, maternal and neonatal characteristics were compared using OR with 95%CI. Statistical analyses were conducted using STATA v16.0.

3.3 Results

3.3.1 Characteristics of the Métis and non-Métis Children

The final study population included 7,875 Métis and 31,184 non-Métis children. Table 1 presents the maternal and neonatal characteristics of the study cohort. Métis children's mothers were significantly younger at delivery (mean age of 27.19; SD= 5.5) than non-Métis children's

mothers (mean age of 29.69; SD = 5.4). Métis children's mothers were more likely to be from rural areas (37.1%) and have smoked and used drugs or alcohol during pregnancy (30.5% and 6.1%) compared to non-Métis children's mothers (24.3%, 13.9%, and 2.9% respectively). When comparing material deprivation, more Métis children and mothers were within the most and second most deprived quintile of material deprivation (26.5% and 22.7%) compared to non-Métis children and mothers (20.8% and 18.5%), while a smaller proportion of Métis children and mothers were within the least deprived quintile of material deprivation (10.1% versus 18.3%). More Métis children were part of the second most deprived quintile of social deprivation compared to non-Métis children (27.4% versus 21.9%).

For neonatal characteristics, Métis children were born heavier (mean weight: 3418g; SD: 565.4) than non-Métis children (mean weight: 3353.0g; SD: 550.9). The mean number of visits to health care was higher among Métis children (mean: 25.38; SD: 17.6) compared to non-Métis children (mean: 23.85; SD: 17.3). Fewer Métis children were born small for gestational age (7.0%) and by caesarean section (25.6%) compared to non-Métis children (9.24% and 27.9%, respectively).

3.3.2 Prevalence of NDD/D among Métis and non-Métis Children

Overall, the crude prevalence of NDD/D for the whole study period was 3.30% among Métis children compared to 2.75% among non-Métis children (Table 2). Prevalence estimates were 0.22% and 0.18% for the motor domain, 0.70% and 0.67% for the speech/communication domain, 1.83% and 1.36% for the learning-cognition domain, 0.33% and 0.45% for the social domain, 0.18% and 0.11% for the sensory domain, and 0.38% and 0.29% for the neuropsychological domain, respectively (Table 2). For the prevalence of specific conditions, Métis children had

increased odds of FAS and ADHD compared to non-Métis children, while no significant differences were identified for other conditions (Table 3).

The crude prevalence OR comparing NDD/D prevalence among Métis and non-Métis children indicated marginally greater prevalence among Métis children (OR: 1.21; 95%CI 1.05, 1.39), but after adjusting for important study covariates, there were no differences in the prevalence of NDD/D between the two groups (aOR: 1.15; 95%CI 0.98, 1.34). Additionally, no differences were found in domain-specific NDD/D prevalence between Métis and non-Métis children.

3.3.3 Characteristics of Métis and non-Métis children with NDD/D

When comparing maternal and prenatal characteristics for NDD/D between Indigenous and non-Indigenous children, Indigenous children with NDD/D had 2.04 times the odds of being born to a mother who was younger than 20 years (95%CI: 1.31, 3.18) and 1.58 times the odds of living in a rural location (95%CI: 1.14, 2.19) (Figure 3; Table 4). Odds of maternal smoking (OR: 2.22; 95%CI: 1.64, 3.01) and substance use (OR: 2.16; 95%CI: 1.33, 3.51) were greater among Indigenous children with NDD/D compared to their non-Indigenous counterparts. Mothers of Indigenous children with NDD/D had greater odds of living in areas of severe material deprivation classified in quintiles 5 (OR: 2.19; 95%CI:1.36, 3.53), 4 (OR: 2.28; 95%CI: 1.40, 3.73), and 3 (OR: 1.79; 95%CI 1.08, 2.98) compared to mothers of non-Indigenous children with NDD/D.

For neonatal factors, Métis children with NDD/D had 55% increase in odds (OR:1.55; 95%CI: 1.04, 2.32) of being born preterm compared to non-Métis children with NDD/D (Figure 3; Table 4) For caesarean section, Métis children with NDD/D had lower odds of being born by caesarean section than non-Métis children with NDD/D (OR: 0.63; 95%CI: 0.46, 0.86).

3.4 Discussion

To the best of our knowledge, this is the first study in Canada that evaluated the prevalence of NDD/D among Métis children compared to non-Métis children aged 0-10 years old. Our study found that 3.30% of Métis children born between 2006 and 2016 had an NDD/D. There were no significant differences between Métis and non-Métis children in the overall and domain-specific NDD/D prevalence. On the condition level, we identified that Métis children had a higher prevalence of FAS and a marginally higher prevalence of ADHD compared to non-Métis children. Our study also compared maternal and neonatal characteristics of Métis and non-Métis children with NDD/D. We found that compared to non-Métis children, Métis children with NDD/D in our cohort had a greater likelihood of being born to mothers who were younger than 20 years old, lived in a rural location, were from the most materially deprived areas, and who smoked and used alcohol or drugs. Métis children with NDD/D were also more likely to be born preterm than non-Métis children with NDD/D.

In this study, we found that Métis children born in Alberta had similar likelihood of having an NDD/D or domain-specific functional limitation compared to non-Métis children. This result suggests that the neurodevelopmental health of Métis children may be similar to non-Métis children which is somewhat inconsistent with published literature which explored the burden of disability among Indigenous children. A previous study by Burstyn et al. conducted using Alberta health databases found that Indigenous children had lower rates of ASD compared to non-Indigenous children.[12] This study used an aggregated definition of Indigeneity including First Nations, Inuit, and Métis children, whereas our study focused on the Métis population, perhaps explaining our differential results. On the other hand, the Aboriginal Peoples Survey, a post-enumeration survey, showed that Métis individuals 15 years and older were affected more by developmental and learning disabilities compared to non-Indigenous individuals.[25] Discrepant

results with our study findings could likely be explained by the differences in the age of the study population. Some NDD/D may not be diagnosed until a child is older due to psychometric limitations of developmental assessments.[26] Alternatively, as our study population and outcomes are dependent on access to healthcare (i.e., emergency room, general practitioners, hospitalizations), our results may reflect limited access to services or the lack of appropriate care that result in under-representation in health databases[27] and underestimation of existing health disparities that exist. Geographic barriers (e.g., living in rural or remote areas), experiences of culturally inappropriate care,[28] and use of diagnostic assessment tools which lack cultural sensitivity[29] are barriers for Indigenous people to accessing healthcare, which subsequently could limit our understanding of the true burden of NDD/D among Métis children.

When analyzing prevalence of specific conditions, we found that FAS was more prevalent among Métis children compared to non-Métis children. This result is in line with the study finding that Métis children with NDD/D had increased likelihood of being born to mothers who used substances including alcohol during pregnancy. Previous reports that have found that fetal alcohol spectrum disorder (FASD), an umbrella term which FAS falls under, disproportionately affect some Indigenous communities in Canada.[30, 31] Some evidence suggests that perpetuating stigma among Indigenous communities and racial biases when accessing healthcare can lead to overdiagnosing FASD over other neurodevelopmental disorders among Indigenous individuals.[32] Another explanation for the higher prevalence of FAS among Métis children in this cohort may reflect coping mechanisms used by Métis mothers against the experiences of the effects of colonialism and intergenerational trauma.[33] Métis mothers have been found to be more likely to use substances (i.e., alcohol and drugs) during pregnancy compared to non-Métis mothers.[17] Community-led education on the adverse effects of substance use during pregnancy on offspring

development may help decrease FAS risk among Métis children. Our study also found marginally increased odds of ADHD among Métis children compared to non-Métis children. This finding is consistent with a previous study by Baydala et al. that found a higher prevalence of ADHD symptoms among Indigenous children in Canada.[11] Future research is needed to better understand the relationship between ADHD and Métis children.

