Predicting Hypertension by Twenty Years Postpartum Using Perinatal Data

by

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Abstract

Study Design

For a population-based cohort of 90,316 women with deliveries recorded in the Nova Scotia Atlee Perinatal Database between 1988 and 2009, pregnancy-related data were linked with provincial administrative data to identify new diagnoses of hypertension. Cox regression was used to model the risk of hypertension and estimate hazard ratios for the associations between pregnancy factors and hypertension. The model was simplified through backwards elimination, then translated into a risk score.

Results

Hypertensive disorders of pregnancy were the strongest pregnancy-related predictors of hypertension, particularly if they recurred in more than one pregnancy. Other pregnancy-related predictors included parity, gestational diabetes, and breastfeeding. The ability of this simplified model to discriminate women who developed hypertension from those who did not was moderate (c-statistic = 0.72).

Conclusion

Individualized predictions of hypertension risk up to 20 years after pregnancy can be generated from clinical information routinely available at the time of pregnancy.

List of Abbreviations Used

AIC	Akaike Information Criterion
BMI	Body Mass Index
CARDIA	Coronary Artery Risk Development in Young Adults Study
CCHS	Canadian Community Health Survey
CCDSS	Canadian Chronic Disease Surveillance System
CI	Confidence Interval
CIHI	Canadian Institute of Health Information
CRP	C-reactive Protein
DAD	Discharge Abstract Database
DBP	Diastolic Blood Pressure
GDM	Gestational Diabetes Mellitus
GERD	Gastroesophageal Reflux Disease
GHTN	Gestational Hypertension
HCN	Health Card Number
HDNS	Health Data Nova Scotia
HDP	Hypertensive Disorders of Pregnancy
HR	Hazard Ratio
ICD	International Classification of Disease
IOM	Institute of Medicine
LGA	Large for Gestational Age
MSI	Medical Services Insurance Program
NHANES	United States National Health and Nutrition Examination Survey
NICE	National Institute for Clinical Excellence
NSAPD	Nova Scotia Atlee Perinatal Database
OR	Odds Ratio
r	Pearson's correlation coefficient
RCP	Reproductive Care Program of Nova Scotia

SBP	Systolic Blood Pressure
SGA	Small for Gestational Age
SOGC	Society of Obstetricians and Gynecologists of Canada
T2DM	Type 2 Diabetes Mellitus
USA	United States of America

Chapter 1 - Introduction

Hypertension represents an increasing threat to the health of modern populations, with sequelae that include heart attack, renal disease, stroke, and death (1,2). With the rates of hypertension increasing (3), and increasing disproportionately in young people (4), significant efforts continue to be directed at identifying and treating hypertension to reduce its long-term sequelae. Overall, women experience hypertension more frequently than men (5), and yet are dramatically under-represented in existing studies aimed at predicting individuals at high risk of hypertension (6). Furthermore, women experience unique risk factors including hypertensive disorders of pregnancy (7), preterm birth (8), or other complications of pregnancy (9,10), which have well-documented associations with future hypertension. While numerous guidelines recommend that sex-specific risk factors such as preeclampsia be considered in evaluating a woman's overall risk of hypertension and its sequelae (11–13), guidance as to how to weigh pregnancy-related risk factors against traditional risk factors to evaluate a woman's overall risk is lacking. Furthermore, limited data regarding the absolute risk of hypertension in high- and low-risk young women exist to guide recommendations around the frequency of screening in these populations. Currently, recommendations concerning the screening for hypertension in young Canadian women remain vague. For example, the Canadian Task Force for Preventative Health recommends screening for hypertension "at all appropriate health care visits" (14), with no guidance regarding a minimum frequency for hypertension screening in asymptomatic young women who might otherwise have little reason to be in regular contact with the health care system outside of pregnancy. Accurate data regarding the incidence of hypertension in young women at average or high risk would inform recommendations regarding optimal screening strategies in this population.

Study Objectives

The objectives of this study were:

1) to describe the risk of hypertension in a population-based cohort of women followed for twenty years after their first pregnancy,
2) to describe the associations of pregnancy-related conditions with future hypertension risk, and,
3) to develop a user-friendly tool to predict women's risk of developing hypertension within twenty years postpartum using clinical data available at the time of pregnancy.

Chapter 2 - Background and Study Rationale

Hypertension

As an independent risk factor for heart failure, coronary artery disease, stroke, renal disease, peripheral arterial disease, and dementia (1,2), hypertension is implicated in 13-15% of all deaths (1) and is a leading cause of disability worldwide (15). In the year 2000, hypertensive heart disease was estimated to cost approximately 2.3 billion dollars in Canada alone when the costs of hospital care, drugs, physician care, premature death and long term disability were taken into account (16).

In recent history, hypertension has increased disproportionately in younger adults. Between 1994 and 2005, the overall Canadian population saw a 77% increase in the prevalence of hypertension, while the increase was 127% in adults aged 35 to 49 and 261% amongst young Canadians aged 12-34 (4). Furthermore, young adults had worse awareness, treatment, and control of their hypertension compared with older adults in the 1999-2014 National Health and Nutrition Examination Surveys (NHANES) in the United States of America (USA) (17). The shifting demographics of the "at risk" population, along with the high prevalence of risk factors such as physical inactivity and elevated body mass index (BMI) (16), are converging in what the Canadian Heart and Stroke Foundation has called "a perfect storm" that threatens to create an "unprecedented burden" on Canada's cardiovascular care system (18). Hypertension is highly amenable to both primary and secondary prevention (18). Changes in lifestyle can reduce the incidence of hypertension (19), and lifestyle interventions or pharmacologic therapy can reduce its associated morbidity and mortality (20), but only if these are effectively prioritized and implemented.

Defining a Threshold for Hypertension Diagnosis

Given that incremental increases in blood pressure above approximately 115 mmHg systolic or 75 mmHg diastolic are associated with a continuously increasing risk of

adverse effects (1), any threshold-based definition of hypertension is somewhat arbitrary. Canadian guidelines recommend diagnosis and treatment of hypertension when systolic blood pressure exceeds 140 mmHg or when diastolic blood pressure exceeds 90 mmHg on the average of five readings at a physician's office (15), consistent with definitions recommended in the US (21) and Europe (22). In some patients, for example those with diabetes, the recommended thresholds for treatment are lower (23). Fewer readings are required for a diagnosis of hypertension if the blood pressure readings are very high. For example, only two evaluations are required if the systolic blood pressure is ≥180 mmHg or the diastolic is ≥110 mmHg (15).

Although the blood pressure thresholds for defining hypertension are relatively consistent between studies, epidemiologic studies of hypertension have variably defined hypertension by patient self-report (24), administrative data (25), chart review, history of antihypertensive medication use (26), or measuring blood pressure directly (27). When blood pressures have been measured directly to diagnose hypertension for research purposes, fewer measurements are generally taken than the recommended criteria for a clinical diagnosis (28–32).

Validity of Administrative Data to Ascertain Hypertension

The International Statistical Classification of Diseases and Related Health Problems (ICD) provides a set of standardized diagnostic codes that can be used to compare causes of morbidity and mortality in different settings, and has been in place since 1900 (33). The ninth and tenth revisions were made in 1979 (ICD-9) and 1992 (ICD-10). A Canadian modification has produced ICD-10-CA codes that provide additional detail regarding diagnoses through the addition of digits to the existing ICD-10 codes (33). The accuracy of hypertension diagnosis based on ICD codes from Canadian administrative databases has been well established (34,35).

Administrative data can be used to identify cases of hypertension in Canadians. When provincial health insurance registries, hospital discharge abstracts, physician billing

claims and vital statistics files from six Canadian provinces were used to identify new cases of hypertension, the majority (87.4%) of cases were identified from physician billings claims, with the remaining cases coming from hospital discharge data (9.8%) or both sources (2.8%) (5).

Canadian physician billing records are highly sensitive and specific for the diagnosis of hypertension. A range of administrative case definitions for hypertension, based on one or two physician billings claims recorded within one to three years, with or without the additional criteria of a hospital discharge code, have been compared against a detailed chart review that was considered the reference standard (35). Hypertension was considered to be present in the chart review if either a physician-assigned diagnosis was recorded, an antihypertensive medication was prescribed in the context of an elevated blood pressure reading, or blood pressures that met the Canadian Hypertension Education Program guidelines were recorded. The overall agreement between administrative data and chart review was >80% for all case-definition algorithms. Physician-billing case definitions that required more than one claim for a diagnosis of hypertension resulted in higher specificity and positive predictive value, while adding claims over a longer period resulted in a greater sensitivity. The definitions with the highest specificity were "two physician-billing claims" or "two physician-billing claims or one hospital discharge" in one year, or "two physician-billing claims in two years". Applying those definitions over two instead of one years' time significantly improved the sensitivity of the administrative case definitions compared to the chart review standard. The sensitivity of the administrative case definition was significantly higher when the case definition was satisfied by either one hospital discharge or two physician billings claims, or both, over two years' time.

Canadian hospital discharge records are moderately sensitive and highly specific at identifying cases of hypertension. When the discharge diagnoses coded (with ICD-10 codes) for administrative purposes from 4,008 Alberta hospital admissions were compared to an independent chart review for the diagnosis of hypertension, the administrative data had a 68% sensitivity, 97.8% specificity, 87.7% negative predictive

value, and 93.1% positive predictive value (33). When comparing the administrative case-definition algorithms to self-reported diagnosis of hypertension, the administrative case-definition of "two physician-billing claims or one hospital discharge over two years" was highly concordant with the self-reported diagnoses measured by the Canadian Community Health Survey (CCHS) (35). The Canadian Chronic Disease Surveillance System (CCDSS) uses this definition (36). When the accuracy of "two physician billing claims or one hospital discharge claim in two years" recorded in administrative data from in Alberta and British Columbia was evaluated using a review of physicians' charts as the reference standard, this definition demonstrated its validity with a reported sensitivity of 75%, specificity of 94%, positive predictive value of 81% and negative predictive value of 92% (37). The prevalence of hypertension measured by this CCDSS definition has been compared self-reported diagnosis of hypertension in the 2007/2008 CCHS, and data from the 2007/2008 Canadian Health Measures Survey where the diagnosis of hypertension came from a combination of self-report and measured blood pressures. All three sources produced very similar estimates of the prevalence of hypertension, ranging from 18.2% to 20.3% (38).

Traditional Risk Factors for Hypertension

Traditional risk factors for hypertension include both non-modifiable attributes such as age, race, and family history, modifiable attributes such as smoking habits, income and education, BMI, and the presence of other disease such as diabetes. The strength of the associations between several traditionally-described risk factors and hypertension are summarized in Table 1.

Cigarette Smoking

The association between smoking status and hypertension has been debated in the past few decades. While some studies have shown increased rates of prehypertension and hypertension, and higher ambulatory blood pressures in smokers compared with non-smokers (39–41), others have shown no independent association between smoking and

hypertension (31,42,43). Biologically plausible mechanisms by which smoking may promote hypertension include its effects on adrenergic activity (39), renal function (40), and its ability to cause damage to the vascular endothelium and trigger endothelial dysfunction (44). By contrast, potential confounding factors such as obesity (41,43,45) are differentially distributed between smokers and non-smokers (16), making it difficult to assess the nature of any observed association between smoking and hypertension. The Coronary Artery Risk Development in Young Adults (CARDIA) study, a prospective community-based cohort study investigating predictors of cardiovascular disease in young adults in the USA, found positive association between current smoking and hypertension, with an adjusted hazard ratio (HR) of 1.35 (95% CI 1.18-1.54) (46). By contrast, the association between current smoking and hypertension was not significant in a study of NHANES survey data, also from the USA, with an adjusted odds ratio (OR) of 1.0 (95% CI 0.6-1.4) (31). Whether or not the sometimes-observed association is due to a causal relationship, smoking status may serve as a predictor of hypertension and is included in several of the current hypertension risk prediction tools (47,48).

Age

Age has consistently been shown to be a key determinant of hypertension risk (4,49,50). In a study of the epidemiology of hypertension in women aged 20 to 44 in the USA, based on NHANES survey data, age was the risk factor most strongly associated with hypertension. As compared to women aged 20-34 in that study, women aged 35-39 had three times the odds of hypertension (OR 3.3, 95% CI 2.1-5.2), and women aged 40-44 had eight times the odds (OR 8.2, 95% CI 5.0-13.3) (31).

Diabetes

A strong relationship between diabetes and hypertension is well established and complex, involving interactions between genetic predisposition, lifestyle factors (such as diet and sedentary behaviour), biological factors (such as sodium retention), abdominal obesity, autonomic function, and other underlying physiological processes in both conditions (23).

In the above-mentioned study of hypertension using NHANES survey data, diabetes was associated with hypertension with a multivariable adjusted OR of 3.4 (95% CI 1.9-6.1) (31).

Obesity

Obesity has also been consistently associated with hypertension, with a "dose-dependent" relationship between BMI and hypertension risk in epidemiologic studies. In the Framingham Heart Study, obese individuals (BMI ≥30) were three times more likely to have hypertension than those with normal blood pressure and the prevalence of hypertension among participants increased with each BMI category (51). In the NHANES data, the prevalence of hypertension increased nearly linearly with increasing BMI; the only risk factor more strongly associated with hypertension than BMI was age (31). The epidemiologic associations are supported by an emerging understanding of the underlying biologic mechanisms. Adipocytes have been shown to produce angiotensinogen, leading to vasoconstriction and increased blood pressure. Other mediators in the renin-angiotensin pathway affect the differentiation of adipocytes, leading to dysfunctional large adipocytes that produce more mediators of obesity-associated hypertension. Large adipocytes also produce inflammatory cytokines, reactive oxygen species and hormones that are thought to influence other mediators of cardiovascular disease in a complex interaction between hypertension and obesity (52).

Over the past 30 years, overweight and obesity have become increasingly common in Canada (16) and worldwide (53). From 2004-2011, approximately 46% to 47% of Nova Scotian women who became pregnant had BMIs classified as overweight or obese (54). Because obesity is the most strongly associated modifiable risk factor for hypertension, it is of particular interest in risk prediction.

Hypertension in Canadian Women

Both biological and behavioral risk factors contribute to different patterns of hypertension in women than in men. While the risk of hypertension is slightly higher in men than in women prior to the age of 50, this pattern is reversed as women age (55) and overall, more women than men are diagnosed with hypertension in Canada (5). Women in Nova Scotia are at particular risk, with an age-standardized prevalence of hypertension of 23.6% in women over 20 years between 2006-2007, exceeding the national average of 19.8% (55). While hypertensive women are more likely to be aware of their diagnosis than hypertensive men, there are still significant gaps in awareness, particularly amongst young adults (56).

Modifiable risk factors for hypertension are common in Canadian women, with 52.5% reporting physical inactivity in their leisure time and 60% reporting excess sodium consumption (16). Although central obesity, high total cholesterol, and low high-density lipoprotein concentrations are risk factors for hypertension in both sexes, these conditions are more prevalent in women than men (57). Hypertension may also affect young women in different ways than it does men, as target organ damage (i.e., microalbuminuria and left ventricular hypertrophy) have been reported to occur more commonly in hypertensive women aged 18 to 45, as compared with hypertensive men (58).

Pregnancy-Related Risk Factors for Hypertension

Younger women appear to experience hypertension risk differently than older women. Not only does overall risk of hypertension change with age, climbing in women around the average age of menopause, (55) but the risk factors for hypertension also appear to differ between populations of younger, predominantly premenopausal women compared with older women. Pregnancy-related risk factors have been more strongly associated with hypertension in younger women. In the NHANES study cohort, an overall increased risk of hypertension was described in women who delivered low birth weight

infants as a result of preterm delivery (8). In subgroup analyses, this association was mainly confined to premenopausal women and was not statistically significant in menopausal women or in women whose last pregnancy was greater than 10 years earlier (8). The association between breastfeeding and hypertension has also been described to differ in women less than 50 years of age (expected to be predominantly premenopausal), as compared with women over 50 years of age. While breastfeeding for at least 24 months (cumulative) was associated with a strong protective effect in the younger women with an OR of 0.53 (95% CI 0.40-0.79), a weaker association was observed in the older women with an OR of 0.79 (95% CI 0.61-1.04) (59).

Due to the profound physiologic changes it elicits, pregnancy is frequently described as a physiological "stress test" (60–62) with the potential to unmask a predisposition for later-onset disease. Pregnancy outcomes have been associated with a host of future cardio-metabolic conditions including cardiac death, stroke, diabetes, and hypertension (60,63,64). In the case of hypertension, it is unknown whether pre-existing subclinical vascular changes or pre-existing risk predispose to both complications in pregnancy and future vascular disease, or whether it is the complications in pregnancy trigger vascular changes that lead to future hypertension, or both (62,65). Regardless of the nature of the association, pregnancy outcomes may serve to predict future hypertension outside of pregnancy.

Hypertensive Disorders of Pregnancy

In Canada, terminology surrounding pre-existing hypertension, gestational hypertension, and preeclampsia are defined by the Society of Obstetricians and Gynecologists of Canada (SOGC), and were last updated in 2014 (66). In the current Canadian classification, hypertension that pre-dates pregnancy, or is diagnosed before 20 weeks of pregnancy, is classified as pre-existing hypertension. Hypertension that develops at ≥20 weeks' gestation is considered gestational hypertension (66,67). If either gestational hypertension or pre-existing hypertension are accompanied by indicators of organ dysfunction (such as new onset proteinuria and/or clinical symptoms and/or laboratory

abnormalities of the haematological, hepatic, cardiorespiratory, renal and nervous systems), preeclampsia is diagnosed. The Canadian Hypertension Society classifications (last updated in 1997) do not include the term "preeclampsia", but classify gestational hypertension as with or without proteinuria, and with or without adverse conditions (67).

