The Proportion of Preterm Birth Attributable to Modifiable Risk Factors:

A Retrospective Cohort Study in Nova Scotia, 2005-2019

by

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DEDICATION PAGE

This thesis is dedicated to my mom and grandparents. Thank you, mom, gramma, and poppy, for continuously encouraging me to be curious and guiding me with your endless knowledge and wisdom.

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ABSTRACT

Background and Objectives: Preterm birth (PTB), occurring at <37 weeks' gestation, is a leading cause of child morbidity and mortality. A study conducted in multiple countries estimated that 37% of PTB can be attributed to known risk factors, but no estimates have been made locally. The objective was to estimate the population attributable risk percent (PAR%) and population impact fraction (PIF%) of modifiable risk factors for PTB in Nova Scotia.

Methods: A population-based retrospective cohort of women and singleton infants delivered from 2005 to 2019 was conducted using the Nova Scotia Atlee Perinatal Database. Theoretically modifiable risk factors included: maternal age, smoking, alcohol use, drug use, pre-pregnancy body mass index, income, depression, pre-existing diabetes, gestational diabetes, chronic hypertension and assisted reproductive technology. Poisson regression models were used to estimate the probability of PTB (p_0) in the population under scenarios where risk factors were removed; the PAR% was calculated as $100*(p_{obs}-p_0)/p_{obs}$. The PIF% was similarly derived to estimate the reduction in PTB under scenarios where the level of continuous risk factors was reduced.

Results: A total of 123607 singleton infants were included in the study who were born between the years 2005-2019 in Nova Scotia. Of the cohort, 8053 (6.5%) infants were born preterm. Multiple imputations were used in analysis with ten imputed data sets. Of the risk factors studied, pre-existing type 2 diabetes had the largest adjusted relative risk (aRR) for PTB at 3.00 (95% confidence interval [CI]: 2.55-3.54), compared to women without the condition. The largest PAR estimated was for the complete elimination of maternal smoking during pregnancy associated with 5.8% (95% CI: 4.6-7.0) of PTB. Results varied for many of the risk factors across time periods (2005-2009, 2010-2014 and 2015-2019) as well as between primiparous and multiparous women.

Conclusion: Only a small proportion of PTB was estimated to be attributable to the risk factors studied. These findings can be used to inform which risk factors may be targeted to reduce PTB in Nova Scotia.

LIST OF ABBREVIATIONS USED

ART	Assisted Reproductive Technology
BMI	Body Mass Index
CCI	Canadian Classification of Health Interventions
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
CPSS	Canadian Perinatal Surveillance System
ICD-10-CA	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada
IVF	In Vitro Fertilization
NSAPD	Nova Scotia Atlee Perinatal Database
OR	Odds Ratio
PAR	Population Attributable Risk
PIF	Population Impact Fraction
PPROM	Preterm Prelabour Rupture of Membranes
PTB	Preterm Birth
QAIPPE	Quintile Area Income Per Person Equivalent
RR	Relative Risk
aRR	Adjusted Relative Risk
SET	Single Embryo Transfer
SOGC	Society of Obstetricians and Gynaecologists of Canada

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CHAPTER 1: INTRODUCTION

Birth occurring at less than 37 weeks' gestation, or preterm birth (PTB), is a leading cause of neonatal and childhood death[1–5]. PTB is a syndrome composed of multiple etiologies, contributing to multiple phenotypes[5,6]. Therefore, PTB can be attributable to multiple risk factors, related to maternal or pregnancy characteristics. While many risk factors may not be considered modifiable, many may be; examples of modifiable risk factors for PTB include maternal age and gestational diabetes.

Due to its importance as a key public health indicator, rates of PTB are tracked provincially, nationally, and internationally over time. While these data are important for identifying possible concerning trends, generating hypotheses, and planning healthcare resources, they do not provide information about the extent to which the rate could be reduced through the modification of risk factors. This information can be provided through the estimation of the population attributable risk (PAR), the proportion of PTB that theoretically can be prevented through the elimination of a causal risk factor in a population. The PAR depends not only on the strength of the association between a risk factor and the outcome, but also on the prevalence of the risk factor in the population. Previous international studies estimate that 37% of PTB can be explained by known risk factors. Studies estimating the PAR tend to be done sporadically for publication in academic journals; however, ongoing provincial estimates that would more directly inform policy and programs are not available.

Therefore, the primary objective of the proposed study was to estimate the percent of PTB that could be prevented if known modifiable risk factors had been absent in Nova Scotia over a 15-year period.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

2.1 Prevalence of Preterm Birth

The World Health Organization defines PTB as the birth of an infant at less than 37 weeks' gestation[1]. This definition uses an arbitrary gestational age, independent of clinical signs or symptoms[7,8]. Globally, 15 million infants are born preterm each year with a varying prevalence of PTB between 9.6-11.1% across countries[9]. Estimates of the prevalence of PTB within one country are often conflicting due to estimates in many countries being drawn from prediction models, as less than 5% of global births occur in countries with complete vital information[4,10,11].

In countries with reliable vital statistics data, rising PTB rates are seen[1,4,12]. The increase in PTB rates are hypothesized to be attributable to increased maternal age, obesity and diabetes, high blood pressure, intra-uterine growth restriction, use of infertility treatments, and provider-initiated births[1,5].

Canada has a preterm birth rate of 8.2 per 100 live births[1]. Prince Edward Island, British Columbia and Québec showed the lowest rates of PTB in 2013 (7.1%, 7.4% and 7.4%, respectively) with Nunavut, Alberta, Newfoundland and Labrador as well as the Yukon showed the highest rates of PTB (12.6%, 8.6%, 8.3% and 8.1%, respectively)[13,14]. In 2016 Nova Scotia had a PTB rate of 7.6%[15].

2.2 Consequences of Preterm Birth

2.2.1 Mortality and Comorbidities

Worldwide, PTB is a significant perinatal, pediatric and women's health indicator and is a leading etiology of neonatal and childhood mortality[10,12,16]. Specifically, PTB is the second most common cause of death in children under the age of five years independent of a country's income[2,4,9]. Neonatal death (deaths within the first 28 days of life) accounts for 42% of deaths under the age of five years, of which 27-75% are directly associated with PTB, leading to an excess of one million preterm deaths each year[1,2,5,11,13]. Because

the degree of an infant's organ immaturity at time of birth directly correlates with chance of mortality, more than 50% of neonatal mortality is accounted for by infants born at less than 30 weeks' gestation. In comparison, infants born after 32 weeks have survival rates near 100%[11,16].

In addition to the increase in mortality, PTB increases the vulnerability of infants to develop childhood, adolescent and adult comorbidities due to the interaction of immature organ systems with the extrauterine environment. An estimated 50% of long-term morbidities are caused by PTB[5]. Comorbidities most often experienced are those related to the lungs, heart and brain, and inability to meet age-related milestones throughout life[11,17,17]. Infants born preterm may have complications with neurodevelopment and behavioural development as well as chronic conditions, with infants born at an earlier gestational age having an increased risk of these conditions[1]. As one third of an infant's brain growth occurs in the last few weeks of gestation, preterm infants frequently display signs of neurocognitive disorders such as cerebral palsy, neuromotor dysfunction, mental retardations, sensory impairment, neuro sensitivity impairments, and visual and hearing impairments[2,2,5,13,17]. Comorbidities of functional and developmental disorders include a high prevalence of attention deficit-hyperactivity disorder[17,18]. In addition to the direct comorbidities to infants, depression and psychosocial distress is higher in parents of infants born preterm[17].

2.2.2 Health Care Costs

Accompanied with the emotional costs of PTB, economic costs to healthcare systems are significant[2,12,19]. Preterm neonates cost twice the amount per day of a full-term neonate during their hospital stay in Canada[19]. An increased prevalence of chronic conditions in infants born preterm compared to full term leads to an increase in visits to outpatient health centres as well as hospital readmissions[17]. Although the highest expenses are created during hospital stays, preterm neonates continue to create considerable expenses to the health care system throughout their life with specialized programs, continuation of hospital care, maternal and paternal lost household labour market productivity, and specialized care for women in subsequent pregnancies[17,19,20]. The national cost of caring

for preterm infants was estimated to be $587.1 million per year in Canada, based on a retrospective study analysing a cohort of preterm infants born between 1996 and 1997[19].

2.3 Preterm Birth Assessment and Classification

The continuum of stages during pregnancy is identical, regardless of whether the resultant birth is preterm or full-term. These stages are implantation, quiescence, activation, stimulation and involution[21]. Any disruption from a variety of independent or interacting risk factors (genetic predispositions or external) have the potential to initiate one of many pathological processes resulting in the premature activation of the natural cascade to parturition, demonstrating the phenotypic heterogeneity of PTB[5–7,21].

2.3.1 Determination of Gestational Age

To determine the gestational age of a neonate, various pre- and post-birth estimations are used in Canada[22]. Early pre-birth estimations of gestational age are the gold standard as estimation becomes increasingly difficult as the pregnancy progresses[8]. Pre-birth estimations of gestational age include non-sonographic methods as well as sonographic methods. Non-sonographic methods for determining gestational age include Naegel's rule, which takes into consideration the start of the last menstrual period[23]. Clinical history or last menstrual period and ovulation is often not reliable, and on average underestimates gestational age[22]. The second non-sonographic method is uterine size, with different sizes corresponding to various points in the pregnancy[23]. Physical factors such as fibroids and maternal obesity limit the accuracy of uterine measurement in the determination of gestational age[22].

Sonographic methods include first, second and third trimester dating, using various measurements of the fetal anatomy (e.g., crown-rump length, biparietal diameter and femur length) depending on timing in pregnancy[23, 22]. Transvaginal ultrasonography may be used during early first trimester pregnancy and transabdominal ultrasonography during all trimesters[22]. Sonographic determination of gestational age has previously been determined as clinically superior to non-sonographic dating[22].

Methods to determine gestational age after birth include birthweight and best obstetric estimates[1,7,11]. Postnatal techniques also include the Dubowitz method and New Ballard score, which each include physical and neurological assessments, with greater scores indicating greater maturity[23].

2.3.2 Preterm Birth Classification and Phenotypes

Current classification systems of PTB are based on gestational age, clinical presentation at birth, or pathophysiology of clinical conditions. PTB has been routinely classified by gestational age at birth: extreme preterm less than 28 weeks, severe preterm 28-31 weeks, moderate preterm 32-33 weeks, and near term or late preterm 34-36 weeks[5,11]. Of the global PTB, 5% account for extreme preterm, 15% severe preterm, 20% moderate preterm and 60-70% near term or late preterm[5].

Alternatively, clinical presentation of PTB has been used to classify PTB as either spontaneous or provider-initiated. Spontaneous PTB occurs following spontaneous initiation of labour leading to PTB; some classifications also include cases of prelabour rupture of membranes. An estimated 70% of PTB occurs following spontaneous labour[24,25]. Provider-initiated (sometimes termed indicated) PTB occurs due to the clinical interruption of pregnancy to initiate birth in favour of the health of either the woman or fetus. This is often due to pregnancy disorders such as hypertension, maternal bleeding, intrauterine growth restriction or fetal distress. An estimated 30% of PTB are provider-initiated[13,21]. This distinction between spontaneous and provider-initiated PTB is somewhat arbitrary as the physiological conditions that can lead to provider-initiated PTB can go clinically undetected for weeks or longer, and as a result could be documented as spontaneous preterm birth[24].

As no single gene or external risk factor is fully responsible for PTB, PTB is discussed as a syndrome with heterogeneous etiology, largely undetermined, influencing the various complex phenotypes[6]. Because of this complexity, PTB is difficult to classify and often, even when classified, is classified incorrectly as the determination of the original factor or set of factors leading to the PTB is near impossible[8].

Recently, it has been proposed to classify PTB phenotypes based on the pathophysiology of clinical conditions[5,6,17]. Villar et al.[6] proposed a classification system in addition to the routine classification of clinical presentation of labour, based on maternal condition before delivery, fetal condition before delivery, placental pathological condition, and signs of initiation of partition[6]. In a study completed by Barros et al.[26], 80% of all PTB were estimated to be explained by one of the above pathophysiological conditions[26]. These visible clinical conditions listed above are frequently targeted for clinical interventions for the prevention of PTB[6,7].

2.4 Modifiable Risk Factors for Preterm Birth

PTB can be attributed to multiple risk factors influencing any component of a PTB phenotype, maternal or pregnancy related, either modifiable or non-modifiable[5]. Risk factors may be genetic, biological, behavioural, social, environmental or a combination of multiple factors[9,25]. Although preterm birth has a component of genetic determination, many risk factors are potentially modifiable[5,9,27,28].

Modifiable risk factors are of importance as they can be modified through policy and public health or clinical practice interventions[17]. By taking a broad approach to the term modifiable, modifiable risk factors for PTB include: maternal age, smoking, alcohol use, drug use, pre-pregnancy body mass index (BMI), income, depression, pre-existing diabetes, gestational diabetes, chronic hypertension and assisted reproductive technology (ART). The evidence for an association between these factors and PTB is briefly reviewed in the following sections and is summarized in Table 2.1; PAR estimates, where available, are reviewed in the following section (2.5) and are summarized in Table 2.2.

2.4.1 Maternal Age

Both younger and older women are at an increased risk of PTB[29]. As women around the world delay pregnancy for professional or other reasons, average maternal age has risen[29,30]. Delayed childbearing increases the risk of PTB as pregnancy at increased maternal age is physiologically more difficult, bringing additional complications to the

pregnancy. Advanced maternal age (35 years of age or older at delivery) is correlated with chronic hypertension, ART, pre-gestational diabetes (type 2) and gestational diabetes, all factors also associated with PTB[29]. In 2009, women 35 years of age or older had the highest rates of PTB at 9.5%, compared to women in lower age groups[13]. In a retrospective cohort study in the UK completed by Oakley et al. (2014)[30], compared to women 20-24 years of age, women 35-39 years were estimated to have a 33% greater likelihood of PTB (relative risk, RR:1.33, 95% CI:1.15-1.53)[30] and women above the age of 40 years were 64% more likely to have a PTB (RR: 1.64, 95% CI:1.36-1.98)[30] (Table 2.1). In an additional study, Schummers et al.[31] demonstrate the increased absolute risk of PTB at both the lower and upper extremes of maternal age[31].

2.4.2 Smoking

Significant decreases in the rates of smoking during pregnancy have occurred, although it is still prevalent[32]. Nicotine and the chemicals within cigarette smoke, including polycyclic aromatic hydrocarbons, can cross the placental barrier and enter fetal circulation. These compounds severely disrupt natural physiological processes and further disrupt development[33]. It has been hypothesised that nicotine and related chemicals found in cigarettes damage the placenta, restricting fetal growth and initiating inflammatory responses, all of which contribute to PTB[5,34]. The effect of smoking during pregnancy on PTB is both dose, and time dependent with earlier and increased exposure during pregnancy increasing the risk of PTB[32]. In a large cohort study using data from the United States, Liu et al.[35] analysed any smoking during either the first or second trimester[35]. They estimated that, compared to women that did not smoke during pregnancy, women who smoked 1-2 cigarettes in the first trimester had a 31% increased odds of PTB (odds ratio, OR:1.31, 95% CI:1.29-1.33)[35]. A linear trend was observed as women who smoked 20 or more cigarettes a day displayed 53% greater odds of PTB (OR:1.53, 95% CI:1.52-1.55)[35]. Estimating the odds of PTB due to smoking in the second trimester, compared to nonsmokers, women who smoked 1-2 cigarettes per day had a 37% increased odds of PTB (OR:1.37, 95% CI:1.35-1.39)[35]. A linear trend was also observed in the second

trimester, as the women who smoked 20 cigarettes or more a day had an increased odds of 59% compared to nonsmokers (OR:1.59, 95% CI:1.58-1.61)[35] (Table 2.1).

Other studies have shown that by reducing smoking in pregnant women, PTB rates decrease as well[25]. Smoking, like alcohol or drug use during pregnancy, is often not report truthfully and can alter accurate representations of their prevalence in the society[17].

2.4.3 Alcohol Use

International clinical guidelines suggest that pregnant women avoid heavy or binge drinking, as alcohol is a teratogen and can initiate a wide range of disruptions including the initiation of PTB[36]. Light to moderate alcohol consumption during pregnancy is routinely a topic of interest, as trends in alcohol consumption during pregnancy have changed drastically over time[37]. In a systematic review and meta-analysis, Mamluk et al.[36] estimated that light to moderate drinking combined, compared to abstainers, lead to an increase in risk of PTB by 10% (RR:1.10, 95% CI:0.95-1.28)[36] (Table 2.1). Additionally, Patra et al.[38] further estimated that moderate to heavy drinking increased the risk of PTB by 23% compared to abstainers (RR:1.23, 95% CI:1.05-1.44)[38] (Table 2.1), potentially indicating a dose-response relationship with the association of drinking and risk of PTB[38].

2.4.4 Drug Use

Illicit drug use during pregnancy interferes with uterine blood flow, fetal oxygenation, and in the case of crack cocaine, increases levels of oxytocin inducing premature contractions and at times initiating preterm labour[5,39,40]. In addition, illicit drug use either in the case of a single substance user or polysubstance user, significantly alters the physiological pathways of appetite in the woman and consequently alters nutrient flow from woman to fetus[40].

Estimating the association between drug use and PTB is difficult due to the high prevalence of polysubstance uses, making it challenging to determine a reliable estimate of the effect of a single drug[41]. In addition, women may be reluctant to disclose the use of drugs during pregnancy due to the added stigma. In response to this, previous research

used illicit drugs as a composite exposure including both single and polysubstance users and any form of illicit drug. In a retrospective cohort of Canadian women, the use of illicit drugs was estimated to increase the risk of PTB before 32 weeks by 80% (RR:1.8, 95% CI:1.7-2.0)[39] and PTB between 32 and 36 weeks by 60% compared to non-illicit drug users (RR:1.6, 95% CI:1.5-1.6)[39] (Table 2.1).

2.4.5 Pre-Pregnancy Body Mass Index

In line with many other health conditions, pregnancy is significantly affected by the weight of the woman. The obesity epidemic has led to the increase in maternal obesity, possibly influencing similar trends in PTB[42]. Worldwide, women on average have higher rates of obesity compared to men[42]. Approximately 8% of reproductive aged women live with obesity, with 17% and 24.2% of pregnant women in Canada and Nova Scotia having obesity, respectively[43–46]. Having obesity while entering a pregnancy is associated with significantly more risk compared to weight gained during pregnancy[2,5,44,47]. Obesity may lead to an increased risk of PTB due to ill-functioning metabolic pathways in the reproductive system of the woman, lack of substantial nutrients delivered to the fetus, in utero constraints as well as the relationship between obesity and adverse conditions such as chronic hypertension, pregnancy induced hypertension, pre-existing diabetes, and gestational diabetes[5,42,48,49]. Similarly to maternal age, women at both ends of the BMI continuum are at an increased risk of PTB, with underweight women unable to provide adequate nutrient delivery for proper fetal development[42]. Controversy exists with the appearance of an obesity PTB paradox where a number of studies have reported obesity as a protective factor of PTB. Lutsiv and colleagues concluded this paradox to be the result of the confounding by unknown factors associated with comorbidities of obesity relating to PTB[45].

Lutsiz et al.[45] estimated that women who had class 3 obesity (BMI 40 or greater) compared to class 1 obesity (BMI 30-34) were at a 31% increased risk of having a PTB (RR:1.31, 95% CI:1.19-1.43)[45], while Han et al.[50] in a systematic review of 78 studies estimated that underweight women compared to normal weight women had a 29% increased risk of PTB (RR:1.29, 95% CI:1.15-1.46)[50] (Table 2.1).

2.4.6 Income

In Canada, area-level income can be analysed using a postal code conversion to census data within dissemination areas, census subdivisions, census tracts as well as other factors such as immigrant tertiles. Neighbourhood income quintiles (Quintile Area Income Per Person Equivalent, QAIPPE) at the level of dissemination area are commonly used, and Statistics Canada regularly updates these data[51].

Income and other socioeconomic measurements are well-established risk factors for various health conditions, including PTB[5]. Low socioeconomic status is associated with additional risk factors that negatively influence pregnancy (e.g., smoking and alcohol use)[52]. Level of deprivation is an important risk factor and is associated with an increase in risk of PTB even in women that would otherwise be at low risk[52]. Determined in a 2009 Canadian survey, PTB rates decreased as neighbourhood income levels increased[13]. Huynh et al.[53] estimated that compared to least deprived women, the most deprived women were at a 16% increased odds of PTB (OR:1.16, 95% CI:1.10-1.21)[53] (Table 2.1).

2.4.7 Depression

Depression is a common comorbid condition during pregnancy, with the global prevalence of antenatal depression ranging from 15% to 65%[54]. Multiple factors contribute to the elevated prevalence of antenatal depression including: depression being more common in females, depression being more common in the age category when reproduction occurs compared to younger and older age categories of women, as well as the increased enhancement of depressive symptoms during pregnancy due to the fluctuation of hormones[54]. Maternal depression leads to the dysregulation in the hypothalamic pituitary adrenal axis[54]. This dysregulation creates high levels of cortisol in the woman, hindering the flow of nutrients to the fetus, decreasing immune response and subsequently increasing risk of harmful infection and PTB[54]. One systematic review demonstrated that a dose-effect relationship exists with severity of depressive symptoms and risk of PTB, with the use of antidepressants increasing the risk of PTB[55]. In a

systematic review and meta-analysis, Dadi et al.[54] estimated that compared to women who did not experience antenatal depression, women who experienced depression were at a 40% increased risk of having a PTB (RR:1.40, 95% CI:1.16-1.69)[54] (Table 2.1).

2.4.8 Diabetes

Various types of diabetes exist, classified by time of onset as well as physiological dysregulation. Regardless of the type of diabetes, all lead to dysglycemia[56]. Pre-existing diabetes is a health condition appearing before pregnancy and continues to be present during a woman's pregnancy. Pre-existing type 2 diabetes is caused by the resistance of human cells to insulin, often linked to poor diet and obesity[57]. Gestational diabetes affects 7-8% of pregnancies, and is caused by impairment of the beta cell functioning due to hormone imbalances in the body during pregnancy[58]. Gestational diabetes is correlated with increased maternal age and obesity[58]. Care for diabetics during pregnancy includes optimal glycemic control to reduce the risk of PTB as high levels of glucose creates a hostile environment for the fetus and consequently frequently leads to PTB[56,59].

In a cohort study of a Canadian population, Metcalfe et al.[57] estimated that women with pre-existing type 2 diabetes were 2.4 times more likely to have a PTB (RR:2.40, 95% CI:2.31-2.49)[57] and women with gestational diabetes were 32% more likely to have a preterm birth compared to non-diabetic women (RR:1.32, 95% CI:1.30-1.34)[57] (Table 2.1). Although studies analysing the risk between type 1 diabetes and PTB exists, this association will not be discussed as type 1 diabetes displays limited modifiability.

2.4.9 Hypertension

Similar to diabetes, hypertension during pregnancy can be due to chronic hypertension originating before conception[60,61]. Diagnoses of hypertension are associated with systematic adverse effects, resulting in an increased risk of PTB[60,62]. Both obesity and increased maternal age are associated with chronic hypertension[60].

In a systematic review and meta-analysis, Bramham et al.[60], estimated that women with chronic hypertension are 2.7 times more likely to have a PTB compared to women

without chronic hypertension (RR:2.7, 95% CI:1.9-3.6)[60] (Table 2.1). Similarly, in a study completed by Berger et al., women with pre-existing hypertension were 3.81 times more likely to experience a PTB (adjusted relative risk, aRR:3.81, 95% CI:3.55-4.11)[63]. Due to the complexities of gestational hypertension and pre-eclampsia, the conditions will not be included in the study as these conditions are difficult to act on, and frequently lead to provider-initiated PTB.