The development of NDD/D is multifactorial, involving genetics, lifestyle, and environmental factors (social determinants of health) that influence neurodevelopment from conception to early life.[34] While the prevalence of NDD/D was similar between Métis and non-Métis children, several maternal and neonatal characteristics were more common among Métis children with NDD/D including being born preterm and to mothers who were young, from rural areas, who smoked, used substances, and who lived in areas that were most materially deprived (i.e., proxy for education attainment, unemployment, and household income). Many of these determinants of health have previously been found to be higher among Métis mothers and children[16] as well as being associated with influencing brain development.[20, 22, 35] It is likely that these factors act synergistically. Previously, Raoufi et al.[10] found that children in disadvantaged circumstances, such as lower SES, poor housing, and under difficulties accessing healthcare, were more likely to report more severe NDD/D. Furthermore, a study by Amjad et al. found that adolescent mothers of lower SES and from rural areas are more likely to smoke and use substances during pregnancy and have adverse birth outcomes such as preterm birth.[36] Lower SES may also be a barrier to healthcare such as prenatal care,[37] where opportunities to stop unhealthy maternal behaviours that affect neurodevelopment can be made to foster healthy pregnancies. Additionally, barriers to healthcare may limit the early identification of children at risk for neurodevelopmental problems and limit early intervention that minimize motor, cognitive, and emotional impairment.[38]

Increased exposure to the social determinants of health is considered one of the key determinants of Indigenous children's health and reflects the effects of colonialism.[15, 39] Colonialism has systematically disrupted the lives of Indigenous peoples in Canada through loss of language and culture, displacement of communities, and discriminatory policies that disadvantage them.[40] These important contributing factors to neurodevelopmental health should be taken into account when creating programs and services to support Métis children.

Clinicians should be aware of circumstances that may influence the neurodevelopmental health of Métis children. Métis-led psychosocial interventions should be created to support Métis women during pregnancy and children after birth to foster better neurodevelopmental health among Métis children. Future research should be done in partnership with Métis communities to understand the mechanisms between social inequalities and the neurodevelopmental health of Métis children and find creative solutions to address them that are rooted in Métis ways of knowing and being.

3.4.1 Study Limitations and Strengths

Several limitations should be considered when interpreting these study results. In this cohort, non-Métis children included other Indigenous children in Alberta, including First Nations and Métis children whose mothers were not members of the MNA. Additionally, although the NDD/D case definition and ascertainment algorithm has been previously used within an electronic health database,[8] it has not been widely validated. As such, these sources of misclassification bias can affect the association between Métis children and NDD/D. The use of the Pampalon deprivation index which measures SES at a dissemination area level does not properly reflect the individual level SES of participants in our cohort. Finally, the generalizability of these results is

limited to children from mothers who are members of the MNA as the Métis cohort is identified based on registration with the MNA.

Nevertheless, our study has several strengths. As the Métis children cohort was identified through the linkage between the MNAIR and administrative health databases, children with the Métis cohort are verified to have connections with the Métis Nation. Additionally, the use of a DAG to select for covariates to be included in the regression model limited overadjustment. Our study also fills a gap in knowledge regarding the burden of NDD/D in Métis children and provides important information regarding possible factors which influence their neurodevelopmental health.

3.4 Conclusion

This study identified that the burden of NDD/D is similar between Métis children and non-Métis children aged 0-10 years old in Alberta after accounting for important study covariates. Métis children with NDD/D were more likely to face social inequalities rooted in Indigenous peoples' experiences in Canada. More research is needed to better understand the impact of social inequalities on the neurodevelopmental health of Métis.

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Table 3.1 Maternal and Neonatal Characteristics of the Cohorts of Métis and non-Métis Children

	Métis (n= 7,875)	Non-Métis (n= 31,184)	Test; p-value
Maternal Factors			
Maternal Age (mean years; SD)	27.19 (5.5)	29.69 (5.4)	**z-test; p=0.000***
Maternal Age; n (%)			
<19	748 (9.5)	1,241 (4.0)	
20-34	6,416 (81.5)	24,715 (79.3)	
35+	711 (9.0)	5,228 (16.8)	**Chi-square; p=0.000***
Type of location			
Urban	5,062 (64.3)	23,968 (76.9)	
Rural	2,772 (35.2)	7,073 (22.7)	**Chi-square; p=0.000***
Missing	41 (0.5)	143 (0.5)	
Maternal Smoking			
Yes	2,402 (30.5)	4,330 (13.9)	
No	5,401 (68.6)	26,650 (85.5)	**Chi-square; p=0.000***
Missing	72 (0.91)	204 (0.65)	
Substance Use			
Yes	482 (6.12)	892 (2.9)	
No	7,393 (93.9)	30,292 (97.1)	**Chi-square; p=0.000***
Material Deprivation Quintiles			
1 (Least Deprived)	795 (10.1)	5,707 (18.3)	
2	1314 (16.7)	5,799 (18.6)	
3	1521 (19.3)	5,881 (18.9	
4	1791 (22.7)	5,777 (18.5)	
5	2088 (26.5)	6,477 (20.8)	**Chi-square; p=0.000***
Missing	366 (4.65)	1,543 (4.95)	
Social Deprivation Quintiles			
1 (Least Deprived)	970 (12.3)	4,117 (13.2)	
2	1,144 (14.5)	5,945 (19.1)	
3	1,615 (20.5)	6,755 (21.6)	
4	2,160 (27.4)	6,822 (21.9)	
5	1,620 (20.6)	6,002 (19.3)	**Chi-square; p=0.000***
Missing	366 (4.65)	1,543 (4.95)	
Neonatal Factors			
Sex			
Female	3,938 (50.0)	15,282 (49.0)	
Male	3,937 (50.0)	15,902 (51.0)	Chi-square; p=0.113
Preterm (<37 weeks gestational weeks)			
Yes	569 (7.2)	2,196 (7.0)	
No	7,306 (92.8)	28,988 (93.0)	Chi-square; p=0.571
Birth Weight (mean grams; SD)	3418.9 (565.4)	3353.0 (550.9)	**z-test; p=0.000***
Low Birth Weight (<2500g)			
Yes	381 (4.8)	1,643 (5.3)	
No	7,494 (95.2)	29,541 (94.7)	Chi-square; p=0.123
Small for Gestational Age			
Yes	551 (7.0)	2,881 (9.24)	
No	7,308 (92.8)	28,266 (90.64)	**Chi-square; p= 0.000***
Missing	16 (0.20)	37 (0.12)	
Caesarean Section			
Yes	2,019 (25.6)	8,707 (27.9)	
No	5,856 (74.4)	22,477 (72.1)	**Chi-square; p=0.000***
5-minute Apgar Score (>7)			
>=7	7,689 (97.6)	30,423 (97.6)	
<7	186 (2.36)	761 (2.4)	Chi-Square; p=0.686
Number of Visits to Health Care	25.38 (17.6)	23.85 (17.3)	**t-test; p=0.000***

Data are presented as numbers with percentages (%) or mean with standard deviations
Missing values were declared where they exist
*Statistically significant difference ($p<0.05$)
SD = standard deviation