An association between preeclampsia and long-term risk of hypertension has been documented as far back as 1961 (68), and contemporary epidemiologic studies consistently demonstrate this association. Two meta-analyses, published in 2007 and 2013, have found relative risks of 3.70 (95% CI 2.70-5.05) (69) and 3.13 (95% CI 2.51-3.89) (7) for hypertension after a pregnancy complicated by preeclampsia indicating an association at least as strong as most traditional risk factors for hypertension (see Table 1). Approximately 5-6% of pregnancies are complicated by gestational hypertension, and 1-2% are complicated by preeclampsia (66). Similarly, in Nova Scotia, the incidence of gestational hypertension with significant proteinuria ranged from 1.4 to 1.9% of pregnancies between 2002 and 2011 (54). Preeclampsia is more common in a first pregnancy than in subsequent pregnancies, with preeclampsia recurring in only about 15% of women. Recurrent hypertensive disorders have been associated with an increased risk of future hypertension (70).

Although the pathophysiology of hypertensive disorders of pregnancy is complex, multifactorial, and incompletely understood, it is believed to involve a mismatch between the utero-placental blood supply and fetal demand (66). This ultimately results in the production of soluble factors that cause activation and dysfunction of the endothelial cells in maternal blood vessels, leading to generalized vasoconstriction and altered blood flow (66,71). Although antihypertensive medications given in pregnancy reduce the immediate risks of uncontrolled hypertension, only delivery of the infant and placenta resolve the condition (66).

While gestational hypertension and preeclampsia generally resolve by 6 weeks to 6 months postpartum (66), several markers of inflammation, thrombosis, and angiogenesis are reported to remain persistently abnormal years after delivery (71,72). It is

hypothesized that an ongoing risk of hypertension and cardiovascular disease in women with a history of preeclampsia is at least in part related to activity of these factors and the accompanying endothelial dysfunction (71). Whether gestational hypertension and preeclampsia represent a spectrum of the same disease process with preeclampsia representing the more severe state, or whether the two conditions develop through different mechanisms, remains contentious (73). The majority of studies describing associations between hypertensive disorders of pregnancy and future hypertension have either focussed only on a history of preeclampsia or have looked at hypertensive disorders as a group without isolating the association of gestational hypertension in the absence of preeclampsia.

Presently several clinical bodies, including the American Heart Association (74), SOGC (66), and the United Kingdom's National Institute for Clinical Excellence (NICE) guidelines (75) suggest that a history of hypertensive disorders in pregnancy be considered as part of the overall assessment of a woman's cardiovascular disease risk, though evidence or guidelines for how these should be incorporated or what (if any) further screening should be initiated is lacking.

Preterm Birth

Preterm birth is the most common cause of low birth weight in developed countries (76) and may develop spontaneously or be iatrogenic (generally due to a complicated pregnancy). A history of preterm delivery has been associated with hypertension in cohorts from several developed countries, including the United States (8), United Kingdom (77), Sweden (78) and Norway (26). Inflammation and endothelial activation have been implicated in the pathogenesis of spontaneous preterm birth (79), as well as in the pathogenesis of hypertension (80). Some (81–83), but not all (84), studies have shown a persistent elevation in the inflammatory marker C-reactive protein (CRP) in women with a history of preterm birth.

Small for Gestational Age

The term small for gestational (SGA) age refers to infants whose growth falls beneath the 10th percentile for gestational age and sex (85). The most common cause of pathological fetal growth restriction in the third trimester is under-perfusion of the utero-placental unit (86). Delivery of a SGA baby is associated with an increased risk of hypertension (10,87) in some, but not all (8), studies. A Danish registry-based study of 782,287 women demonstrated an increased risk of hypertension in women with SGA babies with hazard ratios up to 1.24 (95% CI 1.16-1.32) for mothers of babies with fetal growth 2.0 to 3.0 standard deviations below the mean (87). Delivery of a SGA infant was also associated with an increased risk for other cardiovascular disease in that and several other studies (87–90).

Large for Gestational Age

The term large for gestational age (LGA) refers to infants weighing greater than the 90th percentile for gestational age and sex. Independent risk factors for fetal overgrowth include pre-gestational BMI and pre-gestational diabetes, each established traditional risk factors for hypertension, as well as excessive weight gain during pregnancy and gestational diabetes (91). Only a few studies have examined the association between delivery of a LGA infant and hypertension or cardiovascular disease, with conflicting results. The large Danish study cited above also noted an association between gestational age-standardized birthweight of 2.0 to 3.0 and ≥3.0 SD above the mean and hypertension, with HRs of 1.17 (95% CI 1.01-1.35) and 1.38 (95% CI 1.04-1.84) (87). By contrast, a Swedish registry-based study demonstrated no association between delivery of a LGA infant and subsequent maternal cardiovascular disease (76).

Stillbirth

In Canada, rates of stillbirth (the death of a fetus more than 20 weeks' gestation, or more than 500 g prior to birth) range from 4 to 5 per 1000 total births (92). Between 4% and

9% of stillbirths are attributable to pre-existing hypertension (93). Stillbirth may also indicate a severe case of other pregnancy conditions thought to be associated with hypertension, such as preeclampsia (94), placental abruption, or pathological growth restriction (93). Although the risk for subsequent hypertension in women with a history of stillbirth has not yet been well-studied, stillbirth in a first pregnancy has been associated with an increased risk of future cardiovascular disease (76).

Placental Abruption

Approximately 1% of pregnancies in Nova Scotian women are complicated by placental abruption (54). Abruption refers to the premature separation of the placenta from the uterus. Depending on its extent, placental abruption can be associated with a range of clinical presentations during pregnancy, from mild to life threatening. Abnormal development of the spiral arteries at the utero-placental interface is associated with placental abruption and infarction, along with hypertensive disorders and fetal growth restriction, leading some authors to group these conditions together with terms such as "maternal placental syndromes" (95) or "ischemic placental disease" (96,97). The abnormal transformation of the spiral arteries is associated with the release of mediators that affect vascular function locally and sometimes systemically (97). Placental abruption and/or infarction has been associated with an increased risk of cardiovascular disease in the long term (98,99). Few studies have looked at the association between placental abruption and hypertension; in one Swedish cohort study, although it was not associated with a higher adjusted odds for hypertension, placental abruption was associated with a higher measured diastolic pressure (78).

Parity

Parity has been variably associated with hypertension in different populations. For example increased parity (parity ≥ 2 compared with nulliparity) was associated with a small increased age-adjusted HR for subsequent hypertension in a Norwegian cohort study (26), while primiparity was not. By contrast, in both the CARDIA study and a

Swedish cohort study, increased parity was associated with lower postpartum blood pressure (46,78). Increasing parity has also been variably associated with risk of mortality from hypertensive diseases and the incidence of diseases of the circulatory system such as ischemic heart disease (64,100). These associations may be at least partially related to environmental and behavioural factors as indicated by the fact that the number of children fathered by a man has also been associated with an increase in cardiovascular disease (101). In British men and women aged 60 to 79, a "J-shaped" association between the number of children and risk of coronary heart disease was seen, with parents of two children having the lowest risks, although the association was attenuated by adjusting for metabolic and lifestyle factors (102).

Gestational Weight Gain

More than half of Nova Scotian women experience gestational weight gain that would be considered excessive according to Health Canada guidelines, (54) and this may have long-term impacts on maternal cardiac and metabolic health. Excess weight gain in pregnancy is associated with retention of that weight in the short term, with long term excess weight ≥ 15 years postpartum (103), and with visceral fat accumulation (104) in mothers. As these are established risk factors for hypertension in women, excess gestational weight gain may be a useful predictor of future hypertension risk readily identified in the perinatal period. The relationship between gestational weight gain and hypertension in women may be complicated by the fact that women who are already overweight or obese prior to pregnancy are more likely to experience excess gestational weight gain (105).

Breastfeeding

Although the majority of Nova Scotian mothers are breastfeeding at the time of hospital discharge (75-76% in 2008-2009) (54), significantly fewer women continue breastfeeding beyond six weeks postpartum (106). In a survey of all mothers of singleton newborns born in 2008/2009 in the Cape Breton District Health Authority and Guysborough

Antigonish Straight Health Authority, only 48.2% reported breastfeeding at one to six weeks postpartum and 26.4% reported breastfeeding beyond six weeks postpartum (106).

Breastfeeding has been associated with postpartum weight loss in several high-quality studies, although this result has not been consistent across the literature (107). In a study of healthy US women aged 45-58 years, women who never breastfed not only had higher BMIs, but had 40% greater visceral adiposity (as measured by CT imaging) than women who had breastfed all their children for at least three months (108). Breastfeeding may therefore be expected to exert an effect on future hypertension risk by altering maternal weight and energy expenditure (109), glucose tolerance and lipid metabolism, (110) and inflammatory markers such as CRP (111). Several of the hormones involved in lactation, including oxytocin, prolactin, and cortisol affect blood pressure (110). It is therefore biologically plausible that breastfeeding may contribute causally and thereby help predict a woman's future risk of hypertension.

In epidemiologic studies, breastfeeding has been associated with a decreased risk of later hypertension in a dose-dependent manner. When breastfeeding was defined by self-reported history, nursing for a total of at least 24 months was associated with an OR for hypertension of 0.53 (95% CI 0.40-0.79), while nursing for shorter durations was protective to a lesser magnitude (59). The negative association between breastfeeding and hypertension has similarly been described in ethnically and geographically diverse populations from the United States (112,113), Norway (59), and Korea (114). It is possible that breastfeeding also represents a marker for other unmeasured behaviours, which confounds the association between breastfeeding and hypertension (115). Even if this is the case, in whole or part, it does not detract from the potential for breastfeeding to predict future hypertension.

Predicting Future Hypertension

The first multivariable model to predict the onset of hypertension, the Hopkins score, was published in 1990 (24). Since then, more than 16 different tools to predict hypertension

have been published (27,30,47,50,116–118), yet only the Framingham hypertension risk prediction score (50) was developed in a population that included women younger than 35 years old (6). Risk factors included in existing risk prediction tools for hypertension are summarized in Table 2, and include measures of: age, current and/or previous blood pressure, family history of hypertension, BMI, smoking, ethnicity, diet, dyslipidemia, alcohol use, sedentary lifestyle and serum biomarkers (6). None of the published tools evaluated the impact of obstetrical history as a predictor of hypertension.

The discriminative ability of each of the existing risk prediction tools is acceptable to good, with c-statistics (area under the receiver operator curve) that range from 0.70 to 0.80 (6). Only two of the currently available tools, the Framingham hypertension risk prediction score and the Hopkins score have been externally validated, with c-statistics ranging from 0.71 to 0.84 (32,46,116). When the Framingham hypertension risk prediction score was validated in US participants of the Multi-Ethnic Study of Atherosclerosis, it had a reasonable ability to discriminate between individuals' different risks of incident hypertension (c-statistic 0.78, 95% CI 0.77-0.80). However, this represented only a small and not statistically significant improvement over measuring systolic blood pressure on its own (c-statistic 0.77 95% CI 0.75-0.79]) (32). While existing tools indicate the potential for multivariable regression methods to develop successful risk prediction models, they also indicate room to improve the performance of these models.

Value of Prognostic Information for Women at Risk of Hypertension

Identifying women at risk of developing hypertension and potentially more serious cardiovascular disease should be an urgent goal. Because hypertension is most often asymptomatic until complications are established (15), effective screening is necessary to recognize and treat this condition. Hypertension is common, and carries serious risks that can be effectively reduced through physical exercise, weight reduction, reduced alcohol consumption and dietary changes (15).

Hypertension awareness remains suboptimal in the general Canadian population, with almost one in five Canadians with hypertension being unaware of their condition (119). The Canadian Task Force on Preventive Health Care recommends blood pressure measurement at all appropriate primary care visits (14); however, routine physical exams are not recommended and are not insured services in Nova Scotia (120), therefore "appropriate primary care visits" to assess blood pressure in asymptomatic women are likely to be infrequent. At present, the only primary care visits that are routinely indicated in otherwise young, asymptomatic (and non-pregnant) women may be for cervical cancer screening which is currently recommended every three years in low risk women (121). There is a lack of evidence to guide what screening interval should be recommended in young women at average and higher risk for hypertension, and current screening recommendations may be inadequate. Since there is strong evidence that treating hypertension can reduce mortality from cardiovascular events, particularly stroke (20), recognizing hypertension in any susceptible population must be a priority.

Interventions directed towards high-risk individuals have been shown to effectively reduce hypertension and future cardiovascular disease (i.e., "primordial prevention"). For example, in the Trials of Hypertension Prevention, Phase II, women with elevated BMI received interventions including counselling targeted towards weight loss, reducing sodium intake, or both. Four years after the intensive intervention, the relative risk of hypertension was 0.85 for individuals who received the combined intervention, and 0.86 for individuals who received the sodium reduction intervention, both of which were statistically significant compared with the usual care group (122) and indicate the potential for targeted interventions to reduce the incidence of hypertension. In Nova Scotia, participants of the ANCHOR study (123) (A Novel Approach to Cardiovascular Health by Optimizing Risk Management) received an individualized assessment of their cardiovascular risk based on a modification of the Framingham Risk Score for cardiovascular events. Those in the moderate and high-risk categories received behavioural change counselling and, if needed, pharmacological intervention for twelve months. Nearly all modifiable risk factors for cardiovascular disease improved and a significant proportion of patients had shifted categories to a lower Framingham Risk

Score for cardiovascular events by the study end. Although comparison to a control group was not possible in this study, (123) its findings support the potential for targeted interventions to reduce the risk of hypertension and cardiovascular disease in high risk individuals.

Hypertension commonly clusters with other cardiovascular risk factors, further increasing the risk of stroke, diabetes, heart disease and mortality (22). Insulin resistance, abdominal obesity, hypertension and dyslipidemia often coexist as the "metabolic syndrome" (124), and even non-obese individuals with hypertension are at increased risk of insulin resistance (125). Identifying individuals with or at risk of hypertension may also prompt improved screening of these individuals for other serious, treatable conditions, magnifying the benefit of identifying these women.

Pregnancy as a Teachable Moment

Pregnancy is an important transition point in a woman's life and can be a time of positive lifestyle changes that last beyond the pregnancy itself (126). However, pregnancy alone is often not sufficient incentive without additional interventions (127). Qualitative studies have demonstrated that the majority of women with preeclampsia were unaware of the association with future cardiovascular disease, but were eager to learn and to take steps to reduce their risk (128).

Recognizing the need to intervene in groups at high risk of future cardiovascular disease, an interdisciplinary clinic was established in Alberta in 2010 to follow women with a recent diagnosis of preeclampsia. Their primary goals were patient education regarding long term health implications following preeclampsia, assessment, and management of modifiable cardiovascular risk factors through counselling about lifestyle modifications such as diet and exercise, and with pharmacologic therapy if necessary (129). Even in a small cohort followed for a short time, they were able to show a significant increase in the number of women who reported participating in regular physical activity, from 19% of women reporting participating in regular physical activity pre-pregnancy to 76.2% of

the women being followed up in clinic at six months. A small decrease in BMI was reported in that cohort, although it was not statistically significant (129).

These findings emphasize not only the potential for pregnancy to serve as a window for positive lifestyle changes, but also the importance of developing a tool that effectively identifies young women at high risk of future hypertension so that they can receive adequate education and support after delivery to reduce their risk of hypertension and its serious sequelae. While preeclampsia has been singled out as a trigger for referral to postpartum counselling clinics in Canada (129,130), it is unclear how to best incorporate this and other known risk factors to identify women most likely to benefit from counselling and intervention postpartum to reduce their risk of future hypertension. Incorporating pregnancy-associated risk factors with traditional risk factors to produce a risk prediction tool for hypertension that is relevant to young women may fill this void.

Chapter 3 - Methods

Study Design and Cohort

A historical cohort study was designed to determine whether data routinely collected during pregnancy could predict a diagnosis of hypertension in the twenty-year period following pregnancy. This cohort included all Nova Scotian women aged less than or equal to 55 years at the time of their first delivery, who gave birth for the first time between January 1st, 1988 and December 31, 2009 to babies weighing at least 500 g and achieving at least 20 weeks of gestational age at delivery. The cohort was followed via administrative data through to December 31, 2014, to determine if and when they developed hypertension. Women with a diagnosis of hypertension, recorded on the prenatal record at the time of pregnancy or identified through administrative data, prior to the onset of their first pregnancy were excluded from the cohort. Perinatal data were obtained from the Nova Scotia Atlee Perinatal Database (NSAPD), while data concerning follow-up time and the outcome of hypertension were obtained from four provincial administrative databases: Vital Statistics, Registry of Insured Persons, Medical Services Insurance (MSI) Physicians Billings, and the Canadian Institute for Health Information (CIHI) Hospital Discharge Abstract Database (DAD). The cohort was restricted to women who remained covered under the provincial insurance plan (MSI) for at least two years following their first pregnancy to ensure this minimum period of follow-up for each woman. Nova Scotian women covered under federal health insurance plans and not MSI were excluded from the cohort.

Data Linkage

Relevant variables from the five data sources (NSAPD, Vital Statistics, Insured Patient Registry, CIHI DAD and MSI Physician Billings) were linked at the individual level by Health Data Nova Scotia (HDNS). This linkage was achieved through a crosswalk file maintained by Medavie Blue Cross with encrypted individual health card numbers (HCNs). Health Data Nova Scotia maintains access to CIHI Hospital Discharge Abstract

Database on behalf of CIHI as well as Nova Scotia Vital Statistics data on behalf of the provincial Department of Health and Wellness. Data from the NSAPD were transferred from the Reproductive Care Program of Nova Scotia (RCP) to HDNS, who carried out an individual-level linkage of these databases using the encrypted patient HCNs and who provided a de-identified dataset to our research team for analysis. The variables included in the dataset used for analysis included a study identifier for each mother, the start and end dates for each follow-up period, date of death or end of MSI coverage, variables specifying the diagnosis of hypertension, and variables describing candidate predictors that were pre-selected as plausible predictors of hypertension.