2.4.10 Assisted Reproductive Technologies

ART, used in 1.4% to 7% of pregnancies, is often defined as the handling of sperm and/or eggs outside the human body and includes in vitro fertilization; sometimes it also includes other fertility treatments such as ovarian stimulations[64,65]. ART is sought out when couples experience infertility, when it is biologically impossible for a couple or person to conceive naturally, or by same-sex couples[66].

A systematic review and meta-analysis completed by Pandey et al.[67] concluded that pregnancies resulting from in vitro fertilization (IVF) were at a 54% increased risk of PTB (RR:1.54, 95% CI:1.47-1.62)[67], pregnancies conceived by frozen embryo transfer were at 39% increased risk (RR:1.39, 95% CI:1.20-1.61)[67] and pregnancies conceived by a routine single embryo transfer (SET) were at 53% increased risk (RR:1.54, 95% CI:1.40-1.67)[67] (Table 2.1), compared to spontaneous conception. The indirect impact of infertility, versus the reproductive technologies themselves, during ART on PTB is unknown[64].

2.5 Population Attributable Risks for Preterm Birth

2.5.1 Concept and Methodology to Determine Population Attributable Risk

The PAR is the proportion of a disease, outcome or condition that theoretically can be prevented through the elimination of a causal risk factor in a population. The PAR depends not only on the strength of the association between a risk factor and the outcome, but also on the prevalence of the risk factor in the population[68]. In interpreting the PAR, it

is required that the exposure be a causal factor of the disease at study[68]. A counterfactual scenario is an unobservable theoretical situation contrary to fact held within one variable while estimating a measure of effect[69]. In the case of the PAR, this counterfactual situation is a zero prevalence of exposed individuals. This counterfactual situation can be alternatively manipulated (e.g., lowering the prevalence but not completely eliminating the risk factor, or shifting the level of a continuous risk factor) to estimate additional parameters.

Two methods to estimate the PAR include the Levin's equation and the average PAR. PARs can be estimated using Levin's equation (Equation 2.1) where Pe represents the prevalence of exposure over a specified time period and RR the relative risk of the exposed over non-exposed during the same time period[68,70,71]. Levin's equation can only be used for a complete reduction of the prevalence of the exposure. Therefore, the average PAR equation is the preferred method of estimation, although used more infrequently due to the necessity of an original dataset as opposed to being able to use a previously reported RR as can be used in Levin's equation[70]. The equation for the average PAR can be seen in equation 2.2 and can include any counterfactual situation.

$$\%\, PAR = \; 100\, x \left(\frac{Pe\ (RR - 1)}{1 + Pe(RR - 1)} \right)$$

Equation 2.1. Levin's equation for the estimation of the proportion of a disease attributable to a risk factor in the counterfactual scenario of the risk factor of interest having a prevalence of zero[68].

$$\%\ PAR/PIF = 100\ x \left(\frac{Probability\ of\ PTB_{observed} - Probability\ of\ PTB_{counterfactual}}{Probability\ of\ PTB_{observed}} \right)$$

Equation 2.2. Average PAR/PIF equation for the estimation of the proportion of a disease attributable to a risk factor in a counterfactual of zero or reduced prevalence [70].

A generalization of the PAR concept is that of population impact fractions (PIF). Whereas the PAR represents the potential of eliminating a risk factor, the PIF estimates the percent of a disease that could be prevented if the level of a risk factor were reduced by a certain extent. Because of this, PIF estimates provide a more realistic view of possible reductions of PTB through interventions to reduce risk factors[72]. For example, in estimating the PAR for women with obesity, all women with obesity in the population would be reduced to not having obesity, whereas a PIF may be estimated for a 10% reduction of body weight in women with a BMI of 25 kg/m^2 or greater.

Counterfactual situations applied to the PIF estimations can be based on multiple considerations including feasibility, economics and reductions previously observed. To determine these PIF counterfactual scenarios and apply them to equations, a proportional shift, distributional shift or RR shift may be applied to the prevalence of the exposed group. Similar to the PAR, many equations may be used to estimate the PIF depending on the type of shift applied (counterfactual scenario). Using equation 2.2 allows any counterfactual scenario to be applied.

PARs and PIFs are of value in public health as their estimations help quantify the impact of a risk factor. Using estimations of PAR or PIF, interventions can be determined that have the potential to reduce the prevalence of a certain risk factor, ultimately providing the maximum reduction of the disease or condition in the population[68,70].

2.5.2 Population Attributable Risk and Population Impact Fraction Estimates for Preterm Birth

In a previous international study by Ferrero et al.,[9] 4.1 million singleton pregnancies from four countries were analysed. It was estimated that on average 37% of the PTB cases could be explained by 21 individual known risk factors, and the remaining 63% PTB

cases were due to unknown risk factors[9]. Maternal education, maternal single status, age, smoking, BMI, poverty, no prenatal care before 20 weeks, and use of illicit drugs were determined to be modifiable through policy and public health and accounted for anywhere between 14% to 39% of PTB depending on the country[9]. Risk factors managed through clinical practice (pre-existing and gestational diabetes, pre-existing and pregnancy induced hypertension, previous Caesarean section, and ART) accounted for anywhere between 2% to 12% of PTB depending on the country[9]. Estimates of the proportion of PTB that can be attributed to modifiable risk factors similar to the ones studied by Ferrero et al.[9] have not been studied in Nova Scotia.

Apart from the study conducted by Ferrero et al.,[9] studies on PAR and PIF of PTB are limited. Additionally, in existing studies, the prevalence of PTB varies across geographical region and time, contributing to the difficulty of summarizing and comparing published estimations of PARs and PIFs of modifiable risk factors of PTB.

2.5.2.1 Maternal Age

In a retrospective cohort study in the UK between 2004 and 2012, Oakley et al.[30] analysed the effect of maternal age on risk of PTB for 51,225 singleton deliveries (including 312 stillbirths)[30]. PTB occurred in 0.87% of births occurring to women aged 20-24, 1.39% in women aged 25-29, 1.8% in women aged 35-39 and 1.33% of women aged 40 or older[30]. Using a Poisson regression, and adjusting for parity, women's ethnicity, BMI, smoking status, marital status and area deprivation, Oakley et al.[30] determined births to women aged 25-29, 30-34, 35-39, and above 40 years and older contributed to 0.9%, 1.7%, 5% and 2.6% of PTB respectively (Table 2.2)[30]. These estimations were estimated by applying the risk of PTB from the 20-24 age group to all maternal age groups.

Similarly, in a cross-sectional study conducted using Canadian and American survey data from 2005 and 2006, Garn et al.[73] estimated that 6.2% of PTB in Canada can be attributed to the risk factor of advanced maternal age (above 35 years old), determined by applying a zero prevalence of maternal age above 35 years old as the counterfactual scenario (Table 2.2)[73]. This sample consisted of 34,020 live singleton births in the USA

and 6,421 live singleton births in Canada, where 7.6% of births in the USA were PTB and 4.9% of births in Canada were PTB[73].

2.5.2.2 Smoking

In 2016, Lengyel et al.[74] conducted a retrospective study in the USA in which 393,441 live singleton births were analysed between 2006 and 2011. In this sample, 10.1% of births were PTB[74]. It was estimated that if all smokers became non-smokers, 8.96% of PTB would be prevented (Table 2.2)[74]. A further study in 2019 estimated that 9% of PTB could be attributable to smoking (Table 2.2)[75]. This estimate was determined using data from 28,119 singleton live births in Australia from 1998-2010, in which the prevalence of PTB was 13% of births[75].

2.5.2.3 Alcohol and Drug Use

Although few studies have reported on PARs for alcohol and illicit drug use and PTB, Gibberd et al.[75] analysed a large population of aboriginal Western Australians. During the years 1998 to 2010, this study analysed 28,119 singleton live births, where the prevalence of PTB was 13%[75]. Gibberd et al.[75] estimated that 1% of PTB can be attributed to alcohol use during pregnancy and 5% to illicit drug use among the studied cohort (Table 2.2)[75].

2.5.2.4 Pre-Pregnancy Body Mass Index

As BMI tends to be a risk factor frequently analysed in studies, there are many reports on PARs for BMI and PTB. In a study conducted by Dzakpasu et al.[76] in Canada, 5,930 women were analysed over the years 2005 and 2006. In this retrospective cohort, with a PTB prevalence of 6.1% of births, it was estimated that underweight women contributed to 2.6% of PTB, while having obesity contributed to 0.3% of PTB[76]. In a study conducted by Lengygel et al.[74] in the United States using data from 393,441 singleton live births from 2006 to 2011, it was estimated that 10.1% of births were PTB, and if all underweight women became normal weight, 2.2% of PTB would be prevented (Table

2.2)[74]. Lengygel et al.[74] also determined that obesity is attributable to 0.88% of PTB[74]. Similar results were estimated by Garn et al.[73] who estimated that 1.9% of PTB could be attributable to women being underweight[73]. This American population of 34,020 and Canadian population of 6,421 had a PTB prevalence (including spontaneous and provider-initiated) of 7.6% in the USA and 4.9% in Canada[73].

2.5.2.5 Income

PAR of income on PTB is rarely documented, since preventable fraction, the inverse of PAR when the exposure can be of benefit to a population, is more appropriately used[77]. Brownell et al.[77] analysed the effects of financial support given to women living in poverty during pregnancy in Manitoba, Canada during the years 2003 to 2010, and the influence of this unconditional financial support on rates of PTB[77]. The prevalence of PTB in this population was 19.5% of births[77]. Although a PAR was not estimated in this quasi experimental retrospective cohort, it was determined that PTB was reduced by 17.5% (95% CI:11.2-23.8)[77] in the low income exposed group when low income families received prenatal social assistance, compared to low income women who did not receive the social assistance[77].

2.5.2.6 Depression

When depression and anxiety are analysed together as a composite risk factor of ‘stress’, Lilliecreutz et al.[78] determined that 23% of PTB is attributable to ‘stress' during pregnancy in the exposed group[78]. This study was conducted in Sweden and included 340 women from 2010[78]. As this study was a case control study, estimates of the PAR or PIF were not determined[78].

2.5.2.7 Diabetes

Metcalfe et al.[57] published a retrospective cohort study for the years 2004 to 2015 analysing 285,6401 Canadian births[57]. They estimated that type 2 diabetes contributed to

0.82% (95% CI:0.77-0.87) of PTB and gestational diabetes 1.91% (95% CI:1.78-2.03) of PTB[57] (Table 2.2).

Scime et al.[62] analysed gestational diabetes stratified by provider-initiated and spontaneous PTB, and estimated that gestational diabetes accounted for 2% of spontaneous PTB (95% CI:1.2-2.7) and 4.9% (95% CI:3.8-6.0) of provider-initiated PTB[62] (Table 2.2). These estimates were completed in a cross-sectional study of 152,246 singleton live births in the years 2014-2017, where the prevalence of spontaneous PTB was 4.0% and indicated PTB 2.8%[62].

2.5.2.8 Hypertension

Pre-existing chronic hypertension has been estimated to contribute to 0.19% (95% CI: 0.007-0.31)[79] of spontaneous PTB, 0.26% (95% CI:0.09-0.43)[79] of premature rupture of membranes and 2.03% of provider-initiated PTB (95% CI:1.79-2.26)[79] (Table 2.2). The above estimates were derived from a retrospective cohort study of 580,765 singleton live born infants to non-aboriginal women in Australia from 1984-2006[79]; the prevalence of PTB in this study was 3.5%[79]. A 2020 Canadian study, Berger et al. estimated that 1.40% (95%CI: 1.25-1.55) of PTB was attributable to pre-existing hypertension[63].

2.5.2.9 Assisted Reproductive Technologies

A retrospective cohort study conducted by the Center of Disease Control and Prevention in 2016, analysing data from the USA and Puerto Rico, demonstrated that in 2016, 9.9% of births were PTB[80], while 5.3% of PTB were attributable to ART use (Table 2.2)[80].

2.6 Interventions to Reduce Preterm Birth

Due to the overlapping and complexity of risk factors for PTB, a single intervention known to reduce rates of PTB to the greatest extent does not exist[6]. Currently, primary and secondary interventions exist to help prevent PTB. Previously, a focus on tertiary intervention efforts existed as these interventions act on visible clinical phenotypes such

as maternal bleeding or shortening of the cervix, granting time for health care providers to transfer women to hospitals with resources for preterm delivery. Although survival of preterm infants has increased over the years due to tertiary interventions, these interventions do not reduce the rates of PTB itself[8,9,24,27]. Interventions with the opportunity to prevent the occurrence of PTB lie in primary prevention that occur through preconception care and secondary prevention through antenatal care[1]. Primary prevention efforts aim to prevent PTB by modifying the prevalence of modifiable risk factors through policy and public health, tackling the upstream occurrence of these risk factors as a primordial preventative approach. Recent reports have suggested an increase in research be directed at determining what risk factors contribute the largest to PTB in order to determine the most effective prevention measures[24,34].

2.6.1 Preconception Prevention

Preconception care is health care provided to women of childbearing age and is a general continuum of care to promote and encourage health of women and, in turn, newborns[1]. Preconception care targets modifiable social and behavioural risk factors to promote health[1]. As outlined in the World Health Organization document, *Born Too Soon*, preconception care takes into account underlying and intermediate as well as immediate approaches to prevent PTB[1]. Underlying prevention plans for PTB include educating women on their health through clinical and social means. Preconception care takes advantage of the long term continuum of care approach and allows time for behavioural interventions to disseminate through social and peer support groups[1,24,26,34].

Born Too Soon further discusses intermediate prevention plans, including healthy physical activity and proper nutrition for all women. Immediate prevention targets include: providing knowledge and resources on contraceptives, management and screening of chronic disease and risk factors such as diabetes[1], as well as promoting proper mental health, preventing and treating substance use and minimizing smoking and second-hand smoke exposure[1]. Recently, it has been emphasized that access to preconception care is not universal: socially economic disadvantaged populations tend to not gain the advantages that this continuum of care intends to deliver. Promoting the

expansion of preconception care out of tertiary clinics and into public health resources aims to increase access to greater knowledge and more frequent support for a larger percentage of women[1].

2.6.2 Antenatal Care

The *Born Too Soon* document as well as the Global Strategy for Women's, Children's and Adolescent's Health emphasize that through proper antenatal care, preventative efforts may be used to reduce PTB[1,81]. Antenatal care can additionally provide financial and social support to at-risk women through counselling for risk factors such as smoking cessation as well as providing clinical treatments for chronic diseases such as diabetes and hypertension[24]. With the proper resources, trained professionals, data resources and access to antenatal care, achieving targeted care to women based on known risk factors will reduce PTB rates[1].

2.6.3 Clinical Guidelines Interventions

Using Canadian clinical practice guidelines, examples of current recommendations for some risk factors of PTB include: obesity, hypertension, diabetes, and alcohol use. The Society of Obstetricians and Gynaecologists of Canada (SOGC) states that preconception counselling for weight is the most effective method to promote healthy weight changes in women[82]. Programs that the SOGC recommends includes weight control programs that focus on diet and exercise before pregnancy. A loss of 5% to 10% in weight before getting pregnant (if a woman is living with obesity) is considered extremely beneficial to prevent the occurrence of adverse outcomes such as PTB[82]. By targeting and screening for obesity before a woman becomes pregnant, health care professionals can help prevent the occurrence of additional comorbidities that can arise in pregnancy, including hypertension and diabetes[82]. If a woman wishing to become pregnant has a BMI above 30, the SOGC recommends exploring medical therapy or pharmacology treatments before pregnancy in order to lose weight. Health care providers are encouraged to promote healthy weight during pregnancy[82].

The SOGC includes intervention recommendations for hypertension such as proper blood pressure measurements, routine urine testing, antihypertensive therapy if needed, as well as in patient care during severe cases of hypertension[83].

Diabetes during pregnancy is not uncommon, and the SOGC contains preventative measures to best deal with this risk factor in controlling for adverse neonatal events such as PTB. Preconception care surrounding a woman's pre-existing diabetes is extremely important. This allows for an open dialogue with the woman and health care professionals regarding appropriate medication options for antihyperglycemic agents[84]. Ensuring the woman is competent in managing strict glucose levels is extremely important in aiming to preventing PTB. The SOGC recommends screening for gestational diabetes in the first trimester of all pregnancies to arrest any adverse events that can be influenced by inadequate blood glucose levels.

Alcohol use is a difficult risk factor to treat during pregnancy. The SOCG recommends screening for alcohol use during pregnancy early in the first trimester[85]. Biological markers such as urine or blood can also be used. Providing access to motivational and supportive groups if the woman does abuse alcohol during pregnancy is an extremely important preventative measure[85].

Although interventions on PTB risk factors exist, it is understood that the complete elimination of these risk factors is not possible, restricting the influence of the preventative measures described above at reducing the prevalence of PTB.

2.7 Surveillance of Preterm Birth

Surveillance programs are extremely important in monitoring PTB. These programs inform and evaluate clinical practice, policies, programs, and research to reduce PTB rates and subsequent co-morbidities[86]. Components of surveillance systems include: data collection, analysis, interpretation and response[87]. It is through surveillance methods that the burden of PTB can be measured, and provide opportunities to enhance clinical practice and help guide and develop programs and interventions to reduce PTB[86].

The Canadian Perinatal Surveillance System (CPSS), administered through the Government of Canada is part of the Health Canada initiative to enhance and strengthen

national health surveillance capacity, with a goal of improving the health of pregnant women and infants[87]. Led by provincial experts in perinatal health and epidemiology, the CPSS has identified 52 perinatal health indicators that include maternal fetal and infant health determinants, and currently reports on 27 of these perinatal health indicators (e.g. maternal smoking, alcohol consumption and maternal age at birth), as well as health outcomes such as PTB. The CPSS utilizes the Canadian Institute for Health Information data, and specifically discharge abstracts databases. Because of these data sources, the CPSS has limited access to additional modifiable risk factors for PTB documented on health record chart abstracts during pregnancy and delivery.

In Nova Scotia, rates of PTB are tracked provincially using the Nova Scotia Atlee Perinatal Database (NSAPD). Collected data are important for identifying possibly concerning trends, generating hypotheses, and planning healthcare resources. Data are collected from multiple chart abstracts during a woman's pregnancy and delivery, and therefore contain information on a variety of risk factors for PTB. Although the NSPAD includes a number of modifiable risk factors, indication of the proportion of PTB that could be reduced through the elimination or reduction of modifiable risk factors has yet to be determined.

2.8 Study Rationale

This study is the first to quantify the burden of several modifiable risk factors and to estimate the degree to which PTB can be prevented in Nova Scotia. Its findings will allow comparison of modifiable risk factors with respect to their contribution to the PTB rate on a population level to assist policy makers in focusing their preventive efforts; this research is intended to encourage the development of primary interventions and prevention efforts. In partnership with the Reproductive Care Program (RCP) of Nova Scotia, the project will inform ongoing and active enhanced surveillance methods for PTB using the PAR and PIF, in hope to promote the evaluation of clinical practices, policies, research and programs and enhancing evidence-based population-level health planning. Findings will be accompanied by interpretations suitable for clinicians, patients,

communities, and public health, and thus advocating for all children to obtain the best possible start in life.

Table 2.1. Previous measures of association between modifiable risk factors and PTB, from literature search focussed on systematic reviews and meta-analyses as well as large retrospective cohort studies in Canada.

Risk Factor	Reference	Country	Study Design	Year of Study	Reference	Regression Estimates (95% CI)
Maternal Age	Oakley et al. 2016	UK	RC	2004-2012	20-24 years	25-29: aRR:1.06 (0.92-1.21) 30-34: aRR:1.09 (0.95-1.24) 35-39: aRR:1.33 (1.15-1.53) ≥ 40: RR: 1.64 (1.36-1.98)
Smoking	Liu et al. 2020	USA	RC	2011-2018	No smoking	First trimester: 1-2 cigarettes a day: aOR:1.31 (1.29-1.33) 20 or over a day: aOR:1.53 (1.52-1.55) Second trimester: 1-2 cigarettes/day: aOR:1.37 (1.35-1.39) ≥20 cigarettes/day: aOR:1.59 (1.58-1.61)
Alcohol Use	Mamluk et al. 2017		SRMA		Abstainers	Light to moderate: RR:1.10 (0.95-1.28)
	Patra et al. 2011		SRMA		Abstainers	Moderate to heavy: RR:1.23 (1.05-1.44)
Drug Use	Baer et al. 2018	CA	RC	2007- 2012	No drug use	PTB before 32 weeks: Any drug use aRR:1.8 (1.7-2.0) PTB between 32-36 weeks: Any drug use aRR:1.6 (1.5-1.6)
Pre-Pregnancy BMI	Lutsiv et al. 2015		SRMA		Varies	BMI≥40 compared to 30-34.9: RR:1.31 (1.19-1.43) BMI≥40 compared to 30-39.9: RR: 1.20 (1.13- 1.27)
	Han et al. 2011		SRMA		Normal weight	Underweight: aRR:1.29 (1.15-1.46)
Income	Huynh et al. 2018	CA	CS	2010-2014	Least deprived	Most deprived: aOR: 1.16 (1.10-1.21)
Depression	Dadi et al. 2020		SRMA		Unaffected	aRR:1.40 (1.16-1.69)
Pre-Existing Type 2 Diabetes	Metcalfe et al. 2017	CA	RC	2004-2015	Unaffected	aRR:2.4 (2.31-2.49)
Gestational Diabetes	Metcalfe et al. 2017	CA	RC	2004 - 2015	Unaffected	aRR:1.32 (1.3-1.34)
Pre-Existing Hypertension	Bramham et al. 2014		SRMA		Unaffected	RR:2.7 (1.9-3.6)
	Berger et al. 2020	CA	RC	2010-2016	Unaffected	RR:3.81 (3.55-4.10)
ART	Pandey et al. 2012		SRMA		Spontaneous conception	IVF: RR:1.54 (1.47-1.62) Frozen embryo: RR:1.39 (1.20-1.61) SET: RR:1.53 (1.40-1.67)

aOR, adjusted odds ratio; aRR, adjusted risk ratio; ART, assisted reproductive technologies; CI, confidence interval; CS, cross-sectional; IVF, in vitro fertilization; RC, retrospective cohort; SET, single embryo transfer; SRMA, systematic review and meta-analysis.

Table 2.2. Previous estimates of the proportion of PTB attributable to modifiable risk factors in a zero-prevalence scenario, as well as a reduced prevalence scenario. Literature search focussed on systematic reviews and meta-analyses as well as large retrospective cohort studies in Canada.