Table 3.2 Prevalence of NDD/D among Métis and non-Métis Children

	Métis	**Non-Métis**	**Crude OR (95%CI)**	**Adjusted OR (95%CI)[a]**
NDD/D (All)	3.30% (260)	2.75% (859)	**1.21 (1.05, 1.39)***	1.15 (0.98, 1.34)
Motor Domain	0.22% (17)	0.18% (55)	1.22 (0.71, 2.11)	1.16 (0.64, 2.10)
Speech/Communication Domain	0.70% (55)	0.67% (208)	1.04 (0.78, 1.41)	1.17 (0.85, 1.61)
Learning Domain	1.83% (144)	1.36% (425)	**1.34 (1.11, 1.63)***	1.18 (0.86, 1.62)
Social Domain	0.33% (26)	0.45% (140)	0.73 (0.48, 1.11)	0.83 (0.53, 1.29)
Sensory Domain	0.18% (14)	0.11% (35)	1.58 (0.85, 2.94)	1.68 (0.87, 3.23)
Neuropsychological Domain	0.38% (20)	0.29% (91)	1.30 (0.86, 1.98)	1.35 (0.86, 2.14)

[a]Adjusted for maternal age, area of residence, material and social deprivation, smoking, substance use, preterm birth, caesarean section, small-for-gestational age, 5-minute Apgar score, and number of visits to healthcare
*Statistically significant difference ($p<0.05$)
CI= confidence interval; OR = odds ratio

Table 3.3 Prevalence of each Diagnosis within NDD/D Domains

			Prevalence % (number of cases)			
Domain	**Disease**	**Diagnostic Code (ICD9/ICD10)**	**Métis**	**Non-Métis**	**Prevalence Difference [95%CI]**	**Prevalence Odds Ratio [95%CI]**
Motor	All		0.22 (17)	0.18 (55)	0.04 [-0.07, 0.15]	1.22 [0.71, 2.09]
	Cerebral Palsy	343/G80.9	0.06 (5)	0.06 (20)	0 [-0.06, 0.06]	0.99 [0.38, 2.55]
	Spina Bifida	741/Q05.9	0.05 (4)	0.03 (10)	0 [-0.03, 0.07]	1.58 [0.53, 4.77]
	Lack of Coordination	781.3/R27.8	0.08 (6)	0.06 (19)	0 [-0.05, 0.08]	1.25 [0.51, 3.04]
	Muscular Dystrophies	359/G71.0	0.03 (2)	0.02 (6)	0 [-0.03, 0.04]	1.32 [0, 5.72]
Speech-language	All		0.70 (55)	0.67 (208)	0.03 [-0.17, 0.23]	1.05 [0.77, 1.41]
	Speech Disturbances	784/R47.8	0.08 (6)	0.08 (24)	0 [-0.07, 0.07]	0.98 [0.42, 2.36]
	Aphasia	784.2/R47.01	0.01 (1)	0.01 (2)	0 [-0.02, 0.03]	1.98 [0, 15.01]
	Developmental speech or language disorder	315.3/F80	0.62 (49)	0.59 (183)	0.04 [-0.15, 0.22]	1.06 [0.77, 1.45]
	Problems with voice production	V41.4/R47.89	0.01 (1)	0.02 (5)	0 [-0.03, 0.03]	0.79 [0, 5.11]
Language-Cognition	All		1.83 (144)	1.36 (425)	0.47 [0.14, 0.79]	1.35 [1.11, 1.63]
	Developmental disorder of scholastic skills	315.9/F81.9	0.05 (4)	0.06 (18)	-0.01 [-0.06, 0.05]	0.88 [0.31, 2.48]
	Mental and behavioral problems with learning	V40.0/F81.9	0.06 (5)	0.09 (27)	-0.02 [-0.09, 0.04]	0.73 [0.29, 1.84]
	Fetal alcohol syndrome / Newborn affected by maternal alcohol use	760.71/Q86.0/P04.3	0.32 (25)	0.09 (29)	0.22 [0.10, 0.35]	**3.42 [2.01, 5.81]**
	Signs and symptoms involving cognition	799.5/R41.8	0.08 (6)	0.10 (32)	-0.02 [-0.09, 0.04]	0.74 [0.32, 1.73]
	ADHD	314.0/F90	1.30 (102)	1.02 (318)	0.27 [0.01, 0.55]	**1.27 [1.02, 1.59]**
	Down Syndrome	758.0/Q90	0.14 (11)	0.09 (29)	0.05 [-0.04, 0.14]	1.50 [0.76, 2.97]
Social	ASD	299/Q90	0.33 (26)	0.45 (140)	-0.11 [-0.26, 0.03]	0.73 [0.48, 1.11]
Sensory	All		0.18 (14)	0.11 (35)	0.65 [-0.03, 0.16]	1.58 [0.86, 2.92]
	Deafness	389.0/H91.9	0.10 (8)	0.04 (13)	0.06 [-0.01, 0.13]	**2.44 [1.03, 5.73]**
	Blindness	369/H54.0/H54.7	0	0.01 (4)	n/a	n/a
	Problems with special senses and other special functions	V41	0.08 (6)	20 (0.06)	0.01 [-0.06, 0.08]	1.19 [0.49, 2.87]
Neuropsychological	All		0.38 (20)	0.29 (91)	0.09 [-0.06, 0.24]	1.31 [0.87, 1.97]
	Epilepsy	345/G40	0.32 (25)	0.25 (79)	0.06 [-0.07, 0.20]	1.25 [0.80, 1.96]
	Tourette's	307.23/F95.2	0.06 (5)	0.04 (12)	0.03 [-0.03, 0.08]	1.65 [0.61, 4.49]

Table 3.4 Maternal and Neonatal Characteristics of Métis and non-Métis Children with NDD/D