Sample Size and Power Calculation

Between 1988 and 2009, there were 98,094 mothers whose first deliveries were recorded in the NSAPD. Based on previous work linking the NSAPD database with the CIHI and MSI databases for Nova Scotia mothers who delivered between 1991 and 2003, approximately 92% (90,270 women) were expected to have their records linked successfully (131). Approximately 1% of Nova Scotia mothers were expected to be excluded due to pre-existing hypertension at the time of pregnancy, leaving approximately 89,378 women for analysis. From an estimated prevalence for hypertension of 6.1%, 5,451 cases of hypertension were expected during the study period. A priori, the study thus had a power of 80% to detect HRs less than 0.93 or greater than 1.08 with statistical significance, accepting a type 1 error rate < 0.05.

Potential Predictors of Hypertension

Candidate predictors of hypertension in this analysis included the traditional risk factors for hypertension available from the data sources, pregnancy outcomes potentially associated with an increased risk of hypertension or cardiovascular disease, and demographic variables that may serve as indicators of individuals' lifestyle or health status.

Demographic variables collected by the NSAPD that were considered as potential predictors of hypertension included: year of delivery, month of delivery, quintile of annual income per person equivalent (132), urban residence, and marital status. Traditional risk factors for hypertension or cardiovascular disease that we considered included: age, pre-pregnancy weight, pre-existing diabetes mellitus, pre-existing renal disease complicating pregnancy, and smoking status during pregnancy.

A woman was considered to have diabetes preceding pregnancy if any diagnosis of diabetes (type 1 or type 2 or diabetes mellitus with type unspecified, or White Classification B, C, D, F or R) was recorded as a pre-existing condition in the NSAPD, or if such a diagnosis was identified from the administrative data (even if not also noted in NSAPD). A diagnosis of diabetes was considered to have occurred when ≥ 1 hospitalization or ≥2 physician claims for diabetes were identified from the administrative data sources within two years and at least 120 days prior to the onset of her pregnancy, consistent with the definition used by the CCDSS (36). Although smoking status is captured by the NSAPD prior to and at various time points during pregnancy, to avoid the inclusion of multiple variables that provided overlapping information and to minimize missing values, smoking status was treated as a single binary variable where a woman was considered to have smoked in her pregnancy if the number of cigarettes smoked per day was recorded as greater than zero at one or more of the initial prenatal assessment, the twenty week assessment, or a hospital admission while pregnant.

The following conditions collected from the NSAPD that either complicated pregnancy or were pregnancy-related were considered as potential predictors of hypertension: parity, alcohol or drug use, anxiety or depression, gastroesophageal reflux disease (GERD), multiple gestation, gestational diabetes mellitus (GDM), gestational hypertension without proteinuria, eclamptic seizure, placental infarction, placental abruption, placenta previa, chorioamnionitis, oligohydramnios, polyhydramnios, male sex, gestational weight gain, preeclampsia, thromboembolic event, delivery by cesarean section, breastfeeding,

stillbirth, neonatal death, delivery of a SGA infant (<3% or <10%), delivery of a LGA infant (>90% or >97%), and infant's gestational age at delivery.

The hypertensive disorders of pregnancies were considered in two categories: gestational hypertension without proteinuria, and preeclampsia. The coding of gestational hypertension by the NSAPD changed several times during the study period, which was recategorized as gestational hypertension without proteinuria (an absence of preeclampsia) or preeclampsia. Any code that indicated a diagnosis of gestational hypertension with proteinuria was categorized as preeclampsia in our study.

Evaluating Potential Predictors Over Time

As women in this cohort were followed for up to 20 years following their first pregnancy, many experienced changes in demographic or health status over the study period. Furthermore, many women experienced more than one pregnancy and experienced different outcomes in each pregnancy. To account for these changes, each of the potential predictors was treated as a time-varying covariate over the study period. For potential predictors coded from the administrative data sources (i.e., diabetes), the value of the covariate changed from zero (indicating absence of the condition) to one (indicating the presence of the condition) on the first date a physician billings claim with the diagnosis was made, or the date a hospital discharge with the diagnosis was recorded. For example, if a woman was newly diagnosed with type 2 diabetes by a physician who billed a first visit for type 2 diabetes on January 2, 2008 and a second visit for type 2 diabetes June 4, 2008, her type 2 diabetes status would change from zero (indicating the absence of disease) to one (indicating the presence of diabetes) on the date of the first visit, January 2, 2008. All pregnancy-associated conditions were considered to have occurred on the date of delivery associated with that pregnancy.

Most pregnancy-associated conditions recorded in the NSAPD were stored as binary variables, indicating the absence or presence of the outcome in each pregnancy. In this analysis, these were treated as time-varying variables that could be binary (absent in all

pregnancies/present in any pregnancy), categorical (absent in all pregnancies/present in one pregnancy/present in two or more pregnancies), or integer variables (cumulative number of affected pregnancies). Maternal age at delivery, maternal weight prior to pregnancy, maternal weight gain in pregnancy, and gestational age at delivery were available as continuous variables. Both the continuous form and categorical forms of these variables were considered as candidate predictors of hypertension.

Missing Data

Complete-case analysis was performed in our model-building steps; thus individuals with missing data for candidate predictors required for a particular regression analysis were excluded from those analyses.

Outcome Definition

In keeping with the definition of hypertension used by the CCDSS, the operational definition of hypertension in this study required two physician billings claims of a hypertension-related diagnosis, or one hospital discharge with a diagnosis including hypertension (by ICD-9 or ICD-10 code) within a two-year period. The ICD codes used to indicate a diagnosis of hypertension are listed in Table 3. Women who met these criteria were considered to have hypertension from the date the first physician billings or hospital discharge claim associated with a diagnostic code for hypertension.

Statistical Analysis

Each candidate predictor variable was summarized for the cohort in terms of mean for continuous variables, frequency for binary and categorical variables, minimum and maximum values, and frequency of missing data. Variability was described for continuous variables and reported with the 5^{th} and 95^{th} percentiles. Biologically improbable values (i.e. maternal age <5 at delivery) were replaced with missing values.

Rates of hypertension and candidate predictors were graphed against time to evaluate for patterns that might require further explanation. The mean values or frequencies were evaluated by linear regression against time to further assess whether the mean or frequency of candidate predictors changed linearly over the study period. A change over time in this case was indicated by a non-zero slope of the regression line.

Pearson's correlation coefficients (r) were calculated for each pair of candidate predictors. If highly correlated pairs were identified ($r>0.8$), a single variable from the pair was chosen. Where a choice between highly correlated variables existed, the candidate predictor that was used was the one with less missing data or the one that was felt to be collected more reliably based on clinical experience.

The unadjusted HRs of hypertension associated with each candidate predictor were estimated by Cox proportional hazards regression. The multivariable-adjusted HRs between candidate predictors and hypertension were similarly estimated by Cox proportional hazards regression in our prediction model. Each candidate predictor was assessed graphically to determine if the proportional hazards assumption was violated. Plots of Schoenfeld residuals against survival time were produced. Linear regression of the residuals against time were compared to a zero-slope line where a significant difference would indicate a violation of the proportional hazards assumption (133). Log-log plots of survival against time were produced for each level of categorical variables (or each interval of continuous variables) and if the two curves were not parallel across time these were flagged as potentially non-proportional. Kaplan-Meier survival curves for each level of categorical variables (or each interval of continuous variables) were plotted alongside the Cox-regression predicted survival curves. If the two curves were not parallel, or crossed, these were also flagged as potentially non-proportional over time.

Model Building and Selection

Women entered into the survival analysis at the completion of their first pregnancy (i.e., delivery date). The analysis was based on detecting a single failure event, which

occurred at the time of the first diagnosis of hypertension. Analysis time was right-censored when a woman had her first diagnosis of hypertension, ceased to be eligible for MSI coverage (i.e., lost to follow-up), died, survived to the study's end date of December 31, 2014, or at 20 years after her first delivery. Follow-up time was censored after 20 years to maintain adequate power, as relatively few women were expected to contribute data beyond 20 years of analysis time. Backward elimination, described in detail in the following paragraphs, was used to simplify the model to include only predictors that were independently associated with the risk of developing hypertension. The initial regression model, referred to as the "preliminary model" for convenience, included each candidate predictor coded as a categorical variable. The following model-building steps were followed (in the order given below), to construct the full model:

1) Candidate predictors available as continuous data were included in the model in that form if it improved the model's fit compared with a categorization of the variable.
2) Addition of second order specification of continuous candidate predictors was evaluated and retained in the model if they improved fit.
3) Candidate predictors found to violate the proportional hazards assumption were addressed by adding an interaction term between the candidate predictor and time.
4) The following first-order interactions were evaluated, and retained in the model if they improved its fit:
    a. pre-pregnancy weight and gestational weight gain
    b. gestational hypertension and at least one of the following adverse pregnancy outcomes: preterm birth less than 34 weeks, eclampsia, placental abruption, or stillbirth
    c. preeclampsia and at least one of the following adverse pregnancy outcomes: preterm birth less than 34 weeks, eclampsia, placental abruption, or stillbirth
5) Re-categorization of pregnancy-related variables from binary (present in any pregnancy versus never present) to categorical (never present, present in one pregnancy, and present in two or more pregnancies). At this stage,

multiple gestation and eclamptic seizures were maintained as binary variables due to the rarity of having multiple pregnancies affected by these conditions.

At each step, the modified model was compared to the previous model and the changes to the previous model retained if they improved the model's fit, with a penalty assigned for increased model complexity. If the new model was nested in the old model, models were compared by the likelihood-ratio test and the change retained if the new model demonstrated a significant improvement in fit. When comparing models that were not nested, Akaike's information criterion (AIC) was to define the better fitting model after a penalty for model complexity. Akaike's information criterion is defined as negative two times the natural logarithm of the maximized log-likelihood of the model, plus two times the number of parameters estimated. Thus, a better-fitting model resulted in a lower absolute value of the AIC, while a more complex model will result in a higher absolute value of the AIC (134). The model with the lower absolute value of AIC was carried forward to the next stage of model building. The final model attained through these steps was named the "full prediction model".

The "full prediction model", was simplified through (backward) stepwise elimination of candidate predictors that did not contribute significantly to the model. The stepwise elimination was automated, carried out in Stata (v. 13) (135). At each step, the model was fit on all candidate predictors, and the least significant term was selected for potential removal. Models with and without the selected term were compared by the Wald test. If the significance level of the Wald test was ≥ 0.05, the term was eliminated from the model which was carried forward to the next elimination step.

To evaluate the stability of the model obtained after backward selection, the backward selection procedure was repeated on 100 bootstrapped samples of the same size as the study population, selected with replacement from the study population. Only terms that were included in the simplified models derived from ≥80% of the bootstrapped samples were included the "simplified prediction model".

In addition, a points-based model was developed according to methods previously used and described by the Framingham Study group to convert complex multivariable regression models into integer-values or "points" that could be easily tabulated by clinicians (136). To summarize, a multivariable regression model is used to estimate a regression coefficient for each level of categorical variables and for continuous variables. Continuous variables are categorized into clinically meaningful ranges; in our case, age was categorized in five-year increments and weight was categorized in ten-kg increments. The number of "regression units" associated with each category was calculated (e.g. for maternal age, the number of regression units associated with a five-year change in age was five times the regression coefficient for one year of age). A constant number of regression units would be assigned one "point" in the model. This constant was set as the regression units associated with a five-year increase, so that a five-year increase in age would be assigned one "point" by the model, as this increment was felt to represent a clinically meaningful change hypertension risk. The regression units associated with each other predictor was divided by this constant to produce a continuous variable that was rounded to the nearest integer to indicate the number of "points" that would be added or subtracted when that predictor was present. Any predictors that were associated with zero points after rounding in the points-based model were excluded.

Evaluating Model Performance

The baseline hazard function over time was estimated with the Breslow method (133). This allowed estimation of the 5, 10, and 20-year risks of hypertension in a woman with a given risk profile. The performance of the "full prediction model" and "simplified prediction models" were evaluated over the 20-year period postpartum. Model discrimination and calibration were evaluated graphically by plotting the survival curve predicted by the model against observed hypertension-free survival in women predicted as being low- or high-risk. Model performance was assessed at varying thresholds because the optimum cut-off point to define a "high risk" group of women may vary depending on the setting or goals of model application.

As Harrell's c-statistic cannot be accurately calculated in survival data with late/multiple times of origin or with time-varying covariates, survival time was measured from the date of delivery defined as the origin and analysis time measured in years postpartum. To accommodate for the possibility that the value of the linear predictor may vary over time for a given women in the model, and that the model's performance may change depending on which value of the linear predictor was used, Harrell's c-statistic was calculated using values of the linear predictor derived from the candidate predictors: 1) at the end of a woman's first pregnancy and 2) at the end of a woman's last recorded pregnancy. To estimate the degree of optimism from evaluating the model's discrimination in the same sample it was derived from, the bootstrap-corrected c-statistic was calculated by evaluating the model's discrimination in 100 bootstrap samples of N women, drawn with replication, and the average c-statistic calculated.

Sensitivity Analysis

To evaluate the impact of the decision to use the entire population in our model derivation on the c-statistic evaluated in this population and from bootstrapped samples of this population, the model-building steps were repeated after splitting the population into a derivation cohort and an evaluation cohort. In this sensitivity analysis, the study cohort was randomly split into two. In the half that formed the derivation cohort, each model building step was repeated according to the methods described above. The decision of which predictors to retain in the final simplified prediction model used the same rules described above. The simplified prediction model derived from the split-sample analysis was evaluated in the remaining half of the study population not used for its derivation.

Chapter 4 - Results

Data Linkage

A summary of our data linkage and derivation of the analysis dataset is provided by Figure 1. The NSAPD provided data on 219,634 pregnancies to 133,494 mothers leading to deliveries of infants at a gestational age of least 20 weeks and at least 500g between 1988 and 2009. After excluding women whose first delivery was not captured by the database, 98,094 women (172,782 pregnancies) remained. Of these, 93,760 mothers had records identified from at least one HDNS database. The HDNS data were successfully linked to the NSAPD data for 93,571 mothers. A further 191 women did not meet criteria for inclusion due to being <15 or ≥ 55 years old at the time of their first delivery. There were 567 women excluded whose records indicated a date of entry into our cohort later than the study end date, December 31, 2014, or later than their recorded date of censoring.

Description of Study Cohort

There were 3,335 women with pre-existing hypertension at the time of their first pregnancy, who were excluded from the study cohort. Of these, 2,892 were excluded due to hypertension identified from HDNS diagnostic codes, and a further 1,002 women were excluded because a diagnosis of pre-existing hypertension was recorded in the NSAPD at the time of their first pregnancy. After exclusions, 90,316 women comprised the study cohort.

A description of the study cohort including mean values (for continuous variables) and frequencies (for categorical variables) of candidate predictors are summarized in Table 4. The mean age of women at the time of first delivery was 27.9 years. The number of pregnancies recorded for each woman in the cohort ranged from one to eleven, with a mean value of 1.8 pregnancies per woman. Many of the candidate predictors changed in frequency over time. Women who delivered in later years of the study were more likely

to have multiple gestations, gestational diabetes, preeclampsia, placental syndromes (infarction or abruption), as well as large for gestational age infants. They were more likely to have breastfed, have a higher quintile of annual income per person equivalent, have an urban residence, be married, and be older at the time of their first delivery, than women who delivered in earlier years of the study. Women who delivered in later years of the study were less likely to have smoked in pregnancy, have gestational hypertension without proteinuria, and deliver SGA infants.

Figure 2 shows the observed rates of hypertension-free survival in our cohort. More than half the cohort were followed for at least ten years, and 22.9% were followed for twenty years. A total of 9,811 cases of hypertension were observed during the study period in 90,315 women. The cumulative incidence of hypertension was 3.0% at five years, 6.5% at ten years, 11.3% at fifteen years, and 17.9% at twenty years from their first delivery.

Kaplan-Meier curves of hypertension-free survival, stratified by delivery decade, did not differ significantly (log-rank test $p = 0.09$), indicating that women who delivered in later years of the study had similar patterns of hypertension as women who delivered in earlier years of the study. Therefore, the additional complexity of models stratified by delivery decade was rejected in favour of developing a model that was generalizable over time.

Unadjusted Associations between Candidate Predictors and Hypertension

The unadjusted associations of each candidate predictor with hypertension are shown in Table 5. Most of the candidate predictors were weakly associated with hypertension, with HRs ranging from 0.5 to 2.0. The candidate predictors most strongly associated with hypertension, with unadjusted HRs ≥ 2.0, included: maternal age (over 30 years old versus under 20 years old), pre-pregnancy weight, preeclampsia, diabetes (types 1, 2 and other), gestational hypertension without preeclampsia, eclampsia, gastroesophageal reflux, gestational diabetes, and stillbirth. Alcohol and drug use in pregnancy was the only candidate predictor with a strong negative association with hypertension, as indicated by a HR ≤ 0.5. Candidate predictors that were not significantly associated with

hypertension in the unadjusted analysis were: month of delivery, multiple gestation, chorioamnionitis, neonatal death, and placenta previa.