Risk Factor	Reference	Country	Study Design	Year of Study	Reference	PAR/PIF (95% CI)
Maternal Age	Oakley et al. 2016	UK	RC	2004-2012	Excess PTB that could be prevented if women in all age groups had the same level of risk as those in the 20-24 age group	25-29 years: 0.9% (-2.3-4.0) 30-34 years: 1.7% (-2.3-5.6) 35-39 years: 5% (2.0-7.9) >40: 2.6% (1.3-3.9)
	Garn et al. 2014	CA	CS	2005-2006	No women aged > 35 years	Canada: Aged >35: 6.2% USA: Aged >35: 1.1%
Smoking	Lengyel et al. 2016	USA	RC	2006-2011	All non-smokers	8.96%
	Gibberd et al. 2019	AU	RC	1998-2010	All non-smokers	9%
Alcohol	Gibberd et al. 2009	AU	RC	1998-2010	All abstainers	1%
Drug Use	Gibberd et al. 2009	AU	RC	1998-2010	All no drug use	5%
Pre-Pregnancy BMI	Dzakpasu et al. 2015	CA	RC	2005-2006		Underweight: 2.6% (2.5-5.4) Overweight: -0.4% (-0.6-0.2) Obese: 0.3% (0.1-0.4)
	Lengyel et al. 2016	USA	RC	2006-2011	Normal weight	Underweight: 2.2% Overweight: -0.65% Obese: 0.88%
	Garn et al. 2014	CA	CS	2005-2006	No underweight women	Underweight: 1.9 %
Income	Brownell et al. 2016	CA	Quasi-experimental RC	2003-2010	No reference. Not a fraction.	Reduction in PTB when low income families receive prenatal asocial assistance (not a fraction, preventable in exposed group): 17.5% (11.2-23.8)
Depression	Lilliecreutz et al. 2016	SE	CC	2010	No reference. Not a fraction.	23% of women in the stress group, delivered because they were stressed
Type 2 Diabetes	Metcalfe et al. 2017	CA	RC	2004-2015	No Type 2 diabetes	0.82% (0.77–0.87)
Gestational Diabetes	Metcalfe et al. 2017	CA	RC	2004-2015	No gestational diabetes	1.91% (1.78-2.03)
	Scime et al. 2019	CA	CS	2014-2017	No gestational diabetes	2.0% (1.2-2.7) of spontaneous PTB 4.9% (3.8-6.0) of provider-initiated PTB
Pre-Existing Hypertension	Hammond et al. 2012	AU	RC	1984-2006	No hypertension	0.19% (0.07-0.31) of spontaneous PTB 0.26% (0.09-0.43) of preterm PROM 2.03% (1.79-2.26) of provider-initiated PTB
	Berger et al. 2020	CA	RC	2010-2016	No hypertension	1.40% (1.25-1.55)
ART	CDC 2019	USA	RC	2016	Spontaneous conception	5.3%

ART, assisted reproductive technologies; CDC, Center for Disease Control and Prevention; CI, confidence interval; CS, cross-sectional; PROM, prelabour rupture of membranes; PTB, preterm birth; RC, retrospective cohort.

CHAPTER 3: Objectives

The objectives of the present study were to estimate the proportion of PTB in Nova Scotia from 2005 to 2019 that could be prevented if known modifiable risk factors had been:

1. [Primary] Removed or changed to the category of the lowest risk: a) individually; or b) as a set;
2. [Secondary] Reduced in prevalence or level, but not completely eliminated, to an extent according to selected scenarios.

CHAPTER 4: METHODS

4.1 Design Overview

A population-based retrospective cohort study of Nova Scotia women and singleton infants delivered from 2005 to 2019 was conducted. Data were derived from the NSAPD. PAR and PIFs for PTB were estimated for several modifiable risk factors.

4.2 Population

The population included all live born infants resulting from a singleton pregnancy from January 1st, 2005 to December 31st, 2019 to women residing in Nova Scotia at time of the infant's birth.

4.3 Data Source

The NSAPD, starting in 1980 and becoming provincial in 1988, is a province-wide perinatal database that collects data on all births after 20 weeks' gestation or of weight at least 500 g[88]. Demographic and clinical data are collected, including determinants of maternal and fetal health, labour and delivery characteristics, as well as perinatal and neonatal morbidities. Data from hospitals across the province, with or without maternity facilities, and services in New Brunswick frequently used by Nova Scotians, are entered and coded from standardized provincial prenatal records, antenatal admissions, hospital delivery and postpartum admission chart abstracts. The NSAPD uses its own codes for data entered from both prenatal and hospital records in addition to International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) and Canadian Classification of Health Interventions (CCI) codes based on data entered from the hospital admission for the Canadian Institute for Health Information Discharge Abstract Database. The coding and quality of the data are maintained by the RCP of Nova Scotia.

4.4 Risk Factors

Risk factors analysed included risk factors that are theoretically modifiable. The risk factors of interest are listed in Table 4.1 and the definitions are provided in the following sections. NSAPD and ICD-10-CA codes used to define variables are listed in Appendix A.

4.4.1 Maternal Age

Maternal age was defined as the woman's age at the time of delivery in years and was calculated from maternal date of birth and date of infant delivery. It was categorized following Statistics Canada categories (<20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥45 years). When necessary to ensure the privacy of the women represented in the database, the last two categories were collapsed.

4.4.2 Smoking

Smoking was primarily defined as any tobacco smoking at either pre-pregnancy, first antenatal visit, 20 weeks' gestation, or delivery, using NSAPD codes. Smoking during pre-pregnancy, first antenatal visit, and at 20 weeks is recorded on the Nova Scotia Prenatal Record; smoking at delivery is recorded on the maternal admission assessment at time of delivery. In additional analyses, the number of cigarettes smoked was considered.

4.4.3 Alcohol Use

Alcohol was defined as any drinking of alcohol during any point in pregnancy derived from the NSAPD or ICD-10-CA codes recorded on the Prenatal Record.

4.4.4 Drug Use

Illicit drug use included: cannabis, opioid use (codeine, heroin, Demerol, Dilaudid, morphine, OxyContin), or other drug use (cocaine, crack, solvents, diazepam, ecstasy, lorazepam, prescription medication abuse, other specified abuse) during pregnancy,

recorded on either on the Prenatal Record or Admission records, and entered into the NSAPD with RCP-specific codes or ICD-10-CA codes.

4.4.5 Pre-pregnancy Body Mass Index

Maternal pre-pregnancy weight and height are recorded on the Prenatal Record at the first antenatal appointment, either recalled or self-reported, extracted from the physician's records, or measured at that point. BMI was calculated as weight (kg) divided by the square of the height (metres). Pre-pregnancy BMI was categorized following the World Health Organization Classification of BMI: underweight <18.5 kg/m^2, normal weight 18.5 kg/m^2 to 24.9 kg/m^2, overweight 25.0 kg/m^2 to 29.9 kg/m^2, or obese as larger or equal to 30 kg/m^2 [89].

4.4.6 Area-level Income

Area-level income is derived using Statistics Canada data. For each dissemination area captured on census forms, the average household income adjusted for household size is ranked into quintiles. This variable, determined by Statistics Canada, is termed QAIPPE[51]. This information is linked with the woman's postal code information recorded in the NSAPD using the Postal Code Conversion File Plus, which links postal codes of Canadians to dissemination areas using an algorithm that determines the probability that a Canadian lives in one area or another if postal codes contain overlapping dissemination areas[51].

4.4.7 Depression

Depression was defined as any diagnosis of, or medication use for depression or anxiety derived from the NSAPD codes, from information recorded on the Prenatal Record, Hospital Admission Record or Discharge Summary.

4.4.8 Diabetes

Pre-existing type 2 diabetes is recorded on the Prenatal Record or Discharge Summary, and derived from a diagnosis recorded with either the NSAPD or ICD-10-CA codes.

4.4.9 Hypertension

Pre-existing hypertension was defined as a history of hypertension before 20 weeks' gestation, recorded with either NSAPD or ICD-10-CA codes. Pre-existing hypertension is recorded on the Prenatal Record or Discharge Summary.

4.4.10 Gestational Diabetes

In Nova Scotia, gestational diabetes is screened and diagnosed following the guidelines of Diabetes Canada (formerly Canadian Diabetes Association)[90]. Gestational diabetes was defined as diabetes first diagnosed during pregnancy and entered into the NSAPD with either and RCP-specific code or ICD-10-CA code. A diagnosis of gestational diabetes is recorded on the Prenatal Record or Discharge Summary.

4.4.11 Assisted Reproductive Technologies

ART was defined using ICD-10-CA codes as the use of any of the following artificial techniques to conceive: ovulation induction, intracytoplasmic sperm injection, embryo transfer, or in vitro fertilization. Use of ART is recorded on the Hospital Delivery Admission Record.

4.5 Outcome

The outcome of this study was PTB defined by a gestational age less than 37 weeks, including both spontaneous and provider-initiated PTB. Subgroup analysis by severity of PTB (gestational age at birth) was not included as the focus of the current study was to analyse multiple modifiable risk factors of PTB as a whole. As risk factors that routinely lead to provider-initiated PTB may go undetected in spontaneous PTB, subgroup analysis by type of PTB was not analysed[24].

Gestational age in the NSAPD is estimated using an algorithm that includes: last menstrual period, fetal ultrasound, and clinical estimates. The algorithm is displayed in Figure 4.2, adapted from the RCP[91]. The algorithm begins by examining the method used to conceive. If the pregnancy was conceived through ART, gestational age is determined using date of birth and date of conception for intracytoplasmic sperm injection (ICSI) and for IVF date of birth, date of egg transfer as well as embryo age.

If the pregnancy did not occur through ART, the algorithm uses estimations from fetal ultrasounds from 14 weeks (or transabdominal 8-13 weeks), 14-17 weeks, 18-20 weeks or 21-24 weeks. If the estimated due date from the woman's last menstrual period minus the estimated due date from the ultrasound is less than or equal to a specified number of weeks depending on the week of ultrasound being used, gestational age is determined using the infant's date of birth a well as the date of the last menstrual period. If the estimated due date from the last menstrual period minus the estimated due date from the ultrasound is greater than the specified number of weeks, the gestational age is determined using both the infant's date of birth, date of the ultrasound as well as the gestational age given from the ultrasound.

If the woman did not receive any fetal ultrasound before 24 weeks' gestation, the algorithm uses the woman's last menstrual period as well as the best clinical estimate of gestational age of the infant. If the infant's date of birth minus the date of the woman's last menstrual period minus the gestational age of the best clinical estimate is less than or equal to 20 weeks, then the gestational age is determined using the date of birth and the date of the last menstrual period. If the date of the infant's birth minus the date of the woman's last menstrual period minus the gestational age of the best clinical estimate is greater than 20 weeks, then the gestational age is equal to the clinical estimate.

If the woman's last menstrual period is unknown, health care providers use the best clinical estimates of gestational age. Best clinical estimate is based on physical examination of the infant by the health care provider. If the clinical estimates were not accounted for or not recorded, then the gestational age of the infant was recorded as missing.

4.6 Other Variables

Other variables were used for the purposes of stratifying the results (parity) as well as auxiliary variables in multiple imputation (e.g., modifiable risk factors studied that were observed in previous pregnancies) or to control for confounding of non-modifiable risk factors (pre-existing type 1 diabetes).

4.7 Analysis

Statistical analysis was performed using Stata 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.)

4.7.1 Descriptive Statistics

Descriptive characteristics of the cohort as a whole and by PTB status were summarized using counts and proportions.

4.7.2 Multiple Imputation

Multiple imputation with chained equations was used for missing data. The imputation model included all risk factors of interest and confounding variables, and values from the risk factors from a woman's previous pregnancies (if any) as auxiliary variables. Area-level income, previously documented area-level income and parity were imputed using ordinal logistic regression. Pre-pregnancy BMI, previous pre-pregnancy weight, previous weight at delivery, smoking, gestational age for previous births and interpregnancy interval time were imputed using predictive mean matching. Although the missing at random assumption cannot be verified as the mechanism behind the missing values cannot be known, it is assumed that the data are missing at random. For example, for the variable of smoking, younger women (e.g., those under 18 years) may be less likely to answer questions concerning their smoking status, making smoking missing at random. Ten imputed datasets were generated, with 10 iterations used in the chained equations.

The *mi estimate* command in Stata was used on the ten imputed datasets, which uses Rubin's rule to pool parameter estimates, estimating the average value for point estimates (e.g., descriptive statistics and regression coefficients) across imputed data sets while accounting for the variation between and within imputations while estimating standard errors[92,93]. Analyses with the complete cases were also conducted and presented.

4.7.3 Regression Models

Poisson regression with robust standard errors was used to model the outcome PTB on all indicated modifiable risk factors. Both pre-pregnancy BMI and maternal age were modelled as continuous variables as their individual relationships with PTB were nonlinear, determined using Lowess plots. Quadratic and cubic terms for both maternal age and pre-pregnancy BMI were explored to improve model fit. For maternal age, the quadratic term was significant and kept in the model. For BMI, both the quadratic and cubic terms were significant and kept in the model. Area-level income was not modeled using a multilevel model. No adjustments were made to account for women having multiple pregnancies during the time period studied, as the unit of analysis was live births which was determined to be the most appropriate unit of analysis for determining PARs and PIFs.

Individual Poisson models for each specific risk factor (maternal age, smoking, alcohol use, drug use, pre-pregnancy BMI, area-level income, depression, pre-existing diabetes, pre-existing hypertension, gestational diabetes, and ART) with the appropriate minimal set of variables to control for confounding were developed. The minimum sets of covariates to reduce confounding for each risk factor model (Table 4.2) were determined from a directed acyclic graph (Figure 4.1), using the R package *dagitty*[94]. Relationships between risk factors shown in Figure 4.1 were informed from previous research as well as discussion with committee members. All assumptions of Poisson regression were investigated and met before continuing with the analysis including the model adequately fitting the data and no influential outliers. RR estimates were derived from these models.

Using the regression models, the probability of PTB under the counterfactual scenarios was estimated, from which the PARs and PIFs of interest were estimated. With

the regression models developed for each risk factor, a woman's probability of PTB in the counterfactual scenarios of interest (described in the following sections) was estimated in each delivery; the mean of these probabilities represents the prevalence of PTB estimated under the counterfactual scenarios. The difference between the observed probability of PTB in the population and the estimated counterfactual probability was then divided by the observed probability of PTB and multiplied by 100 to obtain the PAR/PIF (equation 4.1). Confidence intervals for estimated PAR and PIFs were generated using 200 bootstrapped samples in the complete case analysis and using pooled standard error estimates derived from the delta method in the multiply imputed data set analysis.

$$\%\ PAR/PIF = \ 100\ x\ \left(\frac{Probability\ of\ PTB_{observed} - \ Probability\ of\ PTB_{counterfactual}}{Probability\ of\ PTB_{observed}}\right)$$

Equation 4.1. PAR/PIF equation for the estimation of the proportion of a disease attributable to a risk factor in a counterfactual scenario[70].

4.7.4 Objective 1a: Population Attributable Risk

Population attributable risks were estimated using Equation 4.1 for dichotomous variables (smoking, alcohol use, depression, hypertension, gestational diabetes, gestational hypertension, drug use, pre-existing diabetes, and ART) with a counterfactual scenario of zero exposure. The Stata package, *punaf*[95], was used to estimate the PARs for binary risk factors in the complete case analysis. To estimate the PARs for continuous variables, the user-written code, *punaf*, was not applied but the process was generalized to allow for any counterfactual scenario of interest and to allow the extraction of the population unattributable fraction ($P_{observed}/P_{counterfactual}$), the log of which was the estimate that was pooled using Rubin's rules across the imputed datasets as estimates being pooled must be normally distributed; PAR was then calculated as $100*(1-\exp(\log(P_{observed}/P_{counterfactual})))$ (Appendix B).

For variables that were not dichotomous (maternal age, income, and BMI), PARs were estimated based on a complete elimination of the most-at-risk category (shifted to the lowest risk category, as seen in Table 4.3). Additionally, when applying counterfactual scenarios to continuous variables (e.g., maternal age and pre-pregnancy BMI) observations were brought to the edges of the respective categories. For example, for the counterfactual scenario of all women 40 or above becoming the age of those in the category 25-29, women 40 or above were brought to the age of 29. Analyses stratified by parity and in 5-year periods were additionally completed for Objective 1.

To estimate the proportion of PTB that is due to modifiable risk factors, the estimated probabilities of PTB from a scenario where no women have any of the risk factors or the risk factors are set to the level with the lowest risk were compared (using the generalized process adapted from the *punaf* code) to the observed population prevalence of PTB.

4.7.5 Objective 2: Population Impact Fraction

Table 4.3 shows the counterfactual scenarios for which PIFs were estimated. The main counterfactual scenario used for every risk factor was a 25% relative reduction in prevalence. Observations used to apply these counterfactual scenarios were randomly selected; although these values would be equivalent to one-quarter of the PAR, these estimates were generated for the purpose of demonstrating a more feasible counterfactual scenario than the complete elimination of the risk factor represented by the PAR. For smoking, we also used the counterfactual scenario of a 50% reduction in quantity smoked by mothers. For BMI, a 10% decrease in weight for mothers who were overweight or living with obesity was used. The number of cigarettes smoked was found to have a linear relationship with PTB, and therefore no quadratic or cubic terms were added to the model. As an example of how the PARs for continuous variables and all PIFs were estimated, the Stata code used for the PIF estimation of a reduction of all cigarettes smoked by smokers by 50% is appended (Appendix A).

4.7.6 Sample Size and Power

The sample size was the number of live born singleton infants born to Nova Scotia resident women from January 1st, 2005 to December 31st, 2019. With a sample size of 120000 deliveries, a PTB rate of 8%, with an alpha of 0.05 and a beta of 0.2, the smallest RR that could be detected for risk factors with a range of prevalence between 2% and 50% is shown in Table 4.4. The RR that could be detected with the lowest risk factor prevalence of 2% is a RR of 1.20, which is similar in magnitude to the RRs of risk factors for PTB reported in the literature.

4.8 Data Access and Ethics Approvals

This project has undergone review and has received approval from the RCP's Data Access Committee and the IWK Research Ethics Board (REB file #1026339).

Table 4.1. Description and categorizations of risk factors to be analysed.

Risk Factor	Description	Variable type
Maternal Age	Women's age at delivery categorized as: <20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥45 years	Categorical and continuous
Smoking	Maternal smoking status at 1st prenatal appointment, 20-week appointment, and delivery	Binary
Alcohol Use	Alcohol use	Binary
Drug Use	Drug use includes: cannabis, opioids (codeine, heroin, Demerol, Dilaudid, morphine, OxyContin) or other drug use during pregnancy (cocaine crack, hash, solvents, diazepam, ecstasy, lorazepam, prescription medication abuse or other specified abuse)	Binary
Pre-Pregnancy BMI	Underweight <18.5 kg/m^2, normal weight 18.5 kg/m^2 to 24.9 kg/m^2, overweight 25.0 kg/m^2 to 29.9 kg/m^2, and obese as larger or equal to 30.0 kg/m^2	Categorical and continuous
Area-Level Income	QAIPPE	Categorical (quintiles)
Depression	Diagnosis of or medication use for maternal depression or anxiety	Binary
Pre-Existing Type 2 Diabetes	Pre-existing Type 2 diabetes	Binary
Pre-Existing Hypertension	Hypertension before 20 weeks' gestation	Binary
Gestational Diabetes	Diabetes diagnosed during the first trimester	Binary
ART	Ovulation induction, intracytoplasmic sperm injection, embryo transfer or in vitro fertilization	Binary

ART, assisted reproductive technologies; BMI, body mass index; QAIPPE, Quintile Area Income Per Person Equivalent.

Table 4.2. Minimal adjustment sets for multiple regression models.

Risk factor	**Minimal Adjustment Set**
Maternal Age	Area-Level Income
Smoking	Alcohol Use, Depression, Drug Use, Area-Level Income, Maternal Age
Alcohol Use	Depression, Area-Level Income, Maternal Age
Drug Use	Alcohol Use, Depression, Area-Level Income, Maternal Age
Pre-Pregnancy BMI	Depression, Maternal Age, Area-Level Income, Diabetes (Type 1), Smoking
Area-Level Income	None
Depression	Area-Level Income
Pre-Existing Type 2 Diabetes	Pre-Pregnancy BMI, Maternal Age, Area-Level Income, Smoking
Pre-Existing Hypertension	Pre-Pregnancy BMI, Pre-Existing Type 2 Diabetes, Diabetes (Type 1), Gestational Diabetes, Area-Level Income, Maternal Age, Smoking
Gestational Diabetes	Pre-Pregnancy BMI, Maternal Age, Area-Level Income
ART	Pre-Pregnancy BMI, Area-Level Income, Maternal Age

ART, assisted reproductive technologies; BMI, body mass index.

Table 4.3. Counterfactual scenarios for Objectives 1 (complete elimination of risk factor) and Objective 2 (relative reduction in prevalence and/or level and/or quantity).

Risk Factor	**Counterfactual scenario (Objective 1: Elimination or reduction to lowest risk category)**	**Counterfactual scenarios (Objective 2: Relative reduction in prevalence and/or level and/or quantity)**
Maternal Age	i) All women under 20 to 25-29 age group ii) All women 40 or older to 25-29 age group iii) All women under 20 or 40 or older to 25-29 age group	i) 25% of women under the age of 20 to 25-29 age group ii) 25% of women 40 or older to 25-29 age group
Smoking	All non-smokers	i) Prevalence of any smoking reduced by 25% ii) 50% reduction in the amount smoked
Alcohol Use	All non-alcohol users	25% of alcohol users become nonusers
Drug Use	All no drug users	25% of users become nonusers
Pre-Pregnancy BMI	i) All underweight women become normal weight ii) All overweight and obese women become normal weight iii) All underweight, overweight and obese women become normal weight	i) 25% of underweight women become normal weight ii) 25% of obese and overweight women become normal weight iii) Women with BMI>25 lose 10% of their body weight
Area-Level Income	All women in income quintiles 1 and 2 receive incomes equivalent to quintile 3	i) 25% of women in quintile 1 receive incomes equivalent to quintile 3 ii) 25% of women in quintile 1 receive incomes equivalent to quintile 2
Depression	All not depressed	25% of depressed women become non depressed
Pre-Existing Type 2 Diabetes	All no pre-existing Type 2 diabetes	25% of women with Type 2 diabetes become nondiabetic
Pre-Existing Hypertension	All no hypertension	25% of women experiencing hypertension become normotensive
Gestational Diabetes	All no gestational diabetes	25% of women with gestational diabetes become nondiabetic
ART	All conceived spontaneously	25% of infants conceived from ART become conceived spontaneously

ART, assisted reproductive technologies; BMI, body mass index.

Table 4.4. Estimations of the minimally detectable relative risk using a sample size of 120000, prevalence of PTB of 8%, alpha of 0.05, and beta of 0.2.

Risk Factor Prevalence	**Minimally Detectable RR**
2%	1.20
5%	1.13
10%	1.09
15%	1.08
25%	1.06
50%	1.06

RR, relative risk.

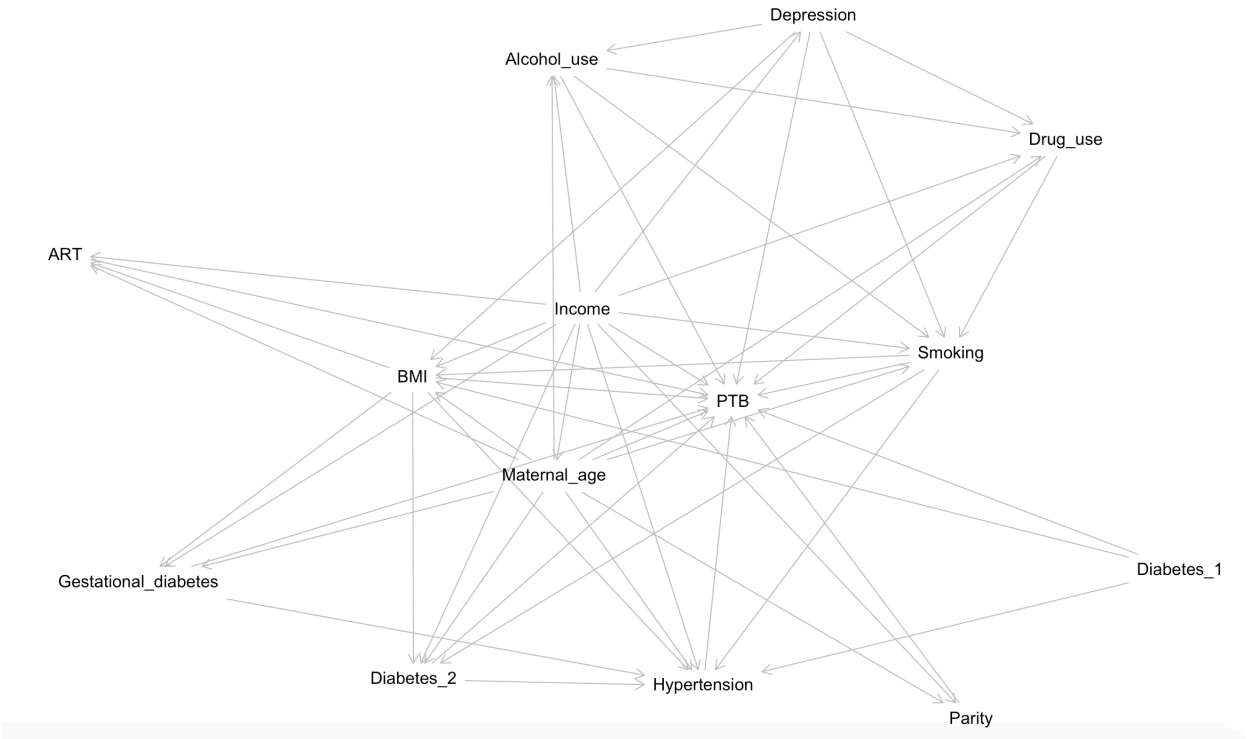

Figure 4.1. Directed acyclic graph demonstrating relationships between modifiable risk factors and PTB. ART, assisted reproductive technologies; BMI, body mass index; Diabetes_1, pre-existing type 1 diabetes; Diabetes_2, pre-existing type 2 diabetes; Hypertension, pre-existing hypertension; Income, area-level income; PTB, preterm birth.

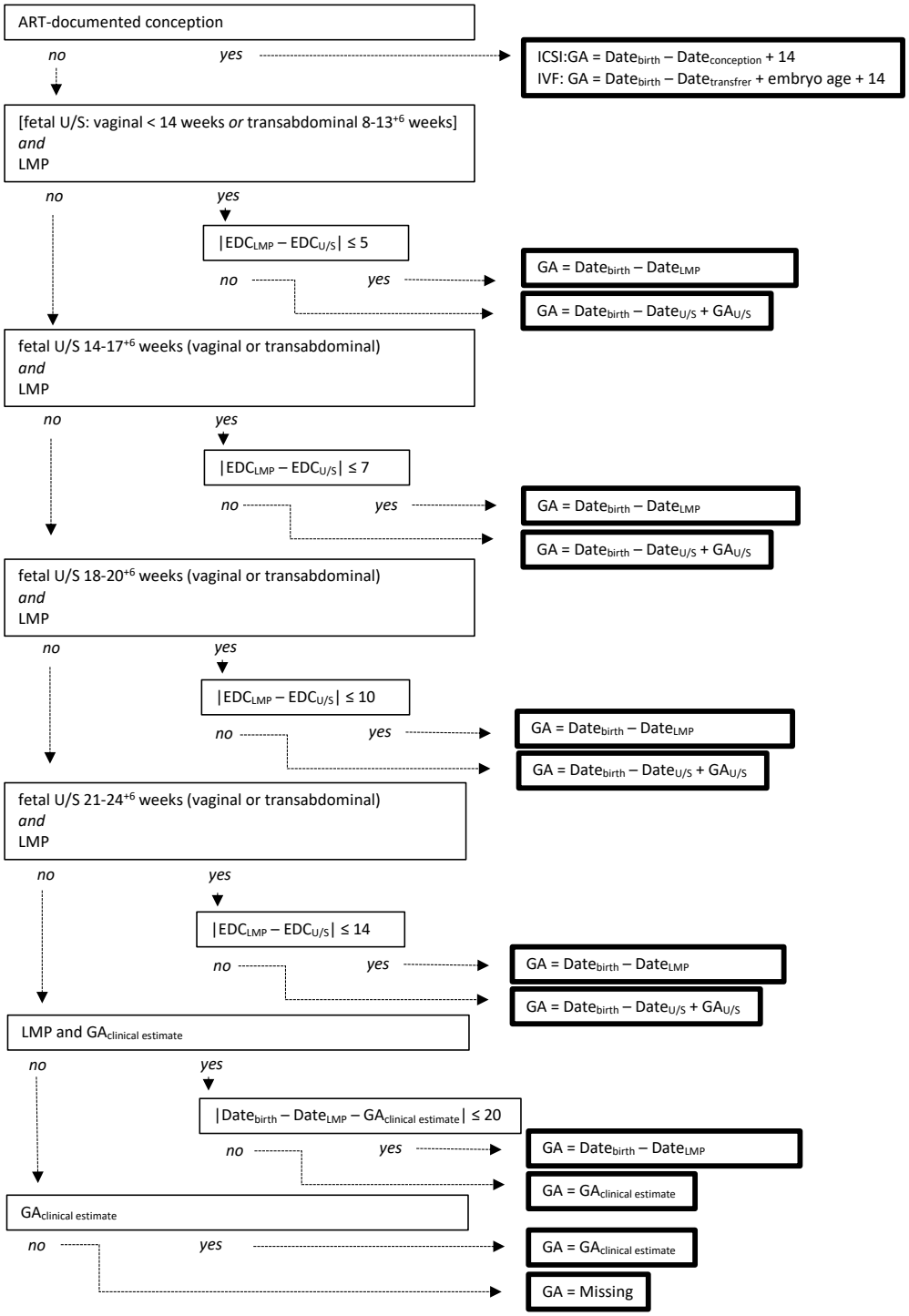

Figure 4.2. Algorithm for determination of gestational age used by the NSAPD[91]. ART, assisted reproductive technologies; EDC, estimated date of confinement; GA, gestational age; ICSI, intracytoplasmic sperm injection; IVF, invitro fertilization; LMP, last menstrual period; U/S, ultrasound.

CHAPTER 5: RESULTS

5.1 Cohort Characteristics

The cohort consisted of 123607 singleton infants born between 2005-2019. After dropping those infants with missing gestational age (231 infants), there were 123376 infants of which 8053 (6.5%) were born preterm (Table 5.1). The number of infants born over the time periods studied, 2005-2009, 2010-2014 and 2015-2019 were 42300, 41999 and 39187, respectively. The largest proportion of women, 31.8%, were in the 30-34 years of age group. Of the cohort women 24.3%, 0.5% and 3.0% smoked, used alcohol, and used illicit drugs, respectively. In the cohort, 37.9% of women had a normal weight, and 22.2% lived in an area with a median income in the third quintile. Of the cohort women 10.9%, 0.5% and 1.2% had depression, pre-existing type 2 diabetes, and pre-existing hypertension, respectively. Gestational diabetes was seen in 5.7% of the cohort, and 1.2% of pregnancies were conceived through ART. Cohort characteristics varied slightly when stratified by parity and time periods.

5.2 Missing Values and Multiple Imputation

In the cohort, 31780 (25.7%) of the recorded deliveries had at least one missing value for the risk factors studied. Of the variables included in the study, missing values were observed for maternal smoking, pre-pregnancy BMI, and area-level income (5.4%, 20.4%, and 2.4%, respectively; Table 5.1). Gestational age (and therefore PTB status) was missing in 0.19% of the cohort; these few infants were excluded from the study. The results from the analyses using the ten imputed datasets will be discussed in the sections. Results from the complete case analyses were in agreement with results obtained from the imputed data (Appendix C-J).

5.3 Relative Risks for the Association between the Risk Factors and Preterm Birth

The estimated RRs of PTB are seen in Tables 5.2-5.4. Over the entire study period (Table 5.2), the risk of PTB was 2-3 times higher in women with pre-existing type 2 diabetes and pre-existing hypertension compared to women without the respective condition (aRR 3.00, 95% CI: 2.55-3.54 and aRR 2.44, 95% CI: 2.17-2.75, respectively). Women in the highest area-level income quintile were 11% less likely to have a PTB relative to the third area-level income quintile (aRR 0.89, 95% CI: 0.83-0.96). Women who were 45 years old or older were 50% more likely to have a PTB rather than 25-29 years old (aRR 1.50, 95% CI: 0.90-2.37). The risk of PTB moderately increased in women who smoked, drank alcohol, or used illicit drugs, compared to women who abstained from these activities (aRR 1.33, 95% CI: 1.26-1.41, aRR 1.54, 95% CI: 1.23-1.94 and aRR 1.47, 95% CI: 1.33-1.63, respectively).

Compared to women with a normal BMI, women with a pre-pregnancy BMI classified as underweight were 44% more likely to have a PTB (aRR 1.44, 95% CI: 1.30-1.59). The risk of PTB in women who experienced depression, gestational diabetes or used ART to conceive was moderately increased compared to women without these conditions (aRR 1.37, 95% CI: 1.29-1.45, aRR 1.53, 95% CI: 1.42-1.66 and aRR 1.39, 95% CI: 1.18-1.64, respectively).

5.3.1 Relative Risks for the Association between the Risk Factors of Interest and Preterm Birth: By Parity Status

Both the prevalence as well as the RR of PTB for some of the risk factors studied were not consistent between primiparous and multiparous women (Table 5.3). The prevalence of smoking (15.7% vs. 19.3%) and drug use (2.3% vs. 3.8%) were lower in primiparous women compared to multiparous women. At the same time, the RRs for the individual associations between smoking and PTB and drug use and PTB were higher in multiparous women, aRR 1.55 vs. aRR 1.15 and aRR 1.71 vs. aRR 1.31, respectively. Women who were overweight, compared to those who were normal weight, were 6% more likely to have a PTB if they were primiparous but 12% less likely if they were multiparous (aRR

1.06 and aRR 0.88). Compared to primiparous women, the risk of PTB was elevated in multiparous women who were living in the lowest area-level income quintile as well as those living with depression, aRR 1.05 vs. aRR 1.22 and aRR 1.15 vs. aRR 1.59, respectively.

5.3.2 Relative Risks for the Association between the Risk Factors and Preterm Birth: By Time Periods

Across time periods (Table 5.4), the prevalence of risk factors as well as the risk for PTB was not consistent for multiple risk factors. The RRs for the association between maternal age and PTB increased for woman younger than 20 years (aRR 0.98 to 1.30), 20-24 years (aRR 0.94 to aRR 1.07), 35-39 years (aRR 1.02 to 1.04), 40-44 years (aRR 0.92 to 1.34) and 45 years or older (aRR 1.05 to 1.43), compared to women aged 25-29 years from the time periods 2005-2009 to 2015-2019, respectively. The prevalence of smoking decreased over this time period, from 20.9% in 2005-2009 to 14.1% in 2015-2019. At the same time, the RRs for the association between smoking and PTB increased in magnitude (aRR 1.22 to aRR 1.50). The association between alcohol consumption during pregnancy and PTB decreased from 240% to 30% more likely in 2005-2009 to 2015-2019 (aRR 2.40 and aRR 1.30). The prevalence of drug use, depression and gestational diabetes increased from, 1.8% to 4.8%, 5.9% to 15.9% and 3.7% to 8.2%, from 2005-2009 to 2015-2019, respectively.

5.4 Objective 1a: Population Attributable Risk

Objective 1a aimed to estimate the proportion of PTB that was attributable to selected modifiable risk factors (Table 5.5). The largest and smallest proportion of PTB that was estimated to be attributable to the studied risk factors was smoking with an estimated PAR of 5.8% (95% CI: 4.6-7.0) and alcohol use with an estimated PAR of 0.3% (95% CI: 0.1 - 0.5).

PARs were similar in primiparous and multiparous women, with the exception of the PARs for variables smoking, depression and area-level income (Table 5.6). In primiparous women, the proportion of PTB estimated to be attributable to smoking was 2.3% (95% CI: 0.7-3.8), and 10.2% (95% CI: 8.4-12.0) in multiparous women. A similar trend was observed for depression, to which 1.6% (95% CI: 0.5-2.7) of PTB could be attributed in primiparous women and 6.2% (95% CI: 4.9-7.4) in multiparous women. The proportion of PTB estimated to be attributable to being in the lowest two area-level income quintiles (compared to the middle quintile) was 1.4% (95% CI: -1.8 - 4.6) in primiparous women, and 4.3% (95% CI: 1.1-7.4) in multiparous women.

Across time periods PARs were generally consistent, with the exception of maternal age, smoking, drug use, pre-pregnancy BMI, depression, and gestational diabetes (Table 5.7). The proportion of PTB estimated to be attributable to women under the age of 20 years and 40 years or older, rather than the ages of those in the 25-29 years of age group, was 0.3% (95% CI: -0.6 - 1.2) in 2005-2009, 2.3% (95% CI: 1.4-3.3) in 2010-2014, and 1.7% (95% CI: 0.9-2.6) in 2015-2019. The proportion of PTB estimated to be attributable to smoking increased from 4.6% (95% CI: 2.3-6.7) in 2005-2009 to 6.8% (95% CI: 4.8-8.7) in 2015-2019. For the risk factor of pre-pregnancy BMI, the proportion of PTB estimated to be attributable to being underweight, overweight or obese (compared to a normal weight) increased from 1.1% (95% CI: -2.2 - 4.3) in 2005-2009 to 3.4% (95% CI: 1.2-5.6) in 2015-2019. Estimated PARs for the risk factors of depression, gestational diabetes, and drug use in pregnancy increased over study periods 2005-2009 to 2015-2019 (Table 5.7).

5.5 Objective 1b: Modifiability of PTB

Objective 1b aimed to estimate the proportion of PTB that could be eliminated if all selected modifiable risk factors had been removed or moved to the lowest level of risk in the population over the entire study period. Using the eleven variables studied, it was estimated that 14.2% (95% CI: 12.5-15.8) of PTB could theoretically be eliminated.

5.6 Objective 2: Population Impact Fraction

Objective 2 addressed the proportion of PTB estimated to be attributable to a 25% relative reduction in the prevalence of selected modifiable risk factors in the population and, in addition, a reduction in quantity for pre-pregnancy BMI and smoking (Table 5.8). Reduction in prevalence of individual risk factors provided PIF estimates around 25% of estimated PARs. The proportion by which PTB could be lowered by a reduction in quantity of cigarettes smoked by 50% was 2.2% (95% CI: 1.7-2.7). Almost no PTB reduction was estimated if all women who were overweight or living with obesity lost 10% of their body weight (PIF 0.0%, 95% CI: -0.8 - 0.7).

Across time periods PIFs were generally consistent (Table 5.9), with the proportion of PTB that was estimated to be attributable to a reduction in quantity of cigarettes smoked by 50%, being 1.2% (95% CI: 0.3-2.2) in 2005-2009 and increasing to 2.6% (95% CI: 1.8-3.4) of PTBs in 2015-2019.

Table 5.1. Prevalence of risk factors of interest and preterm birth in the cohort.

Risk Factor	N (%)	Preterm %
Number	**123376**	(6.5)
Year of Delivery		
2005- 2009	42300 (34.3)	(6.6)
2010- 2014	41889 (34.0)	(6.3)
2015- 2019	39187 (31.8)	(6.7)
Missing	0	
Parity		
Primiparous	56007 (45.4)	(7.1)
Multiparous	67359 (54.6)	(6.1)
Missing	10 (0.01)	SUP
Maternal Age (years)		
<20	4658 (3.8)	(7.6)
20- 24	21128 (17.1)	(6.7)
25- 29	34750 (28.2)	(6.5)
30- 34	39222 (31.8)	(6.1)
35- 39	19710 (16.0)	(6.8)
40- 44	3747 (3.0)	(7.6)
≥45	161 (0.1)	(9.3)
Missing	0	
Smoking		
No	93386 (75.7)	(5.7)
Yes	23311 (18.9)	(8.5)
Missing	6679 (5.4)	(11.7)
Alcohol Use		
No	122787 (99.5)	(6.5)
Yes	589 (0.5)	(11.2)
Missing	0	
Drug Use		
No	119681 (97.0)	(6.5)
Yes	3695 (3.0)	(10.6)
Missing	0	
Pre-Pregnancy BMI (kg/m^2)		
<18.5	4163 (3.4)	(8.3)
18.5- 24.9	46733 (37.9)	(6.0)
25.0- 29.9	24121 (19.6)	(5.8)
≥30	23244 (18.8)	(6.3)
Missing	25115 (20.4)	(8.1)

Risk Factor	N (%)	Preterm %
Area-Level Income (quintiles)		
1 (lowest)	22452 (18.2)	(7.3)
2	25347 (20.5)	(6.6)
3	27371 (22.2)	(6.5)
4	26543 (21.5)	(6.3)
5 (highest)	18686 (15.1)	(5.8)
Missing	2977 (2.4)	(6.6)
Depression		
No	109902 (89.1)	(6.4)
Yes	13474 (10.9)	(8.6)
Missing	0	
Pre-Existing Type 2 Diabetes		
No	122795 (99.5)	(6.5)
Yes	581 (0.5)	(20.5)
Missing	0	
Pre-Existing Hypertension		
No	121935 (98.8)	(6.5)
Yes	1441 (1.2)	(18.0)
Missing	0	
Gestational Diabetes		
No	116370 (94.3)	(6.4)
Yes	7006 (5.7)	(9.6)
Missing	0	
ART		
No	121843 (98.8)	(6.5)
Yes	1533 (1.2)	(9.1)
Missing	0	

ART, assisted reproductive technologies; BMI, body mass index; SUP, suppressed due to low cell count.

Table 5.2. The association between the risk factors of interest and preterm birth, 2005-2019.

Risk Factor	Risk Factor (%)	Preterm (%)	uRR (95% CI)	aRR (95% CI)
Maternal Age (years)				
<20	3.8	7.6	1.17 (1.05 - 1.30)	1.15 (1.03 - 1.28)
20-24	17.0	6.7	1.04 (0.97 - 1.10)	1.02 (0.96 - 1.09)
25-29	28.2	6.5	Reference	Reference
30-34	31.8	6.1	0.94 (0.89 - 1.00)	0.96 (0.90 - 1.01)
35-39	16.0	6.8	1.05 (0.98 - 1.12)	1.07 (1.00 - 1.15)
40-44	3.0	7.6	1.17 (1.04 - 1.32)	1.20 (1.06 - 1.35)
≥45	0.1	9.3	1.44 (0.89 - 2.33)	1.50 (0.90 - 2.37)
Smoking				
No	82.3	6.1	Reference	Reference
Yes	17.7	8.6	1.42 (1.35 - 1.50)	1.33 (1.26 - 1.41)
Alcohol Use				
No	99.5	6.5	Reference	Reference
Yes	0.5	11.2	1.72 (1.37 - 2.16)	1.54 (1.23 - 1.94)
Drug Use				
No	97.0	6.5	Reference	Reference
Yes	3.0	10.6	1.65 (1.50 - 1.82)	1.47 (1.33 - 1.63)
Pre-Pregnancy BMI (kg/m^2)				
<18.5	4.7	9.7	1.54 (1.40 - 1.70)	1.44 (1.30 - 1.59)
18.5-24.9	47.0	6.3	Reference	Reference
25.0-29.9	24.6	6.2	0.98 (0.92 - 1.04)	0.96 (0.90 - 1.02)
≥30	23.6	6.6	1.05 (0.99 - 1.11)	1.01 (0.94 - 1.07)
Area-Level Income (quintiles)				
1 (lowest)	18.6	7.4	1.14 (1.07 - 1.21)	1.14 (1.07 - 1.21)
2	21.0	6.6	1.02 (0.95 - 1.09)	1.02 (0.95 - 1.09)
3	22.7	6.7	Reference	Reference
4	22.1	6.3	0.97 (0.91 - 1.04)	0.97 (0.91 - 1.04)
5 (highest)	15.6	5.8	0.89 (0.83 - 0.96)	0.89 (0.83 - 0.96)
Depression				
No	89.1	6.4	Reference	Reference
Yes	10.9	8.6	1.38 (1.30 - 1.50)	1.37 (1.29 - 1.45)
Pre-Existing Type 2 Diabetes				
No	99.5	6.5	Reference	Reference
Yes	0.5	20.5	3.17 (2.70 - 3.73)	3.00 (2.55 - 3.54)
Pre-Existing Hypertension				
No	98.8	6.5	Reference	Reference
Yes	1.2	18.0	2.80 (2.50 - 3.13)	2.44 (2.17 - 2.75)
Gestational Diabetes				
No	94.3	6.4	Reference	Reference
Yes	5.7	9.6	1.52 (1.41 - 1.64)	1.53 (1.42 - 1.66)
ART				
No	98.8	6.5	Reference	Reference
Yes	1.2	9.1	1.40 (1.20 - 1.64)	1.39 (1.18 - 1.64)

aRR, adjusted relative risk; ART, assisted reproductive technologies; BMI, body mass index; CI, confidence interval; uRR, unadjusted relative risk.

Table 5.3. The association between the risk factors of interest and preterm birth, by parity.

	Primiparous			Multiparous		
Risk Factor	**Risk Factor (%)**	**Preterm (%)**	**aRR (95% CI)**	**Risk Factor (%)**	**Preterm (%)**	**aRR (95% CI)**
Maternal Age (years)						
<20	7.5	7.5	1.08 (1.96 - 1.22)	0.7	7.9	1.25 (0.91 - 1.72)
20-24	23.6	6.7	0.96 (0.88 - 1.05)	11.8	6.7	1.08 (0.98 - 1.20)
25-29	29.9	6.9	Reference	26.7	6.1	Reference
30-34	27.3	7.1	1.03 (0.95 - 1.12)	35.5	5.5	0.93 (0.86 - 1.00)
35-39	9.9	8.1	1.19 (1.07 - 1.32)	21.0	6.3	1.07 (0.99 - 1.17)
40-44	1.7	8.1	1.19 (0.95 - 1.48)	4.1	7.4	1.26 (1.09 - 1.46)
≥45	0.08	12.8	1.90 (0.89 - 3.95)	0.2	7.9	1.33 (0.71 - 2.50)
Smoking						
No	84.3	6.9	Reference	80.7	5.4	Reference
Yes	15.7	8.0	1.15 (1.05 - 1.25)	19.3	9.0	1.55 (1.44 - 1.67)
Alcohol Use						
No	99.4	7.1	Reference	99.6	6.1	Reference
Yes	0.6	10.6	1.45 (1.07 - 1.99)	0.4	12.0	1.67 (1.19 - 2.34)
Drug Use						
No	96.2	7.0	Reference	97.7	6.0	Reference
Yes	3.8	9.5	1.31 (1.14 - 1.51)	2.3	12.1	1.71 (1.50 - 2.00)
Pre-Pregnancy BMI (kg/m^2)						
<18.5	5.7	9.5	1.39 (1.20 - 1.61)	3.9	10.0	1.51 (1.30 - 1.76)
18.5-24.9	50.4	6.7	Reference	44.2	6.0	Reference
25.0-29.9	23.6	7.2	1.06 (0.98 - 1.16)	25.5	5.4	0.88 (0.80 - 0.96)
≥30	20.3	7.3	1.05 (0.96 - 1.15)	26.4	6.2	0.99 (0.91 - 1.08)
Area-Level Income (quintiles)						
1 (lowest)	18.4	7.4	1.05 (0.96 - 1.15)	18.8	7.3	1.22 (1.12 - 1.34)
2	21.5	7.2	1.02 (0.93 - 1.12)	20.7	6.1	1.01 (0.94 - 1.11)
3	22.9	7.2	Reference	22.6	6.3	Reference
4	22.3	7.0	1.00 (0.91 - 1.09)	21.9	5.7	0.95 (0.97 - 1.04)
5 (highest)	15.0	6.6	0.94 (0.84 - 1.04)	16.1	5.2	0.86 (0.77 - 0.95)
Depression						
No	89.3	7.0	Reference	88.9	5.9	Reference
Yes	10.7	8.1	1.15 (1.05 - 1.26)	11.1	9.1	1.59 (1.47 - 1.72)
Pre-Existing Type 2 Diabetes						
No	99.6	7.1	Reference	99.5	6.0	Reference
Yes	0.4	21.6	2.88 (2.22 - 3.74)	0.5	19.8	3.03 (2.45 - 3.74)
Pre-Existing Hypertension						
No	98.9	7.0	Reference	98.8	6.0	Reference
Yes	1.1	18.9	2.33 (1.96 - 2.78)	1.2	17.1	2.47 (2.10 - 2.92)
Gestational Diabetes						
No	95.2	7.0	Reference	93.6	6.0	Reference
Yes	4.8	11.2	1.60 (1.43 - 1.80)	6.4	8.6	1.48 (1.33 - 1.64)
ART						
No	98.2	7.1	Reference	99.2	6.1	Reference
Yes	1.8	9.4	1.25 (1.03 - 1.53)	0.8	8.5	1.40 (1.05 - 1.86)

aRR, adjusted relative risk; ART, assisted reproductive technologies; BMI, body mass index; CI, confidence interval.

Table 5.4. The association between the risk factors of interest and preterm birth, by time period.

Risk Factor	2005-2009			2010-2014			2015-2019		
	Risk Factor (%)	Preterm (%)	aRR (95% CI)	Risk Factor (%)	Preterm (%)	aRR (95% CI)	Risk Factor (%)	Preterm (%)	aRR (95% CI)
Maternal Age (years)									
<20	4.5	6.8	0.98 (0.82 - 1.17)	4.3	7.8	1.27 (1.06 - 1.51)	2.5	8.8	1.30 (1.05 - 1.62)
20-24	18.3	6.5	0.94 (0.85 - 1.05)	17.9	6.6	1.08 (0.97 - 1.21)	28.6	7.2	1.07 (0.95 - 1.20)
25-29	28.6	6.8	Reference	27.7	6.0	Reference	28.3	6.6	Reference
30-34	30.8	6.3	0.94 (0.86 - 1.04)	31.5	5.9	1.00 (0.91 - 1.11)	33.2	6.1	0.93 (0.84 - 1.03)
35-39	14.9	6.8	1.02 (0.91 - 1.15)	15.5	6.8	1.16 (1.03 - 1.30)	17.7	6.8	1.04 (0.93 - 1.17)
40-44	2.8	6.1	0.92 (0.73 - 1.16)	3.1	7.8	1.34 (1.09 - 1.64)	3.2	8.8	1.34 (1.11 - 1.63)
≥45	0.1	7.0	1.05 (0.35 - 3.12)	0.1	11.1	1.86 (0.87 - 3.95)	0.2	9.4	1.43 (0.67 - 1.08)
Smoking									
No	79.1	6.2	Reference	82.2	5.9	Reference	85.9	6.1	Reference
Yes	20.9	8.0	1.22 (1.11 - 1.34)	17.8	8.4	1.35 (1.23 - 1.50)	14.1	10.0	1.50 (1.33 - 1.63)
Alcohol Use									
No	99.8	6.6	Reference	99.4	6.3	Reference	99.4	6.7	Reference
Yes	0.2	17.6	2.40 (1.56 - 3.68)	0.6	9.9	1.43 (0.97 - 2.10)	0.6	9.8	1.30 (0.89 - 1.90)
Drug Use									
No	98.2	6.5	Reference	97.5	6.3	Reference	95.2	6.6	Reference
Yes	1.8	12.3	1.70 (1.34 - 2.10)	2.5	9.5	1.35 (1.10 - 1.65)	4.8	10.5	1.46 (1.27 - 1.70)
Pre-Pregnancy BMI (kg/m^2)									
<18.5	4.8	10.0	1.52 (1.28 - 1.81)	4.8	8.8	1.28 (1.07 - 1.54)	4.6	10.6	1.52 (1.28 - 1.82)
18.5-24.9	48.2	6.3	Reference	47.6	6.3	Reference	45.1	6.3	Reference
25.0-29.9	24.6	6.4	0.97 (0.87 - 1.08)	24.2	6.0	0.93 (0.84 - 1.04)	25.0	6.2	0.97 (0.86 - 1.08)
≥30	22.5	6.6	0.98 (0.87 - 1.09)	23.2	6.2	0.94 (0.84 - 1.05)	25.3	7.1	1.09 (0.98 - 1.22)
Area-Level Income (quintiles)									
1 (lowest)	19.2	7.4	1.16 (1.04 - 1.30)	18.3	7.2	1.13 (1.01 - 1.27)	18.5	7.4	1.12 (1.00 - 1.25)
2	21.2	6.5	1.01 (0.90 - 1.23)	21.0	6.4	1.00 (0.89 - 1.12)	20.9	7.0	1.05 (0.93 - 1.18)
3	22.3	6.7	Reference	22.8	6.6	Reference	30.0	6.9	Reference
4	21.5	6.5	1.01 (0.90 - 1.23)	22.4	6.3	0.99 (0.88 - 1.10)	22.4	6.2	0.93 (0.82 - 1.04)
5 (highest)	15.8	6.0	0.94 (0.83 - 1.06)	15.5	5.3	0.82 (0.82 - 0.94)	15.4	6.1	0.91 (0.80 - 1.04)
Depression									
No	94.1	6.5	Reference	88.7	6.2	Reference	84.1	6.5	Reference
Yes	5.9	9.7	1.52 (1.34 - 1.72)	11.3	8.1	1.32 (1.19 - 1.47)	15.9	8.6	1.35 (1.23 - 1.48)
Pre-Existing Type 2 Diabetes									

Risk Factor	2005-2009				2010-2014				2015-2019			
	Risk Factor (%)	Preterm (%)	aRR (95% CI)		Risk Factor (%)	Preterm (%)	aRR (95% CI)		Risk Factor (%)	Preterm (%)	aRR (95% CI)	
No	99.6	6.6	Reference		99.6	6.3	Reference		99.5	6.6	Reference	
Yes	0.4	17.1	2.58	(1.87 - 3.56)	0.4	30.0	3.97	(3.10 - 5.11)	0.5	18.8	2.62	(1.96 - 3.51)
Pre-Existing Hypertension												
No	98.8	6.5	Reference		98.9	6.3	Reference		98.9	6.6	Reference	
Yes	1.2	17.0	2.55	(2.09 - 3.11)	1.1	17.9	2.36	(1.91 - 2.93)	1.1	18.9	2.39	(1.94 - 2.94)
Gestational Diabetes												
No	96.3	6.5	Reference		94.6	6.2	Reference		91.8	6.5	Reference	
Yes	3.7	8.2	1.27	(1.06 - 1.51)	5.4	10.5	1.77	(1.55 - 2.02)	8.2	9.7	1.51	(1.34 - 1.69)
ART												
No	99.8	6.6	Reference		98.3	6.3	Reference		98.2	6.7	Reference	
Yes	0.2	5.0	0.78	(0.33 - 1.84)	1.7	9.9	1.56	(1.24 - 1.96)	1.8	8.8	1.32	(1.04 - 1.68)

aRR, adjusted relative risk; ART, assisted reproductive technologies; BMI, body mass index; CI, confidence interval.

Table 5.5. Estimated proportion of preterm birth attributable to selected risk factors, 2005-2019.

Risk Factor	CF Scenario	Risk Factor (%)		Preterm (%)		% PAR (95% CI)
		Actual	CF	Actual	CF	
Maternal Age	i) <20 to 25-29 years	3.8	0	6.527	6.484	0.7 (0.4 - 0.9)
	ii) ≥40 to 25-29 years	3.1	0	6.527	6.477	0.8 (0.4 - 1.1)
	iii) <20 or ≥40 to 25-29 years	6.9	0	6.527	6.434	1.4 (0.9 - 2.0)
Smoking	All non-smokers	17.7	0	6.527	6.146	5.8 (4.6 - 7.0)
Alcohol Use	All non-alcohol users	0.5	0	6.527	6.508	0.3 (0.1 - 0.5)
Drug Use	All no drug users	3.0	0	6.527	6.425	1.6 (1.1 - 2.0)
Pre-Pregnancy BMI	i) All <18.5 become 18.5 (normal)	4.7	0	6.527	6.475	0.8 (0.5 - 1.2)
	ii) All ≥25 become 24.9 (normal)	48.2	0	6.527	6.428	1.5 (-0.5 - 3.5)
	iii) All <18.5 and ≥25 become normal	52.9	0	6.527	6.412	1.8 (-0.3 - 3.9)
Area-Level Income	All women in quintiles 1 and 2 receive incomes equivalent to quintile 3	39.6	0	6.527	6.338	2.9 (0.6 - 5.1)
Depression	All not depressed	10.9	0	6.527	6.272	3.9 (3.1 - 4.7)
Pre-Existing Type 2 Diabetes	All no pre-existing diabetes (Type 2)	0.5	0	6.527	6.463	1.0 (0.7 - 1.2)
Pre-Existing Hypertension	All no hypertension	1.2	0	6.527	6.404	1.9 (1.5 - 2.3)
Gestational Diabetes	All no gestational diabetes	5.7	0	6.527	6.337	2.9 (2.3 - 3.5)
ART	All conceived spontaneously	1.2	0	6.527	6.496	0.5 (0.2 - 0.8)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PAR, population attributable risk.

Table 5.6. Estimated proportion of preterm birth attributable to selected risk factors, by parity.

		Primiparous			Multiparous		
Risk Factor	**CF Scenario**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/CF**	**% PAR (95% CI)**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/CF**	**% PAR (95% CI)**
Maternal Age	All women <20 or ≥40 to 25-29 years	9.3/0	7.087/6.995	1.3 (0.4 - 2.1)	5.0/0	6.062/5.971	1.5 (0.9 - 2.1)
Smoking	All non-smokers	15.7/0	7.087/6.927	2.3 (0.7 - 3.8)	19.3/0	6.062/5.443	10.2 (8.4 - 12.0)
Alcohol Use	All non-alcohol users	0.6/0	7.087/7.067	0.3 (0.0 - 0.6)	0.4/0	6.062/6.044	0.3 (0.0 - 0.5)
Drug Use	All no drug users	3.8/0	7.087/7.000	1.2 (0.5 - 1.9)	2.3/0	6.062/5.946	1.9 (1.3 - 2.5)
Pre-Pregnancy BMI	All <18.5 become 18.5 (normal)	5.7/0	7.087/7.030	0.8 (0.4 - 1.2)	3.9/0	6.062/6.014	0.8 (0.3 - 1.2)
Area-Level Income	All women in quintiles 1 and 2 receive incomes equivalent to quintile 3	39.9/0	7.087/6.985	1.4 (-1.8 - 4.6)	13.4/0	6.062/5.799	4.3 (1.1 - 7.4)
Depression	All not depressed	10.7/0	7.087/6.971	1.6 (0.5 - 2.7)	9.1/0	6.062/5.688	6.2 (4.9 - 7.4)
Pre-Existing Type 2 Diabetes	All no pre-existing diabetes (Type 2)	0.4/0	7.087/7.033	0.8 (0.5 - 1.1)	0.5/0	6.062/5.989	1.2 (0.8 - 1.6)
Pre-Existing Hypertension	All no hypertension	1.1/0	7.087/6.963	1.7 (1.2 -2.2)	1.2/0	6.062/5.940	2.0 (1.5 - 2.5)
Gestational Diabetes	All no gestational diabetes	4.8/0	7.087/6.882	2.9 (2.1 - 3.7)	6.4/0	6.062/5.883	2.9 (2.0 - 3.9)
ART	All conceived spontaneously	1.8/0	7.087/7.053	0.5 (0.0 - 0.9)	0.8/0	6.062/6.043	0.3 (0.0 - 0.6)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PAR, population attributable risk.

Table 5.7. Estimated proportion of preterm birth attributable to selected risk factors, by time period.

		2005-2009			2010-2014			2015-2019		
Risk Factor	**CF Scenario**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/CF**	**% PAR (95% CI)**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/CF**	**% PAR (95% CI)**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/ CF**	**% PAR (95% CI)**
Maternal Age	All women <20 or ≥40 to 25-29 years	7.4/0	6.574/6.556	0.3 (-0.6 - 1.2)	7.5/0	6.338/6.190	2.3 (1.4 - 3.3)	5.9/0	6.678/6.562	1.7 (0.9 - 2.6)
Smoking	All non-smokers	20.9/0	6.574/6.275	4.6 (2.3 - 6.7)	17.8/0	6.338/5.946	6.2 (4.1 - 8.2)	14.1/0	6.678/6.227	6.8 (4.8 - 8.7)
Alcohol Use	All non-alcohol users	0.2/0	6.574/6.550	0.4 (0.1 - 0.7)	0.6/0	6.338/6.321	0.3 (-0.1 - 0.6)	0.6/0	6.678/6.664	0.2 (-0.1 - 0.6)
Drug Use	All no drug users	1.8/0	6.574/6.489	1.3 (0.6 - 2.0)	2.5/0	6.338/6.276	1.0 (0.2 - 1.7)	4.8/0	6.678/6.518	2.4 (1.4 - 3.4)
Pre-Pregnancy BMI	All <18.5 and ≥25 become normal	51.9/0	6.574/6.501	1.1 (-2.2 - 4.3)	52.2/0	6.338/6.273	1.0 (-1.3 - 3.3)	54.9/0	6.678/6.451	3.4 (1.2 - 5.6)
Area-Level Income	All women in quintiles 1 and 2 receive incomes equivalent to quintile 3	40.4/0	6.574/6.363	3.2 (-0.7 - 7.0)	39.3/0	6.338/6.186	2.4 (-1.6 - 6.2)	39.4/0	6.678/6.471	3.1 (-0.9 - 7.0)
Depression	All not depressed	5.9/0	6.574/6.378	3.0 (1.9 - 4.0)	11.3/0	6.338/6.114	3.5 (2.1 - 5.0)	15.9/0	6.678/6.324	5.3 (3.5 - 7.1)
Pre-Existing Type 2 Diabetes	All no pre-existing diabetes (Type 2)	0.4/0	6.574/6.528	0.7 (0.3 - 1.1)	0.4/0	6.338/6.254	1.3 (0.9 - 1.8)	0.5/0	6.678/6.615	0.9 (0.5 - 1.4)
Pre-Existing Hypertension	All no hypertension	1.2/0	6.574/6.447	1.9 (1.3 - 2.5)	1.1/0	6.338/6.222	1.8 (1.2 - 2.5)	1.1/0	6.678/6.552	1.9 (1.2 - 2.5)
Gestational Diabetes	All no gestational diabetes	3.7/0	6.574/6.511	1.0 (0.2 - 1.7)	5.4/0	6.338/6.092	3.9 (2.8 - 5.0)	8.2/0	6.678/6.411	4.0 (2.7 - 5.3)
ART	All conceived spontaneously	0.2/0	6.574/6.578	-0.1 (-0.2 - 0.1)	1.7/0	6.338/6.278	0.9 (0.4 - 1.5)	1.8/0	6.678/6.639	0.6 (0.0 - 1.2)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PAR, population attributable risk.

Table 5.8. Estimated proportion of preterm birth attributable to reductions in selected risk factors, 2005-2019.

Risk Factor	CF Scenario	Risk Factor (%)		Preterm (%)		% PIF (95% CI)
		Actual	CF	Actual	CF	
Maternal Age	i) 25% of women <20 to 25-29 years	3.8	2.9	6.527	6.516	0.2 (0.1 - 0.2)
	ii) 25% of women ≥40 to 25-29 years	3.1	2.3	6.527	6.515	0.2 (0.1 - 0.3)
Smoking	i) 25% of smokers become nonsmokers	17.7	13.3	6.526	6.325	3.1 (2.6 - 3.5)
	ii) 50% reduction in the amount smoked	17.7	17.7	6.526	6.441	2.2 (1.7 - 2.7)
Alcohol Use	25% of users become nonusers	0.5	0.4	6.526	6.521	0.1 (0.0 - 0.1)
Drug Use	25% of users become nonusers	3.0	2.3	6.526	6.500	0.4 (0.3 - 0.5)
Pre-Pregnancy BMI	i) 25% of underweight women become normal weight	4.7	3.5	6.526	6.514	0.2 (0.1 - 0.3)
	i) 25% of obese and overweight women become normal weight	48.2	36.2	6.526	6.435	1.4 (-0.5 - 3.3)
	iii) Women with BMI>25 lose 10% of their body weight	48.2	32.3	6.526	6.528	0.0 (-0.8 - 0.7)
Area-Level Income	i) 25% of women in quintile 1 receive incomes equivalent to quintile 3	18.6	14.0	6.526	6.484	0.6 (0.3 - 1.0)
	ii) 25% of women in quintile 1 receive incomes equivalent to quintile 2	18.6	14.0	6.526	6.489	0.5 (0.2 - 0.9)
Depression	25% of depressed women become non depressed	10.9	8.2	6.526	6.462	1.0 (0.8 - 1.2)
Pre-Existing Type 2 Diabetes	25% of women with type 2 diabetes become nondiabetic	0.5	0.4	6.527	6.512	0.3 (0.2 - 0.3)
Pre-Existing Hypertension	25% of women with hypertension become normotensive	1.2	0.9	6.526	6.497	0.4 (0.3 - 0.5)
Gestational Diabetes	25% of women with gestational diabetes become nondiabetic	5.7	4.3	6.526	6.483	0.7 (0.5 - 0.8)
ART	25% of infants conceived from ART become conceived spontaneously	1.2	0.9	6.526	6.518	0.1 (0.1 - 0.2)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PIF, population impact fraction.

Table 5.9. Estimated proportion of preterm birth attributable to selected risk factors, by time period.

		2005-2009			2010-2014			2010-2015		
Risk Factor	**CF Scenario**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/ CF**	**% PIF (95% CI)**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/CF**	**% PIF (95% CI)**	**Risk Factor (%) Actual/ CF**	**Preterm (%) Actual/ CF**	**% PIF (95% CI)**
Maternal Age	i) 25% of women <20 to 25-29 years	4.5/3.4	6.574/6.573	0.0 (-0.1 - 0.1)	4.3/3.2	6.338/6.321	0.3 (0.1 - 0.4)	2.5/1.9	6.678/6.667	0.2 (0.1 - 0.3)
	ii) 25% of women ≥40 to 25-29 years	2.9/2.2	6.574/6.572	0.0 (-0.1 - 0.2)	3.2/2.4	6.338/6.320	0.3 (0.2 - 0.4)	3.4/2.6	6.678/6.662	0.2 (0.1 - 0.4)
Smoking	i) 25% of smokers become nonsmokers	20.9/15.7	6.574/6.499	1.1 (0.6 - 1.7)	17.8/13.4	6.338/6.240	1.5 (1.0 - 2.1)	14.1/10.6	6.678/6.568	1.7 (1.2 - 2.1)
	ii) 50% reduction in the amount smoked	20.9/20.9	6.574/6.493	1.2 (0.3 - 2.2)	17.8/13.4	6.338/6.157	2.9 (1.9 - 3.8)	14.1/10.6	6.678/6.506	2.6 (1.8 - 3.4)
Alcohol Use	25% of users become nonusers	0.2/0.2	6.574/6.569	0.1 (0.0 - 0.2)	0.6/0.5	6.338/6.334	0.1 (0.0 - 0.2)	0.6/0.5	6.678/6.675	0.1 (0.0 - 0.1)
Drug Use	25% of users become nonusers	1.8/1.4	6.574/6.553	0.3 (0.2 - 0.5)	2.5/1.9	6.338/6.323	0.2 (0.1 - 0.4)	4.8/3.6	6.678/6.638	0.6 (0.3 - 0.9)
Pre-Pregnancy BMI	i) 25% of underweight women become normal weight	4.8/3.6	6.574/6.558	0.3 (0.1 - 0.4)	4.8/3.6	6.338/6.326	0.2 (0.1 - 0.3)	4.6/3.5	6.678/6.665	0.2 (0.1 - 0.3)
	i) 25% of obese and overweight women become normal weight	47.1/35.3	6.574/6.513	0.9 (-2.2 - 4.0)	47.4/35.6	6.338/6.289	0.8 (-1.4 - 2.9)	50.3/37.7	6.678/6.477	3.0 (0.9 - 5.1)
	iii) Women with BMI>25 lose 10% of their body weight	47.1/30.85	6.574/6.608	-0.5 (-1.7 - 0.7)	47.4/31.7	6.338/6.355	-0.3 (-1.2 - 0.7)	50.3/34.4	6.678/6.626	0.8 (-0.2 - 1.8)
Area-Level Income	i) 25% of women in the quintile 1 receive incomes equivalent to quintile 3	19.2/14.4	6.574/6.526	0.7 (0.2 - 1.3)	18.3/13.7	6.338/6.300	0.6 (0.1 - 1.1)	18.5/13.9	6.678/6.643	0.5 (0.0 - 1.1)
	ii) 25% of women in quintile 1 receive incomes equivalent to quintile 2	19.2/14.4	6.574/6.529	0.7 (0.1 - 1.2)	18.3/13.7	6.338/6.299	0.6 (0.1 - 1.2)	18.5/13.9	6.678/6.657	0.3 (-0.3 - 0.9)
Depression	25% of depressed women become non depressed	5.9/4.4	6.574/6.525	0.7 (0.5 - 1.0)	11.3/8.5	6.338/6.282	0.9 (0.5 - 1.2)	15.9/11.9	6.678/6.590	1.3 (0.9 - 1.8)
Pre-Existing Type 2 Diabetes	25% of women with type 2 diabetes become nondiabetic	0.4/0.3	6.574/6.563	0.2 (0.1 - 0.3)	0.4/0.3	6.338/6.318	0.4 (0.2 - 0.5)	0.5/0.4	6.678/6.663	0.2 (0.1 - 0.4)

		2005-2009			2010-2014			2010-2015		
Risk Factor	**CF Scenario**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/ CF**	**% PIF (95% CI)**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/CF**	**% PIF (95% CI)**	**Risk Factor (%) Actual/ CF**	**Preterm (%) Actual/ CF**	**% PIF (95% CI)**
Pre-Existing Hypertension	25% of women with hypertension become normotensive	1.2/0.9	6.574/6.543	0.5 (0.3 - 0.7)	1.1/0.8	6.338/6.310	0.4 (0.2 - 0.6)	1.1/0.8	6.678/6.648	0.5 (0.3 - 0.6)
Gestational Diabetes	25% of women with gestational diabetes become nondiabetic	3.7/2.8	6.574/6.559	0.2 (0.0 - 0.4)	5.4/4.1	6.338/6.277	1.0 (0.7 - 1.3)	8.2/6.2	6.678/6.611	1.0 (0.7 - 1.3)
ART	25% of infants conceived from ART become conceived spontaneously	0.2/0.2	6.574/6.575	0.0 (0.0 - 0.0)	1.7/1.3	6.338/6.323	0.2 (0.1 - 0.4)	1.8/1.4	6.678/6.668	0.1 (0.0 - 0.3)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PIF, population impact fraction.

CHAPTER 6: DISCUSSION

6.1 Summary of Results

Results from this study show that a small proportion of PTB could theoretically be prevented through the complete elimination of selected modifiable risk factors. As expected due to the results of the PARs, this study also showed a small percent of PTB that could be eliminated through a 25% relative reduction in risk factor prevalence (PIFs), roughly 25% of the estimated PARs. When stratified by time periods and parity, the prevalence, RR, and PAR of several risk factors were heterogeneous across strata. Overall, while eliminating all risk factors together, this study found that the total modifiability of PTB was low (14.2%).

6.2 Main Results: Population Attributable Risk and Population Impact Fraction

6.2.1 Maternal Age

Due to the inconsistencies in study methodology as well as heterogeneity in the categorization of maternal age (as well as choice of reference group), it is difficult to compare results from the current study to those previously reported (e.g., Garn et al. 2015 and Oakley et al. 2016)[30,73]. In one large retrospective cohort study conducted in the UK, Oakley et al. estimated a general trend in increasing PAR as age category increased (reference category 20-24 years)[30] (Table 2.2). For reference, the authors estimated that the proportion of PTB attributable to women over the age of 40 (compared to 20-24 years) was 2.6%[30] (Table 2.2). In the current study, 1.4% of PTB was estimated to be attributable to delivering at ages of less than 20 years or 40 years or older (rather than at the age of 25-29 years). Overall, the maternal age distribution was similar between the UK cohort and the Nova Scotia cohort, with the RR of PTB in each age group in the UK cohort elevated compared to the current study[30] (Table 2.1). This increase in RR would agree with the elevated PAR estimated by Oakley et al. The authors may have estimated a more dramatic PAR due to modeling maternal age as a categorical variable; when

applying a counterfactual scenario of 20-24, it is, in truth, the mean age in this category. In comparison, the current study modeled maternal age as a continuous variable, and the counterfactual scenario was to bring women to the nearest boundary of the category (e.g., 25 for women under 20, and 29 for women 40 and older), potentially leading to a smaller PAR estimate.

In the current study, the PAR for maternal age was heterogeneous across the time period. Specifically, the proportion of PTB estimated to be attributable to deliveries to women under the age of 20 years and 40 years or older (rather than at the age of 25-29 years) was estimated to be 0.3%, 2.3% and 1.7% of PTB in the three 5-year time periods. While the proportion of women in each category of maternal age remained relatively constant (apart from a reduction in the prevalence of women younger than 20 years), the aRR of PTB in each age group increased over time (with the highest aRR for ≥40 years during 2010-2014). The PAR was lowest in 2005-2009 as the aRRs for all age categories were lowest during this time.

6.2.2 Smoking

In the current study, it was estimated that if maternal smoking was eliminated, 5.8% of PTB could theoretically be prevented. This estimate is lower compared to previously recorded estimates. In a large retrospective cohort study in the United States, Lengyel et al. estimated that the proportion of PTB attributable to maternal smoking was 8.96%[74] (Table 2.2). Similarly, in a retrospective cohort by Gibberd et al., the PAR for smoking was estimated to be 9%[75] (Table 2.2). The magnitude of the association between smoking and PTB in the two studies (Lengyel aRR 1.39 and Gibberd OR 1.26)[74,75] was similar to the current study, aRR 1.33. The discrepancy seen in estimates of the PAR between the current study and those previously reported is, therefore, due to differences in prevalence of smoking: Lengyel et al.[74] reported 25% and Gibberd et al.[75] reported 47% as compared to 17% in the current study. The prevalence of maternal smoking during pregnancy globally has declined over the years, and this is reflected by the time periods of these studies (Lengyel et al., 2006 to 2011; Gibberd et al., 1998 to 2010) (Table 2.2). The

current study is more recent, and the lower prevalence of smoking led to an ultimately smaller PAR[32].

Within the time period of the current study, the prevalence of smoking decreased from 20.9% in 2005-2009 to 14.1% in 2015-2019, but the aRR for the association between smoking and PTB increased (aRR 1.22 to 1.50). As a result, the proportion of PTB estimated to be attributable to smoking during pregnancy increased from 4.6% to 6.8%. While a decrease in prevalence of maternal smoking during pregnancy is reassuring, suggesting that current public health measures to encourage smoking cessation during pregnancy is effective, the increasing aRR of PTB among smokers leading to increasing PARs is concerning[96].

This observed increase in the aRR of PTB in relation to smoking has multiple potential explanations. Firstly, estimates of the PAR using a binary variable of smoking in pregnancy do not capture the effect of the quantity or duration for which smoking had been present before pregnancy. For example, a pregnant woman who currently smokes during pregnancy may have been a smoker for 15 years or for 2 years before entering pregnancy, with each scenario having varying impacts on the probability of PTB. Over the time period of the current study, the smoking group could have been composed increasingly of women who have smoked the longest, and therefore women potentially had the highest aRR of PTB due to long-lasting negative effects of smoking from prolonged use[32].

It is also possible that, although the prevalence of smoking decreased, the prevalence of smoking through the time periods became increasingly composed of women who smoked the largest quantity of cigarettes a day. An increased quantity of cigarettes could have been the explanation to this increased aRR as previous studies have estimated an increased probability of PTB with an increase in cigarettes smoked throughout pregnancy[97]. However, the data show that the mean quantity of cigarettes smoked at the first antenatal appointment, 20-week appointment and at delivery slightly decreased over the study period.

Like many conflicting findings, it is possible that not all confounding variables of the association between smoking during pregnancy and PTB have been controlled. It is possible, as the current study did not have data on vaping, that differing types of vaping

during pregnancy have changed in prevalence over the years and are confounding the relationship between smoking and PTB. Also, it is possible that with the legalization of marijuana over the study period, women who smoked in pregnancy additionally used cannabis. In the population of women studied who reported smoking, 4.8% reported cannabis use in 2005-2009, which increased to 16.6% in 2015-2019. In a previous study, the risk of PTB in a Canadian population was increased in women who used cannabis during pregnancy compared to those who did not[98]. Future studies should analyse smoking cigarettes in combination with smoking cannabis and the effect on PTB. However, measurement error could have influenced cannabis data since, the legalization of marijuana, women are likely asked more frequently if they use cannabis as well as feeling less pressure to withhold true cannabis use status. An additional confounding variable may be paternal smoking during pregnancy, which has shown to be associated with adverse perinatal events due to the passive inhalation of toxins by the woman[99]. While current research has not determined an increased risk of PTB for infants born to fathers who smoked during pregnancy[99–101], paternal smoking may be a confounder in the current study.

An underlying change in distribution of potential effect modifiers may have effected an increase in the association between smoking and PTB. In a retrospective study completed in Indonesia with data from 1993 to 2007, place of residence was identified as a modifier of the association between smoking and PTB[100]. Women who smoked and lived in a rural community were at an increased likelihood of having a PTB compared to women who smoked in urban communities[100]. Infants born preterm to women who smoked and lived in rural communities were also on average born at an earlier gestational age compared to those infants born preterm to women who smoked and lived in urban communities[100]. It is possible in the current study that the distribution of mothers living in a rural vs. urban area changed over time. However, as this variable was not analysed, it is unknown if this factor is acting as an effect modifier in the current study.

Finally, the decrease in prevalence of maternal smoking in the current study may be due to a reduction in disclosure of smoking status over time. As it becomes more apparent with continuing research that smoking during pregnancy has harmful effects on

a growing fetus, women may be more likely to withhold true smoking status out of fear of stigmatization.

In the analysis stratified by parity, the proportion of PTB attributable to smoking during pregnancy was estimated to be 2.3% in primiparous women and 10.2% in multiparous women. This difference is due to both the elevated prevalence of smoking and aRR of PTB in multiparous women. In primiparous women, 15.7% smoked during pregnancy with the risk of PTB being 15% higher compared to non-smokers. In multiparous women, 19.3% smoked during pregnancy with the risk of PTB being 55% higher than women that did not smoke. This higher aRR among multiparous women could be due to a higher quantity of cigarettes smoked than in multiparous women. On average multiparous women smoked approximately two cigarettes more per day compared to primiparous women (7-8 vs. 9-10), as recorded at the first antenatal appointment, 20-week appointment and delivery.

The proportion of PTB estimated to be attributable to a reduction in quantity of cigarettes smoked by smokers by 50% was 2.2%, which is lower in comparison to the proportion estimated to be possible if 25% of smokers were able to quit or avoid smoking during pregnancy (3.1%). To conclude that risk prevention, however, may be more effective than risk reduction depends on the feasibility and effectiveness of harm reduction vs. smoking cessation interventions. For example, if harm reduction programs could effect a 60% reduction in the quantity of cigarettes smoked, a much larger PIF would be estimated. A 2019 Cochrane review found that neither a reduction in amount smoked or abruptly quitting resulted in a higher frequency of long term smoking cessation rates[102]. Therefore, before interventional programs for smoking cessation are developed, future research should be completed with counterfactual scenarios that consider long-term success rates.

6.2.3 Alcohol Use

Gibberd et al. examined the association between alcohol and PTB in their retrospective cohort study completed over the years 1998-2010 in a specific cohort of Aboriginal Western Australian women. The authors estimated the odds of PTB among alcohol users

was 60% higher than non-alcohol users, with the prevalence of alcohol use at 3%[75] (Table 2.1). In the current study, PTB among alcohol users was 54% more likely than non-alcohol users, with the prevalence of alcohol use at 0.5%. With a lower prevalence as well as a weaker association between alcohol and PTB, the current study estimated that a lower proportion of PTB was attributable to alcohol use during pregnancy than Gibberd et al.[75] (0.3% vs. 1% of PTB, respectively).

Over the time periods studied, the risk of PTB among alcohol users compared to non-alcohol users decreased (aRR 2.40 to 1.30), while the prevalence of alcohol use increased slightly (0.2% to 0.6%). As a result, the estimated proportion of PTB attributable to alcohol remained constant over time. Because previous studies have shown a dose response relationship with alcohol and PTB[38], the aRR may have decreased if women reporting alcohol use consumed less alcohol over the time period, reducing the negative effects of alcohol use during pregnancy.

6.2.4 Drug Use

The proportion of PTB estimated to be attributable to illicit drug use during pregnancy in the current study was 1.6%, lower than previous reports of 5% of PTB estimated by Gibberd et al.[75] (Table 2.2). This discrepancy in PAR estimates is seen as the prevalence of illicit drug use in the cohort was half the amount as in the Western Australian Aboriginal cohort (3% vs. 6%)[75]. Women using illicit drugs in the Australian cohort were more than 2 times more likely to have a PTB compared to women not using drugs (Table 2.1), whereas the estimate in the current study showed that women using illicit drugs were almost 1.5 times more likely to have a PTB compared to women not using drugs. Women included in the study by Gibberd et al. may have used a higher proportion of drugs that are more strongly associated with PTB. The prevalence of drug use among Australians could have been higher with a potential disclosure rate higher than what was seen in the current study.

In the cohort studied, the proportion of PTB estimated to be attributable to illicit drug use was not consistent over the three time periods (1.3%, 1.0% and 2.4%). The increase in PAR in 2015-2019 is most likely due to the increased prevalence of illicit drug use among pregnant women (4.8%), as the aRR between drug use and PTB remained

relatively constant over time (aRR 1.70, 1.35, 1.46). This elevated prevalence in drug use during pregnancy seen during 2015-2019 may be related to the legalization of marijuana, with less stigmatization towards marijuana users.

The risk of PTB among multiparous women who used illicit drugs was higher than in primiparous women (aRR 1.71 vs. 1.31). This may be due to unmeasured confounding variables such as person-level income as well as other factors differently affecting drug use in women with more children compared to those without children. However, as the prevalence of drug use among primiparous women was higher than multiparous women (3.8% vs. 2.3%), the difference in strength of association did not result in a difference in PAR between the two groups.

6.2.5 Pre-pregnancy BMI

In a retrospective study of almost 6,000 women in Canada, Dzakpasu et al. estimated that if all underweight women achieved a BMI of normal weight, all overweight women achieved a BMI of normal weight, and all women living with obesity achieved a BMI of normal weight, 2.6%, -0.4% and 0.3% of PTB could have been eliminated, respectively[76] (Table 2.2). In the current study, the proportion of PTB that was estimated to be attributable to all underweight women becoming normal weight was 0.8% of PTB, all women overweight or living with obesity becoming normal weight was 1.5% of PTB and all underweight, overweight and women living with obesity achieving a BMI within normal range, was 1.8% of PTB. The difference in PAR estimates between these studies is likely due to the lower prevalence of underweight women in the current study (4.7% vs. 6%), leading to a lower PAR for underweight women. This decreased PAR may be due to Dzakpasu et al. modeling BMI as a categorical variable, therefore applying a counterfactual scenario of the mean of the normal BMI category. In the current study, BMI was modelled as a continuous variable with a counterfactual scenario of women achieving a BMI just within the normal range (e.g., the counterfactual for women with a BMI >25 was 24.9), creating a less dramatic change and potentially resulting in a less dramatic PAR.

Across the time periods studied, the PAR for all underweight, overweight and women living with obesity becoming normal weight increased from 1.1% to 3.4%, which was most likely due to both the prevalence and aRR of women living with obesity being the highest during 2015-2019.

All currently published studies (although they vary in study methodology, years studies and geographical location) found the measure of association between pre-pregnancy BMI and PTB highest for being underweight relative to normal weight, and lowest for overweight relative to normal weight[73,74,76]. In the current study, women who were underweight were 44% more likely to have a PTB compared to women of normal weight, with women who were overweight being 4% less likely to have a PTB compared to women of normal weight. Similarly, Dzakpasu et al. found that the odds of having a PTB were 44% higher among underweight women, and 2% lower among overweight women[76]. In their large retrospective cohort study, Lengyel et al. found similar results, that women who were underweight were 53% more likely to have a PTB, with women who were overweight being 3% less likely to have a PTB[74] (Table 2.1). Similar results were also seen in a study by Garn et al.[73]

Although the risk of PTB was lowest in women who were overweight, it is not recommended to become overweight before pregnancy to decrease the risk of PTB, due to other adverse outcomes associated with being overweight. Pre-pregnancy BMI also shows a non-linear relationship with PTB, and the aRR of PTB in women who are overweight to be only slightly lower than women of normal weight. Tsur et at.[49] and Banack et al.[103] stated that relationships like the one observed for pre-pregnancy BMI and PTB could be due to conditioning on a comorbidity (such as pre-existing type 1 diabetes in the current study), including collider bias in the association between obesity and PTB. However, when analyses were repeated without conditioning on the comorbidity of pre-existing type 1 diabetes in the present study, the same findings were observed.

The increased risk for PTB among women entering a pregnancy underweight is most likely due to an intrauterine environment lacking proper nutrients for the fetus to grow and develop[42,50]. Women who are underweight may have unhealthy dietary patterns, leading to fewer nutrients supplied to themselves and the fetus[104]. A 2017 Chinese study showed that women who were underweight had lower levels of vitamin E and healthy fats

compared to normal weight women, both of which are essential for maintaining the health of the woman and optimizing fetal growth[105].

The risk of PTB in primiparous women who were overweight was estimated to be 6% higher than in primiparous women of normal weight; in multiparous women who were overweight, risk of PTB was 22% lower compared to multiparous women of normal weight. This discrepancy may be a result of weight gained during a previous pregnancy and retained, or weight gained between pregnancies in parous women not having the same negative effects on PTB as weight gained through avenues before pregnancy in nulliparous women.

This study was the first to analyse the combined impact of a percent reduction in weight among women who were overweight or living with obesity. No PTB was estimated to be attributable to all women who were overweight or living with obesity losing 10% of their body weight. Although a risk reduction management strategy is potentially more attainable and sustainable than the complete elimination of the most at-risk women, the risk reduction currently estimated does not confer any reduction in PTB.

6.2.6 Area-level Income

As expected from previous research, the risk of PTB was lowest in women who lived in an area with a median income in the 4th or 5th income quintile, and highest if they lived in an area with a median income in the 1st or 2nd income quintile (compared to those living in an area with an income in the middle quintile, the 3rd quintile). Among primiparous women, those who lived in an area with a median income in the lowest quintile were 5% more likely to have a PTB compared to those living in an area with a median income in the middle quintile. In multiparous women living in an area with an income in the lowest income quintile, women were 22% more likely to have a PTB compared to multiparous women living in an area with a median income in the middle quintile. This difference between primiparous and multiparous women impacted the estimated PAR for women living in an area with a median income in the lowest quintile. In primiparous women, the proportion of PTB estimated to be attributable to living in an area with a median income in the lowest quintile was 1.4%, but in multiparous women this proportion rose to 4.3% of PTB. The variable used to represent income is termed QAIPPE which stands for quintile

area income per person equivalent, and is often used as a surrogate for person-level and other neighbourhood characteristics (e.g., pollutant levels, access to public transit and quality of green spaces and parks) as well as being an imperfect indicator of person-level income. Multiparous women living in an area with a median income in the lowest quintile may be affected more than nulliparous women by adverse neighbourhood context, as it may influence the health and wellbeing of their existing children, increasing stress and anxiety in pregnancy and potentially increasing the aRR and PAR of PTB.

Estimates from the current study are difficult to compare to previous research. The only similar study studied the effects of an income supplement; the estimated risk difference would be comparable to an attributable [impact] proportion (PTB that could be prevented in the low income group) (Table 2.2)[77].

Estimating the PAR of area-level income has some limitations. As QAIPPE is an aggregated variable and multilevel models were not used, PAR/PIF estimates may be overestimated. Overall, the current study found that the proportion of PTB that was estimated to be attributable to all women living in an area with a median income in the lowest or second lowest quintile, rather than living in an area with a median income in the middle quintile, was 2.9%. An intervention on QAIPPE per se could mean displacing families from the lowest two quintiles into areas with higher area-level incomes. In practice, however, an intervention rather could be improving neighborhoods in the lowest two quintiles so differences in the underlying factors that influence the risk of PTB (e.g., material circumstances and neighborhood characteristics) would be minimized for women. Public health policies that could achieve these changes would be challenging, restricting the modifiability of area-level income in practice.

6.2.7 Depression

The current study is the first to estimate a PAR for depression and PTB. Estimates showed that women with depression during pregnancy are 37% more likely to have a PTB compared to women without depression, and overall, the proportion of PTB estimated to be attributable to depression was 3.9%. The prevalence of depression increased from 5.9% in 2005-2009 to 15.9% in 2015-2019, while the aRR of PTB

remained relatively constant (1.52 to 1.35). As a result, the PAR increased over the study years, from 3.0% in 2005-2009 to 5.3% in 2015-2019. The prevalence of depression in Nova Scotia may have been affected by an increase in awareness about mental health issues, influencing more women to discuss their mental health problems with health care providers, leading to more diagnoses of depression as the years progressed.

In the present study, depression was associated with a 15% increased risk of PTB in primiparous women and with a 59% increased risk in multiparous women. The prevalence of depression was consistent between primiparous and multiparous women. Thus, the proportion of PTB estimated to be attributable to depression was higher in multiparous women (6.2% as compared to 1.6% in primiparous women). This difference in aRR over parity could be due to reduced access to mental health resources following diagnosis, due to family/children commitments.

6.2.8 Pre-existing Type 2 Diabetes

In a Canadian retrospective cohort study that used national hospitalization data (excluding Québec), Metcalfe et al. estimated that women with pre-existing type 2 diabetes were 2.4 times more likely to have a PTB compared to women without the condition, and that 0.82% of PTB could be attributed to it (Tables 2.1 and 2.2)[57]. In the present study, women with type 2 diabetes were 3 times more likely to have a PTB and 1.0% of PTB could be attributed to type 2 diabetes. Although the aRR of PTB in women with type 2 diabetes is higher than the risk of other studied risk factors, the PAR is not as large due to the low prevalence of type 2 diabetes (0.4% of pregnant women).

6.2.9 Pre-existing Hypertension

In the current study, women were 2.4 times more likely to have a PTB if they had pre-existing hypertension. With a prevalence of 1.2% in the population, the proportion of PTB estimated to be attributable to the condition was 1.9%. Findings from the current study are similar to those reported in an Ontario cohort study that estimated that women with pre-existing hypertension were 3.8 times more likely to have a PTB, compared to women without the condition, and the PAR was 1.40%[63]. Results from the current study

are difficult to compare to the study by Hammond et al., as the authors divided the outcome of PTB into spontaneous, preterm prelabour rupture of membranes (PPROM) and provider-initiated PTB. PARs for pre-existing hypertension estimated from this study were 0.19% of spontaneous, 0.26% of PPROM, and 2.03% of provider-initiated PTB (Table 2.2)[79].

6.2.10 Gestational Diabetes

In the present study, women with gestational diabetes were 1.5 times more likely to have a PTB compared to women without gestational diabetes, and 2.9% of PTB were estimated to be attributable to gestational diabetes. Metcalfe et al. estimated a similar association, but a lower estimate of the PAR (RR, 1.32; PAR, 1.91%; Tables 2.1 and 2.2)[57]. The difference in the prevalence of gestational diabetes in the two studies contributes to the heterogeneity in the PAR estimates, being higher in the current study at 5.7% (compared to 5.2%)[57]. In another Canadian study, Scime et al. estimated that 2.0% of spontaneous PTB and 4.9% of provider-initiated PTB could be attributable to gestational diabetes[62].

The proportion of PTB estimated to be attributable to gestational diabetes increased over the study period from 1.0% to 4.0% in the present study, likely due to the increase in prevalence (3.7% to 8.2%). The increase in prevalence of gestational diabetes is a result of the increased prevalence of overweight and obesity[106] and a change in diagnostic criteria that was applied toward the end of 2014 in Nova Scotia. The estimated prevalence of gestational diabetes in primiparous women was less than in multiparous women (4.8% vs. 6.4%). This observation could be a result of multiparous women having a higher prevalence of overweight and obesity compared to primiparous women.

6.2.11 Assisted Reproductive Technologies

ART is not routinely studied as a risk factor for PTB, as it is a complex risk factor composed of both the ART used, as well as the underlying fertility problems. In a 2016 Center for Disease Control and Prevention report on births in the US and Puerto Rico, it was estimated that 5.3% of PTB could be attributed to using ART to conceive (Table

2.2)[80]. In the current study, this proportion was estimated lower at 0.5% of PTB, likely due to a lower prevalence of ART (1.2% vs. 9.9% in the US study).

In the current study, the prevalence of ART rose during the study periods from 0.2% to 1.8%. This increase in prevalence among Nova Scotia women agrees with the slight increase in ART use among Canadians documented by the Canadian Fertility and Andrology Society[107]. The prevalence of ART was higher in primiparous women (1.8%) compared to multiparous women (0.8%); this would be expected as fertility issues are normally presented at first attempt at pregnancy, and therefore it is reasonable to assume that women with fertility issues are less likely to have more children and therefore less likely to use ART to successfully conceive again.

6.3 Modifiability of Preterm Birth

In the current study, the overall modifiability of PTB was 14.2%. This estimation was completed through the elimination of the eleven modifiable risk factors simultaneously. The current study is the first to examine exclusively modifiable risk factors, and therefore difficult to compare to previous studies which included both modifiable and non-modifiable risk factors of PTB. The PAR estimated in the current study is nearly half that estimated by Ferrero et al. to be attributable to known risk factors (37%).[9] Contributing to this discrepancy is the quantity and selection of risk factors used in each study. In the current study, focus was on risk factors that theoretically can be modified before or in early pregnancy (e.g., smoking and drug use), while Ferrero et al. selected a broader set of risk factors including all known risk factors for PTB[9]. For example, the authors included risk factors that were not available for the current study (e.g., no prenatal care before 20 weeks' gestation) and risk factors generally not considered modifiable (e.g., pregnancy induced hypertension and previous Caesarean section). Some risk factors included by Ferrero et al. were strongly associated with PTB (e.g., pregnancy induced hypertension), which would also contribute to an increased overall PAR. Although the current study and that completed by Ferrero et al. are difficult to compare, the presented results nonetheless add to the existing findings that only a small percent of PTB can be attributable to known modifiable risk factors.

Although the factors leading to the remaining 63% of PTB are currently unknown, multiple hypotheses may apply. Currently, research is attempting to uncover the heritability of PTB[5,18,24]. In previous sibling studies, if one sister had a PTB, the other sister was at a 80% higher risk for herself of having a PTB[5]. Overall heritability of PTB has been estimated to be between 17% and 36% in twin studies, indicating that a potentially large proportion of PTB can be due to genetics[108–110]. Additionally, single nucleotide polymorphisms (single nucleotide changes in germlines cells) in several genes have been associated with PTB[5,108,109]. Gene-environment interactions may also contribute to PTB, for example a particular polymorphism in the tumor necrosis factor-alpha gene, which encodes a protein used by the immune system, may interact with bacterial vaginosis to affect PTB risk[5]. Unknown environmental risk factors (e.g., area pollution levels) have also surfaced as potential risk factors contributing to PTB. Previous research has estimated that 60% of PTB may be attributable to individual environmental factors (defined as factors not related to genetics)[110]. Finally, it is possible that the remaining proportion of PTB not attributable to the risk factors measured in this and other studies is explained by measurement error. For example, the population impact of risk factors such as smoking, alcohol and drug use may potentially be underestimated so the true proportion of PTB attributable to currently known risk factors may be underestimated. Gaps in the global understanding and knowledge of factors influencing PTB warrant continued investigation of PTB globally and in our communities.

Modifiability of PTB through each individual risk factor, as estimated by the PAR and PIF, rely on a causal relationship between the risk factor and PTB. Although existing research demonstrates consistent and often strong associations between each risk factor studied and PTB, causal relationships between risk factors and PTB are difficult to fully conclude. Therefore, the modifiability of PTB through some risk factors studied may not be truly representative of what is possible. For example, pre-pregnancy BMI is a complex risk factor in women both underweight as well as women overweight or living with obesity; adverse events such as PTB are associated with women entering pregnancy with unhealthy weights, but it is difficult to confirm a causal relationship to PTB.

Additionally, the modifiability of PTB may not be truthfully represented, as estimates of the PAR and PIF of modifiable risk factors assume individuals were never

exposed to risk factors, when in truth there could exist exposure history. For example, never having smoked (assumed while completing PAR/PIF estimates) would have a different effect on a woman compared to quitting smoking at the start of pregnancy (what the presented estimates more truthfully display). Interventions previously discussed are targeting risk factors at the start of pregnancy (e.g., SOGC guidelines referring to weight counselling at beginning of pregnancies) in comparison to interventions that would meet the assumption of eliminating any previous history of the risk factors (e.g., nutrition and physical education in elementary school to promote healthy weights of girls and woman throughout life). Also, for some risk factors (e.g., ART, are-level income and age), interventions are difficult to implement as their modifiability imposes on a women's autonomy and life course decisions. Therefore, similar to the issue of causality, the modifiability of PTB through some risk factors studied may not be truly representative of what is possible due to the difficulty of implementing interventions that meet the assumption of the risk factor never having existed, or interventions that influence the risk factor without restricting personal life decisions of women.

6.4 Strengths

This study is the first in Canada to estimate the potential modifiability of PTB, both of individual risk factors as well as together as a set. Strengths of this study in addressing the listed objectives include the nature of the dataset, the variables available for analysis, and the method used for analysis.

The NSAPD is a population-based dataset representing the Nova Scotian population. Because of this, results from this study are generalizable to the entire Nova Scotian population of pregnant women. The data are obtained from standardized records during pregnancy, delivery and post-delivery, allowing data coded into the dataset to be consistent across time. Additionally, the NSAPD undergoes ongoing quality assurance and is both reliable and contains good quality data to perform such analysis[88].

An additional strength of this study includes the variety of risk factors available for use and the depth of information each variable contains. The NSAPD contains continuous forms of many variables of interest, permitting the application of various

levels of counterfactual scenarios. For example, due to the nature of the variable smoking in the NSAPD, analysis of the counterfactual scenarios of both a complete elimination of smoking as well as a reduction in the amount of smoking of each woman by 50% were completed. By having access to a variety of risk factors, multiple risk factors were included in the model; this not only allowed us the opportunity to study the effects of individual risk factors on PTB while controlling for other confounding factors, but also the overall modifiability of PTB.

And finally, the method used to estimate both the PARs and PIFs is a strength of this study as the average PAR/PIF equation provided the opportunity to incorporate any counterfactual scenario, which allowed us to explore multiple PIF estimations such as relative reductions in prevalence and quantity of risk factors.

6.5 Limitations

This study includes several limitations related to the availability of variables as well as measurement error. Although the NSAPD contains a long list of modifiable risk factors, an exhaustive list was not available. Modifiable risk factors that have been previously determined to impact the risk of PTB include: occupation (including how physically demanding a woman's job is before and during pregnancy), level of regular physical activity of the woman before and during pregnancy, and access to prenatal care. Additionally, potentially modifiable risk factors that were not available in the NSAPD include a woman's individual or household income and education. Thus, the overall PAR may be misestimated. Acknowledging that unmeasured variables cannot be included in the analysis, some level of confounding will not be adjusted for in the analyses of the individual risk factors investigated, thereby misestimating the aRRs, PARs and PIFs.

Risk factors that are theoretically modifiable were included, but for which modifiability could be socially or ethically questionable. For example, maternal age during pregnancy is theoretically modifiable by encouraging women to have children earlier in life. However, due to reasons such as continuing education as well as more women entering increasingly demanding occupations, women may not wish to act on this modifiable risk factor and have children earlier in adulthood.

In this study, measurement error exists in the estimation of gestational age. As the NSAPD uses an algorithm as described above to estimate gestational age, multiple variables contribute to the estimation allowing many routes for measurement error, impacting potential measurement bias. For example, as seen in the algorithm, the last menstrual period of the woman is used in many cases to determine gestational age, and it is not confirmed by dating ultrasounds in all women. The exact date of the last menstrual period of the woman is sometimes not known and even if known, recall errors exist. In addition, even if a woman's last menstrual period date is known, the number of days in a woman's menstrual cycle may not be comparable to other women or comparable to the average number of days that the algorithm includes as number of days in a woman's cycle. An additional variable that is included in the algorithm is gestational age dating based on ultrasounds. Measurement error exists in ultrasound dating as gestational age is based on measurements taken during the ultrasound such as crown-rump length.

Determination of gestational age may be differential depending on the level of a risk factor. For example, in Nova Scotia not all women have ultrasound dating to confirm gestational age. It is possible that women with unplanned pregnancies, which are more likely to occur at a younger age, will have a reduced likelihood of receiving an ultrasound earlier during pregnancy. This has the potential to introduce differential measurement error into the determination of gestational age as the dating ultrasound is conducted later during pregnancy when it is less accurate, or not done at all.

An additional social factor that may introduce measurement error differentially based on level of risk factor includes women who use alcohol. It could be that women who use alcohol during pregnancy delay presenting for antenatal care and receiving their first ultrasound out of fear of stigma. Similarly, to the risk factor of maternal age, this may introduce measurement error as the first estimate of gestational age could be determined later throughout the pregnancy leading to a less accurate gestational age estimate.

Measurement error may also be present in the risk factors studied. It is possible that the prevalence of risk factors which hold stigma during pregnancy (such as alcohol use and smoking) have been underrepresented in the study, underestimating both the PARs and PIFs. It is also possible that measurement error exists in the measurement of

risk factors such as gestational diabetes or hypertension through inaccurate readings from the instruments used to diagnose these conditions. However, previous studies have concluded high validity in diagnostic testing for these conditions, and therefore measurement error is likely not present.

6.6 Future Directions

As the current study did not categorize PTB by gestational age at birth (e.g., extreme preterm <28 weeks' gestation), possible future directions include analysing the population impact that selected modifiable risk factors have on PTB by weeks' gestation, as different risk factors may differentially effect PTB by gestational age at birth.

Results from the current study show that a large proportion of PTB is not attributable to the selected modifiable risk factors studied. Applying a broader lens to this study, future exploration could include determining the percent of PTB in Nova Scotia that is attributable to all currently known risk factors, modifiable or non-modifiable. Examples of this could include risk factors included in the study by Ferrero et al.[9] such as pregnancy-induced hypertension and previous Caesarean section. As previously discussed, a large gap in knowledge exists as to what risk factors constitute the remaining percentage of PTB cases. A genetic component as well as environmental risk factors are most likely at play and focusing research on these two families of variables should be a priority.

As the counterfactual scenarios that were chosen in this study were used as a demonstration, and not based off previous knowledge or literature as to reductions possible with currently available or feasible interventions, future research could explore additional counterfactual scenarios that may be more plausible and meaningful to the Nova Scotia population. To inform plausible counterfactual scenarios future research may include an in-depth chart analysis of women (both pregnant and not pregnant) who have successfully reduced risk factors such as smoking, and in what quantity and timeline. Future research could include discussions with health care providers as to goals they encourage their patients to achieve, or success rates of interventional programs. Other factors that should be considered while establishing future counterfactual scenarios would

be cost of delivery for such interventional programs as well as universal access to these programs by Nova Scotia women. This research would create more realistic and plausible counterfactual scenarios that would help inform comparable PARs/PIFs between risk factors, specific to the Nova Scotia population.

Finally, as this study shows support for an enhanced routine surveillance system, future studies could complete annual duplications of the current project, continuing to capture the impact that risk factors have on our population, adapting interventions and redirecting focus of health care professionals and patients on the most impactful risk factors seen in a timely manner.

6.7 Impact

PTB is a key indicator of perinatal health and a strong predictor of long-term health in children. As previously mentioned, PTB is the second most common cause of death in children under the age of 5 years[2,4,9]. In addition to mortality, morbidities are often experienced in children born preterm[5]. The individual and social burden of PTB is widespread, affecting families, the healthcare system and society.

Because of the strong impact PTB has on a population, determining ways in which PTB can be reduced is extremely important. To determine effective and efficient ways that PTB can be reduced through acting on modifiable risk factors, both the prevalence and the risk associated with a respective risk factor should be considered through the estimation of PARs and PIFs. To date, limited and sporadic studies exist in the estimation of PARs and PIFs of modifiable risk factors on PTB. This is the first study to estimate PARs and PIFs of modifiable risk factors of PTB on a Nova Scotia population.

Although results from this study show limited modifiability of PTB through the risk factors studied, it nevertheless contributes to researchers', health care professionals' and policy makers' knowledge concerning risk factors that should be targeted in our population. For example, the largest percent of PTB can be attributed to maternal smoking. If maternal smoking during pregnancy was eliminated in the population, around 6% of PTB could be eliminated. Comparing the impact of this risk factor with a less impactful risk factor, for example, alcohol use with a PAR of 0.3%, allows healthcare and

population health professionals to focus and target the development of primary prevention measures and interventions that will reduce PTB most efficiently. Through the emphasis of primary preventative measures as listed by the SOGC for selected risk factors, results from this research shows the importance of periconceptional and antenatal care actions, counselling and encouraging women and families to decrease the prevalence of modifiable risk factors and subsequently halting the occurrence of PTB. Although this study focused on the single perinatal outcome of PTB, chosen because of its importance, the risk factors identified are associated with other perinatal outcomes, and estimating which risk factors are most prevalent, as well as most strongly associated with the outcome studied in our population, may help future similar research with other perinatal outcomes.

The importance of ongoing enhanced surveillance for PTB was shown in this research. Prevalence of risk factors as well as aRRs were shown to result in PARs varying over time. For example, in estimating the PAR for smoking, the prevalence decreased while the risk of PTB among smokers (compared to non-smokers) increased, a trend that would not have been captured if neither the PAR, nor the aRR was tracked over time. The continuation of tracking provincial estimates as an ongoing enhanced surveillance system are encouraged, as their completion will help with the continuation of informing policy and programs in Nova Scotia, which has the potential to improve health services for pregnant women and their newborns on an individual level and reduce the prevalence of PTB on a population level by adapting targeted modifiable risk factors over time, that have the greatest impact on the health of Nova Scotians.

CHAPTER 7: CONCLUSION

This study aimed to estimate the percent of PTB that can be attributed to selected modifiable risk factors in the population. Overall, only a small percent of PTB can be attributed to the selected theoretically modifiable risk factors. As differences were seen in PARs over time, this study supports an enhanced surveillance program that considers both the prevalence of the risk factor and measure of association between the risk factor and PTB to properly analyse trends, and more appropriately plan future primary prevention efforts to maximize reduction of PTB in Nova Scotia. By enhancing surveillance programs and most efficiently reducing PTB in Nova Scotia, we are one step closer to providing all children with the best possible start in life.

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Appendix A. NSAPD and ICD-10-CA codes used to define modifiable risk factors.

Risk Factor	NSAPD Codes		ICD-10-CA Codes	
Maternal Age	N/A		N/A	
Smoking	dlpresmk	Number of cigarettes smoked a day - pre-pregnancy	N/A	
	dlvs1smk	Number of cigarettes smoked a day - 1st prenatal appointment		
	smoke_20	Number of cigarettes smoked a day - 20 weeks prenatal appointment		
	admitsmk	Number of cigarettes smoked a day - delivery		
Alcohol Use	R005_00100	Alcohol abuse - chronic or binge (not social)	Z72.1	Alcohol use
	R005_01800	Alcohol abuse - chronic	F10	Acute intoxication from alcohol use
	R005_01900	Alcohol abuse - binge		
	R005_02000	Alcohol abuse - unknown binge or chronic		
Drug Use	R005_00200	Ativan	F11	Acute intoxication due to opioids
	R005_00300	Cocaine/Crack	F12	Acute intoxication due to cannabinoids
	R005_00400	Codeine	F13	Acute intoxication due to sedatives or hypnotics
	R005_00500	Demerol	F14	Acute intoxication due to cocaine
	R005_00600	Dilaudid	F15	Acute intoxication due to stimulants (including caffeine)
	R005_00700	Hash	F16	Acute intoxication due to hallucinogens
	R005_00800	Heroin	F18	Acute intoxication due to volatile solvents
	R005_01000	Methadone		
	R005_01100	Morphine		
	R005_01200	Prescription medication abuse		
	R005_01300	Solvents		
	R005_01400	Valium		
	R005_01500	Other specified abuse		
	R005_01600	OxyContin		
	R005_01700	Ecstasy		
	R005_00900	Marijuana		
Pre-Pregnancy BMI	N/A		N/A	

Risk Factor	NSAPD Codes		ICD-10-CA Codes	
Area-Level Income	[QAIPPE (Statistics Canada)]			
Depression	R016_00200 R016_00100 R004_00200 R004_01300	Depression Anxiety disorders Anti-depressives Anti-anxiety medication		
Pre-Existing Type 2 Diabetes	R014_01000	Pre-existing diabetes mellitus, type 2	O24.1 O24.6 E11	Pre-existing type 2 diabetes mellitus Pre-existing type 2 diabetes mellitus Type 2 diabetes mellitus
Pre-Existing Hypertension	R014_00700 R014_00800	Pre-existing hypertension complicating pregnancy, childbirth and the puerperium Pre-existing hypertensive disorder with superimposed proteinuria	O10 O11 I10 I11 I12 I13 I15	Pre-existing essential hypertension complicating pregnancy, childbirth and the puerperium Pre-eclampsia superimposed on chronic hypertension Essential (primary) hypertension Hypertensive heart disease Hypertensive renal disease Hypertensive heart and renal disease Secondary hypertension
Gestational Diabetes	R014_01300 R014_00700 R014_00800	Diabetes mellitus arising in pregnancy, includes gestational diabetes Pre-existing hypertension complicating pregnancy, childbirth and the puerperium Pre-existing hypertensive disorder with superimposed proteinuria	O24.4 O24.8	Diabetes mellitus arising in pregnancy Other pre-existing diabetes mellitus in pregnancy, childbirth, and the puerperium
ART	N/A		Z31.1 Z31.2 Z31.3 Z37.^^1 Z38.^^1	Artificial insemination In vitro fertilization Other assisted fertilization methods Birth, pregnancy resulting from assisted reproductive technology Product of assisted reproductive technology

Appendix B. Code used to estimate the PIF for a counterfactual scenario of a reduction in the amount smoked by all smokers by 50%.

```
frame copy default cf
frame change cf
replace Numsmk_1app = Numsmk_1app/2 if Numsmk_1app >0
replace Numsmk_del = Numsmk_del/2 if Numsmk_del >0
replace cf=1

count if _mi_m==0
local numsamp=r(N)
replace _mi_id=(_mi_id)+(10*(`numsamp'))
frameappend default

program pif_smk2_mi, eclass

poisson PTB_37 Numsmk_1app Numsmk_del Alcohol Depanx Drug_use ib3.Qaippe
ib3.Magecat_mi if cf==0 , robust irr
est store betas
frame cf: margins, at((asobserved) Numsmk_1app Numsmk_del) over(cf) noesample
post
nlcom ("logPUF":log(_b[1.cf])-log(_b[0.cf])), post

        tempname b V
        mat `b' = _b[logPUF]
        mat `V' = _se[logPUF]^2
        local N = r(N)

        mat colnames `b' = logPUF
        mat colnames `V' = logPUF
        mat rownames `V' = logPUF

        ereturn post `b' `V', obs(`N')
        ereturn local cmd "parf_smk2_mi"
        ereturn local title "logPUF"
end

mi estimate, cmdok: pif_smk2_mi
matrix sss=r(table)
local logPIUF=sss[1,1]
local selogPIUF=sss[2,1]

di "PAF% "       %3.1f 100*(1-exp(`logPIUF'))
di "LCL (PAF%) " %3.1f 100*(1-exp(`logPIUF'+1.96*`selogPIUF'))
di "UCL (PAF%) " %3.1f 100*(1-exp(`logPIUF'-1.96*`selogPIUF'))

program pcf_smk2_mi, eclass
poisson PTB_37 Numsmk_1app Numsmk_del Alcohol Depanx Drug_use ib3.Qaippe
ib3.Magecat_mi if cf==0, robust irr
frame cf: margins, at((asobserved) Numsmk_1app Numsmk_del) over(cf) noesample
post
end

mi estimate, cmdok: pcf_smk2_mi
frame change default
frame drop cf
```

Appendix C: The association between the risk factors of interest and preterm birth, 2005-2019 (complete case analysis).

Risk Factor	Risk Factor (%)		Preterm n (%)		uRR (95% CI)		aRR (95% CI)	
Maternal Age (years)								
<20	3476	(3.8)	227	(6.5)	1.11	(0.97 - 1.27)	1.09	(0.95 - 1.25)
20-24	15744	(17.2)	953	(6.1)	1.03	(0.92 - 1.11)	1.02	(0.94 - 1.10)
25-29	26062	(28.4)	1533	(5.9)	Reference		Reference	
30-34	29151	(31.8)	1633	(5.6)	0.95	(0.89 - 1.02)	0.96	(0.90 - 1.03)
35-39	14563	(15.9)	923	(6.3)	1.08	(0.99 - 1.17)	1.10	(1.01 - 1.19)
≥40	2831	(3.1)	197	(17.9)	1.20	(1.03 - 1.37)	1.20	(1.04 - 1.39)
Smoking								
No	73909	(80.5)	4059	(5.5)	Reference		Reference	
Yes	17918	(19.5)	1407	(7.9)	1.43	(1.35 - 1.52)	1.37	(1.29 - 1.46)
Alcohol Use								
No	91365	(99.5)	5426	(5.9)	Reference		Reference	
Yes	462	(0.5)	40	(8.7)	1.46	(1.08 - 1.96)	1.30	(0.96 - 1.75)
Drug Use								
No	88916	(96.8)	5200	(5.9)	Reference		Reference	
Yes	2911	(3.2)	266	(9.1)	1.56	(1.39 - 1.76)	1.42	(1.25 - 1.61)
Pre-Pregnancy BMI (kg/m^2)								
<18.5	3864	(4.2)	321	(8.3)	1.42	(1.27 - 1.58)	1.33	(1.19 - 1.49)
18.5-24.9	43619	(47.5)	2558	(5.9)	Reference		Reference	
25.0-29.9	22536	(24.5)	1269	(5.6)	0.96	(0.90 - 1.03)	0.94	(0.88 - 1.01)
≥30	21808	(23.8)	1318	(6.0)	1.03	(0.97 - 1.10)	0.99	(0.93 - 1.06)
Area-Level Income (quintiles)								
1 (lowest)	16944	(18.5)	1112	(6.6)	1.10	(1.02 - 1.19)	1.10	(1.02 - 1.19)
2	19376	(21.1)	1156	(6.0)	1.00	(0.93 - 1.08)	1.00	(0.93 - 1.08)
3	20883	(22.7)	1242	(6.0)	Reference		Reference	
4	20226	(22.0)	1177	(5.8)	0.98	(0.91 - 1.06)	0.98	(0.91 - 1.06)
5 (highest)	14398	(15.7)	779	(5.4)	0.91	(0.83 - 0.99)	0.90	(0.83 - 0.99)
Depression								
No	81068	(88.3)	4596	(5.7)	Reference		Reference	
Yes	10759	(11.7)	870	(8.1)	1.43	(1.33 - 1.53)	1.42	(1.35 - 1.52)
Pre-Existing Type 2 Diabetes								
No	91372	(99.5)	5382	(5.9)	Reference		Reference	
Yes	455	(0.5)	84	(18.5)	3.13	(2.58 - 3.81)	2.97	(2.44 - 3.62)
Pre-Existing Hypertension								
No	90773	(98.9)	5288	(5.8)	Reference		Reference	
Yes	1054	(1.2)	178	(16.9)	2.90	(2.53 - 3.32)	2.48	(2.14 - 2.87)
Gestational Diabetes								
No	86420	(94.1)	4974	(5.8)	Reference		Reference	
Yes	5407	(5.9)	492	(9.1)	1.58	(1.45 - 1.73)	1.59	(1.45 - 1.75)
ART								
No	90582	(98.6)	5356	(5.9)	Reference		Reference	
Yes	1245	(1.4)	110	(8.8)	1.49	(1.25 - 1.79)	1.47	(1.22 - 1.76)

aRR, adjusted relative risk; ART, assisted reproductive technologies; BMI, body mass index; CI, confidence interval; uRR, unadjusted relative risk.

Appendix D: The association between the risk factors of interest and preterm birth, by parity (complete case analysis).

	Primiparous (n=42781)			Multiparous (n=49041)		
Risk Factor	**Risk Factor (%)**	**Preterm (%)**	**aRR (95% CI)**	**Risk Factor (%)**	**Preterm (%)**	**aRR (95% CI)**
Maternal Age (years)						
<20	7.3	6.4	1.02 (0.88 - 1.19)	0.7	8.1	1.41 (0.98 - 2.03)
20-24	23.4	6.1	0.99 (0.89 - 1.10)	11.7	5.9	1.03 (0.91 - 1.17)
25-29	30.1	6.2	Reference	26.9	5.6	Reference
30-34	27.4	6.3	1.03 (0.93 - 1.13)	35.5	5.1	0.94 (0.85 - 1.03)
35-39	10.0	7.5	1.22 (1.07 - 1.38)	20.9	5.9	1.08 (0.98 - 1.20)
≥40	1.8	20.2	1.15 (0.88 - 1.50)	4.3	16.8	1.28 (1.08 - 1.52)
Smoking						
No	82.1	6.1	Reference	79.1	4.9	Reference
Yes	17.9	7.4	1.21 (1.10 - 1.33)	20.9	8.2	1.57 (1.44 - 1.72)
Alcohol Use						
No	99.4	6.3	Reference	99.6	5.6	Reference
Yes	0.6	8.8	1.34 (0.91 - 1.96)	0.4	8.4	1.25 (0.77 - 2.01)
Drug Use						
No	96.0	6.3	Reference	97.6	5.5	Reference
Yes	4.0	8.2	1.27 (1.07 - 1.51)	2.4	10.4	1.64 (1.37 - 1.96)
Pre-Pregnancy BMI (kg/m^2)						
<18.5	4.8	7.7	1.26 (1.07 - 1.47)	3.7	9.0	1.44 (1.23 - 1.69)
18.5-24.9	51.0	6.1	Reference	44.4	5.7	Reference
25.0-29.9	23.6	6.5	1.06 (0.97 - 1.16)	25.3	4.9	0.85 (0.77 - 0.93)
≥30	20.5	6.5	1.05 (0.96 - 1.16)	26.6	5.7	0.97 (0.89 - 1.06)
Area-Level Income (quintiles)						
1 (lowest)	18.3	6.5	1.06 (0.94 - 1.19)	18.6	6.6	1.14 (1.03 - 1.27)
2	21.6	6.5	1.05 (0.94 - 1.17)	20.7	5.5	0.96 (0.86 - 1.07)
3	22.9	6.2	Reference	22.7	5.8	Reference
4	22.2	6.5	1.05 (0.94 - 1.17)	21.9	5.2	0.91 (0.81 - 1.01)
5 (highest)	15.1	6.0	0.98 (0.86 - 1.11)	16.2	4.9	0.85 (0.76 - 0.97)
Depression						
No	88.6	6.2	Reference	88.0	5.2	Reference
Yes	11.4	7.6	1.23 (1.11 - 1.37)	12.0	8.5	1.61 (1.47 - 1.77)
Pre-Existing Type 2 Diabetes						
No	99.6	6.3	Reference	99.4	5.5	Reference
Yes	0.4	18.9	2.83 (2.07 - 3.87)	0.6	18.2	3.03 (2.35 - 3.92)
Pre-Existing Hypertension						
No	98.9	6.2	Reference	98.8	5.5	Reference
Yes	1.1	16.5	2.22 (1.78 - 2.76)	1.2	17.2	2.67 (2.20 - 3.25)
Gestational Diabetes						
No	95.0	6.1	Reference	93.4	5.4	Reference
Yes	5.0	10.3	1.66 (1.45 - 1.90)	6.7	8.3	1.54 (1.36 - 1.75)
ART						
No	98.1	6.3	Reference	99.1	5.6	Reference
Yes	1.9	9.4	1.40 (1.12 - 1.75)	0.7	7.8	1.37 (0.98 - 1.91)

aRR, adjusted relative risk; ART, assisted reproductive technologies; BMI, body mass index; CI, confidence interval.