	Métis (n= 260)	Non-Métis (n= 859)	OR (95%CI) or Mean Difference (95%CI)
Maternal Factors			
Maternal Age (mean years; SD)	26.74 (6.3)	28.98 (5.8)	**2.24 (1.42, 3.06)***
Maternal Age; n (%)			
<19	36 (13.9)	60 (7.0)	**2.04 (1.31, 3.18)***
20-34	197 (75.8)	671 (78.1)	ref
35+	27 (10.4)	128 (14.90)	0.72 (0.46, 1.12)
Type of Location			
Urban	189 (73.3)	694 (81.3)	Ref.
Rural	69 (26.7)	160 (18.7)	**1.58 (1.14, 2.19)***
Maternal Smoking			
Yes	92 (35.4)	171 (20.0)	**2.22 (1.64, 3.01)***
No	166 (63.9)	685 (79.7)	Ref.
Missing	2 (0.77)	3 (0.35)	
Substance Use			
Yes	29 (11.2)	47 (5.5)	**2.16 (1.33, 3.52)***
No	231 (88.9)	812 (94.5)	
Material Deprivation Quintiles			
1 (Least Deprived)	30 (11.5)	174 (20.3)	ref.
2	44 (16.9)	154 (17.9)	1.66 (0.99, 2.77)
3	47 (18.1)	152 (17.7)	**1.79 (1.08, 2.98)***
4	59 (22.7)	150 (17.5)	**2.28 (1.40, 3.73)***
5 (Most Deprived)	70 (26.9)	185 (21.5)	**2.19 (1.36, 3.53)***
Missing	10 (3.9)	44 (5.1)	
Social Deprivation Quintiles			
1 (Least Deprived)	31 (11.9)	94 (11.0)	ref.
2	44 (16.9)	163 (19.0)	0.82 (0.48, 1.38)
3	41 (15.8)	168 (19.6)	0.74 (0.44, 1.26)
4	76 (29.2)	198 (23.1)	1.16 (0.72, 1.89)
5 (Most Deprived)	58 (22.3)	192 (22.4)	0.92 (0.56, 1.51)
Missing	10 (3.9)	44 (5.1)	
Neonatal Factors			
Sex			
Male	175 (67.3)	604 (70.3)	0.87 (0.65, 1.17)
Female	85 (32.7)	255 (29.7)	Ref.
Caesarean Section			
Yes	64 (24.6)	294 (34.2)	**0.63 (0.46, 0.86)***
No	196 (75.4)	565 (66.8)	
Preterm Birth			
Yes	40 (15.4)	90 (10.5)	**1.55 (1.04, 2.32)***
No	220 (84.6)	769 (89.5)	
Birth Weight (mean grams; SD)	3322.6 (663.5)	3316.6 (612.9)	-6.04 (-92.88, 80.79)
Low Birth Weight (<2500 g)			
Yes	26 (10.0)	64 (7.5)	1.38 (0.86, 2.22)
No	234 (90.0)	795 (92.6)	
Small for Gestational Age			
Yes	21(8.1)	108 (12.6)	0.61 (0.37, 0.99)
No	239 (91.9)	748 (87.4)	
Missing	0	3 (0.4)	
5-minute Apgar Score			
>=7	249 (95.8)	812 (94.5)	0.76 (0.39, 1.48)
<7	11 (4.2)	47 (5.5)	
Number of Visits to Health Care	38.85 (24.4)	37.3 (21.3)	-1.57 (-4.63, 1.49)

Data are presented as numbers with percentages (%) or mean with standard deviations
Missing values were declared where they exist
*Statistically significant difference ($p<0.05$)

Figure 3.1 Study Flow Diagram for Data Merging and Population Selection

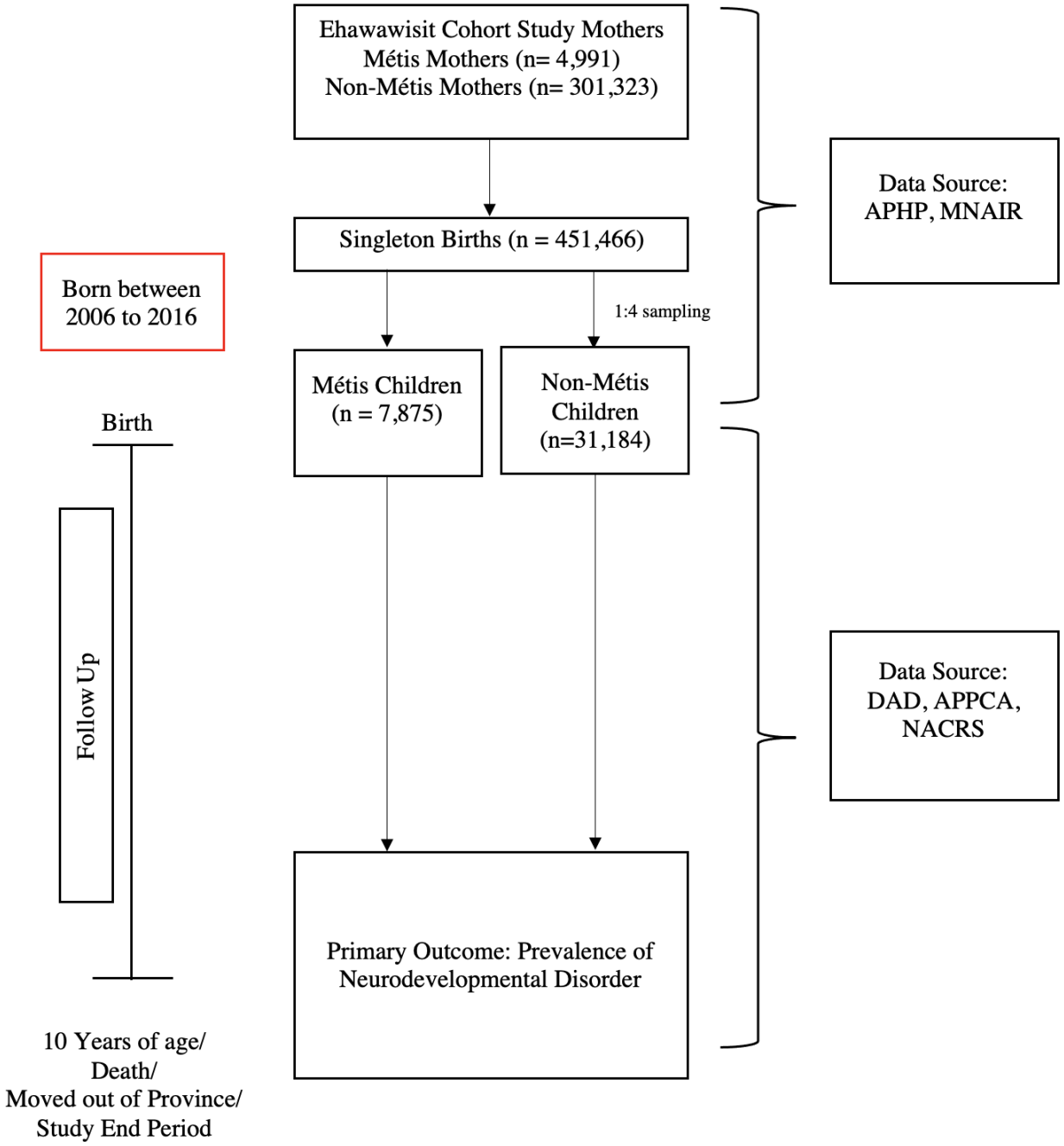
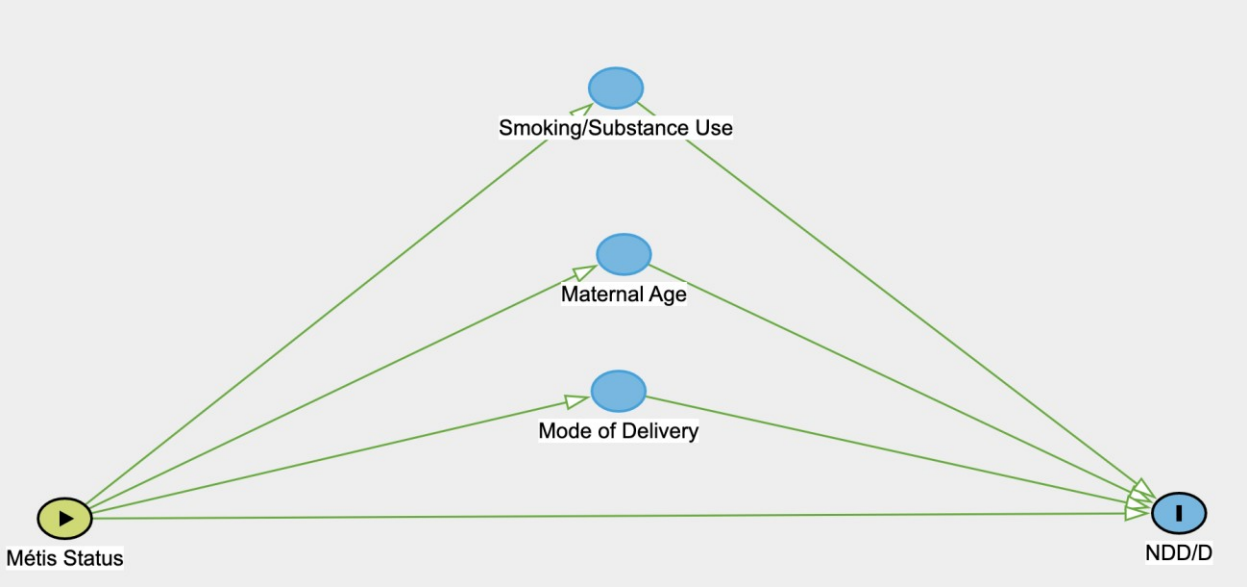
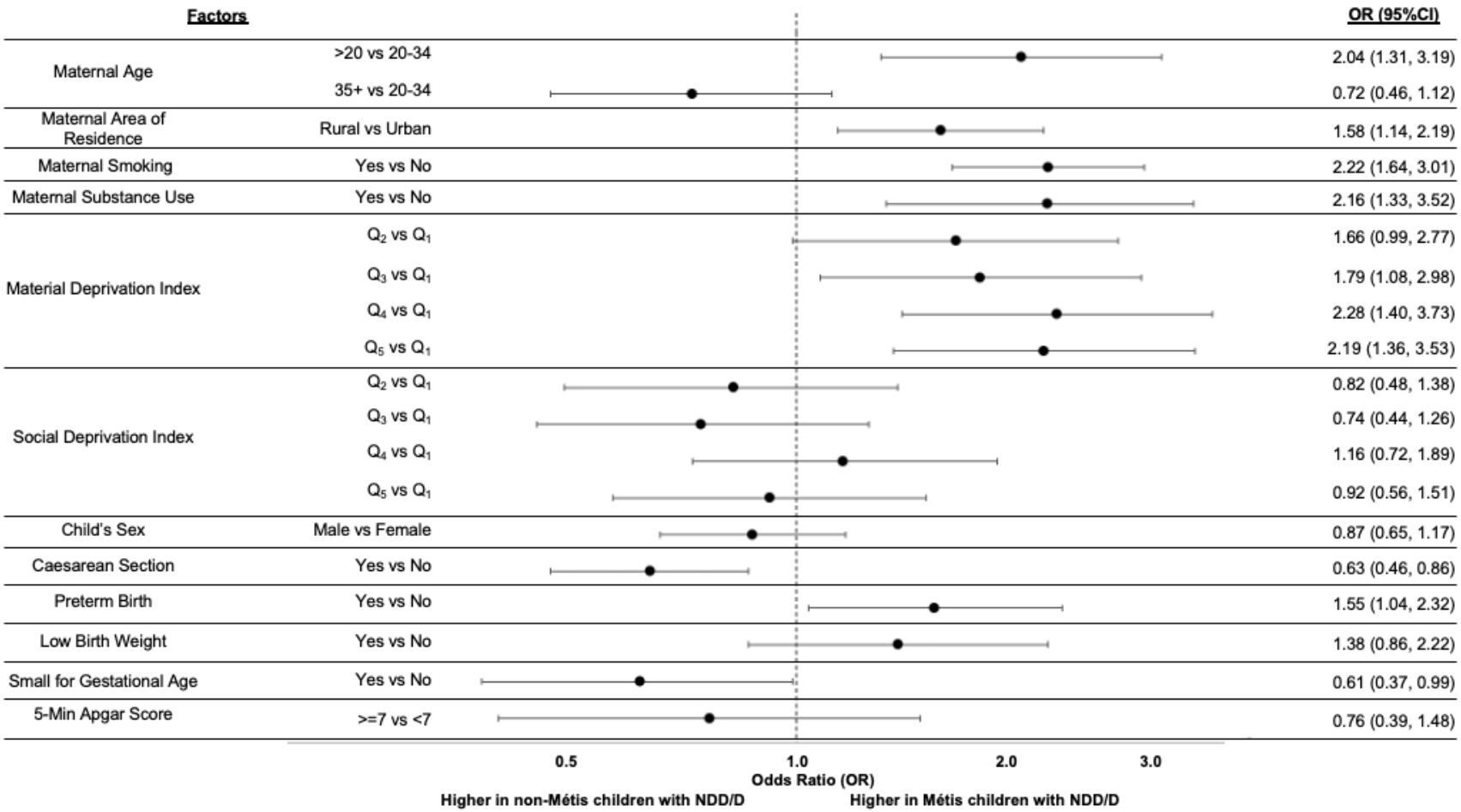