Assessment of Proportional Hazards Assumption

When maternal age categorized in 5- and 10- year intervals, log-log plots of the survival curves suggested a violation in the proportional hazards assumption in women over 50 years old. There were 7 women between 50 and 55 years old at the time of their first delivery which were therefore excluded from the subsequent analyses and model-building steps, and survival data for the remaining women was right-censored when they achieved 50 years of age.

Graphical assessment revealed no violations of the of the proportional hazards assumption for the other candidate predictors, with the exception of: preeclampsia, eclampsia, and gestational hypertension. Figure 3 shows Kaplan-Meier curves stratified by preeclampsia status and gestational hypertension status. Kaplan-Meier curves for each level of the candidate predictor, plotted against survival curves predicted by Cox regression, identified violations in the proportional hazards assumption for these three variables. In each case, the observed survival curve dropped more steeply in the first year than the curve predicted by Cox regression in affected woman than in unaffected women, reversing between 15 and 20 years of follow-up time when the observed survival became greater than the predicted survival. Log-log plot survival curves of categorized candidate predictors suggested no deviations from the proportional hazards assumption for any of the other candidate predictors. Small deviations from the proportional hazards assumption were demonstrated by linear regression of the scaled Schoenfeld residuals against time, which showed a deviation from a zero-slope ($r > -0.1$ or < 0.1) for the candidate predictors: married, pre-pregnancy weight, maternal age, multiple gestation, gestational diabetes, placental abruption, excess gestational weight gain, thromboembolic event, caesarean delivery, smoking prior to pregnancy, and breastfeeding over time. Larger deviations from the proportional hazards assumptions were demonstrated by linear

regression of the Schoenfeld residuals against time for gestational hypertension ($r = -0.18$) and preeclampsia ($r = -0.15$).

Developing the Regression Model

Table 6 summarizes the model building steps, and Akaike's information criterion for each model. The preliminary model (Model 1) included each categorical pregnancy-associated variable as a time-varying binary variable (absent from all pregnancies or present in any pregnancy), while pre-pregnancy weight, maternal age, and age at delivery were treated as continuous variables. In Model 2, each of pre-pregnancy weight, maternal age and gestational age at delivery was included as a continuous variables (versus categorical), as each addition significantly improved the performance of Model 1 (likelihood-ratio test $p < 0.0001$ for each addition). Addition of continuous variables for total gestational weight gain or gestational weight gain in excess of the upper limit of Institute of Medicine recommendations as variables did not improve the fit of Model 1 (likelihood-ratio test $p = 0.11$ and $p = 0.16$, respectively), and these changes were not retained.

Interaction terms were considered for preterm birth prior to 34 weeks, eclamptic seizure, placental abruption or placental infarction and hypertensive disorders, as these adverse pregnancy conditions may indicate the severity of a hypertensive disorder of pregnancy which may further predict future hypertension. First-order interactions between preeclampsia and adverse pregnancy outcomes and between gestational hypertension and adverse pregnancy outcomes, or any hypertensive disorder and adverse pregnancy outcomes did not significantly improve the fit of Model 2 (likelihood-ratio tests $p = 0.32$, $p = 0.50$, and $p = 0.11$ respectively), and were not carried forward into the next model. A first-order interaction between pre-pregnancy weight and weight gain in excess of recommendations significantly improved the fit (likelihood-ratio test $p = 0.003$), and was retained in Model 3.

Quadratic terms were added to describe each continuous variable to see if these would improve the model's fit, which they did for pre-pregnancy weight and maternal age, and were retained in Model 4. To address the violations of the proportional hazards assumption for preeclampsia, gestational hypertension, and eclampsia, which were concentrated in the first year of delivery, a binary interaction term was created that was assigned a value of 1 (present) if the woman had developed the hypertensive disorder of pregnancy *and* was in her first year postpartum, changing to zero after the first postpartum year. This interaction term was always zero in women who did not develop the condition. This interaction term significantly improved the model's fit, and was retained in Model 5. To reach Model 6 (the Full Prediction Model), the binary variables indicating pregnancy-related outcomes were recoded as categorical variables (never present/present in one pregnancy/present in two or more pregnancies), which improved the model's performance as indicated by AIC.

The Full Prediction Model was simplified by stepwise elimination carried out in 100 bootstrapped samples. If a candidate predictor was retained after backwards selection in over 80% of the bootstrapped samples, the predictor was included in the Simplified Prediction Model. The variables that would have been retained if backwards elimination had been performed only in the original sample but were eliminated due to not being consistently retained in the backwards elimination in bootstrapped samples were: area-level income quintile (eliminated in 20% of samples), marital status (eliminated in 46%), alcohol or drug use (eliminated in 31%), and renal disease (eliminated in 30%). Elimination of these variables produced Model 7, the Simplified Prediction Model.

Simplified Prediction Model

The HRs estimated by the Simplified Prediction Model are shown in Table 7. The strongest positive predictors of hypertension were: age at delivery, (HR = 1.65 per five year increase, 95% CI 1.51-1.79), primiparity (HR = 1.52, 95% CI 1.43-1.63), and the hypertensive disorders of pregnancy (description of hazard ratios below). Other pregnancy-related predictors positively associated with hypertension, each with adjusted

hazard ratios between 1 and 1.5 were: gestational diabetes and delivery of a small-for-gestational-age infant less than the tenth percentile. Pregnancy-related variables negatively associated with hypertension were: multiple gestation, smoking in pregnancy, delivery of a large-for-gestational-age infant greater than the ninetieth percentile, and breastfeeding. Type 2 diabetes was included with a hazard ratio of 1.43 (95% CI 1.28-1.61), which was adjusted for each of the other predictors, including gestational diabetes. Other continuous variables included in the Simplified Prediction Model were maternal pre-pregnancy weight and gestational age at delivery. The only demographic variable retained was urban residence, which was negatively associated with hypertension.

The association between preeclampsia or gestational hypertension and a diagnosis of post-pregnancy hypertension was extremely strong in the first year postpartum, and these remained the strongest predictors of hypertension detected in the next 20 years postpartum by our model. These conditions were particularly strong predictors if they recurred in more than one pregnancy. For preeclampsia, the hazard ratio for hypertension was 40.5 (95% CI 32.7 – 50.1) in the first year postpartum, and 2.14 (95% CI 1.93-2.36) in years two through twenty postpartum after a single affected pregnancy or 4.93 (95% CI 3.24-7.51) after two or more affected pregnancies. For gestational hypertension, the hazard ratio for hypertension in the first year postpartum was 52.3 (95% CI 43.9-62.4), and for years two through twenty postpartum the hazard ratios were 2.18 (95% CI 2.06-2.30) after one affected pregnancy and 4.06 (95% CI 3.59-4.60) after two or more affected pregnancies.

When women were classified as “high risk” if the value of the linear predictor calculated by the Simplified Prediction Model fell within the top 10% for the cohort, their risk of developing hypertension was 23.2% (95% CI 22.2%-24.4%) by ten years following their first pregnancy, and 45.6% by twenty years, (95% CI 44.1%-47.1%), compared with only 4.2% (95% CI 4.0-4.3%) by ten years and 13.5% (95% CI 13.2-13.9%) by twenty years in the remaining cohort. Among the high-risk women, 65% had a history of a hypertensive disorder in at least one pregnancy. By contrast, only 55% of women with a hypertensive disorder in at least one pregnancy would be classified as high risk indicating

that other predictors remained important to a woman's overall risk assessment. Figure 4 illustrates the proportion of women developing hypertension over time stratified by high- or low-risk status based on the ninetieth percentile of predicted risk, and further stratified by history of hypertensive disorders in pregnancy.

Points-Based Model

The Points-Based Model included eight predictors, as each other predictor in the final model contributed zero points after rounding to the nearest integer. Table 8 shows the allocation of points in this model. The included predictors were: maternal age at delivery, pre-pregnancy weight, history of type two diabetes, history of hypertensive disorder of pregnancy, primiparity, preterm delivery less than 34 weeks at last delivery, history of multiple gestation, and breastfeeding history.

In the study cohort, the mean number of points allocated to each woman was 2.09, with 95% of women scoring between 0 and 5 points. Less than 1% of women scored less than -1 point, and less than 1% of women scored more than 7 points. The observed rates of hypertension at 10 and 20 years in women from this cohort scoring between -1 and 7 points are summarized in Table 9. The c-statistic for the Points-Based Model was 0.67.

Model Performance

Figure 5 illustrates the model's ability to successfully discriminate between low-risk and high-risk women, and to accurately predict their risk of hypertension during the twenty years after delivery of a first child. The model's predicted hypertension-free survival is well calibrated over time in all groups, except for the very highest-risk women (>99th percentile for predicted risk). In the women whose calculated linear predictor was in the highest one percentile, the model underestimated the incidence of hypertension over first ten years postpartum, but accurately predicted hypertension-free survival between 10 and 20 years postpartum.

After excluding women who were right censored due to death or emigration from the province prior to the study's end date, the c-statistic was 0.722 when calculated based on values for the candidate predictors measured the end of the women's first pregnancies. This improved slightly to 0.723 if it was calculated from the end of the women's last recorded pregnancies. When the model's discrimination was assessed in 100 bootstrapped samples drawn with replacement from the original study sample, the mean of the c-statistics (calculated from the time of the last recorded pregnancies) was 0.713. When the ninetieth percentile for predicted risk is used as the threshold to define high risk women, the positive predictive value of a high-risk classification was 55.4%, while the negative predictive value was 87.1%. The model loses some of its discriminative accuracy when it is translated from a continuous measure to a dichotomized risk prediction tool. Table 10 illustrates the effects on the model's performance when different thresholds from the 50^{th} percentile through 95^{th} percentile are used to identify "high risk" women.

Chapter 5 - Discussion

Summary of Results

This study is the first to report a risk prediction model for hypertension that uses clinical variables, with an emphasis on pregnancy-specific conditions, to predict a future diagnosis of hypertension in women under the age of 50. The pregnancy-specific conditions included in this model were: primiparity, multiple gestation, smoking in pregnancy, gestational diabetes, gestational hypertension, preeclampsia, gestational age at delivery, SGA (<10th percentile), LGA (>90th percentile), and breastfeeding. Additional predictors included in the final model included: type 2 diabetes, maternal age at delivery, pre-pregnancy weight, and urban residence.

The strongest individual predictors of a future diagnosis of hypertension were preeclampsia and gestational hypertension, particularly if these recurred in more than one pregnancy. As estimated by the Simplified Prediction Model, a woman with one pregnancy affected by preeclampsia had a HR of 2.14 for a future diagnosis of hypertension, comparable to a non-preeclamptic mother 10.4 years older. If a woman had a history of two preeclamptic pregnancies, the HR for future hypertension was 4.93, equivalent to the HR conferred by being 35.7 years older. Importantly, the HR for being diagnosed with hypertension within the first year after a pregnancy affected by a hypertensive disorder was 40.5 after a pregnancy affected by preeclampsia and 52.3 after a pregnancy affected by gestational hypertension. The most likely explanation for this observation is that some cases of hypertension initially classified as a hypertensive disorder of pregnancy actually represented the identification pre-existing hypertension that had gone undiagnosed until regular blood pressure screening took place in pregnancy. After being identified as hypertensive in pregnancy, these women may have gone on to be diagnosed with hypertension if their elevated blood pressures did not resolve in the postpartum period. The HR conferred by gestational hypertension without preeclampsia was similar in magnitude to that conferred by preeclampsia, indicating that

all hypertensive disorders of pregnancy should be treated as similarly strong predictors of a future diagnosis of hypertension, whether or not there were features of preeclampsia.

When the Simplified Prediction Model was evaluated in this study population, it discriminated between women who did and did not develop hypertension, and accurately predicted the rates of hypertension observed in our study population up to 20 years postpartum. The c-statistic calculated at the time of a woman's last recorded pregnancy was 0.72, which is comparable to other available hypertension risk prediction tools (137). The mean c-statistic when the Simplified Prediction Model was evaluated in 100 bootstrapped samples from this study population was 0.71. This model produces a continuous linear predictor, which could be categorized at any chosen cut-point(s) to define groups based on future risk of hypertension. When the linear predictor was dichotomized at the 90th percentile, the positive predictive value for a diagnosis of hypertension within 20 years postpartum was 46.3%, while the negative predictive value was 87.1%.

Application of the Simplified Risk Prediction Model

Figure 6 illustrates how the Simplified Prediction Model predicts the risk of incident hypertension over 20 years for three different (hypothetical) women, based on clinical data available at the time of pregnancy. While a 20 year old woman weighing 50 kg with an uncomplicated pregnancy has a small risk of developing hypertension within the next 20 years, a woman who is average in other respects (28 years old at the time of delivery, weighing 68 kg pre-pregnancy) with a history of preeclampsia and delivery of a SGA infant in each of two pregnancies, has a predicted risk of hypertension of almost 30% by the age of 38, and almost 60% by the age of 48. Some Canadian centres have already established postpartum clinics where women with hypertensive disorders of pregnancies, or other pregnancy-related conditions associated with an increased risk of chronic disease later in life are invited to undergo assessment and counselling for risk-reduction (129,138). The ability to provide individualized prediction of hypertension risk in the postpartum period could inform individualized recommendations regarding the frequency

of ongoing screening for hypertension outside the immediate postpartum period. Applying this model may also improve the identification of women at high risk of future hypertension for referral postpartum counselling clinics, which may include some but not all women with hypertensive disorders of pregnancy, as well as women with risk factors other than the hypertensive disorders such as age or elevated pre-pregnancy weight. Identifying women whose overall risk of hypertension is the highest may help target resources for more intensive screening and intervention to the women most likely to benefit from these.

Comparison to the Existing Literature on Observed Associations of Pregnancy-Related Conditions with Future Hypertension

Recently, 60,027 Norwegian women (41% of the eligible population) were observed for ten years postpartum to determine the association between various lifestyle and pregnancy-related covariates and subsequent pharmacologically treated hypertension (26). To our knowledge that study was the first, and only study prior to this one, to describe the associations between pregnancy-related conditions and future hypertension that was carried out using national registry-based data in a developed country with universal access to publicly funded healthcare. In the Norwegian study, treated hypertension was identified through the Norwegian Prescription Database. In their cohort, 2.5% of the women developed pharmacologically treated hypertension, which is somewhat less than the 6.5% cumulative incidence in our population by 10 years of follow-up. This may be explained by differences between populations but may also reflect the different outcome of pharmacologically-treated hypertension, which would be expected to represent a subset of more severe cases of hypertension. Many, but not all, of the lifestyle and pregnancy-related covariates included in this study were also included in the Norwegian study. Additional covariates included in the Norwegian study were physical activity pre-pregnancy, dietary intake at 22 weeks pregnancy, oral contraceptive use and, in a subgroup with available data, breastfeeding and weight change from pre-pregnancy weight measured six months postpartum.

Similar to the findings of the current study, the pregnancy-related conditions most strongly associated with future hypertension in the Norwegian study (26) were the hypertensive disorders of pregnancy, with adjusted HRs of 6.00 (95% CI 5.15-6.99) for preeclampsia and 7.13 (95% CI 5.93-8.58) for gestational hypertension. The adjusted HRs from that study cannot be directly compared to the adjusted HRs observed from the Simplified Prediction Model in this study, as the Norwegian study's HRs were adjusted only for maternal age, pre-pregnancy BMI, and several demographic and dietary factors and not the other pregnancy-related conditions adjusted for in this analysis. Those HRs were larger than the unadjusted HR observed in this study for preeclampsia (3.45, 95% CI 3.22-3.71) and gestational hypertension (3.02, 95% CI 2.90-3.15). The HRs observed in this study are more consistent with a recent meta-analysis of studies assessing the association between preeclampsia and future hypertension, which estimated an overall relative risk of 3.13 (95% CI 2.51-3.89) (7) for hypertension after a pregnancy complicated by preeclampsia. While other differences between study methodology and the underlying populations may account for the apparently stronger associations in the Norwegian study, it may be that the more severe states of hypertension requiring treatment which were the outcome in the Norwegian study are particularly strongly associated with preeclampsia and/or gestational hypertension.

The Norwegian study (26) found decreasing HRs for preeclampsia and gestational hypertension (treated as a single condition) over time from 9.40 (95% CI 8.00-11.04) in the first four years of follow-up to 6.38 (95% CI 5.62-7.26) by 10 years of follow-up, although they did not describe the effect of time on the hazard of hypertension in any further detail. Others have similarly reported a weakening association of preeclampsia with hypertension over time. The pattern described in detail in the current study, with an extremely strong association between hypertensive disorders of pregnancy within the first year after delivery, followed by a more stable association thereafter, could explain these observations. It may also be that over time other mechanisms of vascular damage accrue in aging individuals, and the relative impact of the hypertensive disorders of pregnancy on an individual's overall hypertension risk begins to decline.

In the present study, having two or more pregnancies complicated by a hypertensive disorder of pregnancy approximately doubled the HR for developing hypertension compared with a single affected pregnancy. This is consistent with the results of a systematic review and meta-analysis published in 2018 that estimated a pooled relative risk for hypertension of 2.33 (95% CI 1.86-2.92) with recurrent preeclampsia as opposed to preeclampsia followed by an uncomplicated pregnancy (70). This is, to the best of our knowledge, the first study to similarly show an increased risk of future hypertension after recurrent pregnancies complicated by gestational hypertension (without preeclampsia).

The relationship between gestational hypertension and future cardiovascular disease has been less scrutinized than that of preeclampsia, despite the fact that gestational hypertension is a far more common condition (66), affecting 11% of Nova Scotian mothers during the study period. No published meta-analyses have examined the association between gestational hypertension without preeclampsia and a future hypertension diagnosis, and the primary literature in this field has similarly has typically focused on preeclampsia alone or has grouped the two conditions together. In the Avon Longitudinal Study from the UK, gestational hypertension and preeclampsia were distinguished and each was associated with an 8.31 mmHg higher systolic blood pressure 18 years after an index pregnancy as compared with women without a prior hypertensive disorder of pregnancy (95% CI 7.15-9.47 for gestational hypertension and 5.58-11.14 for preeclampsia). The differences in diastolic blood pressures were also similar (139). This is consistent with the current study's finding of similar associations of gestational hypertension with or without preeclampsia on future hypertension risk.

Previous studies have yielded inconsistent results as to whether the severity or timing of onset of a hypertensive disorder in pregnancy influences its association with future cardiovascular disease or cerebrovascular disease (63,69,76). The most recent systematic review showed no significant increase in cardiovascular events in preeclamptic women with a pre-term delivery relative to women with a term delivery (7). The only study thus far to have looked specifically at whether the interaction between preeclampsia and a preterm or SGA delivery was independently associated with future hypertension was the

Norwegian study(26) which, like this one, did not find a statistically significant interaction (26).

In this study's Simplified Prediction Model, delivery of a SGA infant was a weak predictor of hypertension, while delivery of a LGA infant was a weak negative predictor. Neither predictor was retained in the points-based model. Delivery of a SGA infant has been associated with future hypertension in unadjusted analyses from Swedish (78) and American (8) populations, but these associations were not statistically significant in multivariable-adjusted analyses in those populations or in another study of the Norwegian population (26). A SGA delivery was associated with higher measured systolic and diastolic blood pressures in multivariable adjusted analyses (including adjustment for other pregnancy-related conditions) in a British cohort (139). Studies that have looked at this association thus far, including this study, have been registry-based studies relying on secondary use of data with limited the ability to distinguish between constitutionally small or large infants and infants who were small or large secondary to a pathological process, which may be differentially associated with hypertension risk. In the Norwegian study (26), LGA was significantly associated with hypertension when adjusted for maternal age only, but in the model additionally adjusted for BMI and lifestyle factors (but not other pregnancy-related conditions) there was no significant association (HR 0.94, 95% CI 0.81-1.11). There is little data describing the association between delivery of a LGA infant and future hypertension after controlling for maternal height, glucose tolerance, and gestational or postpartum diabetes. Large for gestational age infants represent a mix of pathologically large and constitutionally large infants. Although LGA was a weak negative predictor in our study, it is unclear whether this would have remained significant if we had been able to adjust for maternal height in our analysis, which may have helped control for infants which were LGA constitutionally as opposed to pathologically.

The impact of multiple gestation on future hypertension has not been adequately studied, but women carrying multiple gestations are known to be at increased risk for several of the conditions that were positive predictors of hypertension in this study's Simplified

Prediction Model including: gestational diabetes, hypertensive disorders of pregnancy, preterm birth, and delivery of a SGA infant (140). Thus, multiple gestation as a negative predictor of hypertension in this adjusted model likely does not reflect a protective effect, but a way in which the apparent increased risk of hypertension associated with those other conditions is mitigated by this model if the conditions were provoked by the additional stress of a multiple gestation rather than the same underlying predisposition to hypertension as a woman who developed the condition in the context of a singleton gestation.

The other pregnancy-related predictors of hypertension identified by the Simplified Prediction Model have been consistently associated with hypertension in other Western populations. Preterm delivery has been associated with hypertension in cohorts from the US (31), UK (139), Sweden (78), and Norway (26). Pathologic inflammation has been proposed as a common precursor of both preterm birth and hypertension, and may explain this consistent association (79,81–83). Breastfeeding, a negative predictor of hypertension in our population, has also consistently been associated with a decreased incidence of hypertension in diverse populations from the US (112,113), Norway (59), and Korea (114). The ability of breastfeeding history to predict a decreased risk of hypertension could be explained either by the metabolic effects of breastfeeding itself, by breastfeeding serving as a marker for other health behaviours, or by a combination thereof.

The traditional risk factors of age, weight, and type 2 diabetes included in this study's Simplified Prediction Model have each been consistently associated with hypertension (141) and are included in many existing hypertension prediction models (137). Consistent with this study's findings, gestational diabetes has been associated with hypertension in other populations (26,78). A history of gestational diabetes is also strongly associated with an increased risk of type 2 diabetes (RR 7.4, 95% CI 4.8-11.5) (142). In addition to the hallmark of insulin-resistance, both gestational- and type 2 diabetes are associated with subclinical inflammation, which may contribute to vascular dysfunction (143). The association between diabetes in epidemiologic studies may be

further magnified as, once diagnosed with diabetes, women may be more likely to be screened for and diagnosed with hypertension.

Urban residence was included as a negative predictor in this study's Simplified Prediction Model; it could potentially serve as a surrogate for a complex array of environmental, behavioural and socioeconomic factors that influence hypertension risk. Because the impact of urban residence on environmental and psychosocial factors may differ between countries and populations, the usefulness of urban residence as a predictor may vary between populations. Future study could indicate whether urban versus rural residence is consistently associated with decreased rates of hypertension across Canada and in other populations. If it is consistently associated with decreased rates of hypertension in Canada, this may prompt further investigation into the underlying reasons that individuals in rural settings appear to be at increased risk and whether these are amenable to targeted primary prevention. Urban residence contributed no points to this study's Points-Based Model, reflecting its relatively weaker association with hypertension in the study population, compared with the other predictors described so far.

It is unclear how to explain the fact that cigarette smoking was identified as a negative predictor of hypertension in the Simplified Prediction Model. Although smoking has been associated with an increased risk of cardiovascular disease (144), it has sometimes, but not consistently, been independently associated with hypertension in epidemiologic studies (31,42,43). In the NHANES study of hypertension in reproductive-aged women from the United States (31), smoking was associated with hypertension in the unadjusted analysis, but not in the multivariable-adjusted analysis. By contrast, smoking has been associated with a decreased risk of preeclampsia (66), though this would not explain the apparent negative association in this Simplified Prediction Model. It is possible that smokers are less likely to be diagnosed with hypertension as a result of decreased engagement with the healthcare system, resulting in less screening and detection rather than less disease. Similarly, women who use alcohol in pregnancy may be less engaged with the health care system after their pregnancies and less likely to be diagnosed with hypertension, which may explain negative association of alcohol use with hypertension in

both this study and the Norwegian study of pregnancy-related risk factors associated with hypertension (26). Even if smoking itself was a true negative predictor of hypertension rather than a marker of an underdiagnosed group, its inclusion as a negative predictor in this study's model does not necessarily imply a negative association with disease. Whether smoking was positively, negatively, or not associated with hypertension, it is associated with other predictors identified in this study such as preterm birth, SGA, and placental syndromes. Each of these factors are suggested to arise from either subclinical vascular dysfunction pre-existing the pregnancy or to an underlying susceptibility to vascular dysfunction (i.e., from genetic, lifestyle, or comorbid conditions) that contribute both to abnormal placentation and its complications at the time of pregnancy, and later contribute to hypertension. If smoking increases an individual's risk of developing these adverse pregnancy outcomes, the pregnancy-related predictors may not indicate the same individual predisposition to future hypertension when they arise in smokers as when they arise in non-smokers. Thus, smoking may be a true negative predictor in this model, even if it is not protective against hypertension, if it exists in the model to mitigate the predictive power of other correlated conditions.

Comparison of Risk Prediction with Other Hypertension Risk Prediction Models

Other studies developing risk prediction tools have consistently defined hypertension as either systolic blood pressure ≥ 140 mmHg and/or diastolic hypertension ≥ 90 mmHg and/or use of antihypertensive medications (137). These definitions are consistent with the definition used in study and with current Canadian clinical practice (145). In 2013, a systematic review of 16 risk models aimed at predicting incident hypertension was published (6). By 2017, an updated systematic review identified 27 articles reporting on 48 risk prediction models (some studies reported on more than one alternative model) (137). Among regression tools used in model building, logistic regression was most common, followed by Cox regression which was used in 8 of the 27 published studies as well as in our own analysis. Of the existing risk prediction tools, only one was developed in a cohort of exclusively women (47), and this was limited to women aged 45 and older. Only clinical variables (i.e., history and physical exam, usually consisting of blood

pressure and/or anthropometric measurements) were included in 26 of the existing models. Clinical data combined with biochemical testing (i.e., measures of fasting plasma glucose, inflammatory markers, liver function testing, etc.) were used in 11 of the models, and genetic testing with or without clinical and biochemical was used in the remaining 10 models.

The common predictors included in clinical risk prediction models are age, sex, BMI, systolic blood pressure, diastolic blood pressure, and parental history of hypertension (137). While age was included in this study's Simplified Prediction Model, the present study was unable to consider BMI, SBP, DBP or parental history of hypertension as candidate predictors as these were not available from the population-based data sources used. The c-statistics reported in the systematic review for the non-invasive/clinical models ranged from 0.66 - 0.86 (137). In this study, the c-statistic calculated for the Points-Based Model was 0.67, and for the Simplified Prediction Model was 0.72, suggesting the risk prediction models published in this study discriminate similarly to previously published models.

Among the 27 studies reporting on prediction models, only seven reported the internal validation of their model. All except one used a split sample to validate their model, while the remaining study used fivefold cross-validation (48). Three have been externally validated: the SHIP risk model from Germany was validated in a Danish cohort with an area under the receiver-operator curve of 0.77 (146), the KoGES risk score from Korea was validated in a nationwide Korean cohort (147) and the Framingham Hypertension Risk Prediction Score has been validated in external populations by seven studies (137). Although the Framingham Hypertension Risk Prediction Score performed well in US, German, and British populations, it performed less well in a rural Chinese cohort and a Korean cohort (137). Different genetics, lifestyles and environmental exposures, may limit the generalizability of a model developed in Western populations to these Asian cohorts. For the same reasons, the model developed in this study may perform best in developed countries with predominantly Caucasian populations, similar to the cohort in which this model-building study was carried out.

The authors of both current systematic reviews (6,137) of existing hypertension risk prediction emphasize the fact that none of the current models were developed using prospectively collected data (raising concerns about missing data, accuracy of available data, or appropriate categorization of continuous variables), a limitation shared by this study. Both authors discussed the need for increased assessment of validity, internally but particularly in external populations. Both discussed the difficulties in applying clinical and genetics-based predictors across ethnicities, and between developed or developing countries. Yet surprisingly, despite the fact that both authors acknowledged the paucity of women included in the development of existing risk prediction model, neither included this point in their discussion of the limitations of existing risk prediction tools, and little attention was paid to the paucity of risk prediction tools applicable to a young reproductive-aged population. No risk prediction tool so far has evaluated pregnancy outcomes as candidate predictors, and yet this was not addressed as a limitation of existing models. This may suggest under-recognition of the rising prevalence of hypertension in young women, a lack of emphasis on the impact of hypertension in this population by the mainstream hypertension literature, or a general lack of knowledge about the unique variables (such as obstetrical history) available for incorporation into risk prediction models applicable to young women.

Study Strengths

The survival analysis performed in this study describes the current risk of hypertension in young reproductive-aged women, filling an important gap in an era where this condition is increasingly prevalent amongst young adults. The semi-parametric Cox regression analyses employed in this study made no assumptions about the risk of hypertension over time in young postpartum women. Using the Breslow method, this study described the risk of hypertension in the 20 years after pregnancy in a nearly-complete population-based sample. This addition to the current understanding of the epidemiology of hypertension in young Canadian women may help to plan and allocate resources for the prevention and treatment of hypertension.

While many studies have described the associations of pregnancy-related conditions with future onset hypertension, this represents the largest study published thus far. The most comparable study described the association of pregnancy-related conditions with hypertension up to 10 years following pregnancy (26), while this study described associations over a period twice that long. This is also one of the first studies to evaluate the associations between pregnancy-related conditions and hypertension in a population-based sample, reducing the potential for selection bias. By treating candidate predictors of hypertension as time-varying covariates throughout the study period, this study was able to incorporate changes to an individual's risk profile over time (for example if an individual gained weight between pregnancies or developed an adverse outcome that was not present in their first pregnancy), and was able to evaluate the impact of having one pregnancy versus multiple pregnancies affected by each candidate predictor on an individual's hypertension risk.

The internal validity of the Simplified Prediction Model and Points-Based Model described in this study are comparable to models currently available to predict hypertension, but existing models have not been evaluated in populations of exclusively young pre-menopausal women and it remains to be seen whether existing models would perform as well in this group. These models are the first to be developed in a population of young women and are unique in their consideration of pregnancy-related predictors that may be particularly relevant in this population. Although these models have not yet been externally evaluated, the fact that the majority of predictors included in these models have been demonstrated to be associated with hypertension in other populations suggest these predictors may be generalizable outside this study's population.

Caution in Interpretation of Adjusted Hazard Ratios

The HRs reported in the Simplified Prediction Model are likely to be over-adjusted compared with the true associations of each of these pregnancy-related outcomes with hypertension, as this model includes multiple non-independent covariates and covariates

that are thought to mediate the association between other predictors and the risk of future hypertension. For example, preterm delivery and delivery of a SGA infant are both well-known complications of hypertensive disorders in pregnancy (66), and the HRs reported for the hypertensive disorders of pregnancy in this study's Simplified Prediction Model are adjusted for each of these other predictors. This is acceptable since, unlike previous work, the objective of this study was not to describe the true magnitude of associations between hypertensive disorders of pregnancy and future hypertension, but to develop a prediction model that effectively identified women at high risk of future hypertension based on clinical data available from an obstetrical history.

Study Limitations

While the secondary use of an established perinatal database and administrative databases allowed the study of a large population over a long period of time, it limited what variables were available for consideration as candidate predictors. Key clinical factors that were frequently included in existing hypertension risk prediction models but not available from this study's data sources were measurements of blood pressure, parental history of hypertension, and BMI. While pre-pregnancy weight was evaluated in this study, maternal height (and, therefore, BMI) was not included in the NSAPD until 2003 so was not available for much of this study's period. The Framingham Hypertension Risk Prediction Score and Women's Health Study risk prediction models have been compared to a single measure of blood pressure to predict future hypertension (32,47). While the single measure of blood pressure performed adequately as the only predictor of future hypertension, suggesting that this was a key predictor in these models, both models performed superiorly when the other predictors were included. The inability to include a baseline measurement of blood pressure as a candidate predictor in this study was, therefore, a key limitation of this work and points to a potential opportunity to improve the performance of these models. On the other hand, unless the addition of blood pressure measures significantly improved these models' performance, the fact that these models can be evaluated using only information that can be obtained by a clinical history

(without the requirement of a physical exam), may be a strength of these models making them easily applicable.

Retrospective, secondary use of data in this study limited the ability to control the way in which data were collected. This may have impacted the predictive ability of certain variables. Breastfeeding, for example, has been associated with future hypertension in a dose-dependent manner (59) and, because breastfeeding was only assessed at one time point in this study's data sources (prior to hospital discharge, generally within the first days postpartum), this study was unable to assess the potential impact of the extent or duration of breastfeeding on prediction of future hypertension.

While missing data remain a limitation, the overall rate of missing data was low in this study. Aside from maternal pre-pregnancy weight (missing for 7.2% of women), maternal weight gain in pregnancy (missing in 12.5% of women), and urban residence (missing in 8.2% of women,) each candidate predictor was missing in fewer than 4% of all women.

Pre-pregnancy weight may have been prone to recall or reporting bias in some cases, as it would sometimes have been obtained from self-report. A meta-analysis of studies comparing self-reported pre-pregnancy weight with measured pre-pregnancy weight showed that women tend to underreport their pre-pregnancy weight by 0.34-2.94 kg, but that correlation between self-reported and measured weight was high (r ranging from 0.90-0.99) (148). Bias in this measurement and missing data may have limited the full potential of this predictor, but pre-pregnancy weight nevertheless remained a strong predictor in this study's models consistent with prior literature linking elevated BMI to hypertension (31).

It is possible that some cases of gestational hypertension were misclassified as preeclampsia, or vice versa, as there have been changes in terminology over the study period and the two may sometimes be used imprecisely in clinical documentation. Given that the HRs associated with the two conditions were very similar in this study, and they

ended up being combined into a single predictor (history of hypertensive disorders of pregnancy) in the Points-Based Model, misclassification between these two conditions would not be expected to have a large impact on the models' development or performance. It may, however, have limited this study's ability to detect differences in the predictive strength of gestational hypertension with or without preeclampsia on future hypertension risk.

Due to both the limited collection of maternal race/ethnicity in the NSAPD, and the limited ethnic diversity of the Nova Scotian population, this study was unable to evaluate the performance of the prediction models in women of different race/ethnicities, and these prediction models may be most applicable in Caucasian women.

Because the Simplified Prediction Model and Points-Based Model derived from this study have, so far, only been evaluated in the same population in which they were derived, their discrimination and calibration reported in this study may be overly optimistic (149). This was compensated for, to some extent, by evaluating the Simplified Prediction Model in bootstrapped samples drawn from the population with replacement, which demonstrated that the model performs similarly in randomly selected samples from the population. An alternative approach to evaluating the model's performance would be to split the study cohort into a derivation sample in which the model is derived, and a non-overlapping sample in which it is validated. This is how most hypertension risk prediction tools have been internally validated to date (137). This study chose a different approach, as excluding women from the model's derivation cohort would have reduced the statistical power to evaluate the impact of many candidate predictors, or to evaluate the impact of candidate predictors that were uncommon in the study population. This alternate approach of splitting the study cohort into a model-development cohort and an evaluation cohort was performed in a sensitivity analysis carried out to evaluate the impact of this choice of internal validation methods on the c-statistic reported for the Simplified Prediction Model. When the model-building steps were carried out in a random sample of 50% of the study cohort (the derivation cohort), and the Simplified Prediction Model generated in the derivation cohort was evaluated in the other 50% of

the study cohort (the evaluation cohort), the c-statistic for the Simplified Prediction Model's performance in the evaluation cohort was 0.721, identical to the average c-statistic calculated in bootstrapped samples from our entire cohort.

External validation in a cohort drawn from a different population or a different time period should be carried out in the future. Nevertheless, the biological plausibility of the associations between pregnancy-related predictors, and the consistency with which the majority of the predictors included in the Simplified Prediction Model and Points-Based Prediction Model have been associated with hypertension in other epidemiological studies from outside populations, suggest these models would be generalizable to other populations.

While the prevalence of hypertension is similar between men and women under the age of 50, epidemiologic data show that women experience a distinct increase in rates of hypertension as they age beyond this (55). There is also epidemiologic data that associations between pregnancy outcomes and hypertension were different in subgroup analyses of women younger than 50 years old compared to older women (59). Biologically, there is considerable evidence that estrogens affect endothelial function (150,151). It is therefore plausible that the pathophysiology and predictors of hypertension may differ in pre- and post-menopausal women. This model was specifically developed in women under the age of 50, and may not be applicable to older women. Because the median age of menopause is between 50 and 52 (in Caucasian women from industrialized countries) (152), this model may be predominantly applicable to premenopausal women.

Implications for Current Clinical Practice Guidelines

Current Canadian clinical practice guidelines advocate that women with prior obstetrical complications be counselled about the increased risk of hypertension and other associated cardiovascular and cerebrovascular disease. The 2014 guideline by the SOGC recommends that "women with a history of severe preeclampsia (particularly those who

presented or delivered before 34 weeks' gestation) should be screened for pre-existing hypertension and underlying renal disease", with a II-2B; Low/Weak grade of evidence (66). Based on this study, and other studies demonstrating that women with gestational hypertension without preeclampsia are at similarly increased risk of future hypertension (139), this recommendation should be modified to recommend that all women affected by a hypertensive disorder of pregnancy be screened in the first year postpartum for undiagnosed hypertension. Further, the SOGC guideline goes on to recommend "women with a prior hypertensive disorder of pregnancy (particularly associated with preterm delivery or adverse perinatal outcome) should be informed of their increased future health risks, including: hypertension; cardiovascular and cerebrovascular morbidity and mortality…" (66). In this study, an interaction between hypertensive disorders of pregnancy and adverse pregnancy outcomes did not improve the model's ability to predict future hypertension. Since it remains unclear whether the association with preterm delivery or other adverse perinatal outcomes influences the association between hypertensive disorders of pregnancy and future hypertension risk, and since this emphasis on adverse perinatal outcomes may cause women with hypertensive disorders not complicated by other adverse conditions to have their risk underestimated, the emphasis on preterm delivery or other adverse perinatal outcomes to inform women about increased future risk of hypertension should be reconsidered.

International guidelines consistently recommend that preeclampsia be considered a risk factor for future cardiovascular disease but are not consistent in recommending gestational hypertension also be considered (153). The American College of Obstetricians and Gynecologists (ACOG) advise that preeclampsia, particularly when associated with preterm delivery, should be considered a strong risk factor for [cardiovascular] disease" and recommend "For women with a medical history of preeclampsia who gave birth preterm (less than 37 0/7 weeks of gestation) or who have a medical history of recurrent preeclampsia, yearly assessment of blood pressure, lipids, fasting blood glucose, and body mass index is suggested." (11) With the screening recommendations, the ACOG guideline provides the caveat that "although there is clear evidence of an association between preeclampsia and later-life [cardiovascular] disease,

the value and appropriate timing [of enhanced screening] is not yet established" (11). By contrast, the British NICE Guideline, updated in 2011, recommends counselling women with preeclampsia or gestational hypertension about an increased risk of hypertension (12). Also in 2011, the American Heart Association added both preeclampsia and pregnancy-induced hypertension to their list of cardiovascular risk factors, which already included gestational diabetes (13). At present no guidelines are recommending additional counselling or surveillance regarding the future risk of hypertension or other cardiovascular disease after a preterm delivery, aside from those associated with hypertensive disorders of pregnancy. If the association of preterm birth with future hypertension is replicated in other populations, guidelines should be amended to include this risk factor.

This study may help refine the advice given to women regarding the impact of obstetrical outcomes on their overall risk of future hypertension by:

1) Confirming that pregnancies affected by gestational hypertension, not only preeclampsia, are associated with a significantly increased risk of future hypertension

2) Demonstrating that the recurrence of a hypertensive disorder in more than one pregnancy approximately doubles the risk of future hypertension, compared to a woman with one affected pregnancy, and increases the risk by approximately fourfold compared to no history of hypertensive disorders of pregnancy

3) Demonstrating that, in the absence of other risk factors, women with a history of a hypertensive disorder of pregnancy may still be at low risk of future hypertension overall, and

4) Demonstrating that pregnancy outcomes aside from hypertensive disorders, such as gestational diabetes or preterm birth, may also indicate an increased risk of future hypertension.

Directions for Future Study

A key limitation of existing risk prediction models is their failure to consider pregnancy-related outcomes as candidate predictors of future hypertension in young reproductive-aged women. By contrast, a limitation of the Simplified Prediction Model and Points-Based Prediction Model developed in this study is their inability to consider the traditional risk factors of family history, or a baseline blood pressure measurement. Future research should evaluate the incremental benefit of adding these candidate predictors to the Simplified Prediction Model and Point-Based prediction model for prediction of hypertension in reproductive-aged women. Ideally this would be done on prospectively-collected data collected primarily for research purposes. However, given the time and expense that would be required for such a study, and the routine availability of a blood pressure measurement taken in the first trimester of pregnancy (prior to the usual onset of preeclampsia), a retrospective chart review to obtain this data could provide further information about the likelihood that a baseline measurement of blood pressure would improve the performance of the Simplified Prediction Model or Points-Based Prediction Model.

At this point, these models have only been evaluated in Nova Scotian women under the age of 50. While the predictive power of obstetrical outcomes may be different in older women, future studies should evaluate the impact of obstetrical conditions (such as hypertensive disorders of pregnancy, primiparity, preterm delivery, multiple gestation, and breastfeeding history) on the prediction of hypertension in older and postmenopausal women. These models have not been validated outside of this study cohort; determining their generalizability to other women across Canada and internationally is necessary if they are to become clinically applicable. If these models were to be applied in ethnically diverse populations, the impact of ethnicity as a candidate predictor should be evaluated in external populations.

To determine whether these models can contribute meaningfully to improving the Canadian population's health, prospective research should evaluate whether the

application of these or any hypertension prediction models can lead to targeted interventions that prevent or delay the onset of hypertension or improve its detection at a stage where intervention can decrease its impact. Recently, clinical practice guidelines have emphasized that blood pressures between 120/80 and the traditional definition of hypertension of 140/90 may be important to recognize as these increase the risk of long-term morbidity and mortality (154,155). By contrast, treatment is often not recommended until blood pressures exceed 140/90 (154,155). Future research in hypertension risk-prediction models, particularly prospective studies that evaluate the impact of applying these models to identify and intervene in high-risk groups, should consider what degree of elevated blood pressure is most useful to predict.

Chapter 6 – Tables and Figures

Table 1 – Traditionally Established Risk Factors for Hypertension

Risk Factor		Estimated OR/RR/HR and [95% CI]
Age (40-44 years old vs. 20-34 years old)		OR 8.2 [5.0-13.3]
Prehypertension (SBP 120 to 139, DBP 80 to 89)		HR 6.81 [6.06 to 7.66]
BMI	25 to 30	OR 2.0 [1.1-3.5]
	30 to 35	OR 4.2 [2.4 to 7.2]
	≥ 35	OR 6.1 [3.4 to 10.9]
Diabetes		OR 3.4 [1.9 to 6.1]
Income adequacy (lowest vs. highest quintile)		OR 2.35
Black, Non-Hispanic vs. White, Non-Hispanic		OR 2.3 [1.5-3.5]
Family History of premature cardiovascular disease		HR 1.63 [1.24 to 2.14]
Cigarette Smoking		HR 1.35 [1.18 to 1.54]
Sex (women vs. men)		HR 1.29 [1.15 to 1.46]

OR = odds ratio, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = hazard ratio

Table 2 – Selected Risk Prediction Models for Hypertension

	Hopkins 1990 (24)	Framingham 2008 (50)	WHS (a) 2009 (47)	Whitehall II (b) 2009 (116)	ARIC/ CHS 2010 (30)	Iran (c) 2011 (29)	Taiwan (d) 2011 (156)	Korea 2013 (48)	Swedish (e) 2013 (27)	Japan 2015 (118)
women <50 included		•								
Age	•	•	•	•	•		•	•	•	•
Sex		•		•	•		•	•	•	
Systolic BP	•	•	•	•	•	•	•	•	•	•
Diastolic BP		•	•	•	•	•	•	•	•	•
BMI	•	•	•	•	•		•	•	•	•
Family history	•	•		•	•	•		•	•	•
Dyslipidemia									•	
Smoking		•	•	•	•	•			•	•
Ethnicity		•		•	•					
Diet		•		•	•	•				
Biochemical Markers			•				•			
Diabetes			•						•	
Sedentary Lifestyle			•						•	
Waist					•					
Alcohol									•	•
Heart Rate									•	
Marital Status									•	

(a) Simplified versions of the WHS tool exclude biochemical markers

(b) Modified versions of the Whitehall II tool incorporate repeat, average, or usual values for systolic and diastolic blood pressure

(c) Separate tools for men and women

(d) Clinical model excludes biomarkers

(e) A genetic risk score based on 29 single nucleotide polymorphisms was included in the model, but did not significantly improve the area under the curve

BP = Blood Pressure, BMI = Body Mass Index, WHS = Women's Health Study, ARIC = Atherosclerosis Risk in Communities study, CHS = Cardiovascular Health Study

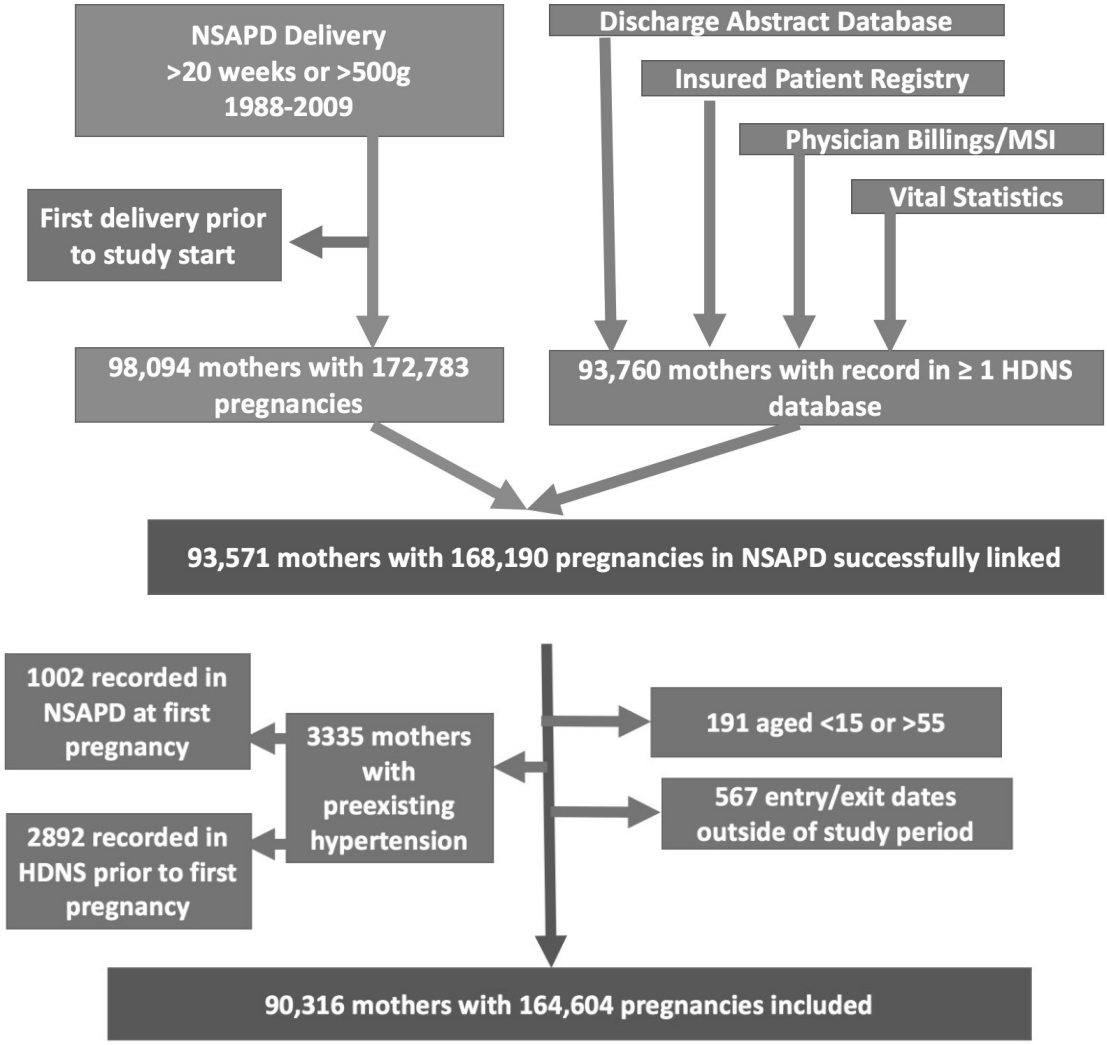
Table 3 – Operational Definition of Hypertension

	ICD-9	ICD-10
Essential (primary) Hypertension	401.-	I10
Hypertensive Heart Disease	402.-	I11.-
Hypertensive Renal Disease	403.-	I12.-
Hypertensive Heart and Renal Disease	404.-	I13.-
Secondary Hypertension	405.-	I15.-

* A code of hypertension was indicated by two physician billings claims within two years or one hospital admission containing one or more ICD codes listed here.

ICD = International Classification of Disease

Figure 1 – Summary of Data Linkage



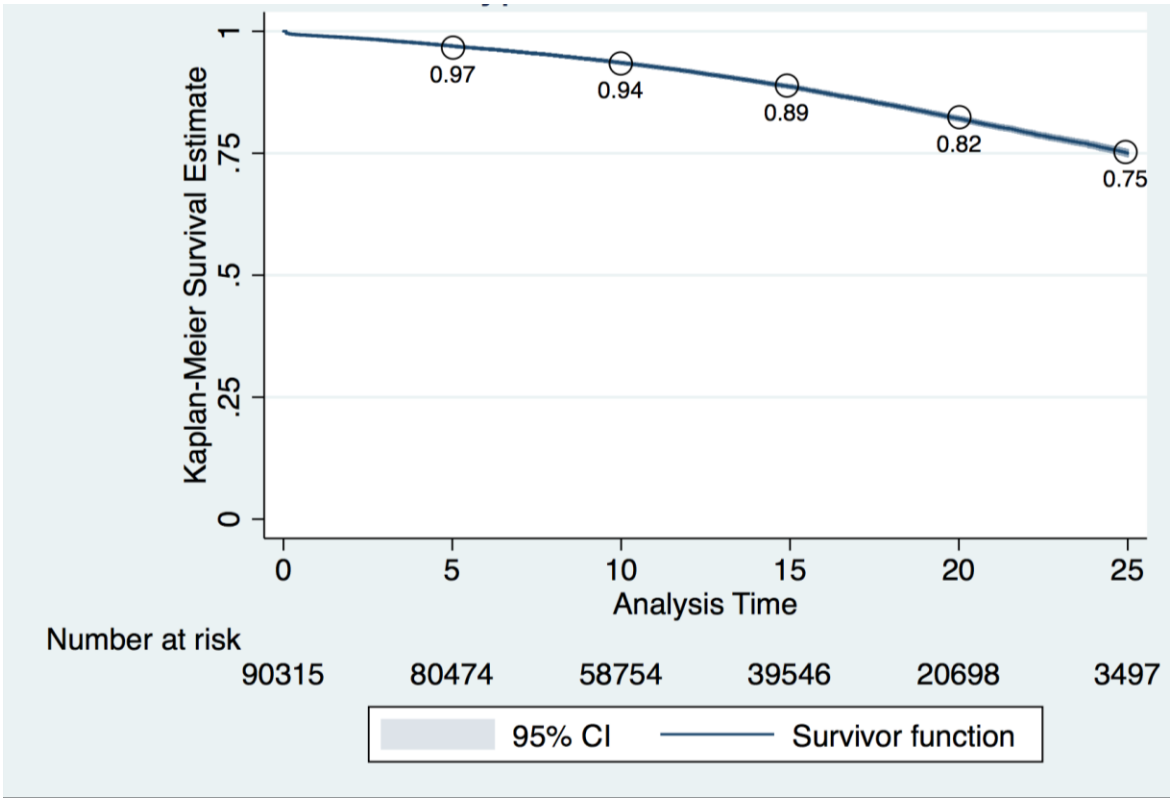
NSAPD = Nova Scotia Atlee Perinatal Database, MSI = Medical Services Insurance Program

Table 4 – Description of Study Cohort

	% Missing data	Mean or proportion	5th percentile – 95th percentile
Demographic Variables			
Maternal age at first delivery, years	0.58%	27.9	18.8 – 37.4
Maternal weight pre- first pregnancy, kg	7.16%	65.7 kg	47.6 – 95.3
Pregnancies in database per woman	-	1.79	1 - 3
Married or common-law	3.88%	71.4%	-
Area-level income quintile	0.57%	2.86	1-5
Urban residence	8.24%	60.2%	
Health Conditions Underlying Any Pregnancy			
Alcohol or drug use	-	1.14%	-
Anxiety or depression	-	3.25%	-
Renal disease	-	0.66%	-
Observed in at Least One Pregnancy			
Smoking in pregnancy	1.34%	30.89%	-
Maternal weight gain in pregnancy, kg	12.5%	14.96 kg	5.44 - 25.4
Gastroesophageal reflux disease	-	0.08%	-
Gestational diabetes	-	4.56%	-
Gestational hypertension (no proteinuria)	-	10.93%	-
Preeclampsia	-	2.64%	-
Eclamptic seizure	-	0.05%	-
Thromboembolic event	-	0.44%	-
Chorioamnionitis	-	1.41%	-
Oligohydramnios	-	3.34%	-
Polyhydramnios	-	0.77%	-
Placental infarction	-	0.39%	-
Placental abruption	-	1.64%	-
Placenta previa	-	0.58%	-

Cesarean delivery	-	28.78%	-
Multiple gestation	-	2.35%	-
Small for gestational age (<10 percentile)	-	14.21%	-
Large for gestational age (>90 percentile)	-	20.32%	-
Gestational age at delivery, weeks	-	39.45	36.29 – 41.86
Preterm birth (< 34 weeks)	-	3.04%	-
Stillbirth	-	0.84%	-
Neonatal death	-	0.53%	-
Breastfeeding	0.76%	70.18%	-
Chronic Health Conditions, Pre-existing or Developed By Time of Last Pregnancy			
Type 1 diabetes	-	0.49%	-
Type 2 diabetes	-	3.12%	-

Figure 2 – Hypertension-Free Survival in Entire Study Cohort



CI = Confidence Interval

Table 5 – Unadjusted Associations between Candidate Predictors and Risk of Hypertension

Continuous Variables	Units	Unadjusted HR	Unadjusted HR 95% CI	Hypertensive by 20 years postpartum	Hypertensive by 20 years postpartum 95% CI
Age at delivery	1 year	1.051	1.05-1.06		
(Maternal Age at Delivery Categorized)	<20	1	-	9.4%	8.1%-10.8%
	20-30	1.99	1.78-2.22	15.8%	15.3%-16.3%
	30-40	2.64	2.36-2.95	20.4%	19.9%-21.0%
	40-50	3.66	3.07-4.35	25.8%	22.6%-29.3%
Pre-pregnancy weight	1 kg	1.03	1.03-1.03		
(Pre-pregnancy weight categorized)	<50 kg	1	-	8.1%	7.3%-9.1%
	50-60	1.39	1.25-1.54	11.2%	10.6%-11.7%
	60-70	1.94	1.75-2.16	15.2%	14.6%-15.9%
	70-80	2.86	2.57-3.18	21.4%	20.5%-22.4%
	80-90	3.90	3.49-4.35	27.5%	26.1%-29.0%
	90-100	5.22	4.65-5.86	33.5%	31.6%-35.6%
	>100	6.04	5.38-6.79	37.1%	34.9%-39.4%
Weight gain in pregnancy	1 kg	0.98	0.98-0.99		
(Maternal weight gain in pregnancy, categorized)	<5 kg	1.57	1.45-1.70	25.6%	23.8%-27.4%
	5-15	1	-	17.3%	16.8%-17.8%
	15-25	0.89	0.86-0.94	15.6%	15.0%-16.2%
	>25 kg	1.08	0.98-1.19	18.9%	17.1%-20.1%
Delivery at < 40 wk	1 week	1.05	1.04-1.06		

Demographic Variables	Category	Unadjusted HR (95% CI)	Unadjusted HR (95% CI)	Hypertensive by 20 years postpartum	Hypertensive by 20 years postpartum
Married or common-law	No	1	-	14.3%	13.6%-15.0%
	Yes	1.32	1.26-1.39	18.3%	17.8%-18.6%
Primiparous	No	1	-	16.7%	15.2%-18.2%
	Yes	1.30	1.24-1.35	19.6%	18.0%-20.3%
Area-level income quintile	1	1	-	17.2%	16.4%-18.0%
	2	1.08	1.01-1.15	17.6%	16.9%-18.4%
	3	1.03	0.97-1.09	17.3%	16.6%-18.1%
	4	1.01	0.94-1.07	17.0%	16.2%-17.8%
	5	0.98	0.92-1.05	17.1%	16.2%-18.0%
Urban residence	No	1	-	18.0%	17.5%-18.6%
	Yes	0.90	0.86-0.94	16.5%	16.0%-17.0%

Underlying Health Conditions	Category	Unadjusted HR	Unadjusted HR 95% CI	Hypertensive by 20 years postpartum	Hypertensive by 20 years postpartum 95% CI
Type 2 Diabetes	No	1		17.3%	17.0%-17.7%
	Yes	3.08	2.84-3.33	43.8%	41.0%-46.7%
Type 1 Diabetes	No	1		17.9%	17.5-%18.2%
	Yes	2.39	1.97-2.90	36.4%	30.1%-43.6%
Pre-existing renal disease	No	1		17.2%	16.9%-17.6%
	Yes	1.25	1.0003-1.57	21.0%	16.6%-26.4%
Anxiety or depression	No	1		17.2%	16.9%-17.6%
	Yes	1.25	1.10-1.42	19.9%	17.3%-22.8%
Alcohol or drug use	No	1		17.3%	17.0%-17.7%
	Yes	0.45	0.32-0.63	8.1%	5.5%-11.8%

Pregnancy Related Outcomes	Category	Unadjusted HR	Unadjusted HR (95% CI)	Hypertensive by 20 years postpartum	Hypertensive by 20 years postpartum
Preeclampsia	No	1		17.3%	(16.9-17.6%)
	Yes	3.45	(3.22-3.71)	43.1%	(40.6-45.7%)
Eclamptic seizure	No	1		17.9%	(17.6-18.3%)
	Yes	2.66	(1.51-4.68)	32.7%	(18.8-52.9%)
GHTN (no proteinuria)	No	1		15.2%	(14.9-15.6%)
	Yes	3.02	(2.90-3.15)	37.7%	(36.5-38.9%)
GERD	No	1		17.9%	(17.6-18.3%)
	Yes	2.11	(1.10-4.07)	32.6%	(14.9-61.9%)
Gestational Diabetes	No	1		17.4%	(17.0-17.7%)
	Yes	2.03	(1.89-2.19)	31.3%	(29.4-33.3%)
Stillbirth	No	1		17.9%	(17.6-18.3%)
	Yes	1.49	(1.26-1.76)	24.0%	(20.4-28.1%)
Cesarean delivery	No	1		16.7%	(16.3-17.1%)
	Yes	1.37	(1.32-1.42)	21.4%	(20.7-22.2%)
Preterm birth (< 34)	No	1		17.9%	(17.5-18.2%)
	Yes	1.29	(1.17-1.42)	20.7%	(18.8-22.7%)
Thromboembolic event	No	1		17.9%	(17.6-18.3%)
	Yes	1.2	(0.96-1.69)	20.8%	(15.7-27.5%)
Polyhydramnios	No	1		17.9%	(17.6-18.3%)
	Yes	1.23	(1.03-1.50)	21.0%	(17.5-25.1%)
Gest weight gain > recommended by IOM	No	1		16.1%	(15.6-16.6%)
	Yes	1.23	(1.19-1.28)	19.5%	(19.0-20.0%)
Gestational weight gain < recommended by IOM	No	1		18.7%	(18.3-19.1%)
	Yes	0.80	(0.77-0.84)	15.3%	(14.6-16.0%)
Placental abruption or infarction	No	1		17.9%	(17.5-18.2%)
	Yes	1.28	(1.14-1.45)	21.9%	(19.4-24.6%)
Oligohydramnios	No	1		17.8%	(17.5-18.2%)
	Yes	1.20	(1.10-1.32)	21.2%	(19.4-23.1%)
SGA (<10 percentile)	No	1		17.8%	(17.5-18.2%)
	Yes	1.03	(0.98-1.10)	18.5%	(17.6-19.4%)

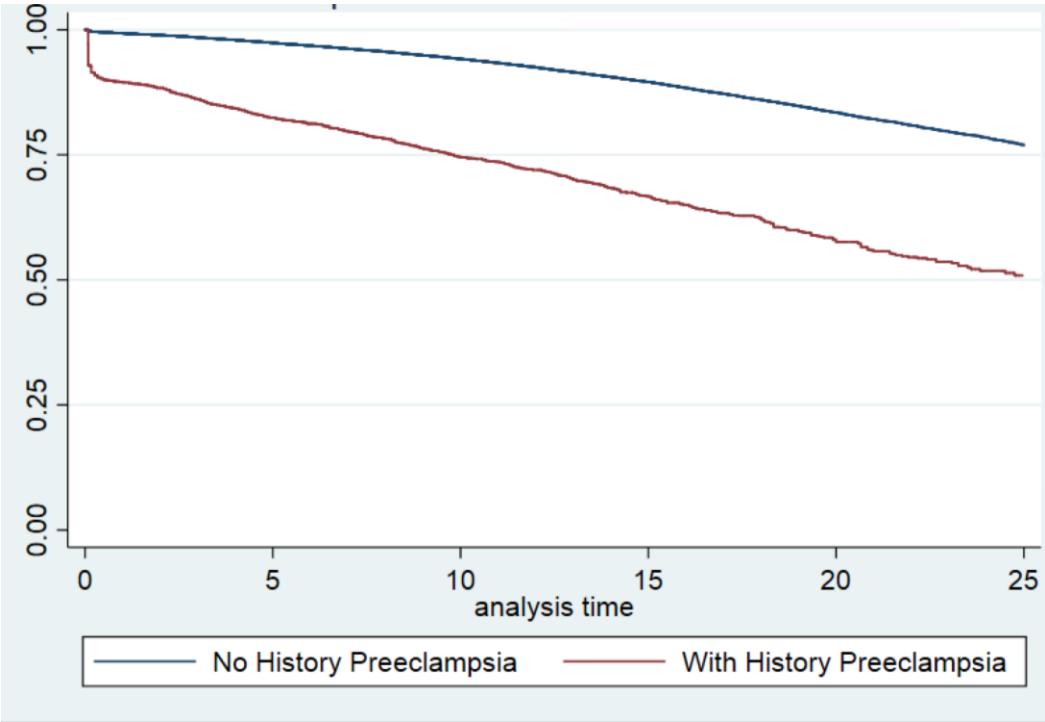
Pregnancy Related Outcomes, continued	Category	Unadjusted HR	Unadjusted HR (95% CI)	Hypertensive by 20 years postpartum	Hypertensive by 20 years postpartum
LGA (>90 percentile)	No	1		17.7%	(17.3-18.1%)
	Yes	1.10	(1.05-1.15)	19.1%	(18.3-19.9%)
Multiple gestation	No	1		18.0%	(17.6-18.3%)
	Yes	1.00	(0.88-1.14)	17.8%	(15.7-20.2%)
Sex of infant	Female	1		19.3%	(18.6-19.9%)
	Male	0.90	(0.86-0.93)	17.4%	(17.0-17.8%)
Placenta previa	No	1		17.9%	(17.6-18.3%)
	Yes	1.06	(0.83-1.35)	18.1%	(14.0-23.3%)
Chorioamnionitis	No	1		17.9%	(17.6-18.3%)
	Yes	0.99	(0.85-1.16)	18.6%	(15.8-21.7%)
Neonatal death	No	1		17.9%	(17.6-18.3%)
	Yes	1.02	(0.80-1.29)	17.9%	(14.0-22.7%)
Breastfeeding	No	1		19.3%	(18.7-19.9%)
	Yes	0.88	(0.84-0.91)	17.2%	(16.8-17.7%)
Smoking in pregnancy	No	1		18.9%	(18.4-19.3%)
	Yes	0.83	(0.79-0.86)	16.0%	(15.4-16.6%)

GHTN = Gestational Hypertension, GERD = Gastroesophageal Reflux Disease,

IOM = Institute of Medicine, SGA = Small for Gestational Age, LGA = Large for Gestational Age

Figure 3 – Kaplan-Meier Curves Stratified According to Hypertensive Disorder of Pregnancy Status

a) **By preeclampsia status**



a) **By gestational hypertension status**

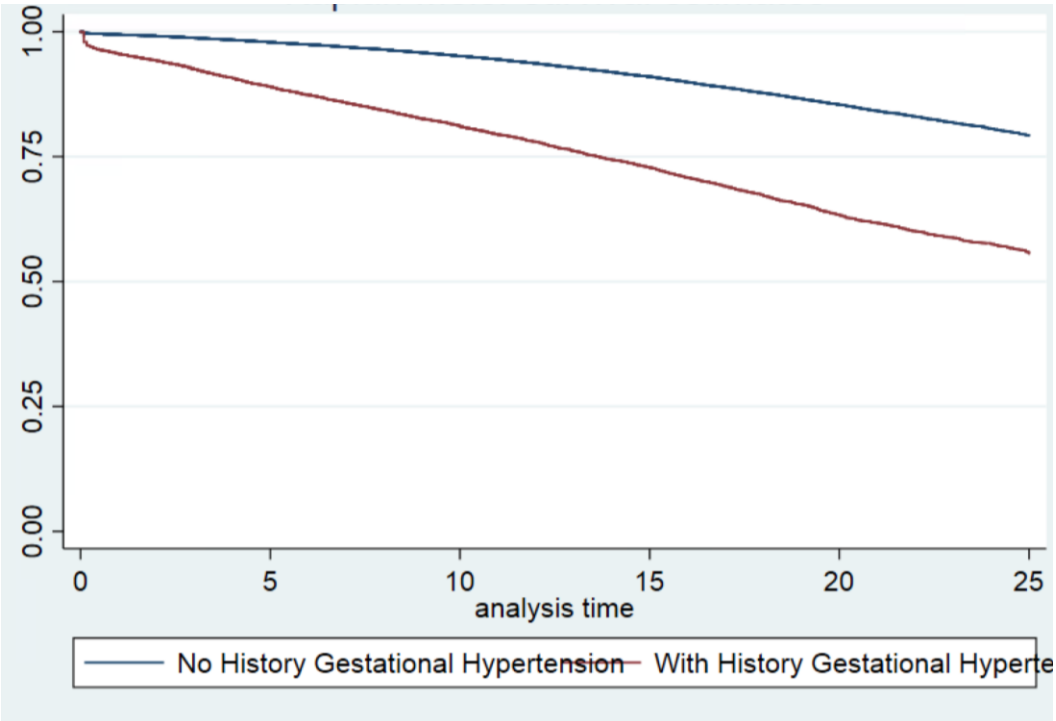


Table 6 – Model Characteristics

Number of candidate predictors	Women contributing to model	Hypertension cases contributing to model	Akaike information criterion (AIC)
Model 1: Each candidate predictor included in categorical form			
36	74,114	7,779	162,394
Model 2: Replacing categorical with continuous forms of pre-pregnancy weight, maternal age, and gestational age			
35	74,114	7,779	162,344
Model 3: Addition of pre-specified interactions, and retention of significant interactions			
36	70,182	7,397	153,674
Model 4: Addition of quadratic terms for pre-pregnancy weight and maternal age			
38	70,182	7,397	153,145
Model 5: Addition of time-varying hazard for preeclampsia, gestational hypertension and eclampsia			
46	70,182	7,397	150,954
Model 6 (Full Prediction Model): Categorization of pregnancy-associated predictors as 0, 1, or ≥ 2 affected pregnancies Included Predictors: maternal age, primiparity, preeclampsia, gestational hypertension, gestational diabetes, SGA infant, multiple gestation, smoking in pregnancy, LGA infant, breastfeeding, T2DM, pre-pregnancy weight, gestational age, urban residence, area-level income quintile, marital status, alcohol or drug use, renal disease			
46	70,182	7,397	150,834

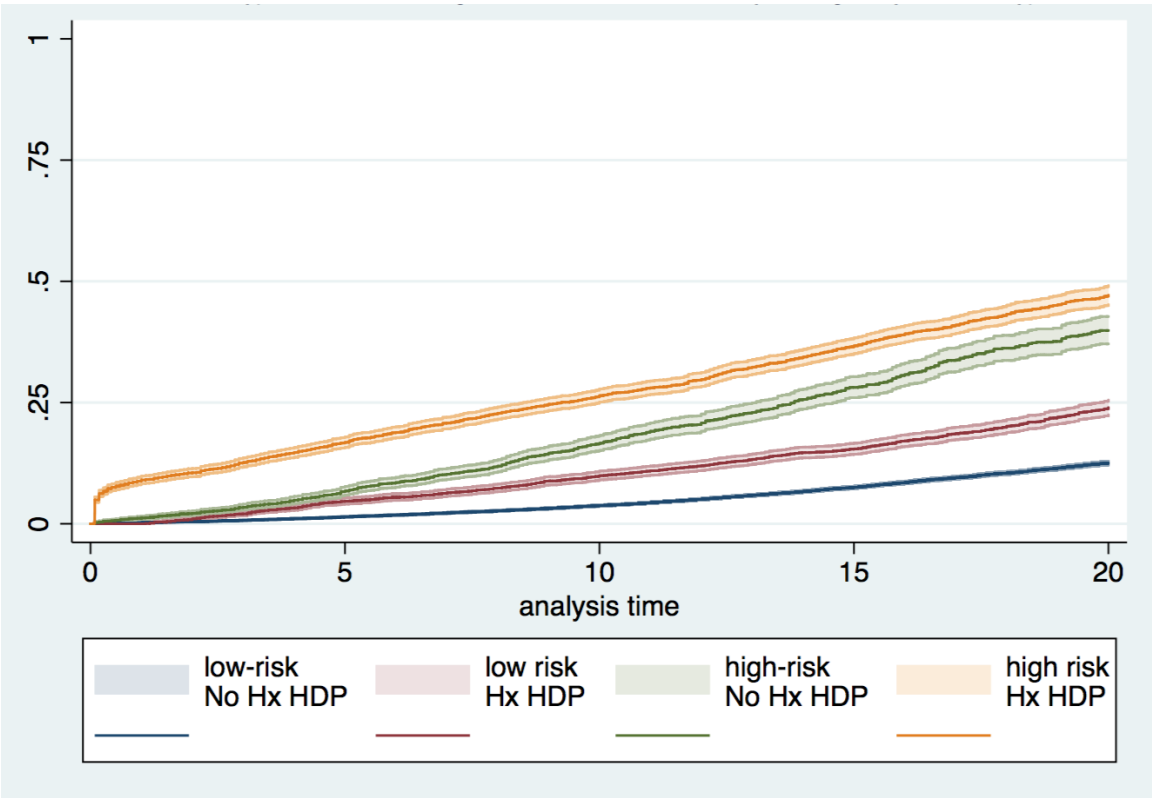
Number of candidate predictors	Women contributing to model	Hypertension cases contributing to model	Akaike information criterion (AIC)
Model 7 (Simplified Prediction Model): Elimination of unstable predictors that were not included in ≥80% of models derived by stepwise elimination from model 5 in 100 bootstrapped samples Included Predictors: Predictors: maternal age, primiparity, preeclampsia, gestational hypertension, gestational diabetes, SGA infant, multiple gestation, smoking in pregnancy, LGA infant, breastfeeding, T2DM, pre-pregnancy weight, gestational age, urban residence			
19	76,907	8,059	165,665
Points-Based Model: Linear predictor approximated with the sum of integer "points" Included Predictors: maternal age, pre-pregnancy weight, T2DM, hypertensive disorder of pregnancy, primiparity, preterm delivery <34 weeks at last delivery, multiple gestation, breastfeeding			
9	90,312	9,453	198,931

LGA = Large for Gestational Age, T2DM = Type 2 Diabetes Mellitus

Table 7 – Simplified Prediction Model

Predictor	Level	Hazard Ratio (95% CI)	
Age at Delivery	/5 years	1.65	(1.51-1.79)
Age at Delivery squared	/25 year^2	0.96	(0.94-0.97)
Weight Pre-Pregnancy	/5 kg	1.23	(1.21-1.25)
Weight Pre-Pregnancy squared	/25 kg^2	0.99	(0.99-0.99)
Gestational Age at Delivery	/week	1.04	(1.03-1.05)
Urban residence	Yes	0.88	(0.84-0.92)
Primiparity	Yes	1.52	(1.43-1.63)
Multiple gestation	1	*0.61	(0.53-0.71)
Smoking in Pregnancy	1	0.92	(0.86-0.98)
	≥2	0.84	(0.78-0.91)
Gestational Diabetes	1	1.17	(1.06-1.23)
	≥2	1.24	(0.999-1.54)
Gestational Hypertension	1	2.18	(2.06-2.30)
	≥2	4.09	(3.61-4.63)
Gestational Hypertension – additional risk of diagnosis in first year		52.5	(44.0-62.6)
Preeclampsia	1	2.14	(1.93-2.37)
	≥2	4.91	(3.23-7.49)
Preeclampsia – additional risk of diagnosis in first year		40.4	(32.6-50.0)
Small for Gestational Age <10th percentile	1	1.15	(1.08-1.23)
	≥2	1.28	(1.09-1.51)
Large for Gestational Age >90th percentile	1	0.91	(0.86-0.97)
	≥2	0.82	(0.73-0.92)
Breastfeeding	1	0.81	(0.77-0.86)
	≥2	0.74	(0.69-0.79)
Type 2 Diabetes Mellitus	Yes	1.43	(1.28-1.61)

Figure 4 – Risk of Hypertension Stratified by Predicted Risk and History of Hypertensive Disorders in Pregnancy



Hx HDP = History of Hypertensive Disorder of Pregnancy

Table 8 – Scoring of Risk in Points-Based Model

Points Derived from Obstetrical History			
	No affected pregnancies	One affected pregnancy	≥ Two affected pregnancies
Hypertensive Disorder of Pregnancy	0	2	3
Primiparous	-	1	-
Preterm Delivery <34w at last pregnancy	-	1	-
Multiple Gestation	0	-1	**
Breastfeeding	0	0	-1

Points Derived from Demographic Variables		
	Category	Points Assigned
Age at Delivery in current pregnancy	15-20y	0
	20-30y	1
	30-50y	2
Pre-pregnancy Weight in current pregnancy	<35kg	-2
	35-45kg	-1
	45-55kg	0
	55-65kg	1
	65-75kg	2
	75-85kg	3
	85-95kg	3
	95-105kg	4
	>105kg	5

Points Derived from Other Medical History	
	Points Assigned
History of Type 2 Diabetes	1

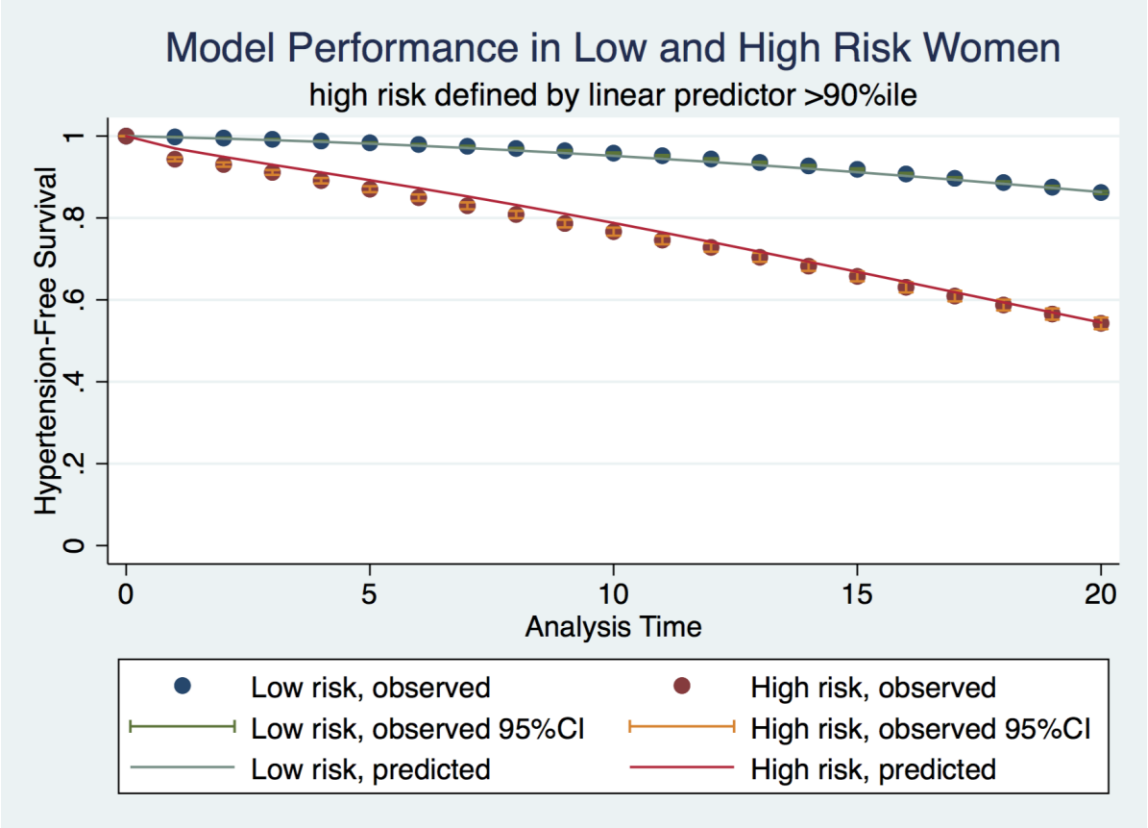
Table 9 – Observed Hypertension Risk Stratified by Points-Based Model Score

Points	Frequency in Population	Observed 10-year Risk	Observed 10-year Risk 95% CI	Observed 20-year Risk	Observed 20-year Risk 95% CI
≤ -3	<0. 1%				
-2	0.3%				
-1	4.3%	1.5%	1.2-1.9%	6.2%	5.3 - 7.2%
0	11.5%	2.3%	2.0-2.7%	8.3%	7.7 - 9.0%
1	25.2%	3.2%	3.0-3.5%	11.1%	10.6- 11.8%
2	23.8%	4.2%	3.9-4.5%	15.2%	14.5- 16.0%
3	15.8%	6.8%	6.3-7.2%	20.7%	19.7% - 21.8%
4	10.4%	11.3%	10.6-12.1%	30.6%	29.1-32.1%
5	4.3%	15.3%	14.1-16.6%	36.2%	34.1-38.5%
6	2.8%	19.0%	17.3-20.8%	42.6%	39.5-45.8%
7	0.8%	26.4%	22.9-30.3%	54.1%	49.0-59.4%
8	0.4%				
≥9	0.5%				

CI = Confidence Interval

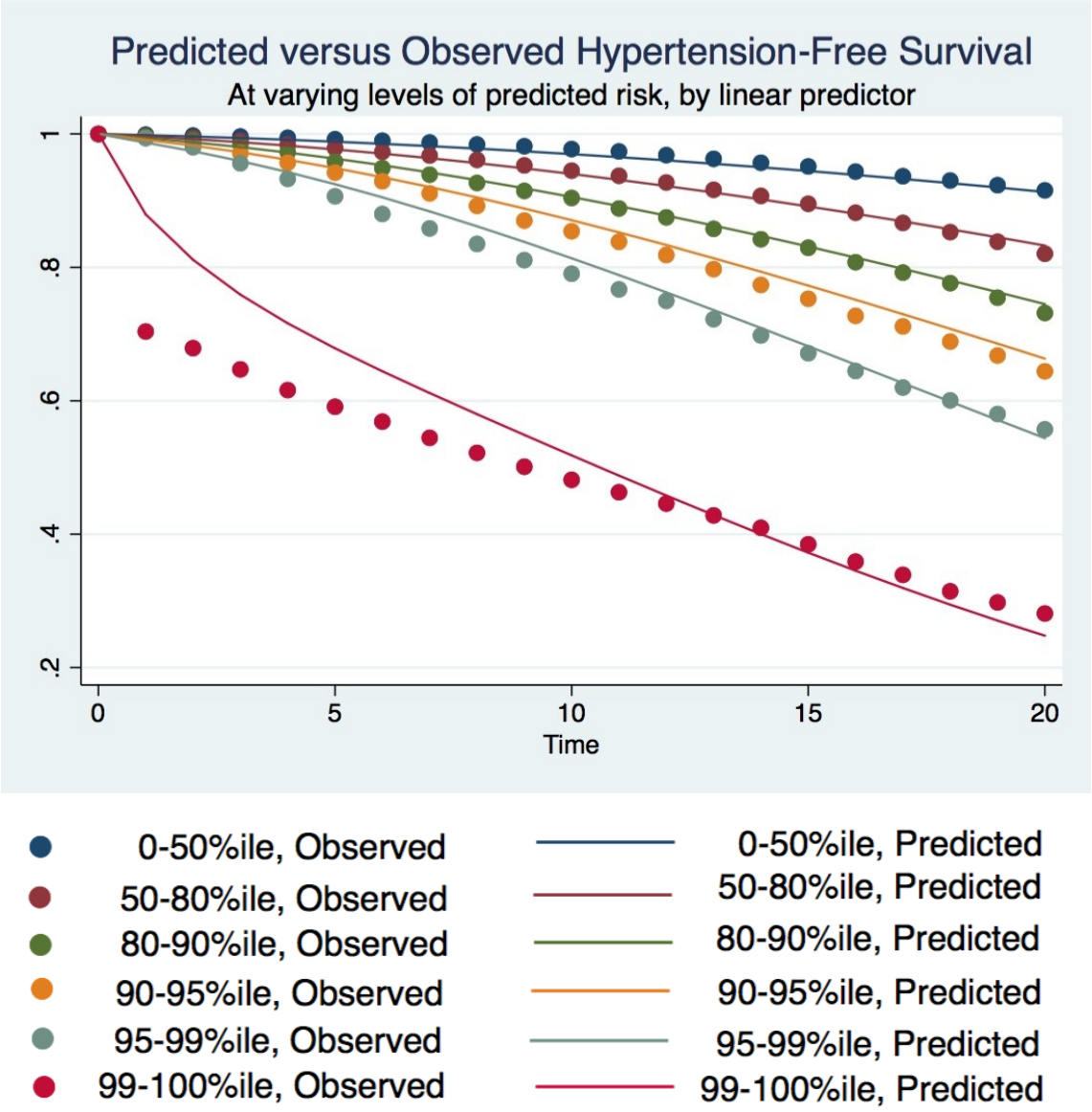
Figure 5 – Performance of Simplified Prediction Model Stratified by Risk Category

a)



CI = Confidence Interval, %ile = Percentile

b)

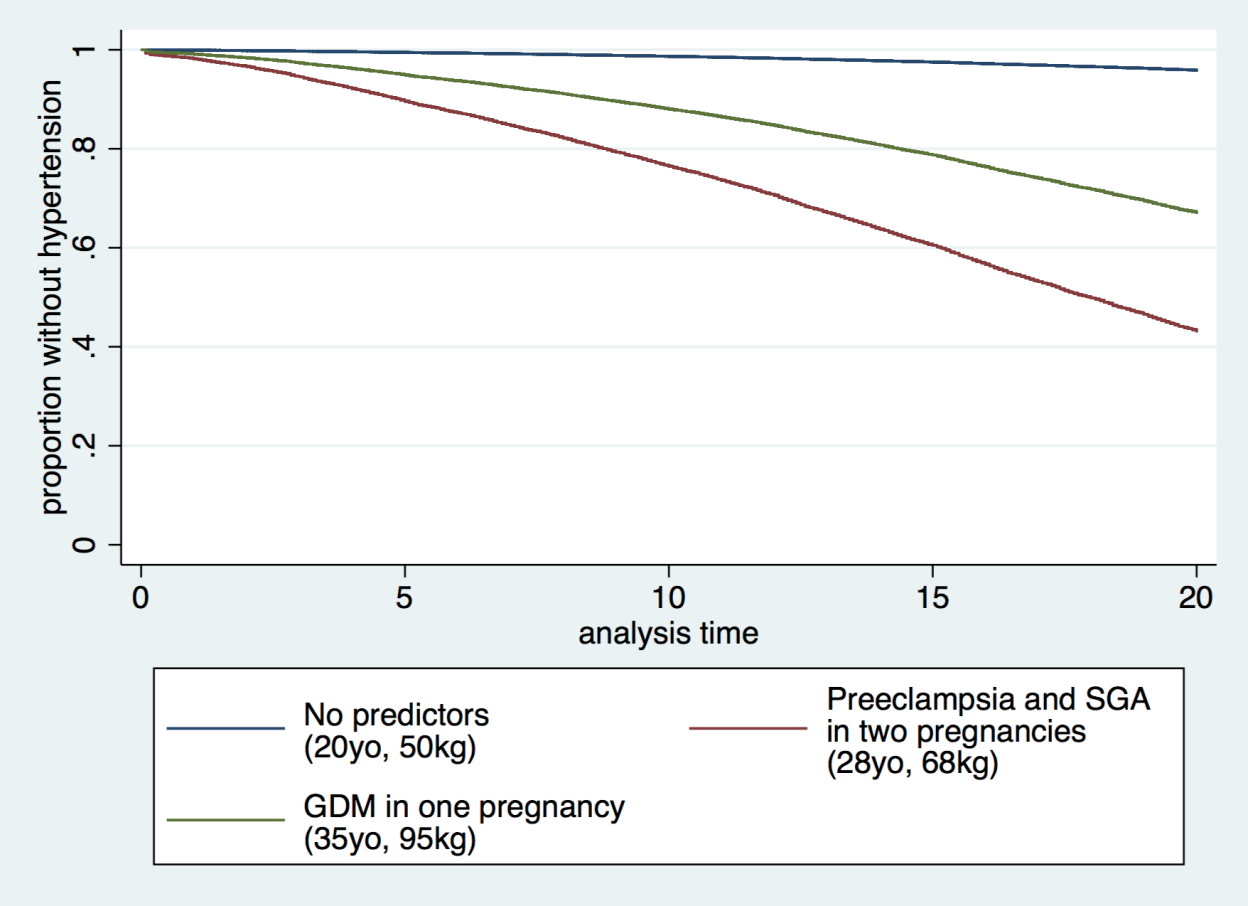


%ile = Percentile

Table 10 – Evaluation of Models' Performance

	c-statistic	"high risk" women per 1000	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Full Prediction Model	0.72					
Simplified Prediction Model	0.72	-	-	-	-	-
Simplified Prediction Model – Mean from bootstrapped samples	0.71					
Points-Based Model	0.67					
Simplified Prediction Model – dichotomized 95%	0.59	50	15.7%	97.3%	55.4%	84.3%
Simplified Prediction Model – dichotomized 90%	0.62	100	26.1%	93.5%	46.3%	87.1%
Simplified Prediction Model – dichotomized 80%	0.65	200	42.6%	84.9%	38.2%	87.1%
Simplified Prediction Model – dichotomized 50%	0.65	500	73.9%	55.4%	27.0%	90.4%

Figure 6 – Application of Simplified Prediction Model for Hypertension Risk



SGA = Small for Gestational Age, GDM = Gestational Diabetes Mellitus

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