Appendix E: The association between the risk factors of interest and preterm birth, by time period (complete case analysis).

Risk Factor	2005-2009 (n=28219)			2010-2014 (n=32501)			2015-2019 (n=31107)		
	Risk Factor (%)	Preterm (%)	aRR (95% CI)	Risk Factor (%)	Preterm (%)	aRR (95% CI)	Risk Factor (%)	Preterm (%)	aRR (95% CI)
Maternal Age (years)									
<20	4.7	5.9	0.97 (0.77 - 1.23)	4.3	6.8	1.23 (1.00 - 1.52)	2.4	7.2	1.12 (0.86 - 1.47)
20-24	18.5	5.6	0.93 (0.81 - 1.07)	17.9	6.0	1.10 (0.96 - 1.25)	15.1	6.6	1.04 (0.91 - 1.19)
25-29	28.8	6.0	Reference	28.0	5.4	Reference	28.4	6.3	Reference
30-34	30.9	5.6	0.95 (0.84 - 1.07)	31.3	5.7	1.06 (0.94 - 1.19)	33.0	5.6	0.90 (0.80 - 1.00)
35-39	14.4	6.1	1.03 (0.89 - 1.20)	15.3	6.4	1.21 (1.05 - 1.38)	17.7	6.5	1.04 (0.92 - 1.19)
≥40	2.8	17.4	0.78 (0.56 - 1.09)	3.0	19.3	1.45 (1.15 - 1.83)	3.4	17.6	1.30 1.04 - 1.62)
Smoking									
No	76.2	5.4	Reference	80.3	5.4	Reference	84.6	5.7	Reference
Yes	23.8	6.9	1.23 (1.10 - 1.38)	19.7	7.9	1.44 (1.29 - 1.60)	15.5	9.2	1.50 (1.34 - 1.67)
Alcohol Use									
No	99.8	5.7	Reference	99.4	5.9	Reference	99.4	6.2	Reference
Yes	0.2	10.6	1.63 (0.80 - 3.31)	0.6	7.7	1.20 (0.74 - 1.98)	0.7	9.0	1.27 (0.82 - 1.98)
Drug Use									
No	98.2	5.7	Reference	97.3	5.8	Reference	95.1	6.0	Reference
Yes	1.8	10.0	1.65 (1.24 - 2.19)	2.7	7.7	1.20 (0.94 - 1.54)	4.9	9.7	1.44 (1.22 - 1.70)
Pre-Pregnancy BMI (kg/m^2)									
<18.5	4.0	8.2	1.39 (1.12 - 1.71)	4.4	7.5	1.18 (0.97 - 1.43)	4.2	9.3	1.45 (1.21 - 1.74)
18.5-24.9	49.4	5.7	Reference	48.2	6.0	Reference	45.1	5.9	Reference
25.0-29.9	24.4	5.6	0.96 (0.85 - 1.08)	24.18	5.6	0.92 (0.82 - 1.02)	25.1	5.7	0.96 (0.85 - 1.07)
≥30	22.2	5.6	0.95 (0.84 - 1.08)	23.3	5.7	0.92 (0.82 - 1.03)	25.6	6.7	1.09 (0.98 - 1.21)
Area-Level Income (quintiles)									
1 (lowest)	19.0	6.3	1.10 (0.95 - 1.27)	18.2	6.7	1.16 (1.02 - 1.32)	18.3	6.8	1.06 (0.93 - 1.21)
2	21.2	5.6	0.98 (0.85 - 1.13)	21.2	5.9	1.02 (0.89 - 1.16)	21.0	6.4	1.01 (0.89 - 1.14)
3	22.3	5.7	Reference	22.9	5.7	Reference	23.0	6.4	Reference
4	21.4	5.7	1.00 (0.86 - 1.15)	22.2	6.0	1.05 (0.92 - 1.19)	22.5	5.7	0.90 (0.79 - 1.02)
5 (highest)	16.2	5.5	0.97 (0.83 - 1.13)	15.6	5.0	0.87 (0.75 - 1.02)	15.4	5.7	0.90 (0.77 - 1.04)
Depression									
No	93.6	5.6	Reference	88.3	5.6	Reference	83.5	5.8	Reference
Yes	6.4	8.6	1.54 (1.32 - 1.81)	11.7	7.6	1.34 (1.19 - 1.51)	16.5	8.3	1.42 (1.28 - 1.57)
Pre-Existing Type 2 Diabetes									
No	99.5	5.7	Reference	99.5	5.8	Reference	99.4	6.2	Reference
Yes	0.5	15.9	2.80 (1.86 - 4.22)	0.5	25.5	4.24 (3.20 - 5.62)	0.6	14.2	2.11 (1.46 - 3.06)

Risk Factor	2005-2009 (n=28219)			2010-2014 (n=32501)			2015-2019 (n=31107)		
	Risk Factor (%)	Preterm (%)	aRR (95% CI)	Risk Factor (%)	Preterm (%)	aRR (95% CI)	Risk Factor (%)	Preterm (%)	aRR (95% CI)
Pre-Existing Hypertension									
No	98.9	5.6	Reference	98.9	5.8	Reference	98.8	6.1	Reference
Yes	1.1	16.9	2.91 (2.25 - 3.77)	1.2	15.6	2.15 (1.66 - 2.79)	1.2	18.3	2.47 (1.94 - 3.14)
Gestational Diabetes									
No	96.3	5.7	Reference	94.5	5.7	Reference	91.8	6.0	Reference
Yes	3.7	8.5	1.56 (1.26 - 1.92)	5.5	9.3	1.68 (1.45 - 1.97)	8.2	9.2	1.52 (1.33 - 1.74)
ART									
No	99.7	5.8	Reference	98.3	5.8	Reference	98.0	6.2	Reference
Yes	0.3	2.6	0.45 (0.12 - 1.79)	1.7	9.5	1.60 (1.22 - 2.08)	2.0	9.0	1.44 (1.11 - 1.87)

aRR, adjusted relative risk; ART, assisted reproductive technologies; BMI, body mass index; CI, confidence interval.

Appendix F: Estimated proportion of preterm birth attributable to selected risk factors, 2005- 2019 (complete case analysis).

Risk Factor	CF Scenario	Risk Factor (%)		Preterm (%)		% PAR (95% CI)
		Actual	CF	Actual	CF	
Maternal Age	i) <20 to 25-29 years	3.8	0	5.952	5.921	0.53 (0.20 - 0.86)
	ii) ≥40 to 25-29 years	3.1	0	5.952	5.910	0.71 (0.35 - 1.07)
	iii) <20 or ≥40 to 25-29 years	6.9	0	5.952	5.878	1.25 (0.65 - 1.84)
Smoking	All non-smokers	19.5	0	5.953	5.535	7.01 (5.53 - 8.50)
Alcohol Use	All non-alcohol users	0.5	0	5.953	5.942	0.17 (-0.06 - 0.40)
Drug Use	All no drug users	3.2	0	5.953	5.867	1.43 (0.82 - 2.05)
Pre-Pregnancy BMI	i) All <18.5 become 18.5 (normal)	4.2	0	5.952	5.932	0.35 (0.19 - 0.51)
	ii) All ≥25 become 24.9 (normal)	48.3	0	5.952	5.932	0.35 (-1.06 - 1.76)
	iii) All <18.5 and ≥25 become normal	52.5	0	5.952	5.911	0.70 (-0.66 - 2.06)
Area-Level Income	All women in quintiles 1 and 2 receive incomes equivalent to quintile 3	39.6	0	5.953	5.835	2.00 (-0.96 - 4.90)
Depression	All not depressed	11.7	0	5.953	5.672	4.72 (3.63 - 5.81)
Pre-Existing Type 2 Diabetes	All no pre- existing diabetes (Type 2)	0.5	0	5.953	5.892	1.02 (0.69 - 1.35)
Pre-Existing Hypertension	All no hypertension	1.2	0	5.953	5.837	1.94 (1.50 - 2.40)
Gestational Diabetes	All no gestational diabetes	5.9	0	5.953	5.753	3.40 (2.57 - 4.14)
ART	All conceived spontaneously	1.4	0	5.953	5.914	0.64 (0.32 - 0.97)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PAR, population attributable risk.

Appendix G: Estimated proportion of preterm birth attributable to selected risk factors, by parity (complete case analysis).

		Primiparous			Multiparous		
Risk Factor	**CF Scenario**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/ CF**	**% PAR (95% CI)**	**Risk Factor (%) Actual/ CF**	**Preterm (%) Actual/CF**	**% PAR (95% CI)**
Maternal Age	All women <20 or ≥40 to 25-29 years	9.1/0	6.349/6.286	0.99 (-0.04 - 2.03)	4.9/0	5.606/5.525	1.44 (0.63 - 2.26)
Smoking	All non-smokers	17.9/0	6.349/6.120	3.60 (1.68 - 5.51)	20.9/0	5.606/4.980	11.2 (8.90 - 13.4)
Alcohol Use	All non-alcohol users	0.6/0	6.349/6.335	0.22 (-0.12 - 0.57)	0.4/0	5.606/5.600	0.11 (-0.17 - 0.40)
Drug Use	All no drug users	4.0/0	6.349/6.278	1.11 (0.18 - 2.05)	2.4/0	5.606/5.507	1.76 (0.95 - 2.60)
Pre-Pregnancy BMI	All <18.5 become 18.5 (normal)	4.8/0	6.349/6.335	0.22 (0.03 - 0.42)	3.7/0	5.606/5.579	0.47 (0.25 - 0.68)
Area-Level Income	All women in quintiles 1 and 2 receive incomes equivalent to quintile 3	39.9/0	6.349/6.218	2.05 (-2.04 - 6.14)	39.3/0	5.606/5.501	1.86 (-1.82 - 5.55)
Depression	All not depressed	11.4/0	6.349/6.184	2.59 (1.24 - 3.94)	12.0/0	5.606/5.220	6.87 (5.35 - 8.40)
Pre-Existing Type 2 Diabetes	All no pre-existing diabetes (Type 2)	0.4/0	6.349/6.299	0.79 (0.38 - 1.19)	0.6/0	5.606/5.536	1.24 (0.79 - 1.70)
Pre-Existing Hypertension	All no hypertension	1.1/0	6.349/6.247	1.60 (1.00 - 2.20)	1.2/0	5.606/5.479	2.25 (1.59 - 2.92)
Gestational Diabetes	All no gestational diabetes	5.0/0	6.349/6.143	3.24 (2.21 - 4.28)	6.7/0	5.606/5.412	3.46 (2.27 - 4.65)
ART	All conceived spontaneously	1.9/0	6.349/6.297	0.82 (0.20 - 1.42)	0.9/0	5.606/5.587	0.32 (-0.07 - 0.72)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PAR, population attributable risk.

Appendix H: Estimated proportion of preterm birth attributable to selected risk factors, by time period (complete case analysis).

		2005- 2009			2010- 2014			2015- 2019		
Risk Factor	**CF Scenario**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/CF**	**% PAR (95% CI)**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/CF**	**% PAR (95% CI)**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/ CF**	**% PAR (95% CI)**
Maternal Age	All women <20 or ≥40 to 25-29 years	7.4/0	5.751/5.757	-0.09 (-1.15 - 0.97)	7.4/0	5.874/5.741	2.25 (1.10 - 3.40)	5.8/0	6.217/6.130	1.40 (0.43 - 2.36)
Smoking	All non-smokers	23.8/0	5.751/5.442	5.38 (2.38 - 8.37)	19.7/0	5.874/5.400	8.06 (5.33 - 10.78)	15.5/0	6.217/5.746	7.58 (5.42 - 9.74)
Alcohol Use	All non-alcohol users	0.2/0	5.751/5.742	0.17 (-0.17 - 0.50)	0.6/0	5.874/5.866	0.13 (-0.23 - 0.50)	9.0/0	6.217/6.205	0.20 (-0.21- 0.61)
Drug Use	All no drug users	0.8/0	5.751/5.680	1.24 (0.33 - 2.15)	2.7/0	5.874/5.839	0.59 (-0.29 - 1.46)	4.9/0	6.217/6.072	2.33 (1.16 - 3.50)
Pre-Pregnancy BMI	All <18.5 and ≥25 become normal	50.6/0	5.751/5.823	-1.35 (-4.01 - 1.32)	51.8/0	5.874/5.892	-0.31 (-2.93 - 2.32)	54.9/0	6.217/6.031	3.00 (0.37 - 5.63)
Area-Level Income	All women in quintiles 1 and 2 receive incomes equivalent to quintile 3	40.2/0	5.751/5.670	1.41 (-3.76 - 6.58)	39.3/0	5.874/5.682	3.26 (-1.10 - 7.62)	39.2/0	6.217/6.139	1.25 (-3.35 - 5.85)
Depression	All not depressed	6.4/0	5.751/5.558	3.37 (1.95 - 4.78)	11.7/0	5.874/5.648	3.84 (2.25 - 5.43)	16.5/0	6.217/5.815	6.48 (4.20 - 8.75)
Pre-Existing Type 2 Diabetes	All no pre-existing diabetes (Type 2)	0.5/0	5.751/5.706	0.79 (0.23 - 1.35)	0.5/0	5.874/5.782	1.56 (1.00 - 2.12)	0.6/0	6.217/6.175	0.68 (0.20 - 1.16)
Pre-Existing Hypertension	All no hypertension	1.1/0	5.751/5.626	2.18 (1.35 - 3.02)	1.2/0	5.874/5.778	1.63 (0.88 - 2.37)	1.2/0	6.217/6.091	2.03 (1.27 - 2.79)
Gestational Diabetes	All no gestational diabetes	3.7/0	5.751/5.638	1.97 (0.78 - 3.15)	5.5/0	5.874/5.665	3.56 (2.25 - 4.87)	8.2/0	6.217/5.958	4.16 (2.55 - 5.78)
ART	All conceived spontaneously	0.3/0	5.751/5.760	-0.15 (-0.33 - 0.03)	1.7/0	5.874/5.813	1.04 (0.31 - 1.76)	2.0/0	6.217/6.164	0.86 (0.10 - 1.62)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PAR, population attributable risk.

Appendix I: Estimated proportion of preterm birth attributable to reductions in selected risk factors, 2005-2019 (complete case analysis).

Risk Factor	CF Scenario	Risk Factor (%)		Preterm (%)		% PIF (95% CI)
		Actual	CF	Actual	CF	
Maternal Age	i) 25% of women <20 to 25-29 years	3.8	2.8	5.952	5.945	0.13 (0.07 - 0.19)
	ii) 25% of women ≥40 to 25-29 years	3.1	2.3	5.952	5.942	0.18 (0.13 - 0.22)
Smoking	i) 25% of smokers become nonsmokers	19.5	14.6	5.952	5.848	1.75 (1.68 - 1.83)
	ii) 50% reduction in the amount smoked	19.5	19.5	5.714	5.630	1.47 (0.95 - 1.98)
Alcohol Use	25% of alcohol users become nonusers	0.5	0.4	5.952	5.950	0.04 (-0.02 - 0.09)
Drug Use	25% of users become nonusers	3.2	2.4	5.952	5.931	0.35 (0.21 - 0.50)
Pre-Pregnancy BMI	i) 25% of underweight women become normal weight	4.2	3.2	5.952	5.947	0.09 (0.05 - 0.14)
	ii) 25% of obese and overweight women become normal weight	48.3	36.2	5.952	5.948	0.08 (-0.26 - 0.42)
	iii) women with BMI>25 lose 10% of their body weight	48.3	32.6	5.952	5.950	0.04 (-0.61 - 0.68)
Area-Level Income	i) 25% of women in quintile 1 receive incomes equivalent to quintile 3	18.5	13.8	5.952	5.924	0.48 (0.12 - 0.83)
	ii) 25% of women in quintile 1 receive incomes equivalent to quintile 2	18.5	13.8	5.952	5.925	0.46 (0.16 - 0.77)
Depression	25% of depressed women become non depressed	11.7	8.8	5.952	5.883	1.17 (0.88 - 1.46)
Pre-Existing Type 2 Diabetes	25% of women with type 2 diabetes become nondiabetic	0.5	0.4	5.952	5.939	0.23 (0.21 - 0.25)
Pre-Existing Hypertension	25% of women with hypertension become normotensive	1.2	0.9	5.952	5.926	0.44 (0.35 - 0.53)
Gestational Diabetes	25% of women with gestational diabetes become nondiabetic	5.9	4.4	5.952	5.904	0.82 (0.69 - 0.95)
ART	25% of infants conceived from ART become conceived spontaneously	1.4	1.0	5.952	5.944	0.15 (0.08 - 0.22)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PIF, population impact fraction.

Appendix J: Estimated proportion of preterm birth attributable to selected risk factors, by time period (complete case analysis).

		2005- 2009			2010- 2014			2010- 2015		
Risk Factor	**CF Scenario**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/ CF**	**% PIF (95% CI)**	**Risk Factor (%) Actual/CF**	**Preterm (%) Actual/CF**	**% PIF (95% CI)**	**Risk Factor (%) Actual/ CF**	**Preterm (%) Actual/ CF**	**% PIF (95% CI)**
Maternal Age	i) 25% of women under the age of 20 to 25-29 age group	4.7/3.5	5.751/5.751	-0.01 (-0.02 - 0.01)	4.3/3.3	5.874/5.860	0.23 (0.09 - 0.36)	2.42/1.81	6.217/6.210	0.11 (0.11 - 0.12)
	ii) 25% of women 40 or older to 25-29 age group	2.8/2.1	5.751/5.752	-0.01 (-0.09 - 0.06)	3.1/2.3	5.874/5.857	0.29 (0.14 - 0.44)	3.39/2.54	6.217/6.205	0.19 (0.06 - 0.33)
Smoking	i) 25% of smokers become nonsmokers	23.8/17.9	5.751/5.676	1.31 (0.67 - 1.94)	19.7/14.8	5.874/5.758	1.97 (1.45 - 2.50)	15.45/11.58	6.217/6.101	1.86 (1.06 - 2.67)
	ii) 50% reduction in the amount smoked	23.8/13.8	5.533/5.5129	0.36 (-0.13 - 0.86)	19.7/19.7	5.590/5.480	1.96 (1.35 - 2.57)	15.45/15.45	6.000/5.880	2.01 (0.57 - 3.46)
Alcohol Use	25% of users become nonusers	0.2/0.2	5.751/5.749	0.03 (0.01 - 0.06)	0.6/0.5	5.874/5.872	0.03 (-0.05 - 0.10)	0.65/0.48	6.217/6.214	0.04 (-0.02 - 0.11)
Drug Use	25% of users become nonusers	1.8/1.4	5.751/5.735	0.28 (0.11 - 0.44)	7.7/5.8	5.874/5.866	0.13 (-0.05 - 0.32)	4.92/3.69	6.217/6.182	0.56 (0.32 - 0.79)
Pre-Pregnancy BMI	i) 25% of underweight women become normal weight	4.0/3.0	5.751/5.748	0.05 (0.0 - 0.11)	4.4/3.3	5.874/5.869	0.08 (0.04 - 0.11)	4.22/3.16	6.217/6.211	0.10 (0.09 - 0.12)
	ii) 25% of obese and overweight women become normal weight	46.6/35.0	5.751/5.774	-0.39 (-0.96 - 0.18)	47.4/35.6	5.874/5.883	-0.16 (-0.70 - 0.37)	50.67/38.00	6.217/6.176	0.67 (0.01 - 1.32)
	iii) women with BMI>25 lose 10% of their body weight	46.6/32.4	5.751/5.799	-0.82 (-2.04 - 0.39)	47.4/31.7	5.874/5.897	-0.39 (-1.46 - 0.68)	50.67/34.78	6.217/6.154	1.01 (-0.04 - 2.07)
Area-Level Income	i) 25% of women in quintile 1 receive incomes equivalent to women in quintile 3	19.0/14.2	5.751/5.726	0.44 (-0.28 - 1.16)	18.2/13.6	5.874/5.832	0.70 (0.28 - 1.11)	18.25/13.68	6.217/6.200	0.27 (0.27 - 0.38)
	ii) 25% of women in quintile 1 receive incomes equivalent to women in quintile 2	19.0/14.2	5.751/5.721	0.53 (-0.28 - 1.35)	18.2/13.6	5.874/5.838	0.61 (0.12 - 1.10)	18.25/13.68	6.217/6.202	0.24 (-0.37 - 0.85)
Depression	25% of depressed women become non depressed	6.4/4.8	5.751/5.706	0.79 (0.74 - 0.84)	11.7/8.8	5.874/5.818	0.95 (0.45 - 1.45)	16.53/12.39	6.217/6.119	1.58 (1.23 - 1.92)
Pre-Existing Type 2 Diabetes	25% of women with type 2 diabetes become nondiabetic	0.5/0.3	5.751/5.741	0.18 (0.14 - 0.22)	0.5/0.4	5.874/5.854	0.34 (0.21 - 0.47)	0.57/0.42	6.217/6.208	0.14 (0.13 - 0.16)

Pre-Existing Hypertension	25% of women with hypertension become normotensive	1.1/0.8	5.751/5.724	0.47	(0.30 - 0.64)	1.2/0.9	5.874/5.852	0.37	(0.24 - 0.51)	1.16/0.87	6.217/6.188	0.48 (0.33 - 0.62)
Gestational Diabetes	25% of women with gestational diabetes become nondiabetic	3.7/2.8	5.751/5.726	0.45	(0.30 - 0.59)	5.5/4.2	5.874/5.825	0.83	(0.56 - 1.09)	8.23/6.17	6.217/6.153	1.03 (0.51 - 1.55)
ART	25% of infants conceived from ART become conceived spontaneously	0.3/0.2	5.751/5.7534	-0.03	(-0.06 - -0.01)	1.7/1.3	5.874/5.861	0.22	(0.09 - 0.35)	1.96/1.47	6.217/6.205	0.19 (0.05 - 0.33)

ART, assisted reproductive technologies; BMI, body mass index; CF, counterfactual; CI, confidence interval; PIF, population impact fraction.

Appendix K. List of equations

Equation 2.1. Levin's equation for the estimation of the proportion of a disease attributable to a risk factor in the counterfactual scenario of the risk factor of interest having a prevalence of zero[68]. 13

Equation 2.2. Average PAR/PIF equation for the estimation of the proportion of a disease attributable to a risk factor in a counterfactual of zero or reduced prevalence[70]…14

Equation 4.1. PAR/PIF equation for the estimation of the proportion of a disease attributable to a risk factor in a counterfactual scenario[70]. 34