Figure 3.2 Directed Acyclic Graph (DAG) for the Association between Métis Status and NDD/D



Green lines represent causal pathways.

Figure 3.3 Comparison of Maternal and Neonatal Factors among Métis and non-Métis Children with NDD/D



Chapter 4: Discussion, Clinical Implications, Future Research Directions, and Knowledge Translation

4.1 Overview of Study Results

This thesis was conducted to help understand the prevalence of NDDs among Indigenous children compared to non-Indigenous children. We conducted two studies to achieve our purpose. The first study was a systematic review which examined the prevalence of NDDs among Indigenous and non-Indigenous children in countries with similar colonial histories. The second study was a retrospective cohort study which evaluated the prevalence of NDD/D among Métis children compared to non-Métis children in Alberta. This final section of the thesis will discuss the results of both studies, the implications of this research and potential areas for future research.

4.2 Systematic Review Results

The systematic review in Chapter 2 evaluated the evidence from observational studies on the prevalence of NDDs among Indigenous children compared to non-Indigenous children in countries with similar histories of colonialism (Australia, Canada, New Zealand, USA). Twelve unique studies were included (two from Australia, one from Canada, four from New Zealand, and five from the USA). Six studies were of retrospective cohort study design, one was a prospective cohort study, four were cross-sectional, and one was an ecological study. Five studies evaluated ADHD prevalence, seven for ASD, three for ID, and one for SLD. The methodological quality of studies varied as most of the cohort and ecological studies had a high risk of bias while all cross-sectional studies had a low risk of bias.

Our systematic review highlighted a considerable gap in the literature on the neurodevelopmental health of Indigenous children living in countries with similar colonial histories. No studies evaluating ADHD, MD, SLD, and CD prevalence among Australian

Aboriginal children compared to non-Aboriginal children were retrieved. ASD was the only condition that has been compared between Indigenous and non-Indigenous children in Canada. No epidemiological studies comparing the prevalence of MD, SLD, and CD were identified for Māori children. No epidemiological evidence has evaluated MD and CD prevalence between AI/AN and White children in the USA. Considering the health disparities between Indigenous and their non-Indigenous counterparts around the world,[1] more well-designed epidemiological studies are needed to address the dearth of research on the neurodevelopmental health of Indigenous children.

4.2.1 Prevalence and Meta-Analysis

Among Australian Aboriginal children, there was evidence of greater prevalence of ID compared to non-Aboriginal children while no differences were found in ASD prevalence in the meta-analysis. In Canada, non-Indigenous children in Canada had a higher prevalence of ASD compared to Indigenous children. For Māori children, evidence suggested that ID prevalence was greater compared to non-Māori children, while there was inconclusive evidence for ADHD and ASD. In the USA, there was evidence that suggested that AI/AN children had a higher prevalence of ID and SLD compared to White children. A lack of consensus was found regarding the prevalence estimates for ASD and ADHD among AI/AN children compared to White children. It is important to note that these results are made based on the small number of studies that estimated the prevalence of NDD among Indigenous children compared to non-Indigenous children.

Our systematic review found that Aboriginal Australian, Māori, and AI/AN children have a higher prevalence of ID than non-Indigenous children. A higher prevalence of SLD was also found among AI/AN children compared to White children. Although these findings were based on a single study for each Indigenous group and more research is needed to provide more robust results, these findings are consistent with reports of health disparities between Indigenous and non-

Indigenous children. For the diverse group of Indigenous children included in these reviews, intergenerational effects of colonialism, which include systematic discrimination/racism, culture loss, and forced removal from traditional land, prevails as one of the most important determinants of health.[1] The effects of colonialism manifest in increased exposure to disadvantaged circumstances (e.g., lower education, income, employment) and increased rates of substance abuse[2] that can affect Indigenous children's neurodevelopmental health.

For ADHD and ASD among Māori and AI/AN children, the prevalence estimates found in the systematic review are not consistent with reports of the health disparities that exist between Indigenous and non-Indigenous children. While one consideration is that Māori and AI/AN children have lower or similar rates of ADHD and ASD compared to their non-Indigenous counterparts, there are likely structural factors that affect the assessment of NDDs in Indigenous communities. Limited access to healthcare and diagnostic services resulting from geographic barriers,[3] lack of culturally sensitive care, and fear of discrimination, racism, and stigma from healthcare professionals[4-6] can result in the underreporting of NDDs among Indigenous children. Racial and ethnic bias in diagnosing specific conditions among Indigenous communities such as FASD[7] and ID[3] can lead underdetection of conditions such as ASD and ADHD that have overlapping characteristics.[7, 8] The lack of culturally appropriate diagnostic tools for Indigenous children may also contribute to underdiagnosis.[9, 10] Additionally, as many Indigenous communities promote diversity and inclusion and conceptualize disability differently from Western models of disabilities, engaging diagnostic services may be altered due to differences in cultural values.[11-14]

4.2.2 Clinical and Public Health Implications of the Systematic Review

Clinicians must be aware that some NDDs are more prevalent among Indigenous children compared to non-Indigenous children. Clinicians must also understand that while the etiology of

NDDs are multifactorial, there may be inherent disadvantages, such as structural determinants of health that inherently increase the risk of NDDs among Indigenous children. Practitioners should also be aware of the possible cultural differences in understanding disability between Indigenous and Western communities and look to frame healthcare that is cognizant of the cultural environment of the child and their families.

Although NDDs are lifelong conditions, early diagnosis and subsequent interventions can minimize motor, cognitive, and emotional impairment.[15, 16] Therefore, it is important to address the barriers that prevent Indigenous children from accessing diagnostic services and neurodevelopmental examinations. Increasing the number of Indigenous health care workers and services within Indigenous communities can increase engagement with accessing healthcare as Indigenous-led services are better situated to provide care that are aligned with values and norms of the communities. Additionally, partnership with Indigenous communities to develop diagnostic tools and clinical practices that are culturally safe is needed to help improve Indigenous people's engagement with support services and the accuracy of NDD diagnoses among Indigenous children.

4.3 Results from the Retrospective Cohort Study

The purpose of the study was to assess the prevalence and maternal and neonatal characteristics of NDD/Ds among Métis children born to women who are members of the MNA compared to a random sample of non-Métis children in Alberta. Children in this cohort were born 2006-2016 and were aged 0-10 years old. The final study population included 7,875 Métis and 31,184 non-Métis children. We found no significant difference between Métis and non-Métis children in the overall and domain-specific NDD/D prevalence. When analyzing condition-specific prevalence, Métis children had a higher prevalence of FAS and a marginally higher prevalence of ADHD than non-Métis children. Métis children with NDD/D were more likely to

have been born preterm and have mothers who were younger than 20 years old, lived in a rural location, from the most materially deprived areas, smoked and used alcohol or drugs compared to non-Métis children with NDD/D.

4.3.1 Métis and NDD/D

After adjusting for important covariates, no significant differences in the overall and domain-specific NDD/D prevalence was found between Métis and non-Métis children. Additional analysis indicated that Métis had higher FAS and ADHD prevalence than non-Métis children.

Our results suggest that the burden of NDD/D is similar among Métis and non-Métis children. These results add to the limited number of epidemiological studies that have been conducted in Canada that compares the prevalence of NDD/D among Indigenous children and non-Indigenous children, which primarily focus on Indigenous children as an aggregate group or among older Métis individuals. However, our results are not similar to results found in those studies. ASD prevalence in Alberta was previously found to be lower among Indigenous children compared to their non-Indigenous counterparts, which was not found in our study.[17] Compared to the Statistics Canada Aboriginal Peoples Survey, our results also do not align with their results that found Métis individuals have elevated developmental and learning disabilities rates compared to non-Indigenous individuals.[18] As discussed in Chapter 3, it may be likely that these discrepancies result from differences in the study populations. Alternatively, discrepancies may reflect the inequities in access to healthcare resulting from geographical barriers[19] and culturally inappropriate care[10] that lead to under-representation of Métis children with NDD/D in healthcare databases and bias results towards the null (no effect).

Higher FAS prevalence among Métis children compared to non-Métis children in our cohort is in line with previous reports of elevated FASD prevalence among Indigenous

communities.[20, 21] These results correspond with previous research that found Métis mothers are more likely to use substances such as alcohol and drugs during pregnancy,[22] which is a common coping mechanism used to manage experiences of colonialism and intergenerational trauma.[23] Increased rates of FAS among Métis children may also be a result of overdiagnosing FASD among Indigenous communities over other conditions due to racial and ethnic biases among healthcare providers, resulting in the over-representation of FAS among Métis communities.[7] Similarly, ADHD symptomology has been found to be more prevalent among Indigenous children.[24] It has been suggested that Indigenous children may have a genetic predisposition for ADHD due to the selection of traits that are useful for hunter-gatherer communities,[24] but further research is necessary to better understand associations between Indigeneity and ADHD.

4.3.2 Maternal and Neonatal Characteristics of Métis children with NDD/D

Several maternal and neonatal characteristics were more common among Métis children than non-Métis children with NDD/D including being born preterm and to mothers younger than 20 years old, from rural areas, who smoked, used substances and who lives in the most materially deprived areas. Most of these characteristics have previously been found to be higher among Métis mothers[22] and well as being risk factors for adverse neurodevelopment.[25] Rather than acting singularly, these factors act synergistically and represent potential risk profiles that influence brain development of Métis children. Children from younger Indigenous mothers from most socio-disadvantaged quintiles have been identified to have a higher likelihood of becoming developmentally vulnerable.[26] These social inequalities also result in differential access to critical resources such as healthcare that contribute to disparities in health between Indigenous and non-Indigenous children.[27] At the root of the increased exposure to the social determinants of health is

the historic and contemporary impacts of colonialism,[1, 27] and future research and policies must look to address these social inequalities.

4.3.3 Clinical and Public Health Implications of the Retrospective Cohort Study

Although NDD/D prevalence may be similar between Métis and non-Métis children in Alberta, clinicians should be aware of the circumstances that may influence the neurodevelopmental health of Métis children. Clinicians should know that Métis mothers may need more education and support to manage their pregnancies and encourage healthy maternal behaviours to foster healthy neurodevelopment. Clinicians should also address potential biases that may affect their diagnostic practices and take time to understand the social determinants of health affect Métis children's health to provide holistic and culturally safe care.

There are also several public health implications of this research. As Métis children and equally impacted by NDD/D as non-Métis children, Métis-specific intervention services and developmental support plans should be developed and designed to meet the needs of Métis children who have functional limitations or are at risk for them. Psychosocial support developed in partnership with the MNA in Alberta should be created to aid Métis women during pregnancy and children after birth to foster better neurodevelopmental health among Métis children. Creating and increasing access to culturally appropriate prenatal care and health education about risk and prenatal care needs specifically tailored to Métis women's needs can improve the brain health of Métis children.

4.4 Future Direction

4.4.1 Understudied NDDs among Indigenous Children

From the systematic review, we found no evidence informing the prevalence of ADHD, MD, SLD, and CD prevalence among Australian Aboriginal compared to non-Aboriginal children.

Evidence on ADHD, MD, SLD, and CD prevalence were not identified for Indigenous children in Canada. There are no studies informing the MD, SLD, and CD prevalence between Māori and non-Māori children. Finally, no epidemiological evidence has evaluated MD and CD prevalence between AI/AN and White children in the USA. Future studies should enhance the current knowledge base on the burden of these understudied NDDs among Indigenous children from countries with similar colonial histories.

4.4.2 Further Longitudinal Follow-up of Métis Children

Results from the retrospective cohort study are limited to children who are aged zero to ten years old. As some NDDs are not detected until later into childhood due to psychometric limitations of developmental assessments,[28] it would be important to conduct a follow-up evaluation on this cohort of children.

4.4.3 Qualitative study on Severity and Impact of NDD among Métis Children

A previous research study had found that children who were within disadvantaged circumstances, such as being from a family with lower SES, from rural areas, and having difficulties accessing healthcare, were related to increasing severity of NDD/D.[29] To further understand the burden of NDD/D among Métis children, a qualitative study can explore the intensity of functional limitations and how NDD/D affects specific aspects of childhood beyond the functional information from the NDD/D classification (e.g., education, physical activities, transportation, social interaction). This information can be used to direct specific services to certain areas of childhood needs among Métis children and improve their quality of life.

4.4.4 Understanding the Mechanism of Social Inequities on Neurodevelopmental Health among Métis Children

Throughout the thesis, we have made speculations of the mechanisms that may influence the neurodevelopmental of Indigenous children from countries of similar colonial histories and among Métis children. However, making causal inferences between the interaction of intergeneration effects of colonialism and social inequalities, and neurodevelopmental health is out of the scope of this thesis. Mixed methods studies which quantify experiences of colonialism and incorporates concepts of the Developmental Origins of Health and Diseases (DOHaD) hypothesis,[30] which looks at the impact of early life exposure from conception to early childhood on disease development, may enhance our understanding of the mechanism of adverse brain development among Métis children.

4.5 Knowledge Translation

The MNA have been actively engaged in developing and conducting the retrospective cohort study, including the genesis of the research questions, approval of the methodologies, and the interpretation of the results. In our research study, we have study results based on the complex histories and contemporary experiences of Indigenous children and Métis people to avoid reductionist approaches to health research among Indigenous peoples that perpetuate negative perceptions and stigma towards Indigenous peoples that has occurred frequently in health research.[31] In addition, partnership with MNA throughout the research process ensured that the methodologies and results reflected the needs of its citizens. The results from the retrospective cohort study will be used to inform the development of strategies and planning of culturally competent action to support the health and well-being of Métis children in Alberta. Research

results will be disseminated through reports and publications that are produced with guidance by the MNA.

4.6 Concluding Remarks

This thesis investigated the burden of NDDs among Indigenous children compared to non-Indigenous children from countries with similar colonial histories and evaluated the prevalence of NDD/D among Métis and non-Métis children in Alberta. In the systematic review, limited evidence suggested that Indigenous children in Australia, New Zealand, and the USA have a greater burden of ID than non-Indigenous children. Evidence also suggests that SLD affects AI/AN children more than White children. There is conflicting and a lack of evidence on the prevalence of the other DSM-5 NDDs in Indigenous children, which may result from structural factors that limit diagnoses among Indigenous children. In the retrospective cohort study, we found that the prevalence of NDD/D is similar between Métis and non-Métis children but identified social inequalities that exist between Métis and non-Métis children with NDD/D. These findings will be useful to inform strategies to improve the neurodevelopmental health of Indigenous children from countries with similar colonial histories and for Métis children in Alberta.

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Appendices

Appendix 1. MEDLINE Search Strategy

OVID Medline(R) ALL 1946-February 15, 2022
Date searched: Feb 15, 2021
Results: 300
Search saved as: Neurodev Indigenous Medline
1. exp Neurodevelopmental Disorders/
2. exp psychomotor disorders/
3. (((developmental* or intellectual* or learning or communication or motor) adj3 (disab* or impair* or delay* or disorder*)) or (mental* adj3 (delay* or impair* or challenged or retard*)) or cognitive* delay* or special needs or mental retardation or autis* or asperger* or pervasive developmental disorder* or cerebral palsy or tourette* or tic-disorder* or attention-deficit* or adhd or language-disorder* or learning disab* or dyslexi* or dyscalculi* or neurodevelopment* or neuro-development*).mp.
4. 1 or 2 or 3
5. exp american native continental ancestry group/ or oceanic ancestry group/
6. ((Native* adj1 (American* or Canadian* or Alaska*)) or (Natives not digital natives) or Tribes or Indigenous or Aborigin* or Inuit* or Inuk or Inupiat* or First Nation or First Nations or Métis or Eskimo* or Aleut* or Amerindian* or (Indian* adj3 America*) or Canadian Indian* or first people* or autochthonous people* or Torres strait islander* or Māori*).mp.
7. 5 or 6
8. epidemiologic studies/ or exp cohort studies/ or cross-sectional studies/
9. incidence/ or prevalence/
10. epidemiologic methods/ or epidemiologic research design/ or epidemiologic study characteristics/ or epidemiological monitoring/
11. (Cohort or longitudinal or follow up or followup or prospective or retrospective or cross-sectional or control group* or observational or incidence or prevalen* or epidemiol* or survey*).mp.
12. 8 or 9 or 10 or 11
13. 4 and 7 and 12
14. limit 13 to yr="2005 -Current"

Appendix 2: Multiple Publications of Studies included in the Systematic Review

13 of 27 included articles were identified as multiple publications.

Studies Associated with Abdullahi 2019
Bourke J, de Klerk N, Smith T, Leonard H. Population-Based Prevalence of Intellectual Disability and Autism Spectrum Disorders in Western Australia: A Comparison With Previous Estimates. *Medicine (Baltimore)* 2016; **95**(21): e3737.
Fairthorne J, de Klerk N, Leonard HM, Schieve LA, Yeargin-Allsopp M. Maternal Race-Ethnicity, Immigrant Status, Country of Birth, and the Odds of a Child With Autism. *Child Neurol Open* 2017; **4**: 2329048X16688125-2329048X.
Leonard H, Petterson B, De Klerk N, et al. Association of sociodemographic characteristics of children with intellectual disability in Western Australia. *Soc Sci Med* 2005; **60**(7): 1499-513.
Leonard H, Nassar N, Bourke J, et al. Relation between intrauterine growth and subsequent intellectual disability in a ten-year population cohort of children in Western Australia. *Am J Epidemiol* 2008; **167**(1): 103-11.
Leonard H, Glasson E, Nassar N, et al. Autism and intellectual disability are differentially related to sociodemographic background at birth. *PloS one* 2011; **6**(3): e17875.
O'Leary C, Leonard H, Bourke J, D'Antoine H, Bartu A, Bower C. Intellectual disability: population-based estimates of the proportion attributable to maternal alcohol use disorder during pregnancy. *Dev Med Child Neurol* 2013; **55**(3): 271-7.
O'Leary C, Lawrence D, Hafekost K, Zubrick SR, Bower C. Maternal alcohol-use disorder and child outcomes. *Pediatrics* 2020; **145**(3).
Study associated with May 2020
Randall M, Sciberras E, Brignell A, et al. Autism spectrum disorder: Presentation and prevalence in a nationally representative Australian sample. *Aust N Z J Psychiatry* 2016; **50**(3): 243-53.
Studies associated with de Brey 2021
Sullivan AL. School-Based Autism Identification: Prevalence, Racial Disparities, and Systemic Correlates. *School Psychology Review* 2013; **42**(3): 298-316.
Travers JC, Tincani M, Krezmien MP. A Multiyear National Profile of Racial Disparity in Autism Identification. *The Journal of Special Education* 2011; **47**(1): 41-9.
Travers J, Krezmien M. Racial Disparities in Autism Identification in the United States During 2014. *Exceptional Children* 2018; **84**(4): 403-19.
Dickerson AS, Dickerson AS. Brief Report: Texas School District Autism Prevalence in Children from Non-English-Speaking Homes. *J Autism Dev Disord* 2020; **50**(4): 1411-7.

Appendix 3: Screening of Title and Abstract Instruction Form

Title and Abstract Screening Form

For each title/abstract, go through the four criteria R1 to R4, in any order. Any article must clearly satisfy all of the criteria below in order to be considered potentially relevant. Stop at the first "No" and classify the study as "Do not retrieve article". Otherwise, classify it as "Retrieve article". If it is unclear whether the article meets any one of the criteria below, the article will be considered eligible for retrieval and further review.

Criteria of Relevance:

Criteria	Yes	No	Unsure
R1: Population/Exposure: Described as Indigenous Children from countries of interest (i.e., Indigenous, First Nations, Inuit, Métis, Māori, Native American, Native Canadian, Alaska Native, Torres Strait Islanders, Aboriginal people, Australian Aboriginal)	1	2	3
R2: Comparison groups: The study should include a control/comparison group (Non-Indigenous Children); **Flag studies with no comparison with non-Indigenous children**	1	2	3
R3: Outcome: Neurodevelopmental Disorders (DSM-5 Categories: Intellectual Disability, Communication Disorder, Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, Specific Learning Disorder, Motor Disorder, Other Neurodevelopmental Disorders)	1	2	3
R4: Study design: Cohort Studies and Cross-Sectional Studies	1	2	3

Decisions:

Retrieve article ☐
Do not retrieve article ☐

Specific instructions:

a) Children aged 0-18 will be considered
b) Exclude Neurodevelopmental Disorders of chromosomal anomaly origin (Down Syndrome, Rett Syndrome, Fragile X Syndrome, Angelman Syndrome)
c) **Flag studies with no comparison with non-Indigenous children**

The article will be considered irrelevant if the article does not include any of the specific terms listed in the list of populations/exposure of interests. See list of examples of relevant populations/exposures below:

Aboriginal people	American Indians
Alaska Native	Autochthonous people
First Nations	First people
First People	Indigenous Children
Inuit	Métis
Native American, Canadian	Torres Strait Islander
Aboriginal Australian	Māori

The article will be considered irrelevant if the article does not include any of the specific terms listed in the list of potentially relevant outcomes. See list of examples of relevant outcomes below:

Language Disorder	Attention-Deficit/Hyperactivity Disorder
Global Developmental Delay	Autism Spectrum Disorder
Intellectual Disability	Communication Disorder
Social (Pragmatic Communication) Disorder	Dyscalculia
Childhood-Onset Fluency Disorder (Stuttering)	Dyslexia
Developmental Coordination Disorder	Persistent (Chronic) Motor or Vocal Tic Disorder
Stereotypic Movement Disorder	Provisional Tic Disorder
Speech Sound Disorder	Specific Learning Disorder
Motor Disorders	Tourette's Disorder

Appendix 4: Study Inclusion Form

Eligibility Criteria Form

Reference ID #:	Author(s):	Reviewer ID #:	Year of Publication:

1. Preliminary			
Does this article contain primary research?	Yes ☐	No ☐	Unsure ☐
2. Study design			
Does the study satisfy any of the following designs? ☐ Prospective/retrospective cohort study with control group ☐ Cross-sectional studies	Yes ☐	No ☐	Unsure ☐
3. Population			
Does the population consist of children aged 0-18?	Yes ☐	No ☐	Unsure ☐
4. Exposure			
Does the study population include Indigenous children *(Check all that apply)*? ☐ Canadian Indigenous Children (First Nations, Inuit, Métis) ☐ Torres Strait Islander, Australian Aboriginal ☐ Māori ☐ American Natives, Alaskan Indians	Yes ☐	No ☐	Unsure ☐
4. Comparator			
Does the study include a non-Indigenous population for comparison? *(If the study include fulfills criteria for population, exposure and outcome, but does not meet the comparator criteria, flag the study*)	Yes ☐	No ☐	Unsure ☐
5. Outcomes			
Did the study report at least one of the following neurodevelopmental disorders? *(Check all that apply).* ☐ Intellectual Disability - Global Developmental Delay ☐ Communication Disorder - Language Disorder - Speech Sound Disorder - Childhood-Onset Fluency Disorder (Stuttering) - Social (Pragmatic Communication) Disorder ☐ Autism Spectrum Disorder ☐ Attention-Deficit/Hyperactivity Disorder ☐ Specific Learning Disorder - With impairment in reading - with impairment in written expression - with impairment in mathematics) ☐ Motor Disorders - Developmental Coordination Disorder - Stereotypic Movement Disorder - Tic Disorders (Tourette's, Motor or Vocal Tic Disorder) - Cerebral Palsy	Yes ☐	No ☐	Unsure ☐

FINAL DECISION

Should this study be included in the next stage? *(Answer yes if all the above are "yes")*	Yes ☐	No ☐	Unsure ☐

Consensus decision:

Yes	No	3rd Party
☐	☐	☐

Appendix 4: Data Extraction Template

Data Extraction Form: Prevalence of Neurodevelopmental Disorder among Indigenous Children: A Systematic Review (Adapted from Cochrane Data Extraction Template)

Study Information:

Covidence ID	
Study ID	
Title Primary	
Authors	
Pub Year	

Characteristics of included studies:

Methods

	Description from report/paper
Study Design	
Study Start Date	
Study End Date	
Study Aim	
Duration of Participation	
Withdrawals and Exclusion	
Funding	

Additional Comments:

Participants

	Description
Country	
Study Setting	
Indigenous Group	
Comparison Group	
Age (specify mean [SD] or median [IQR])	
Age Range	
% Female	

Additional Comments:

Outcomes

	Description			
Type of NDD				
NDD Info Collected from (e.g., survey, EMR)				
NDD Definition				
Time when NDD was measured				
Results	Indigenous Children		Non-Indigenous Children	
	Has NDD	Total in Group	Has NDD	Total in Group
Odds Ratio (95% confidence interval)				
Number of missing participants				
Reason for missing participants				

Additional Comments:

Findings

	Description
Overall Findings	
Statistical Significance?	
Author's Conclusion	

Additional Comments: