Association Between Hypertensive Disorders During Pregnancy and Subsequent Long-term Risk of Hospitalization Due to End-stage Renal Disease: A Population-based Follow-up Study

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ABSTRACT

Hypertensive disorders during pregnancy (HDPs) were reported to be associated with some serious maternal outcomes and adverse long-term consequences. To examine the effect of HDPs on the development of end-stage renal disease (ESRD), we followed up a cohort of women who had delivered in Canadian hospitals between the fiscal years of 1993/1994 and 2002/2003 and identified their subsequent hospitalizations. The study revealed that a significantly higher risk of incidence of subsequent ESRD hospitalization was associated with previous HDPs, and women with pre-eclampsia superimposed on pre-existing hypertension had the highest risk among the women with HDPs. Cox regression analysis was used to adjust for potential confounders, and to estimate the relative risk for ESRD hospitalization associated with previous HDPs and found that gestational hypertension and pre-eclampsia increased the risk which was partially mediated by diabetes mellitus developed after HDPs. In addition, pre-eclamptic pregnancy associated with preterm delivery could substantially elevated risk of an ESRD hospitalization in later life.

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Chapter 1 Introduction

1.1 Hypertensive disorders during pregnancy

Abnormal elevated blood pressure with systolic blood pressure higher than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg is defined as hypertension[1]. Hypertension occurred during pregnancy, known as hypertensive disorders during pregnancy (HDPs), affects 5–10% of all pregnancies[2-4]. In Canada, approximately 5 to 7% of pregnant women experience HDPs, which are the major cause of maternal and perinatal mortality and morbidity in this country[5-7].

Based on the US national guideline published at 2000, HDPs can be classified into four groups: pre-existing (chronic) hypertension, pre-eclampsia/eclampsia, pre-eclampsia superimposed on pre-existing hypertension, and gestational hypertension[8] (Table 1.1.).

Table 1.1. Classification of HDPs with major diagnosis criteria[8]

Gestational hypertension	• de novo arterial hypertension • Temporary hypertension after 20th week of gestation • Return to normal blood pressure postpartum • No proteinuria
Pre-eclampsia/Eclampsia	• Gestational hypertension *plus* proteinuria $\geq$ 300 mg/24 hr (or creatinine ratio $\geq$30 mg/mmol) • Eclampsia: the presence of convulsions
Pre-existing hypertension	• Hypertension that exist prior to pregnancy or is diagnosed before 20th week of gestation • de novo hypertension which fails to settle postpartum
Pre-eclampsia superimposed upon existing hypertension	• de novo proteinuria after 20th week of gestation • a sudden increase in blood pressure

In 2008, Society of Obstetricians and Gynaecologists of Canada (SOGC) updated guideline for hypertension in pregnancy and reclassified this kind of disease into pre-existing hypertension and gestational hypertension according to the different onset of hypertension and emphasized that women may be classified into more than one subgroup (Table 1.2.).

Because the majority of discharge information used in this study was recorded before 2003 with International Classification of Diseases (ICD) 9 coding system, we classified HDPs according to US national guideline in present study[8].

Among HDPs, pre-eclampsia (including eclampsia) is frequently associated with severe pregnant complications, such as preterm delivery and fetal growth restriction, and cause

Table 1.2. Classification of HDPs and definition of pre-eclampsia from SOGC[9]

Primary Diagnosis		Definition of Pre-eclampsia
Pre-existing hypertension (hypertension before 20 weeks' gestation)		
	With comorbidities	
	With pre-eclampsia (onset after 20 weeks' gestation)	• Resistant hypertension • New or worsening proteinuria • One or more adverse condition(s)
Gestational hypertension (hypertension at/after 20 weeks' gestation)		
	With comorbidities	
	With pre-eclampsia (onset after 20 weeks' gestation)	• New proteinuria • One or more adverse condition(s)

long-term severe adverse outcomes[2-4,10-20]. Depending on study populations, pre-eclampsia complicates 3 to 10% of all pregnancies[9,21]. Nulliparity, multiple pregnancy, extreme maternal age (older than 40 years), family history of pre-eclampsia, previous pre-eclamptic pregnancy, ethnicity, obesity (body mass index higher than 35kg/m^2), smoking, diabetes mellitus, kidney disease, essential hypertension and autoimmune disease (such as systemic lupus erythematosus) were found to be associated with an increased risk of developing pre-eclampsia and considered as the common risk factors for pre-eclampsia[17,22-31].

In normal pregnancy, maternal blood pressure usually decreases due to a reduction of the peripheral vascular resistance and slightly elevates later towards previous non-pregnant blood pressure at full-term. In pre-eclampsia, abnormally increased peripheral vascular resistance reverses this vascular change and contributes to hypertension[32]. However, pre-eclampsia is considered as a multi-system disorder of pregnancy and the exact cause remains unknown. For pre-eclampsia usually resolves itself after delivery, placenta is regarded as the pathogenic focus for all manifestations of pre-eclampsia[33,34]. During the early stage of normal gestation, uterine spiral arteries, the vessels supplying blood from uterine arteries to the placenta, are remodelling into sac-like, flaccid uteroplacental vessels with reduced resistance[35]. Successful transformation can decrease the ability of vasoconstrictive and allow greater volumes of blood supplied to placenta with a lower blood pressure than before. However, incomplete transformed spiral arteries, which remain thick-walled and muscular, have been well documented in women with pre-eclampsia. This kind of vessel restricts the enough blood flow to the placenta and consequently leads to placental ischemia[36]. As a response, hypoperfused placenta releases

some anti-angiogentic factors, such as the soluble vascular endothelial growth factor receptor-1 (sFlt-1), into maternal circulation and induced oxidative stress, which contributes to endothelial dysfunction and pro-inflammatory state in pre-eclampsia[37-43]. The increasing content of plasma fibronecin, an indicator of endothelial damage, was detected in women with hypertensive gestation and supported that the integrity of maternal endothelium is impaired in this kind of women[44-47]. The endothelial disorder can induce multi-system dysfunction, and has been suggested to reverse the physiological vasodilatation in pregnancy and responsible for subsequent hypertension and proteinuria[45,48,49].

Gestational hypertension and pre-eclampsia are the major subcategories of HDPs. There are various options about whether they are two different entities or different stages of one disease during development. It has been proposed that gestational hypertension is regarded as latent essential hypertension that is just revealed by pregnancy, while pre-eclampsia is a pregnancy-specific syndrome with a different etiology[3,50]. In clinical, proteinuria can appear very late after the development of gestational hypertension, especially the onset of hypertension prior to 34 weeks' gestation[51]. Gestational hypertension can be a transient status and finally develop into pre-eclampsia. Therefore, pre-eclampsia is also considered as the extreme end of maternal adaptation to pregnancy[51-53].

1.2 Hypertensive disorders during pregnancy and future maternal health

1.2.1 Hypertensive disorders during pregnancy and its long-term implication on cardiovascular disease and diabetes mellitus

Positive relationship between pre-eclampsia and subsequent maternal hypertension was suggested several decades ago[54]. Recently, accumulated evidence has exhibited that abnormally elevated blood pressure during pregnancy is not just associated with maternal and perinatal adverse outcomes, but also implicates the future health problems, especially cardiovascular disease (CVD), for both pregnant women and their offspring[15,55-57]. It is well documented that HDPs and CVD share similar risk factors, including obesity, smoking, extreme age, diabetes mellitus and kidney diseases. Endothelial dysfunction in HDPs could play a key role in the development of subsequent hypertension and other cardiovascular disease. Women with previous pre-eclampsia compared with those without, had a relative risk of 3.70 (95% CI: 2.70 to 5.05) for subsequent hypertension, of 2.16 (95% CI: 1.86 to 2.52) for ischaemic heart disease (IHD) and of 1.81 (95% CI: 1.45 to 2.27) for stroke[55]. The risk of hospitalization for deep venous thromboembolism was reported to be 2.2-fold higher in women with previous pre-eclampsia than women without such a medical condition[58].

Beside cardiovascular diseases, women with previous gestational hypertension or pre-eclamptic pregnancy exhibited insulin resistance even eight years after pregnancy and had a two-fold risk of developing diabetes mellitus later in life[59,60].

1.2.2 Hypertensive disorders during pregnancy and subsequent kidney disease

Kidney is an important organ to excrete waste products, such as creatinine, from body. Kidney with normal function can completely filter and excrete serum creatinine. The level of serum creatinine is measured to estimate the glomerular filtration rate (eGFR). The accumulation of serum creatinine means that the normal renal function is impaired and the ability to filter and excrete serum creatinine decreases. According to various

levels of serum creatinine, chronic kidney disease is classified into five stages and the last stage (defined as eGFR<15 ml/min/1.73 m^2) is usually called end-stage renal disease (ESRD)[61]. At ESRD stage, only approximately 10% of renal function remains, and this is inadequate to support a normal individual's daily life. ESRD patients need to perform hemodialysis or peritoneal dialysis treatment immediately or accept kidney transplantation to survive.

The kidney is one of the main organs affected by hypertensive gestation and appearance of proteinuria is one of the important characteristics of pre-eclampsia. Although pre-eclampsia and proteinuria can resolve after delivery, the microalbuminuria, a marker of renal endothelial injury, can be persistently detected several years after gestational hypertension or pre-eclamptic pregnancy, indicating the renal impairment from hypertensive pregnancy is long-term[62].

Recently, several large population-based epidemiological studies investigated the long-term adverse effect of HDPs on renal function and demonstrated that women with a history of HDPs had a high risk of subsequent renal disease, including ESRD[63-65]. For hypertensive pregnancy and renal disease share some similar risk factors, such as diabetes mellitus, obesity and hypertension, there remains a lack of conclusion on whether hypertensive gestation itself, or underlying pathophysiological risk factors, or combination of both contribute to future renal disease. The evidence for the long-term implications of HDPs on renal disease is detailed in Chapter 3.

Chapter 2 Objective

The present study was aimed to examine the association of HDPs with the risk of subsequent hospitalization due to ESRD. Specifically, the study objectives were:

1. To verify whether HDPs are associated with a higher risk of subsequent ESRD hospitalization;
2. To assess the effect of the various types of HDPs on subsequent ESRD hospitalization;
3. To identify potential pregnancy-related risk factors or comorbidities for subsequent ESRD hospitalization; and
4. To examine whether diabetes mellitus developed after HDPs contributes to the ESRD hospitalization in late life.

Chapter 3 Literature Review

A comprehensive literature search was conducted to identify publications that investigated the relationship between previous HDPs and the risk of ESRD. We searched PubMed/Medline and OvidSP for publications between 1960 and April 30, 2014 using the key words related to HDPs and ESRD (Appendix A). The search tried to find all cohort studies and case-control studies that clearly examined ESRD as a long-term adverse outcome in women with a history of hypertensive disorders during pregnancy.

As shown in Figure 3.1, 353 citations and 336 citations were identified from PubMed/Medline and OvidSP, respectively, in our search. After removal of duplicates, 519 citations remained in study. Among them, 162 citations were further removed because the citations had no author or abstract or were written in language other than English. Based on the results from screening title and abstract, 12 citations were selected to undergo full-text article review. The most common reasons for exclusion during the screening process of title and abstract were that the publication was review paper or the ESRD was not the primary outcome in study. Finally, 5 articles were included in this literature review[64-68] (Table 3.1). These studies had a clear description of selection criteria and study design, contained a comparison group, and explored the statistical significance of study results with adjustment for potential confounders. All reviewed articles were retrospective studies and published between 2008 and 2014. Three studies from Norway had the same first author[65,67,68] and the other two were from Taiwan[64,66]. Among these studies, four studies[64-67] were population-based epidemiological research and one study[68] only selected women with kidney biopsy after last delivery into the study population.

Figure 3.1 Study process of literature review of association of HDPs with subsequent ESRD.

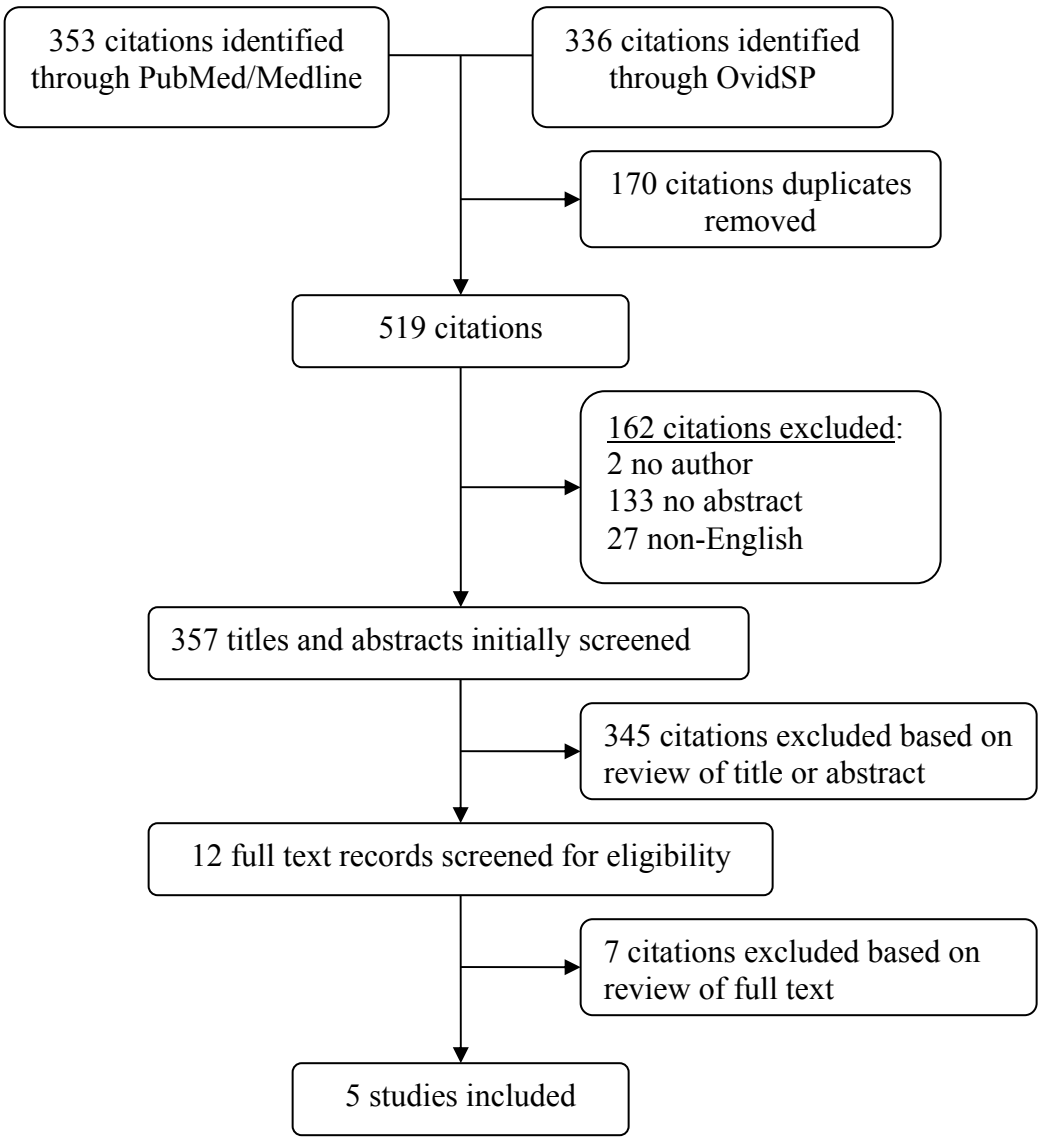


Table 3.1 Characteristics of studies included in literature review

Study	Study period	Population and study design	Exclusion criteria	Data source and exposure classification	Exposure group	Reference group
Wu et al (2014)	1998-2002	Population: women with or without HDPs in their first pregnancy during the study period identified in insurance database; Study design: Retrospective cohort study;	Women with multiple HDPs, diabetes, renal disease, systemic lupus erythematosus, and previous ESRD history	Taiwan National Health Insurance database (ICD-9 CM codes): Gestational hypertension: 642.3; Preeclampsia/Eclampsia: 642.4, 642.5 and 642.6; Pre-existing hypertension: 642.0 and 642.2; Preeclampsia imposed on pre-existing hypertension: 642.7	gestational hypertension: 2,361; preeclampsia: 8,609; pre-existing hypertension: 731; preeclampsia imposed on pre-existing hypertension: 594;	930,841 without hypertensive disorders during pregnancy
Wang et al (2013)	1998-2009	Population: women aged 19-40 years with HDPs in their first pregnancy; women without HDPs were randomly selected (ratio:8:1) with matched maternal age and delivery year of women with HDPs; Study design: Retrospective cohort study;	Women with hypertension, diabetes, kidney disease or lupus.	Taiwan National Health Insurance database (ICD-9 CM codes): 642.3, 6424.4-642.6 and 642.9	gestational hypertension: 8,653; preeclampsia/eclampsia: 17,998	213,397 women without HDPs in their first pregnancy during the study period
Vikse et al (2008)	1967-1991	Population: women with a delivery history identified in the Medical Birth Registry of Norway; Study design: Retrospective cohort study;	Women with multiple deliveries; women with a diagnosis of hypertension, kidney disease, rheumatic disease, or diabetes before first pregnancy were excluded before model analysis	Medical Birth Registry of Norway(ICD-8 codes): Preeclampsia (ICD codes were not provided)	preeclampsia: 20,918	549,515 women without preeclampsia in their first pregnancy during the study period

Table 3.1: cont'd

Study	Study period	Population and study design	Exclusion criteria	Data source and exposure classification	Exposure group	Reference group
Vikse et al (2010)	1967-2005	Population: Women who had a representative kidney biopsy after their last recorded birth and registered in the Norwegian Kidney Biopsy Registry between 1988 and 2005; Study design: Retrospective cohort study;	Women who had had a birth after their kidney biopsies	Medical Birth Registry of Norway(ICD-8, ICD-10 codes): Preeclampsia (ICD codes were not provided)	preeclampsia: 60	522 women without preeclampsia in first birth
Vikse et al (2012)	1967-2008	Population (cohort 1): All women registered with a first birth in the Medical Birth Registry (1967 to 2008) and who had at least one sibling with a registered first birth in the Medical Birth Registry between 1967 and 2008; Study design: Retrospective cohort study;	Cohort 1: women with more than 6 siblings or no siblings; women without siblings with first pregnancies 1967-2008; women with ESRD before first birth; women with a diagnosis of essential hypertension, kidney disease, rheumatic disease, or diabetes before first pregnancy were excluded before data analysis	Medical Birth Registry of Norway(ICD-8, ICD-10 codes): Preeclampsia (ICD codes were not provided)	Cohort 1: preeclampsia: 22,814	Cohort 1: 503,583 women without preeclampsia who had no sibling with preeclampsia

All five studies reported ESRD as a primary outcome in the cohort with pre-eclampsia (Table 3.2). Two studies from Taiwan classified eclampsia into pre-eclampsia and the studies from Vikse et al[65,67,68] never mentioned whether they included women with eclampsia in their study or not. All selected studies in this literature review defined pre-eclampsia as hypertension with proteinuria after 20 weeks of gestation and identified patients from administrative database based on ICD diagnosis codes. In 2008, Vikse et al published a population based epidemiological study paper and clearly revealed an association of previous pre-eclamptic gestation with the risk of ESRD in Norway[65]. They found that after adjustment for potential confounders, pre-eclampsia during the first pregnancy was associated with an increased risk of subsequent ESRD with a relative risk being 3.2 (95% CI: 2.2-4.5). Moreover, among women who had been pregnant three or more times, pre-eclampsia during one pregnancy was associated with a relative risk of ESRD of 5.3 (95% CI: 3.0-9.6). During the estimation of the familial aggregation of risk factors contributed to the subsequent ESRD, Vikse et al[67] utilized the same data source and found that among women whose siblings had no pre-eclampsia, women with pre-eclampsia had an adjusted relative risk of 2.88 (95% CI: 1.69-4.90) when compared with women without pre-eclampsia. A population based study conducted by Wu et al[66] explored Taiwan National Health Insurance administrative database and found that in Taiwan, women with a single pre-eclamptic gestation was associated with a relative risk of ESRD of 15.99 (95% CI: 5.89-43.38) after adjustment for maternal age, delivery type, number of deliveries, preterm delivery and threatened labor. Another study[64] from Taiwan also obtained similar results when they investigated the effect of previous pre-eclampsia on ESRD with the same data source with overlapped study periods. They

Table 3.2 Relative risks of subsequent ESRD among women with HDP

	Wu et al (2014)	Wang et al(2013)	Vikse et al (2008)	Vikse et al (2010)	Vikse et al (2012)
Followup period (year)	Median: 9 (IQR:7.79 - 10.02)	Mean: 6.3	Mean: 26.5 ± 7.5	Mean (duration from first birth to kidney biopsy): 17.3±9.6	Mean:19.6 ± 10.4
ESRD definition and data source	Hemodialysis for >3 moths or catastrophic illness card for ESRD issued by NHI insurance program	ESRD patients registered in the Catastrophic Illness Patients Database	ESRD patients registered in Norwegian Renal Registry	ESRD patients registered the Norwegian Renal Registry	ESRD patients registered Norwegian Renal Registry
ESRD incidence rates (per 100,000 person-year)	No HDPs: 0.26; HDPs: 3.88; GH*: 1.97; Preeclampsia: 3.35; HTN*:6.33; PE+SCH*: 17.20	No HDPS: 0.34; HDPs: 4.72; GH*:3.4; Preeclampsia:5.33	No preeclampsia: 3.3 (2.9-3.6); preeclampsia: 14.5 (11.2-18.1)	No application	No Reported
Relative risk of ESRD for HDPs	Crude HR: 15.23 (11.07-20.95); Adjusted HR: 10.64 (7.53-15.05)*	Crude HR: 14.1 (9.76-10.3); Adjusted HR: 1.91 (1.20-3.07)[b]	No application	No application	No Reported
Relative risk of ESRD for GH*	Crude HR: 7.85 (2.92-21.10); Adjusted HR: 5.82 (2.15-15.77)[a]	Crude HR: 10.2 (5.89-17.6); Adjusted HR: 1.38 (0.74-2.57) [b]	No application	No application	No application
Relative risk of ESRD for preeclampsia	Crude HR: 13.16 (8.69-19.92); Adjusted HR: 15.99 (5.89-43.38) [a]	Crude HR: 15.9 (10.8-23.3); Adjusted HR: 2.17 (1.33-3.54) [b]	Crude HR: 4.7 (3.6-6.1); Adjusted HR: 3.2 (2.2-4.5)[c]	Crude HR: 1.2 (0.63-2.4); Adjusted HR: 1.1 (0.50-2.6)[d]	Crude HR: 5.95 (4.37-8.11); Adjusted HR: 2.88(1.69-4.90)[e]
Relative risk of ESRD for HTN*	Crude HR: 25.02 (9.31-67.29); Adjusted HR: 9.46 (6.10-14.68) [a]	No application	No application	No application	No Reported

Table 3.2: cont'd

	Wu et al (2014)	Wang et al(2013)	Vikse et al (2008)	Vikse et al (2010)	Vikse et al (2012)
Relative risk of ESRD for PE+SCH*	Crude HR: 66.95 (34.36-130.44); Adjusted HR: 44.72 (22.59-88.51) [a]	No application	No application	No application	No Reported

* GH: gestational hypertension; HTN: pre-existing hypertension; PE+SCH: preeclampsia imposed on pre-existing hypertension

[a] Risk was adjusted for age, delivery type, number of deliveries, and complications from delivery (early delivery, threatened labor, and threatened premature delivery)

[b] Risk was adjusted for urban status, coronary artery disease, congestive heart failure, hyperlipidemia, abruption, and hypertension and diabetes which were developed after pregnancy

[c] Women with a diagnosis of pre-existing hypertension, kidney disease, rheumatic disease, or diabetes before the pregnancy were excluded, and the risk was adjusted for year of delivery, maternal age, maternal marital status, stillbirth, and congenital malformation of the infant.

[d] Risk was adjusted for age at biopsy, categorized eGFR, proteinuria, diastolic BP, the known duration of renal disease and interstitial fibrosis and inflammation arteriolosclerosis

[e] Women with a diagnosis of pre-existing hypertension, kidney disease, rheumatic disease, or diabetes before the pregnancy were excluded, and the risk was adjusted for year of delivery, maternal age, maternal marital status, number of siblings, and maternal educational level

reported that women with previous pre-eclampsia had a relative risk for ESRD 14.0 (95% CI: 9.43-20.7) compared with women without, and the relative risk strikingly decreased to 2.17 (95% CI: 1.33-3.54) after adjustment for hypertension and diabetes mellitus developed after pregnancy, which are two important risk factors shared by pre-eclampsia and ESRD[69]. Vikse et al also studied whether pre-eclampsia was associated with an increased risk of progression of established chronic kidney disease toward ESRD[68]. They selected only women with a representative kidney biopsy between 1988 and 2005 since last recorded births and followup whether chronic kidney disease developed into ESRD. The study revealed that in these women, pre-eclampsia in their first pregnancy was not significantly associated with the risk of ESRD with a relative risk being 1.1 (95% CI: 0.50-2.6).

Two studies[64,66] from Taiwan examined the association of gestational hypertension with ESRD. Wu et al[66] in their study reported relative risks of subsequent ESRD in women with gestational hypertension being 7.85 and 5.82 before and after adjustment for covariates. For women with previous HDPs, the risk of subsequent ESRD in women with gestation hypertension was not significantly (p=0.437) different from that in women with pre-eclampsia. The study conducted by Wang et al[64] reported that gestational hypertension was strongly associated with subsequent ESRD with crude relative risk of 10.2 (95% CI: 5.89-17.6). After adjustment for urban status, coronary artery disease, congestive heart failure, hyperlipidemia and abruption, the risk was still 9 times higher among the women with gestational hypertension than among the women without HDPs. This result was similar to the estimated corresponding risk from the study conducted by Wu et al[66]. But after hypertension and diabetes mellitus which was developed after

pregnancy were considered as potential confounders, the relative risk for women with previous gestational hypertension versus without declined to 1.38 (95% CI: 0.74-2.57) and the association became nonsignificant.

Among the selected citations in this literature review, three studies excluded women with pre-existing hypertension [64] [65,67]; one study did not mention whether they include or remove women with pre-existing hypertension during research[68]. Only Wu et al[66] classified pre-existing hypertension (except secondary to renal disease) as an independent risk factor and investigated its influence on the subsequent ESRD. According to the classification of HDPs, Wu et al further divided women with pre-existing hypertension into two cohorts, women with only pre-existing hypertension before index pregnancy and women with pre-eclampsia superimposed on pre-existing hypertension. In univariate analysis, pre-existing hypertension was associated with subsequent ESRD with a crude relative risk being 25.02 (95% CI: 9.31-67.29). After adjustment for maternal age, delivery type, number of deliveries, preterm delivery and threatened labor, the relative risk was 15.99 (95% CI: 5.89-43.38). Although women with pre-existing hypertension showed extremely high chance to develop ESRD in late life in comparison with women without HDPs, the risk did not show statistically significant (p=0.172) difference from the risk for women with gestational hypertension. When women had pre-existing hypertension before their pre-eclamptic index pregnancy, the crude and adjusted relative risks for subsequent ESRD were 66.95 (95% CI: 34.36-130.44) and 44.72 (95% CI: 22.59-88.51), respectively, for women without versus women with HDPs. Moreover, unlike women with pre-eclampsia or pre-existing hypertension, women with pre-eclampsia superimposed on pre-existing hypertension had a significantly increased risk of

subsequent ESRD (hazard ratio, 7.22; 95% CI: 2.21-23.58) than women with gestational hypertension. In this study, Wu et al. also reported that overall HDPs were associated with an increased risk of ESRD (hazard ratio: 10.64; 95% CI: 7.53-15.05).

In this literature review, four population-based epidemiological studies provided the evidence that in comparison with women without HDPs, women with previous pre-eclampsia had a higher risk of ESRD, and the relative risk estimates ranged from 4.7 to 15.9 dependent on study population. For women with chronic kidney disease, previous pre-eclampsia was not associated with an increased risk of progression of chronic kidney disease towards ESRD. Women with previous gestational hypertension had a greater risk of ESRD, which could attribute to the hypertension or diabetes mellitus developed after delivery. Pre-existing hypertension was much strongly associated with the risk of subsequent ESRD compared with temporary hypertension during pregnancy. When pre-existing hypertension combined with pre-eclampsia, the risk of subsequent ESRD was remarkably higher than the risks for other types of HDPs. However, the existing evidence is far from sufficient to reach a conclusion that women with previous HDPs have a high risk of ESRD. All five studies identified were retrospective study in nature and originated from only two regions, Norway and Taiwan. Four studies did not consider pre-existing hypertension as one important type of HDPs and excluded women with this disorder from study. Moreover, only one study considered hypertension and diabetes mellitus as potential confounders, which could significantly bias the estimates the association of HDPs with the risk of subsequent ESRD. Further research is needed to determine whether the increased risk of chronic kidney disease and ESRD for women with previous various

types of HDPs after adjustment for important confounders, including hypertension and diabetes mellitus, in general population.

Chapter 4 Methods

4.1 Data source, quality and linkage

4.1.1 Data source

The present study cohort was from the Discharge Abstract Database (DAD), which collates hospital admission and separation records and is maintained by the Canadian Institute for Health Information (CIHI). The DAD is a national electronic database initially developed in 1963 and contains information about inpatient acute, chronic and rehabilitation cares and day surgery from the majority of acute care institutions in Canada (except Quebec and some parts of Manitoba). At present, over three million discharge abstracts are submitted to the DAD every year, representing approximately 80% of all hospital inpatient discharges in Canada[70]. Each record in the DAD is composed of information about hospital admission, demographic variables and standard clinical records for each instance of a hospital separation. When a patient is readmitted within the same fiscal year (April 1 to March 31), a separate record is created.

One of the major advantages of DAD is that the main data elements in database include the comprehensive information about principal diagnosis, secondary and comorbid diagnoses and interventions or procedures performed during the hospitalization. Diagnose are coded according to the International Statistical Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9 CM] or the International Statistical Classification and Related Health Problems, Tenth Revision, Canada [ICD-10 CA], and procedures are coded using the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedure (CCP) or the Canadian Classification of Health Interventions (CCI). All

corresponding ICD-10 CA codes involved in this study were mapped from the appropriated ICD-9 CM codes.

4.1.2 Data quality

DAD data have been previously validated and widely used for perinatal health surveillance and research in Canada[70-72]. One study on the all discharges in Ontario between 1990 and 1994 showed that a primary ICD-9 code of pre-eclampsia had a sensitivity of 89% (95% CI: 78% to 94%) and a specificity of 67% (95% CI: 59% to 94%)[58]. Several other validation studies also revealed that information in the DAD was complete and high-quality with high sensitivity and specificity for essential hypertension, and any gestational hypertensive disorders[73,74].

In addition, hospitals, governments and academic institutions also take advantages of the information extracted from DAD database for administrative studies, management decisions and various scientific research. Thus, with a good data quality, DAD database is suitable for our present investigation.

4.1.3 Data linkage

Every Canadian citizen has a healthcare number (HCN) issued by the provincial or territorial health authority. In the DAD database, HCN was scrambled but still keep its uniqueness for each person. Moreover, each inpatient stay was recorded separately. Therefore, scrambled HCN can be applied to establish the connection among the different hospital separations from the same patient even within and across fiscal years. In this study, the scrambled HCN and birth year was combined to identify the women's first obstetrical delivery record and identify their subsequent outcome of interest.

4.2 Study population

Women with valid HCN and obstetrical delivery records during the period from the fiscal years of 1993-1994 to 2003-2004 in eight provinces and territories (except the provinces of Quebec and Manitoba due to uncompleted information collected by CIHI) were identified from the DAD database by a published algorithm (Appendix B)[70]. Their first pregnancy during this period was referred as the index pregnancy.

The total number of obstetrical delivery records included in the study was over 1.5 million. These accounted for approximately 98% of all deliveries occurring in the provinces and territories of study during the investigation period[72]. Women with extreme maternal age (younger than 15 years or older than 45 years), multiple gestation, pre-existing diabetes mellitus (DM), gestational diabetes mellitus (GDM), systemic lupus erythematosus (SLE), thrombotic microangiopathy, haemolytic uremia syndrome, obstructive uropathy, glomerulopathy, other nephritis or nephropathy and hypertension secondary to renal disease that complicated pregnancy, childbirth and the puerperium were excluded from study population.

4.3 Explanatory variables

In this study, the primary explanatory variable is the exposure to HDPs complicated index pregnancy. According to classification of HDPs suggested from ISSHP and discharge information on identified obstetrical delivery records from DAD, women who suffered HDPs during the first pregnancy within the study period were classified into five categories: gestational hypertension (ICD-9 CM codes: 642.3; ICD-10 CA codes O13), pre-eclampsia (ICD-9 CM codes: 642.4, 642.5, 642.6; ICD-10 codes: O14, O15), pre-existing hypertension except secondary to renal disease (ICD-9 CM codes: 642.0, 642.1, 642.2, 401, 402, 403, 404, 405; ICD-10 codes: O10, I10, I11, I12, I13, I15), pre-

eclampsia superimposed on pre-existing hypertension (ICD-9 CM code: 642.7; ICD-10 CA code: O11), and unspecific hypertension during pregnancy(ICD-9 CM code: 642.9; ICD-10 CA code: O16). Women without such medical condition were grouped referred as comparison. Because there is yet no explicit diagnostic criterion for unspecific HDP, although its analytic results were shown along with other types of HDPs, the effects of this hypertensive disorder on outcome of interest were not discussed. When multiple HDPs diagnostic codes simultaneously appeared in one obstetrical delivery record and the patients could be classified into more than one category of HDPs for the index pregnancy: the highest priority was set to pre-eclampsia superimposed on chronic hypertension, followed by pre-eclampsia or chronic hypertension and gestational hypertension. Therefore, no overlap appeared among various categories of HDPs in present study.

A number of variables were considered to be potential confounders. They were selected based on their relationships to HDPs and renal disease, which were the exposure and outcome for the main objective, respectively.

Variables for demographic characteristics included maternal age at delivery (<20, 20-24, 25-29, 30-34, 35-39, >=40 years); delivery fiscal year (1993/1994-1994/1995, 1995/1996 - 1996/1997, 1997/1998 – 1998/1999, 1999/2000 – 2000/2001, 2001/2002-2002/2003); delivery region (Atlantic region (Newfoundland, Prince Edward Island, Nova Scotia, and New Brunswick), Ontario, Prairies region (Manitoba, Saskatchewan, and Alberta), Pacific region (British Columbia) and territory region (Northwest Territories, Nunavut Territory, and Yukon Territory)).

Variables for obstetrical conditions and complications included grand multiparity, intrauterine growth restriction (IUGR), preterm delivery, prolong pregnancy, intrauterine fetal death, fetal distress, placenta disorders, placenta abruption, placenta previa, malpresentation of fetus, oligohydramnio, polyhydramnio, rupture of uterus during delivery, premature rupture of membranes, postpartum haemorrhage, hysterectomy, blood transfusion, medical induced delivery, surgical induced delivery, and caesarean delivery (Appendix C).

Variables for comorbid diseases which affected the pregnant women included obesity, hyperlipidemia, disorders of thyroid gland, major puerperal infection, sepsis, deep vein thrombosis, coagulation defects, acute myocardial infarction, stroke, transient cerebral ischemia, acute rheumatic fever, chronic rheumatic heart disease, ischemic heart disease, stroke, and cardiomyopathy (which include pericarditis, endocarditis, myocarditis, conduction disorders, and heart failure).

4.4 Outcome definitions

The outcome of interest in present study was ESRD hospitalization after index pregnancy until March 31, 2012. To minimize the immediate effect of pregnant complications on the outcomes, any hospital admission for ESRD in the first following year was removed from analysis. In the datasets, which utilized ICD-9 coding system to record the diagnosis information, CIHI did not adopt specific ICD diagnostic code of ESRD (ICD-9 code: 585.6) to separate it from other previous stages of chronic renal disease (ICD-9 code: 585.1-585.5). In these datasets, the same three-digital ICD-9 diagnosis code (ICD-9 code: 58.5) represented all stages of chronic renal disease. As a

consequence, ESRD hospitalization could not be directly identified in these records by its ICD-9 diagnosis code.

When a physician certifies ESRD, the patient needs to accept continuous dialysis treatment immediately or kidney transplantation. Therefore, long-term renal replacement therapy - dialysis (ICD-9 CM codes: V451, V560, V561, V568; CCP procedure codes: 512.7, 514.2, 514.3, 519.5, 669.8) and/or kidney transplantation (ICD-9 CM code: V42.0; CCP procedure code: 675.9) for the women with chronic renal disease (ICD-9 CM code: 585) were used to identify ESRD hospitalization from DAD datasets in which ICD-9 coding system was utilized to record the diagnosis/procedure information. In this study, long-term renal replacement therapy means renal dialysis over three months and/or renal transplantation. The date of ESRD onset was defined as the date of hospital admission.

4.5 Statistical analysis

Separate descriptive and multivariable analyses were conducted to investigate the distribution of selected variables in the study population, and examine the associations between various types of HDPs and subsequent ESRD hospitalization. Significance was set at α level of <0.01 due to large study size.

4.5.1 Descriptive analysis

Descriptive analyses were performed to examine the distributions of various types of HDPs, outcome of interest, death, as well as baseline data, including demographic characteristics, pregnancy complications and comorbid diseases. Chi-square test was used for significance test, and distribution differences in selected variables were examined between each exposure cohort (i.e. various types of HDPs) and comparison cohort.

4.5.2 Comparison of incidence of subsequent ESRD hospitalization between women with HDPs and without

The incidence of subsequent ESRD hospitalization was calculated as the number of patients with ESRD divided by the total number of person-years. Absolute-risk estimate was calculated as rate per 100,000 person-years of follow-up. Poisson regression analysis with total person-years as an offset variable was used to calculate incidence rate ratio of subsequent ESRD hospitalization.

4.5.3 Survival analysis

Survival analysis is a set of statistical methods to analyze survival data in which time to event of interest is the outcome variable[75]. Survival analysis of the relationship between the occurrence of events and timing of events is widely used in various research fields, including health and social sciences. In present study, the effects of women with hypertensive gestation on the future ESRD hospitalization were estimated by survival analysis.

Kaplan-Meier estimator is a non-parametric statistic to estimate the survival function and is used to analyze and compare one or multiple groups of survival data[76]. In 1972, Cox extended the Kaplan-Meier method and regression model was introduced to analyze survival data with multiple explanatory variables[77]. Unlike other regression models, Cox regression model is considered as semi-parametric model. This regression model dose not require special assumption about the distribution of baseline hazard from individuals, such as exponential distribution, Weibull distribution or Gompetz distribution, but assumes that the hazard functions between different individuals remained proportional and constant over time.

Event, survival time and censoring are three important fundamental elements in survival analysis[78]. An 'event' usually indicates the outcome of interest, such as death, onset of disease that may occur to any subject in a certain cohort. In this study, hospital admission of ESRD is denoted as the event. The "survival time" means the time spanned from the beginning of the exposure until a studied event occurs. Normally, this parameter is measured by the number of time units (e.g. year, month, week, or day). Chronic renal disease is a disease with slow and irreversible progression and requires 10-20 years to develop into the final stage. Therefore, 'month' was used as the basic unit to measure the time from index pregnancy to the ESRD hospitalization in present study. Censoring is a condition in which an exact individual's survival time is unknown. Right censoring is the most common type of censoring in survival data and occurs when an individual is lost or the event does not occur in the follow-up period. These are also known as loss-to-follow-up censoring and end-of-study censoring, respectively. ESRD is a serious medical condition with low incidence in general population, thus majority of women in this study cohort did not develop into ESRD and became end-of-study censors at the end of follow-up.

4.5.3.1 Survivor function and hazard function

Survivor function and hazard function are used to describe survival data[78,79].

Survivor function describes the probability that an individual survives from the beginning of exposure until a particular time point *t*. The cumulative distribution of survival time can be expressed as $F(t) = P(T < t)$, where T represents the actual survival time. Therefore, survivor function can be defined as $S(t) = P(T \geq t) = 1 - F(t)$ [78].

A hazard function, $h(t)$, expresses the risk of an event occurrence at the particular time point t for the person who has survived until that time point[78]. The formula for hazard function can be expressed as

$$h(t) = \lim_{\sigma t \to 0} \left\{ \frac{P(t \le T < t + \sigma t \mid T \ge t)}{\sigma t} \right\}$$ [78].

4.5.3.2 Kaplan-Meier survival analysis

Graphical summary of survival times is generally used for each individual in every exposure group at the beginning of analyzing survival data. Without any specific assumptions regarding the distribution of the survival time, the Kaplan-Meier survival analysis is routinely used to estimate the survivor function. Based on the time of events, a series of time intervals are created to estimate the Kaplan-Meier estimator[79]. The Kaplan-Meier estimator of survivor function is expressed as $\hat{S}(t) = \prod_{j:t_j \le t} (\frac{n_j - d_j}{n_j})$, where n_j and d_j represent the number of individuals in the risk set at time t_j, and the number of individuals who had event within the same interval, respectively[80]. Survival curve is used to express Kaplan-Meier estimators by plotting estimated survival probabilities against time and only indicates the occurrences of event but not censored observations. Therefore, survival curve can be used to compare the risks among various exposure groups. Log-rank test is generally the most appropriate method to compare the survival of groups, which takes the full follow-up period into account. It examines whether there is a statistically significant difference among the groups in the probability of an event at any follow-up time point[78]. Moreover, log-rank test does not generate bias even the pattern of censoring is different among groups. In this study, survival curves were used to describe the proportion of subjects who remained non-hospitalization for ESRD during the follow-

up period in women with or without HDPs, and log-rank test was applied to compare the risk difference among them.

4.5.3.3 Cox proportional hazards regression analysis

One disadvantage of Kaplan-Meier survival analysis is that it does not allow testing the effects from multiple variables during analysis. Sometimes, the additional characteristics about observations, such as socio-demographic factors, comorbidities conditions or other information, are available in data. These characteristics may considerably affect the survival function, and ignoring the effects from these explanatory variables could seriously bias the final conclusion. Just like the multiple regression analysis, Cox regression analysis enables us to examine the effects of these additional variables on survival times with various exposures.

4.5.3.3.1 Cox proportional hazards regression model

The Cox PH model can be expressed as the hazard function for the individual at time point *t*: $h_i(t) = h_0(t)\exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \ldots + \beta_p x_{pi})$ [78]. The model is composed of two parts: (1) baseline hazard function, $h_0(t)$, describes how the risk of event per time unit changes over time at baseline level; (2) variable-related component describes how the risk alters in response to different sets of explanatory variables.

Unlike other regression model, Cox regression model does not require any special assumption about distribution of survival time. It only assumes that the hazards for any two individual are proportional to each other over the time; therefore, hazards ratio between any two subjects is constant and not interacts with time. This is referred as proportional hazards (PH) assumption. Because individuals share the same baseline hazard function which can be cancelled each other, only the values of the studied

variables determine the hazard ratio for two individuals[78]. The hazard ratio for each explanatory variable can be calculated from the following formula: $hazardratio = \frac{h_i(t)}{h_j(t)} = \exp\left\{\beta_1\left(x_{i1} - x_{j1}\right) + \ldots + \beta_k\left(x_{ik} - x_{jk}\right)\right\}$[78]. If hazards ratio changes with time, the PH assumption can not be hold and Cox regression model become invalid. In this study, Cox PH regression analysis was applied to investigate the association of the risk of an ESRD hospitalization with previous history of HDPs complicated pregnancy.

4.5.3.3.2 Model selection

Collett's model selection approach was applied to choose the variables and build Cox PH regression model for this study[79]. The selection procedure in present study is as follows:

Step 1: the significance of each potential variable for subsequent ESRD was examined by univariate screening procedure with a significance level of 0.2;

Step 2: all significant variable identified from step one were recruited into a Cox regression model along with HDPs, delivery year, delivery region, and maternal age (as primary interest or basic demographic information needed to be adjusted, these variables were forced to remain in model during the following selection procedure and data analysis procedure), and a backward selection procedure was used to eliminate nonsignificant variables with a significance level of 0.1;

Step 3: variables remained after backward selection and nonsignificant variables (*p* value > 0.2) in step one were combined and examined by forward selection procedure with entry criterion of significance level less than 0.1;

Step 4: after the forward selection, stayed variables were screened by stepwise selection with entry and stay criterion of significance level less than 0.1 and 0.01, respectively, to choose the best subset of explanatory variables.

4.5.3.3.3 Assessment of proportional hazards assumption for Cox regression Model

The validation of Cox regression analysis relies on the hazards being proportional. It is very important to verify that the explanatory variables used in model satisfy PH assumption. Many numerical or graphical approaches can be used to assess this assumption and three of them were used in present study:

1) Log cumulative hazard plot. To assess whether an explanatory variable holds the PH assumption for Cox regression analysis, the study population is classified into different groups according to the value of tested explanatory variable and the 'log of negative log of the Kaplan-Meier estimator' for each group plots against the log of survival time[81]. If the PH assumption is satisfied, the constant distance is expected between the different groups over time.

2) Schoenfeld residual. Checking the distribution of Schoenfeld residual is another graphical method to assess PH assumption. When the tested explanatory variable satisfies the PH assumption, its Schoenfeld residuals should not exhibit any apparent trend over time.

3) Examining the time-dependence of explanatory variable in the model. An interaction variable representing the product between tested explanatory variable and survival time is created and introduced in the model. If the effect of tested explanatory variable changes significantly over time, the parameter of interaction variable shows significance and PH assumption might be invalid.

4.5.3.3.4 Stratified Cox PH regression model

When PH assumption is not satisfied, the basic Cox regression model becomes invalid. Advance Cox models, such as stratified Cox regression model or extended Cox regression model, may be considered to manipulate this non-proportional hazards situation. In this study, stratified Cox regression model was applied in analysis of the risks of future ESRD hospitalization for women with HDPs. The main idea of stratified Cox regression model is to split the whole study population into several strata based on the value of explanatory variable which violates PH assumption and then re-estimate the model. Defined in the concept, there are two models — interaction and no-interaction stratified Cox regression models — in the stratified Cox regression analysis[82].

No-interaction stratified Cox regression model assumes that the effects of variables remained in the model have the constant influences across the strata on outcome of interest. In this model, each stratum has its own baseline hazard function, but the coefficients of the explanatory variables are the same for each stratum. The no-interaction model is defined as follows: $h_g(t) = h_{0g}(t)\exp(\beta_1 x_1 + \beta_2 x_2 \cdots + \beta_k x_k)$, $g = 1,2,\cdots,k$, where g represents the strata[82]. In this model, the strata are the different categorizations of the stratification variables which are not included in model, and other explanatory variables stayed in the model are assumed to satisfy the PH assumption.

Interaction stratified Cox regression model can be used to investigate the risk when stratification variable potentially interacts with other explanatory variables stayed in the model. The interaction model is defined as follows: $h_g(t) = h_{0g}(t)\exp(\beta_{1g} x_1 + \beta_{2g} x_2 \cdots + \beta_{kg} x_k)$, $g = 1,2,\cdots,k$. Unlike no-interaction stratification model, each stratum has its own special baseline hazard function and the

coefficients[82]. Therefore, the specific-stratum hazard ratios must be estimated and reported separately.

4.5.3.3.5 Cox regression model diagnosis

Adequacy of a fitted model needs to be assessed before performing inference and diagnostic procedure for model checking is regarded as an essential part of a modeling process. Schoenfeld residual, deviance residual, dfbeta value can be calculated during fitting the Cox regression model and these measures were utilized to examine the Cox PH assumption, identify outliers and determine influential observations in present study.

The final fitted Cox regression model is built based on PH assumption and Schoenfeld residual is widely used to check this assumption[83]. This kind of residuals specifies the difference between the observed and the expected values of the tested explanatory variable for every individual at the failure time. Unlike other kinds of residuals, Schoenfeld residual is only calculated for the individual who had event and has separate residual for each individual per explanatory variable in the model. Due to the time-independence, when the Schoenfeld residuals plot against survival time, a non-random pattern is the evidence that the effect of the explanatory variable changes over time and implies the invalid PH assumption. Grambsch and Therneau suggested standardized Schoenfeld residuals can greatly increase diagnostic power[84]. Therefore, standardized Schoenfeld residuals were applied in graphical diagnostics for PH assumption in this study.

It is also important to identify the potential outlier observations which were poorly fit the final model. Deviance residuals were applied to assess the relative influence of the fitness of the model to each individual in present study[78]. This kind of residuals is derived

from martingale residual which follows the unit exponential distribution and specifies excess failures beyond the expected baseline hazard. Due to highly skewed distribution of martingale residuals, deviance residuals are transformed from martingale residuals and normalized. As a consequence, this kind of residuals successfully avoids the skewed distribution and is widely used to measure the difference between observed and expected hazards. When deviance residuals plot against the variables, residuals representing for censored observations are concentrated around zero and the residuals with large negative or positive value indicate the observations have a lower or higher risk than average, respectively. Extreme low or high values may suggest that the observation is an outlier and need special attention.

In evaluating the adequacy of the fitted model, the parameter of estimated risk could be specifically affected by some particular observations. Therefore, it is better to determine whether any observation has a disproportionate influence on the estimated parameters. Deletion diagnostics is a preferred method to estimate the individual observation influence, which measure the difference (dfbeta) between the regression coefficient estimated from all observations and the coefficient estimated without the that particular individual observation. Dfbeta as the measure of influence has a straightforward interpretation and each observation has a separate dfbeta value for each explanatory variable in the model. If dfbeta value is close to 0, that observation has less influence on that estimated coefficient. To identify the observations with disproportionate influence, the process is repeated for each individual observation and each explanatory variable in the original dataset, and the estimates of dfbeta plot versus observations which are ranked by event-to-time in present study.

4.5.4 Calculation of population-attributable fraction

Population-attributable fractions (PAF) for ESRD due to previous hypertensive gestation were calculated based on the risks estimated by Cox PH regression analysis. In present study, PFA was estimated as $p_d \times (HR-1/HR)$, where p_d represents the proportion of cases exposed to the risk factors and HR represents relative risk. When a confounding variable exists, the formula above is considered more valid than the popular formula $P_e \times (HR-1)/(P_e \times (HR-1)+1)$, where P_e is the proportion of the source population exposed to the risk factor[85].

4.5.5 Assessment of interaction

In epidemiological study, interaction is referred as the extent to which the combined effect of two exposures on outcome of interest is different from the sum of their independent effects. The interaction is explicitly defined as a deviation from additivity on a risk difference scale[86]. Because Cox PH regression analysis applied in present study was performed on a multiplicative scale, the model cannot be directly used to examine additive interactions. To assess the additive interactions between HDPs and other risk factors in relation to subsequent ESRD hospitalization, three different measures, the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP) and the synergy index (S), have been applied to evaluate interaction on an additive scale. The definitions are as follows:

$RERI=HR_{11}-HR_{10}-HR_{01}+1$

$AP=RERI/HR_{11}$

$S=(HR_{11}-1)/[(HR_{10}-1)+(HR_{01}-1)]$

HR_{11} represents the relative risk for women with both of HDPs and potential interacting risk factor, while HR_{10} and HR_{01} represent the relative risks for women with either HDPs or the potential interacting risk factor, respectively. Women with neither HDPs and nor such interacting risk factor were considered as reference group. When no interaction occurs, RERI and AP do not significantly depart from zero and S is close to 1. In this study, Cox PH regression analysis was applied to estimate the relative risks with full adjustment and the 95% CI for each additive measure were calculated using the approach proposed by Andersson et al[87].

4.6 Software

Statistical analysis for this study was performed using SAS 9.1 (SAS Institute, Cary, NC, USA)

4.7 Ethics Approval

CIHI collected, prepared and maintained the DAD database with strict confidentiality guidelines. The data used for this study accessible at the Public Health Agency of Canada (PHAC) is a denominalized version. No individual consent was needed from the patient whose discharge information was recorded in the database, and approval from an ethics review board is not required by either CIHI or PHAC[88-90].

Chapter 5 Results

5.1 Demographic characteristics and comorbid condition of the study population

During the period from the fiscal year 1993/1994 to 2002/2003, a total of 2,351,665 obstetrical delivery records were identified from the DAD database. According to inclusion/exclusion criteria, 1,598,043 women were included in this cohort study and their first pregnancies during the study period were referred as the index pregnancy. During the index pregnancy, 28,548 (1.79%) women were diagnosed with gestational hypertension, 51,614 (3.23%) women experienced pre-eclampsia, 5 236 (0.33%) women had pre-existing hypertension, and 943 (0.06%) women experienced pre-eclampsia superimposed on pre-existing hypertension (Table 5.1).

Women with gestational hypertension or pre-eclampsia and women without HDPs had a similar age distribution with a mean age of approximately 28 years. Approximately 31.80% of women with pre-eclampsia were in the age group of 25-29 years, followed by age groups of 30-34 years (26.06%), 20-24 years (20.26%), 15-19 years (8.31%), and 40-45 years (2.14%). Women with pre-existing hypertension or pre-eclampsia superimposed on pre-existing hypertension were older than other women (median age: 31 years, interquartile range (IQR): 27-35 years *vs.* median age: 28 years, IQR: 24-32 years, $p<0.001$).

Most of the deliveries in women without HDPs were reported in Ontario (54.00%), followed by in Prairie Region (19.35%), Pacific Region (16.71%) and Atlantic Region (9.31%), and Territories Region (0.63%). A similar distribution pattern was found among women with HDPs, except for women with pre-eclampsia superimposed on pre-existing hypertension.

Table 5.1. Demographic characteristics and comorbidities among women with and without HDPs (Canada excluding provinces of Quebec and Manitoba, 1993/1994-2002/2003)

		With HDPs									
	Without HDPs (N=1,500,520)	Gestational hypertension (N=28,548)		Pre-eclampsia/ Eclampsia (N=51,614)		Pre-existing hypertension (N=5,236)		Pre-eclampsia imposed on pre-existing hypertension (N=943)		Unspecific HDP (N=11,182)	
	No. (%)	No. (%)	*P* value[a]	No. (%)	*P* value[a]	No. (%)	*P* value[a]	No. (%)	*P* value[a]	No. (%)	*P* value[a]
Mean age, years[b]	28.01 ± 5.63	28.26 ± 5.72	<.001	27.91 ± 5.78	<.001	30.82 ± 5.78	<.001	31.01 ± 5.81	<.001	28.25 ± 5.74	<.001
Median age, years	28 (24-32)	28 (24-32)		28 (24-32)		31 (27-35)		31 (27-35)		28 (24-32)	
Age group (years)											
15-19	117,333 (7.82)	1,925 (6.74)	<.001	4,289 (8.31)	<.001	167 (3.19)	<.001	18 (1.91)	<.001	805 (7.20)	<.001
20-24	291,616 (19.43)	5,580 (19.55)		10,458 (20.26)		578 (11.04)		119 (12.62)		2,124 (18.99)	
25-29	478,391 (31.88)	9,188 (32.18)		16,414 (31.80)		1,349 (25.76)		247 (26.19)		3,620 (32.37)	
30-34	421,760 (28.11)	7681 (26.91)		13,452 (26.06)		1,703 (32.52)		281 (29.80)		3,011 (26.93)	
35-39	164,777 (10.98)	3440 (12.05)		5,897 (11.43)		1,087 (20.76)		205 (21.74)		1,347 (12.05)	
40-45	26,643 (1.78)	734 (2.57)		1,104 (2.14)		352 (6.72)		73 (7.74)		275 (2.46)	
Period											
1993/1994 1994/1995	44,2496 (29.49)	5,179 (18.14)	<.001	13,420 (26.00)	<.001	1,163 (22.21)	<.001	120 (12.73)	<.001	2,962 (26.49)	<.001
1995/1996 1996/1997	33,6236 (22.41)	4,415 (15.47)		12,208 (23.65)		1,120 (21.39)		171 (18.13)		2,549 (22.80)	
1997/1998 1998/1999	26,4506 (17.63)	4,645 (16.27)		10,514 (20.37)		938 (17.91)		195 (20.68)		2,343 (20.95)	
1999/2000 2000/2001	23,6278 (15.75)	5,280 (18.50)		9,517 (18.44)		1,052 (20.09)		179 (18.98)		2,169 (19.40)	
2001/2002 2002/2003	22,1004 (14.73)	9,029 (31.63)		5,955 (11.54)		963 (18.39)		278 (29.48)		1,159 (10.36)	

Table 5.1: cont'd

	Without HDPs (N=1,500,520)	With HDPs									
		Gestational hypertension (N=28,548)		Pre-eclampsia/ Eclampsia (N=51,614)		Pre-existing hypertension (N=5,236)		Pre-eclampsia imposed on pre-existing hypertension (N=943)		Unspecific HDP (N=11,182)	
	No. (%)	No. (%)	*P* value[a]	No. (%)	*P* value[a]	No. (%)	*P* value[a]	No. (%)	*P* value[a]	No. (%)	*P* value[a]
Region											
Atlantic	139,711 (9.31)	2,394 (8.39)	<.001	7,036 (13.63)	<.001	629 (12.01)	<.001	142 (15.06)	<.001	1,202 (10.75)	<.001
Ontario	810,348 (54.00)	12,004 (42.05)		27,699 (53.67)		2,718 (51.91)		404 (42.84)		6,955 (62.20)	
Prairie	290,304 (19.35)	7,690 (26.94)		9,681 (18.76)		991 (18.93)		183 (19.41)		1,446 (12.93)	
Pacific	250,775 (16.71)	6,138 (21.50)		7,043 (13.65)		863 (16.48)		213 (22.59)		1,539 (13.76)	
Territory	9,382 (0.63)	322 (1.13)		155 (0.30)		35 (0.67)		1 (0.11)		40 (0.36)	
Death											
No	1,495,047 (99.64)	28,463 (99.70)	0.06	51,394 (99.57)	0.02	5,188 (99.08)	<.001	939 (99.58)	0.59	1,1131 (99.54)	0.11
Yes	5,473 (0.36)	85 (0.30)		220 (0.43)		48 (0.92)		4 (0.42)		51 (0.46)	
Deliveries, n											
1	940,354 (62.67)	19,606 (68.68)	<.001	29,667 (57.48)	<.001	3,643 (69.58)	<.001	681 (72.22)	<.001	6,479 (57.94)	<.001
>=2	560,166 (37.33)	8,942 (31.32)		21,947 (42.52)		1,593 (30.42)		262 (27.78)		4,703 (42.06)	
Obesity											
No	1,494,574 (99.60)	27,896 (97.72)	<.001	50,826 (98.47)	<.001	5,012 (95.72)	<.001	889 (94.27)	<.001	1,1022 (98.57)	<.001
Yes	5946 (0.40)	652 (2.28)		788 (1.53)		224 (4.28)		54 (5.73)		160 (1.43)	
Cardiomyopathy											
No	1496,697 (99.75)	28,442 (99.63)	<.001	51,353 (99.49)	<.001	5,167 (98.68)	<.001	924 (97.99)	<.001	11,135 (99.58)	0.001
Yes	3,823 (0.25)	106 (0.37)		261 (0.51)		69 (1.32)		19 (2.01)		47 (0.42)	

Table 5.1: cont'd

	Without HDPs (N=1,500,520)	With HDPs									
		Gestational hypertension (N=28,548)		Pre-eclampsia/ Eclampsia (N=51,614)		Pre-existing hypertension (N=5,236)		Pre-eclampsia imposed on pre-existing hypertension (N=943)		Unspecific HDP (N=11,182)	
	No. (%)	No. (%)	*P* value[a]	No. (%)	*P* value[a]	No. (%)	*P* value[a]	No. (%)	*P* value[a]	No. (%)	*P* value[a]
Deep vein thrombosis											
No	1,499,605 (99.94)	28,532 (99.94)	0.74	51,529 (99.84)	<.001	5,223 (99.75)	<.001	939 (99.58)	0.003	11,171 (99.90)	0.11
Yes	915 (0.06)	16 (0.06)		85 (0.16)		13 (0.25)		4 (0.42)		11 (0.10)	

[a] Compared with those without HDPs; Student *t* test for continuous variables and χ^2 test for categorical variables;
[b] Data are given as mean ± SD;

During the follow-up period 0.37% (n=5,881) of women were reported dead in the cohort. The highest death rate (0.92%, n=48) was founded in women with pre-existing hypertension and was significantly greater (p<0.001) than women without HDPs (0.36%, n=5,473).

Women with any type of HDPs showed significantly increased proportions of obesity in comparison with women without any type of HDPs (1.53% to 5.73% *vs*. 0.4%, p<0.001) and were more likely to had cardiomyopathy during the index pregnancy (0.37% to 2.01% *vs*. 0.25%, p<0.001). About 0.06% (n=915) of women without HDPs suffered deep venous thrombosis during index pregnancy, while the corresponding proportion was significantly higher for women with pre-eclampsia (0.16%), pre-existing hypertension (0.25%) or with pre-eclampsia superimposed on pre-existing hypertension (0.42%). Women without HDPs were more likely to have multiple deliveries during the study period (37.33%) than women with gestational hypertension (31.32%), pre-existing hypertension (30.42%), or pre-eclampsia superimposed on the pre-existing hypertension (27.78%).

5.2 Pregnancy-related complications among women with HDPs

Table 5.2 shows obstetrical conditions by HDPs status. During the index pregnancy, women with any type of HDPs had significantly higher (p<0.001) proportions of caesarean delivery, intrauterine growth restriction, preterm delivery, stillbirth, oligohydramnio, fetal distress, placenta disorders, placenta abruption and postpartum haemorrhages compared with the cohort without HDPs. Except for women with pre-eclampsia superimposed on pre-existing hypertension, a significantly higher (p<0.001) proportion of polyhydramnio was also observed in women with other types of HDPs than

Table 5.2. Pregnancy-related complications among women with and without HDPs (Canada excluding provinces of Quebec and Manitoba, 1993/1994-2002/2003)

	Without HDPs (N=1,500,520)	With HDPs									
		Gestational hypertension (N=28,548)		Pre-eclampsia/ Eclampsia (N=51,614)		Pre-existing hypertension (N=5,236)		Pre-eclampsia imposed on pre-existing hypertension (N=943)		Unspecific HDP (N=11,182)	
	No. (%)	No. (%)	*p* value[a]	No. (%)	*p* value[a]	No. (%)	*p* value[a]	No. (%)	*p* value[a]	No. (%)	*p* value
Delivery type, n											
Natural childbirth	1,209,156 (80.58)	20,186 (70.71)	<..001	32,579 (63.12)	<..001	3,445 (65.79)	<..001	487 (51.64)	<..001	8,118 (72.60)	<..001
Caesarean delivery	291,364 (19.42)	8,362 (29.29)		19,035 (36.88)		1,791 (34.21)		456 (48.36)		3,064 (27.40)	
IUGR											
No	1,468,156 (97.84)	27,080 (94.86)	<..001	47,719 (92.45)	<..001	4,832 (92.28)	<..001	804 (85.26)	<..001	10,658 (95.31)	<..001
Yes	32,364 (2.16)	1,468 (5.14)		3,895 (7.55)		404 (7.72)		139 (14.74)		524 (4.69)	
Preterm delivery											
No	1,433,769 (95.55)	27,017 (94.64)	<..001	45,044 (87.27)	<..001	4,781 (91.31)	<..001	690 (73.17)	<..001	10,711 (95.79)	0.23
Yes	66,751 (4.45)	1,531 (5.36)		6,570 (12.73)		455 (8.69)		253 (26.83)		471 (4.21)	
Stillbirth											
No	1,491,448 (99.40)	28,418 (99.54)	0.001	51,215 (99.23)	<..001	5,140 (98.17)	<..001	926 (98.20)	<..001	11,117 (99.42)	0.75
Yes	9,072 (0.60)	130 (0.46)		399 (0.77)		96 (1.83)		17 (1.80)		65 (0.58)	
Fetal Distress											
No	1,360,147 (90.65)	24,396 (85.46)	<..001	45,357 (87.88)	<..001	4,544 (86.78)	<..001	775 (82.18)	<..001	9,794 (87.89)	<..001
Yes	140,373 (9.35)	4,152 (14.54)		6,257 (12.12)		692 (13.22)		168 (17.82)		1,388 (12.41)	
Placenta disorders											
No	1,484,848 (98.96)	27,948 (97.90)	<..001	50,022 (96.92)	<..001	5,125 (97.88)	<..001	892 (94.59)	<..001	10,971 (98.11)	<..001
Yes	15,672 (1.04)	600 (2.10)		1,592 (3.08)		111 (21.12)		51 (5.41)		211 (1.89)	
Postpartum haemorrhages											
No	1,427,505 (95.13)	26,507 (92.85)	<..001	47,913 (92.83)	<..001	4,887 (93.33)	<..001	854 (90.56)	<..001	10,565 (94.48)	0.001
Yes	73,015 (4.87)	2,041 (7.15)		3,701 (7.17)		349 (6.67)		89 (9.44)		617 (5.12)	

Table 5.2: cont'd

	Without HDPs (N=1,500,520)	With HDPs									
		Gestational hypertension (N=28,548)		Pre-eclampsia/ Eclampsia (N=51,614)		Pre-existing hypertension (N=5,236)		Pre-eclampsia imposed on pre-existing hypertension (N=943)		Unspecific HDP (N=11,182)	
	No. (%)	No. (%)	*p* value[a]	No. (%)	*p* value[a]	No. (%)	*p* value[a]	No. (%)	*p* value[a]	No. (%)	*p* value
Placenta abruption											
No	1,483,212 (98.85)	28,090 (98.40)	<..001	50,437 (97.72)	<..001	5,148 (98.32)	<..001	917 (97.24)	<..001	1,1021 (98.56)	0.005
Yes	17,308 (1.15)	458 (1.60)		1,177 (2.28)		88 (1.68)		26 (2.76)		161 (1.44)	
Oligohydramnio											
No	1,481,645 (98.74)	27,751 (97.21)	<..001	50,001 (96.88)	<..001	4,994 (95.38)	<..001	859 (91.09)	<..001	10,916 (97.62)	<..001
Yes	18,875 (1.26)	797 (2.79)		1,613 (3.12)		242 (4.62)		84 (8.91)		266 (2.38)	
Polyhydramnio											
No	1,495,351 (99.66)	28,357 (99.33)	<..001	51,340 (99.47)	<..001	5,206 (99.43)	0.005	941 (99.79)	0.7777	11,109 (99.35)	<..001
Yes	5,169 (0.34)	191 (0.67)		274 (0.53)		30 (0.57)		2 (0.21)		73 (0.65)	
Prolong pregnancy											
No	1,356,474 (90.40)	26,085 (91.37)	<..001	48,786 (94.52)	<..001	4,908 (93.74)	<..001	928 (98.41)	<..001	10,221 (91.41)	<..001
Yes	144,046 (9.60)	2,463 (8.63)		2,828 (5.48)		328 (6.26)		15 (1.59)		961 (8.59)	
Placenta previa											
No	1,493,434 (99.53)	28,467 (99.72)	<..001	51,432 (99.65)	<..001	5,204 (99.39)	0.14	938 (99.47)	0.64	11,155 (99.76)	<..001
Yes	7,086 (0.47)	81 (0.28)		182 (0.35)		32 (0.61)		5 (0.53)		27 (0.24)	
Hysterectomy											
No	1,499,922 (99.96)	28,532 (99.94)	0.180	51,576 (99.93)	<..001	5,233 (99.94)	0.47	940 (99.68)	0.007	11,179 (99.97)	0.81
Yes	598 (0.04)	16 (0.06)		38 (0.07)		3 (0.06)		3 (0.32)		3 (0.03)	
Transfusion											
No	1498,903 (99.89)	28,502 (99.84)	0.007	51,482 (99.74)	<..001	5,231 (99.90)	0.79	940 (99.68)	0.083	11,164 (99.84)	0.09
Yes	1,617 (0.11)	46 (0.16)		132 (0.26)		5 (0.10)		3 (0.32)		18 (0.16)	

[a] Compared with those without HDPs; χ^2 test for categorical variables;

women without HDPs. Women with pre-eclampsia and with pre-eclampsia superimposed pre-existing hypertension had a higher proportion of hysterectomy than women with other types of HDPs or without HDPs had. Compared with women without HDPs, women with gestational hypertension and with pre-eclampsia were more likely to require blood transfusion and less likely to experience placenta previa during index pregnancy. A significantly decreased ($p<0.001$) proportion of prolong pregnancy was observed in women with HDPs than women without any HDPs.

5.3 Incidence of subsequent ESRD hospitalization associated with HDPs

5.3.1 Comparison of incidences of subsequent ESRD hospitalization between women with HDPs and without

A follow-up study was conducted for subsequent hospital admissions after index pregnancy until March 31, 2013, with median follow-up of 185 months (IQR: 153-214 months) for women with any type of HDPs and 194 months (IQR: 153-214 months) for women without HDPs.

There were 548 women who admitted to hospital for ESRD after the index pregnancy (Table 5.3), of which 147 were women with HDPs. The proportion of ESRD hospitalization in women with HDPs had about five times greater than that in women without HDPs (0.15% vs. 0.027%). Besides, women with HDPs also experienced ESRD hospitalization after index pregnancy earlier than women without such medical conditions (median, 123 months *vs.* 146 months). Incidence of subsequent ESRD hospitalization in women with HDPs was 9.90 per 100,000 person-years, which was approximately six times greater than the rate in women without HDPs (1.7 per 100,000 person-years).

Table 5.3 Comparisons of incidences of subsequent ESRD hospitalization among women with HDPs versus without

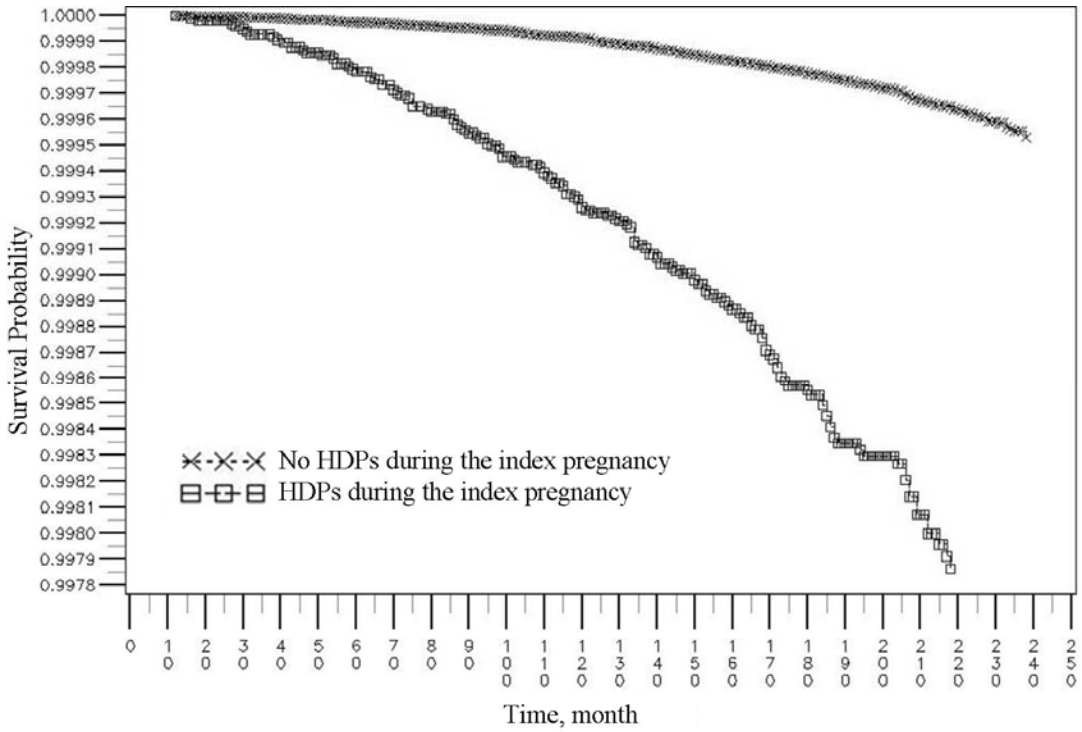
			Classification of HDPs				
Without HDPs (n=1,500,520)	With HDPs (n=97,523)	Gestational hypertension (n=28,548)	Pre-eclampsia/ Eclampsia (n=51,614)	Pre-existing hypertension (n=5,236)	Pre-eclampsia imposed on pre-existing hypertension (n=943)	Unspecific HDPs (n=1,1182)
Person-years						
2,356,5820	1,485,435	408,766	808,604	79,018	13,364	175,682
Length of follow-up, months (interquartile range)						
194 (159-220)	185 (153-214)	167 (137-205)	191 (161-216)	183 (151-212)	168 (138-198)	191 (162-217)
ESRD, n						
401	147	21	82	21	8	15
Median time to ESRD, months (interquartile rang)						
146 (105-185)	123 (84-168)	132 (86-163)	120 (75-162)	120 (89-153)	95.5 (82-142.5)	168 (120-186)
Hospital rate, per 100 000 person-years						
1.7	9.90	5.14	10.14	26.58	59.86	8.54
Hospital rate ratio (95% CI)						
1.00	5.82 (4.81-7.03)	3.02 (1.95-4.68)	5.96 (4.70-7.56)	15.62 (10.07-24.22)	35.18 (17.47-70.83)	5.02 (3.00-8.40)

Kaplan-Meier analysis exhibited that the survival curves of women with HDPs and women without differed since 30 months after index delivery and women without HDPs had a higher proportion of non-hospitalization for ESRD during the follow-up period (Figure 5.1). Log-rank test showed a significant difference between two survival curves (p<0.001).

5.3.2 Comparison of incidences of subsequent ESRD hospitalization between women with various types of HDPs and women without HDPs

Women with gestational hypertension, pre-eclampsia, pre-existing hypertension and pre-eclampsia superimposed in pre-existing hypertension had median follow-up of 167 months (IQR: 137-205 months), 191 months (IQR: 161-216 months), 183 months (IQR:

Figure 5.1 Estimated proportions of women without ESRD hospitalization during the follow-up period among women with and without HDPs. Log-rank test, p<0.001.

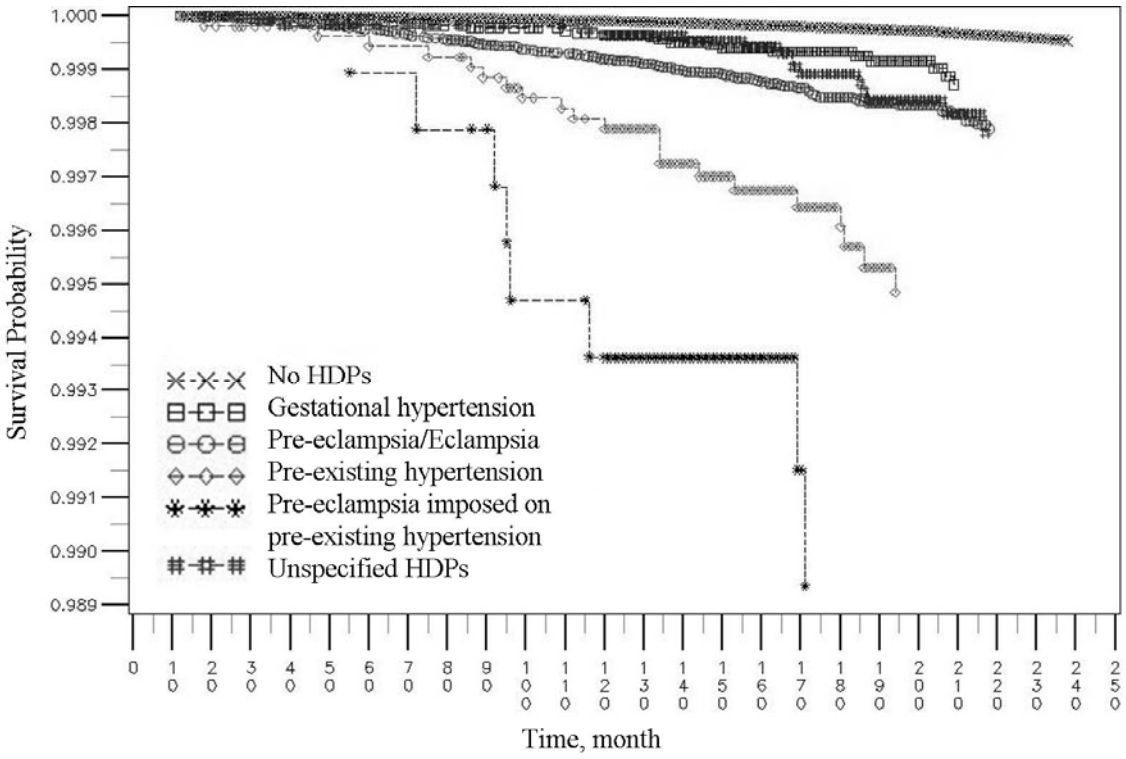


151-212 months), and168 months (IQR: 138-198 months), respectively. As shown in Table 5.3, women with pre-eclampsia superimposed on pre-existing hypertension had the highest proportion of subsequent ESRD hospitalization (0.85%, n=8), followed by women with pre-existing hypertension (0.40%, n=21), pre-eclampsia (0.16%, n=82) and gestational hypertension (0.07%, n=21). The proportion of subsequent ESRD hospitalization from women with any type of HDPs (0.15%, n=147) was higher in comparison with the proportion in the cohort without HDPs (0.03%, n=401).

The incidence of ESRD hospitalization was 1.7 per 100,000 person-years for women without HDPs during index pregnancy. The incidences of subsequent ESRD hospitalization were 59.86, 26.58, 10.14 and 5.14 per 100,000 person-years for women with pre-eclampsia superimposed on pre-existing hypertension, pre-existing hypertension, pre-eclampsia, and gestational hypertension, respectively (Table 5.3). Compared with women without HDPs, women with gestational hypertension and with pre-eclampsia had an increased risk of subsequent ESRD hospitalization with relative risks being 5.96 (95% CI: 4.70-7.56) and 3.02 (95% CI: 19.5-4.68), respectively. Women with pre-existing hypertension and with pre-eclampsia superimposed on pre-existing hypertension has even higher risk of an ESRD hospitalization when compared with those without HDPs, and the corresponding hazard ratios were 15.62 (95% CI: 10.07-24.22) and 35.18 (95% CI: 17.47-70.83), respectively.

The Kaplan-Meier survival plot (Figure 5.2) shows that in comparison with women with any type of HDPs, women without HDPs had a significantly higher overall proportion of non-hospitalization for ESRD during follow-up period (log-rank, $p<0.001$). Among women with different types of HDPs, women with gestational hypertension had

Figure 5.2 Estimated proportions of women without ESRD hospitalization during the follow-up period among women with specified HDPs and without. Log-rank test, $p<0.001$.



the highest proportion of non-hospitalization for ESRD subjects, followed by women with pre-eclampsia, with pre-existing hypertension, and with pre-eclampsia superimposed on pre-existing hypertension. The survival curves began to depart apparently each other 60 months following the index delivery and the survival curves for women with pre-existing hypertension and women with pre-eclampsia superimposed on pre-existing hypertension became much steeper later in comparison with the survival curves for other cohorts.

5.4 Cox PH regression analysis for the incidence of ESRD hospitalization associated with HDPs during index pregnancy

Because the onset of pre-existing hypertension is unavailable from DAD hospital administrative database, the time-to-event for this kind of exposure is undetermined for survival analysis. Therefore, pre-existing hypertension and pre-eclampsia superimposed pre-existing hypertension were not suitable for survival analysis in this study. 6,246 women who had pre-existing hypertension before the index pregnancy were removed from our study population, and the effects of gestational hypertension and pre-eclampsia on the risk of having an ESRD later in life were studied by Cox regression analysis.

5.4.1 Variable selection for Cox PH regression model

The main objective of the present study was to examine the potential associations of various types of HDPs and other medical conditions during pregnancy with the risk of subsequent ESRD hospitalization. As described in method above, a Collett's model selection approach was applied to build Cox regression model[79]. During the univariate screening procedure, 26 variables showed an association with subsequent ESRD hospitalization at the significance level of less than 0.2. The variables selected for the final model are shown in Table 5.4. Besides primary exposure variables of interest and demographic variables, caesarean delivery, preterm delivery, IUGR, deep vein thrombosis, cardiomyopathy, and blood transfusion were positively associated with subsequent ESRD hospitalization. The risk of subsequent ESRD hospitalization in women who had delivered >1 child during the study period was significantly lower than women who had only one delivery during study period.

Because the validation of a Cox regression analysis is based on the PH assumption, the significance of interaction between time and the effect of each identified explanatory variable in the model was evaluated to test whether hazard ratio exhibited a time-

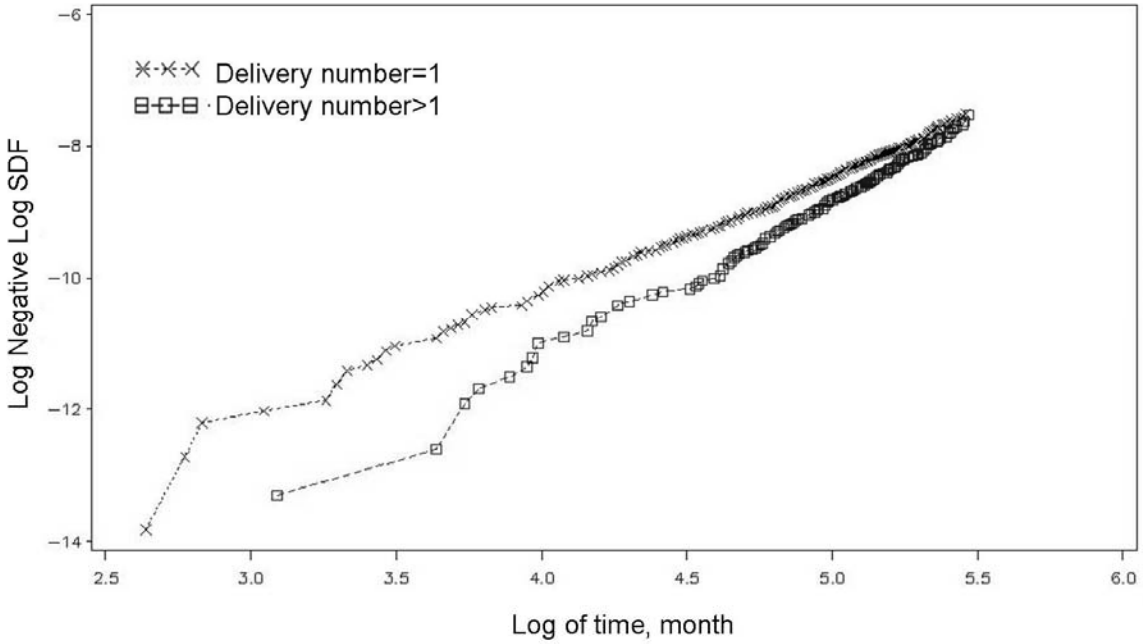
Table 5.4 Cox PH regression analysis for the incidence of ESRD hospitalization associated with HDPs during index pregnancy

Variable	β	SE[a]	Adjusted Hazard Ratio (95% CI)	*p* value	Significance of time-dependence
HDPs					
Gestational hypertension	1.1847	0.2255	3.27 (2.10-5.09)	<0.001	0.625
Pre-eclampsia/Eclampsia	1.5401	0.1275	4.67 (3.63-5.99)	<0.001	0.007
Unspecified HDPs	1.5263	0.2636	4.60 (2.75-7.71)	<0.001	0.646
No HDPs[b]	0	0	1.00		
Age (years)					
15-19	0.1250	0.1846	1.13 (0.79-1.63)	0.4985	0.975
20-24	0.3711	0.1225	1.45 (1.14-1.84)	0.0025	0.781
30-34	-0.0447	0.1207	0.96 (0.76-1.21)	0.7109	0.250
35-39	0.1214	0.1508	1.13 (0.84-1.52)	0.4207	0.267
40-45	0.3115	0.2828	1.37 (0.78-2.38)	0.2707	0.652
25-29[b]	0	0	1.00		
Region					
Atlantic	-0.3907	0.1734	0.68 (0.48-0.95)	0.0243	0.180
Prairie	-0.5326	0.1339	0.59 (0.45-0.76)	<0.001	0.172
Pacific	-0.0515	0.1176	0.95 (0.75-1.20)	0.6612	0.148
Territory	0.1735	0.5048	1.19 (0.44-3.20)	0.731	0.817
Ontario[b]	0	0	1.00		
Period					
1995/1996-1996/1997	-0.0064	0.1158	0.99 (0.79-1.25)	0.956	0.080
1997/1998-1998/1999	0.1124	0.1341	1.12 (0.86-1.46)	0.4022	0.693
1999/2000-2000/2001	-0.0041	0.1591	1.00 (0.73-1.36)	0.9793	0.765
2001/2002-2002/2003	-0.7000	0.2413	0.50 (0.31-0.80)	0.0037	0.532
1993/1994-1994/1995[a]	0	0	1.00		
Caesarean delivery	0.3896	0.0992	1.48 (1.22-1.79)	<0.001	0.200
IUGR	0.6446	0.1796	1.91 (1.34-2.71)	<0.001	0.155
Deep vein thrombosis	1.7557	0.5819	5.79 (1.85-18.11)	0.0026	0.414
Cardiomyopathy	1.2752	0.4123	3.58 (1.60-8.03)	0.002	0.583
Transfusion	1.5464	0.5041	4.69 (1.79-12.61)	0.0022	0.647
Preterm delivery	0.8573	0.1360	2.36 (1.81-3.08)	<0.001	0.216
Delivery number (1 *vs.* >1)	-0.3189	0.0958	0.73 (0.60-0.88)	<0.001	0.001

[a] SE, Standard error;
[b] Reference group.

dependent pattern. Significance of time-dependence shown in Table 5.4 stated that the effects of pre-eclampsia and delivery number variable significantly changed over time (p=0.0067 and p=0.0013, respectively), indicating the risks of subsequent ESRD hospitalization among the strata of these categorical variables is not proportional and the PH assumption of this Cox regression model was unsatisfied. For the variable of delivery number, the violated assumption was apparently observed by a log cumulative hazard plot (Figure 5.3). The distance between two cumulative hazard curves which were represented women with different delivery number (n=1 vs. n>1) became narrow with the time development and finally the hazard curves converged each other at the end of follow-up. This suggested that the hazard ratio of subsequent ESRD hospitalization between the strata of this binary variable was not constant and model need to be revised.

Figure 5.3 Log cumulative risk of ESRD hospitalization after index pregnancy, according to the number of delivery



Due to the significant effect on outcome of interest, the variables that did not hold the PH assumption should not be simply removed from the regression analysis. Two methods can be applied to manipulate non-proportional hazards in Cox regression. One is to introduce the interaction with time for variables which violate PH assumption. This method can identify such variables in the model and solve the problem at the same time, but interpretation of the analytic result is difficult and complicated. Stratification is another routine method to handle the non-proportional situation for survival data. In this method, the study population is split into several strata according to the value of stratification variable which interacts with time. As a consequence, the stratification variable is not implicitly included in the stratification model. All other explanatory variables stayed in the stratified model are assumed to satisfy the PH assumption. Stratification is most natural when the effect of the stratifying variable is not of the primary interest and the variable is categorized by only a few distinct values. Moreover, the interpretation for the stratified Cox regression results is quite straightforward and easy to understand. Therefore, stratified Cox regression analysis was applied to solve the non-proportional hazards problem in present cohort study.

5.4.2 Stratified Cox PH regression analysis for the incidence of ESRD hospitalization associated with HDPs during index pregnancy

As pre-eclampsia is the primary variable of interest, the cohort data was firstly stratified into two strata based on the number of deliveries (1 *vs.* >1).

5.4.2.1 No-interaction Stratified Cox PH regression analysis for the incidence of ESRD hospitalization associated with HDPs during index pregnancy

No-interaction Cox model assumes that the stratification variable has the constant influence across the strata on outcome of interest or that there is no interaction of stratification variable and other explanatory variables. As a consequence, each stratum shares the same coefficients of explanatory variables in model and the hazard ratios are identical. The result of no-interaction stratified Cox regression analysis for this study cohort is shown in Table 5.5. However, if interaction exists, no-interaction model become invalid and stratum-specific coefficients must be reported separately. As compared with women with one-delivery during the study period, women with multiple deliveries might have much better health condition and be less likely to have pregnancy-related complications. The complicated multiple unknown factors which relate to the decision of having a subsequent pregnancy could interact with the remaining explanatory variables in the model and violate the non-interaction stratification assumption. Besides, the effect from pre-eclamptic pregnancy was still significantly (p=0.005, Table 5.5) interacted with time in this no-interaction stratified model, indicating non-interaction stratified model might not be suitable for the data.

5.4.2.2 Interaction Stratified Cox PH regression analysis for the incidence of ESRD hospitalization associated with HDPs during index pregnancy

Interaction stratified Cox regression model considers the potential interaction of stratification variable with other explanatory variables used in the model and investigates the specific-stratum hazard ratios. We split the study population into two strata according to the number of deliveries, and specific-stratum hazard ratios were estimated separately.

The first stratum was composed of 996,063 women who had only one obstetrical delivery record during the study period. Among the women in the cohort without HDPs

Table 5.5 No-interaction stratified Cox PH regression analysis for the incidence of ESRD hospitalization associated with HDPs during index pregnancy

Variable	β	SE [a]	Adjusted hazard ratio (95% CI)	*p* value	Significance of time-dependence
HDPs					
Gestational hypertension	1.1839	0.2255	3.27 (2.10-5.08)	<0.001	0.629
Pre-eclampsia/Eclampsia	1.5386	0.1275	4.66 (3.63-5.98)	<0.001	0.005
Unspecified HDPs	1.5265	0.2636	4.60 (2.75-7.72)	<0.001	0.665
No HDPs [b]	0	0	1.00		
Age (years)					
15-19	0.1191	0.1846	1.13 (0.78-1.62)	0.519	0.946
20-24	0.3679	0.1225	1.45 (1.14-1.84)	0.003	0.822
30-34	-0.0424	0.1207	0.96 (0.76-1.21)	0.725	0.144
35-39	0.1227	0.1508	1.13 (0.84-1.52)	0.416	0.107
40-45	0.3091	0.2828	1.36 (0.78-2.37)	0.274	0.996
25-29 [b]	0	0	1.00		
Region					
Atlantic	-0.3902	0.1734	0.68 (0.48-0.95)	0.024	0.233
Prairie	-0.5218	0.1341	0.59 (0.46-0.77)	<0.001	0.286
Pacific	-0.0519	0.1176	0.95 (0.75-1.20)	0.659	0.159
Territory	0.1692	0.5048	1.18 (0.44-3.19)	0.737	0.753
Ontario [b]	0	0	1.00		
Period					
1995/1996-1996/1997	-0.0065	0.1158	0.99 (0.79-1.25)	0.955	0.093
1997/1998-1998/1999	0.1121	0.1341	1.12 (0.86-1.46)	0.403	0.655
1999/2000-2000/2001	-0.0260	0.1593	0.97 (0.71-1.33)	0.870	0.621
2001/2002-2002/2003	-0.7887	0.2430	0.45 (0.28-0.73)	0.001	0.832
1993/1994-1994/1995 [b]	0	0	1.00		
Caesarean delivery	0.3889	0.0992	1.48 (1.22-1.79)	<0.001	0.250
IUGR	0.6441	0.1796	1.90 (1.34-2.71)	<0.001	0.166
Deep vein thrombosis	1.7482	0.5821	5.74 (1.84-17.98)	0.003	0.452
Cardiomyopathy	1.2737	0.4123	3.57 (1.59-8.02)	0.002	0.553
Transfusion	1.5457	0.5042	4.69 (1.75-12.60)	0.002	0.631
Preterm delivery	0.8564	0.1360	2.36 (1.80-3.07)	<0.001	0.231

[a] SE, Standard error;
[b] Reference group.

(n=940,354), 246 (0.026%) were admitted to hospital for ESRD with a median time of 185 months (IQR: 146-218 months). 1.97% (n=19,606) of women experienced gestational hypertension during the index pregnancy and 14 women (0.07%) were reported subsequent ESRD hospitalization with a median time of 110 months (IQR: 70-132 months). In comparison with women without HDPs, women with gestational hypertension were at an increased risk of an ESRD hospitalization with an adjusted hazard ratio of 3.47 (95% CI: 2.01-5.97) (Table 5.6). In this stratum, 29,667 (2.98%) women suffered a pre-eclamptic pregnancy and 60 (0.20%) of these women were admitted to hospital for ESRD during the follow-up period. With a median time to ESRD of 114 months (IQR: 67-160.5 months), women in the cohort with pre-eclampsia had a risk of subsequent ESRD hospitalization 5.64 times (95% CI: 4.17-7.62) greater than did those without HDPs. For the obstetrical complications, caesarean delivery, IUGR and preterm delivery during the pregnancy were significantly associated the risk ESRD hospitalization later in life with adjusted hazard ratios of 1.61 (95% CI: 1.27-2.04), 1.98 (95% CI: 1.30-3.02), and 2.42 (95% CI: 1.75-3.35), respectively. The risks of having an ESRD later in life in women with deep vein thrombosis or cardiomyopathy during the pregnancy increased by 7.56 times (95% CI: 2.39-23.92) and 4.02 times (95% CI: 1.65-9.81), respectively, than in women without such medical conditions. The time-dependence of each explanatory variable was examined and no one showed a significance of time-dependence at the alpha level of 0.01.

In this stratum, 23.09% of ESRD cases developed after the pregnancy were attributable to the previous HDPs complicated pregnancy (Table 5.6). PAF for subsequent ESRD hospitalization in women with pre-eclampsia was four times higher

Table 5.6 Cox PH regression analysis for the incidence of ESRD hospitalization associated with HDPs during index pregnancy among women who had only one delivery during the study period

Variables	Univariate Cox Regression Model			Adjusted Cox Regression Model			Significance of time-dependence	ESRD, n	PAF for ESRD (%)
	β	SE [a]	Hazard ratio (95% CI)	β	SE [a]	Adjusted hazard ratio (95% CI)			
HDPs									
Gestational hypertension	1.2289	0.2751	3.42 (1.99-5.86)	1.2429	0.2771	3.47 (2.01-5.97)	0.23	14	3.83
Pre-eclampsia/Eclampsia	2.0661	0.1440	7.90 (5.95-10.47)	1.7299	0.1537	5.64 (4.17-7.62)	0.03	60	16.13
Unspecified HDPs	1.7785	0.3226	5.92 (3.15-11.14)	1.6209	0.3235	5.06 (2.68-9.53)	0.91	10	3.13
No HDPs	0		1.00	0		1.00		246	
Age (years)									
15-19	0.0981	0.2557	1.10 (0.67-1.82)	0.1201	0.2567	1.13 (0.68-1.86)	0.41		
20-24	0.3687	0.1675	1.45 (1.04-2.01)	0.3963	0.1679	1.49 (1.07-2.07)	0.72		
30-34	0.1359	0.1512	1.15 (085-1.54)	0.0771	0.1516	1.08 (0.80-1.45)	0.15		
35-39	0.3601	0.1738	1.43 (1.02-2.02)	0.1870	0.1748	1.21 (0.86-1.70)	0.16		
40-45	0.5134	0.3097	1.67 (0.91-3.07)	0.2119	0.3112	1.24 (0.67-2.27)	0.62		
25-29 [b]	0		1.00	0		1.00			
Region									
Atlantic	-0.3040	0.2020	0.74 (0.50-1010)	-0.3755	0.2040	0.69 (0.46-1.03)	0.18		
Prairie	-0.8601	0.1813	0.42 (0.30-0.60)	-0.9205	0.1827	0.40 (0.28-0.57)	0.02		

Table 5.6: cont'd

Variables	Univariate Cox Regression Model			Adjusted Cox Regression Model			Significance of time-dependence	ESRD, n	PAF for ESRD (%)
	β	SE [a]	Hazard ratio (95% CI)	β	SE [a]	Adjusted hazard ratio (95% CI)			
Pacific	0.0457	0.1422	1.05 (0.79-1.38)	0.0267	0.1428	1.03 (0.78-1.36)	0.05		
Territory	0.0463	0.5818	1.05 (0.34-3.28)	0.1197	0.5836	1.13 (0.36-3.54)	0.76		
Ontario[b]	0		1.00	0		1.00			
Period									
1995/1996-1996/1997	0.0778	0.1506	1.08 (0.81-1.45)	-0.0003	0.1514	1.00 (0.74-1.35)	0.37		
1997/1998-1998/1999	0.3299	0.1682	1.39 (1.000-1.93)	0.2107	0.1693	1.24 (0.89-1.72)	0.61		
1999/2000- 2000/2001	0.2167	0.1858	1.24 (0.86-1.79)	0.0502	0.1872	1.05 (0.73-1.52)	0.50		
2001/2002- 2002/2003	-0.5667	0.2494	0.57 (0.35-0.93)	-0.7250	0.2511	0.48 (0.30-0.79)	0.83		
1993/1994- 1994/1995[b]	0		1.00	0		1.00			
Caesarean delivery	0.7367	0.1156	2.09 (1.67-2.62)	0.4738	0.1208	1.61 (1.27-2.04)	0.61	115	13.15
IUGR	1.2437	0.2043	3.47 (2.32-5.18)	0.6836	0.2143	1.98 (1.30-3.02)	0.19	26	3.90
Deep vein thrombosis	2.5836	0.5800	13.25 (4.25-41.28)	2.0223	0.5880	7.56 (2.39-23.92)	0.64	3	0.79
Cardiomyopathy	1.7084	0.4506	5.52 (2.28-13.35)	1.3915	0.4549	4.02 (1.65-9.81)	0.47	5	1.14
Transfusion	1.5511	0.7093	4.72 (1.18-18.94)	1.2488	0.7149	3.49 (0.86-14.15)	0.99	2	0.43
Preterm delivery	1.2533	0.1576	3.50 (2.57-4.77)	0.8851	0.1658	2.42 (1.75-3.35)	0.33	47	8.36

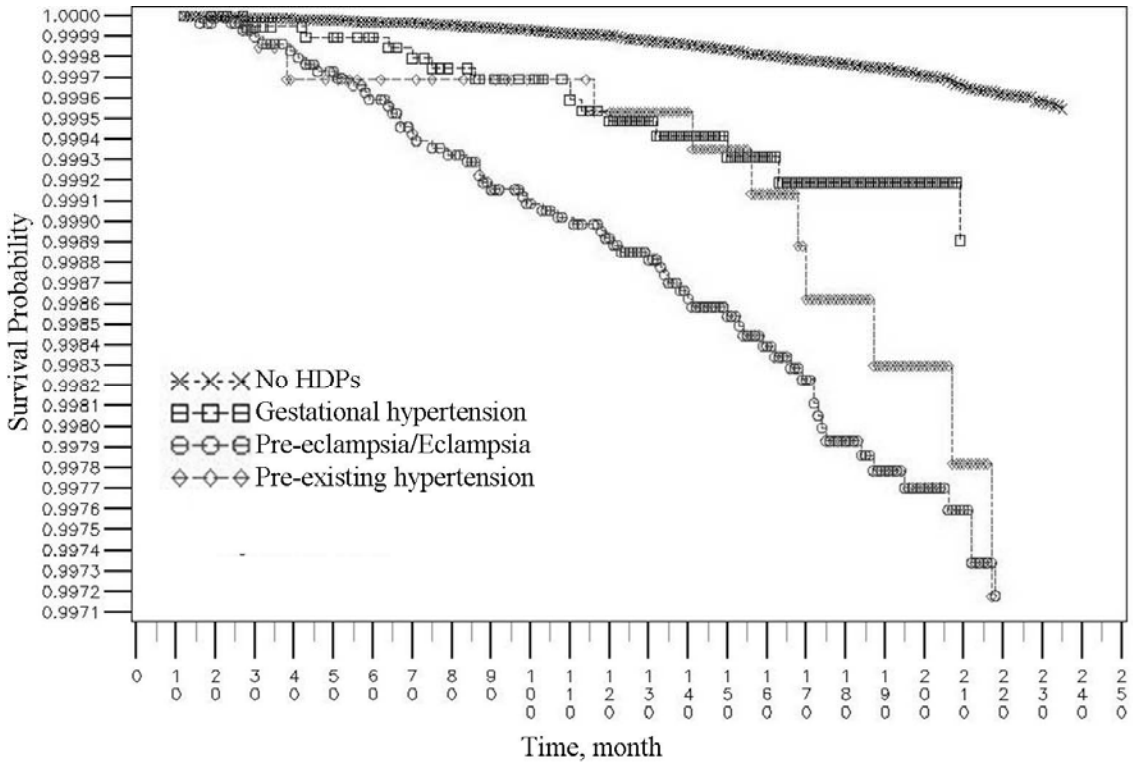
[a] SE, Standard error;
[b] Reference group.

than that PAF in women with gestational hypertension (16.13% vs. 3.83%). Approximately 3.90% and 8.36% of the subsequent ESRD could be attributed to IUGR and preterm delivery, respectively.

The Kaplan-Meier survival analysis showed that overall proportions of non-hospitalization for ESRD after the index pregnancy were significantly different between women with and without HDPs (log-rank<0.001, Figure 5.4). Women without HDPs had the lowest risk of an ESRD hospitalization among all groups. While the survival curve for women with pre-eclampsia slid down more rapidly than any other survival curve, indicating this kind of women had a higher risk as compared with all other women. The results from the Kaplan-Meier plot were consistent with those from Cox regression models that HDPs were associated with greater risks of subsequent ESRD hospitalization and women with pre-eclamptic pregnancy had a worse adverse effect on this long-term outcome as compared with those with pregnancy complicated by gestational hypertension.

The second stratum contained 595,734 women who had one or more deliveries after index pregnancy during the study period. There were 560,166 women without HDPs during their index pregnancy and 0.027% (n=155) of these women were admitted to hospital for ESRD later with a median time of 203 months (IQR: 178-222 months). 1.50% (n=8,942) and 3.68% (n=21,947) of women in this stratum had gestational hypertension or pre-eclampsia during their index pregnancy, respectively. In women with gestational hypertension, seven cases of ESRD hospitalization after the index pregnancy were reported with a median time to ESRD of 187 months (IQR: 137-204 months). The adjusted hazard ratio was 2.98 (95% CI: 1.39-6.38) for women with gestational hypertension in comparison with women without HDPs (Table 5.7). The proportion of

Figure 5.4 Estimated proportions of women without subsequent ESRD hospitalization for women in the stratum of one-delivery during the study period. Log-rank test, $p<0.001$.



subsequent ESRD hospitalization in women with pre-eclampsia was much lower in this stratum as compared with the first stratum (0.10% vs. 0.20%). 22 subsequent ESRD cases were reported in women with pre-eclampsia with a median time of 133 months (IQR: 102-165 months) and yielded an adjusted hazard ratio of 3.19 (95% CI: 2.02-5.05). Caesarean section, IUGR, deep vein thrombosis and cardiomyopathy were positively associated with subsequent ESRD in the first stratum, but the associations became statistically nonsignificant in this stratum. However, blood transfusion during the index delivery was significantly associated with the risk of subsequent ESRD hospitalization (hazard ratio, 6.47; 95% CI: 1.60-26.23) in this stratum. Women with preterm delivery during the index pregnancy still showed an increased risk of an ESRD hospitalization

Table 5.7 Cox PH regression analysis for the incidence of ESRD hospitalization associated with HDPs during index pregnancy among women who had multiple deliveries during the study period

Variables	Univariate Cox regression model			Adjusted Cox regression model			Significance of time-dependence	ESRD, n	PAF for ESRD (%)
	β	SE[a]	Hazard ratio (95% CIs)	β	SE[a]	Adjusted hazard ratio (95% CI)			
HDPs									
Gestational hypertension	1.1275	0.3865	3.09 (1.45-6.59)	1.0913	0.3883	2.98 (1.39-6.38)	0.17	7	2.46
Pre-eclampsia/Eclampsia	1.3067	0.2278	3.70 (2.36-5.77)	1.1604	0.2345	3.19 (2.02-5.05)	0.45	22	7.99
Unspecified HDPs	1.3888	0.4543	4.01 (1.65-9.77)	1.3752	0.4552	3.96 (1.62-9.65)	0.38	5	1.98
No HDPs[b]	0		1.00	0		1.00		155	
Age (years)									
15-19	0.0654	0.2651	1.07 (0.64-1.80)	0.0615	0.2663	1.06 (0.63-1.79)	0.31		
20-24	0.3042	0.1787	1.36 (0.96-1.92)	0.3082	0.1793	1.36 (0.96-1.93)	0.30		
30-34	-0.2728	0.2101	0.76 (0.50-1.5)	-0.2795	0.2102	0.76 (0.50-1.14)	0.56		
35-39	-0.0838	0.3548	0.92 (0.46-1.84)	-0.1190	0.3554	0.89 (0.44-1.78)	0.48		
40-45	1.2966	0.7175	3.66 (0.90-14.92)	1.2568	0.7180	3.51 (0.86-14.35)	0.29		
25-29[b]	0		1.00	0		1.00			
Region									
Atlantic	-0.4133	0.3298	0.66 (0.35-1.26)	-0.4536	0.3316	0.64 (0.33-1.22)	0.90		
Prairie	0.2656	0.1964	1.30 (089-1.92)	0.2255	0.2009	1.25 (0.85-1.86)	0.50		

Table 5.7: cont'd

Variables	Univariate Cox regression model			Adjusted Cox regression model			Significance of time-dependence	ESRD, n	PAF for ESRD (%)
	β	SE[a]	Hazard ratio (95% CIs)	β	SE[a]	Adjusted hazard ratio (95% CI)			
Pacific	-0.1639	0.2078	0.85 (0.57-1.28)	-0.2019	0.2084	0.82 (0.54-1.23)	0.32		
Territory	0.3540	1.0044	1.43 (0.20-10.20)	0.3215	1.0063	1.38 (0.19-9.91)	0.23		
Ontario[b]	0		1.00	0		1.00			
Period									
1995/1996-1996/1997	-0.0819	0.1793	0.92 (0.65-1.31)	-0.1155	0.1812	0.89 (0.63-1.27)	0.07		
1997/1998-1998/1999	-0.0991	0.2210	0.91 (0.59-1.40)	-0.1551	0.2236	0.86 (0.55-1.33)	0.75		
1999/2000- 2000/2001	-0.2735	0.3213	0.76 (0.41-1.43)	-0.3440	0.3240	0.71(0.38-1.34)	0.80		
2001/2002- 2002/2003	-11.1080	240.4265	0 (0-6.72E+199)	-11.5715	284.1493	0 (0-6.96E+236)	1.00		
1993/1994- 1994/1995[b]	0		1.00	0		1.00			
Caesarean delivery	0.2977	0.1750	1.35 (0.96-1.90)	0.1975	0.1792	1.22 (0.86-1.72)	0.46	42	3.98
IUGR	0.8786	0.3250	2.41 (1.27-4.55)	0.5443	0.3324	1.72 (0.90-3.31)	0.96	10	2.22
Deep vein thrombosis	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	
Cardiomyopathy	0.8007	1.0013	2.23 (0.31-15.85)	0.7584	1.0032	2.14 (0.30-15.25)	0.87	1	0.28
Transfusion	2.1350	0.7109	8.46 (2.10-34.07)	1.8676	0.7140	6.47 (1.60-26.23)	0.40	2	0.89
Preterm delivery	0.9140	0.2365	2.49 (1.57-3.97)	0.7562	0.2414	2.13(1.33-3.42)	0.77	20	5.61

[a] SE, Standard error;
[b] Reference group.

(hazard ratio, 2.13; 95% CI: 1.33-3.42) in the second stratum. The time-dependence of each explanatory variable was tested and no variable exhibited significantly interact with time. Therefore, the PH assumption was satisfied.

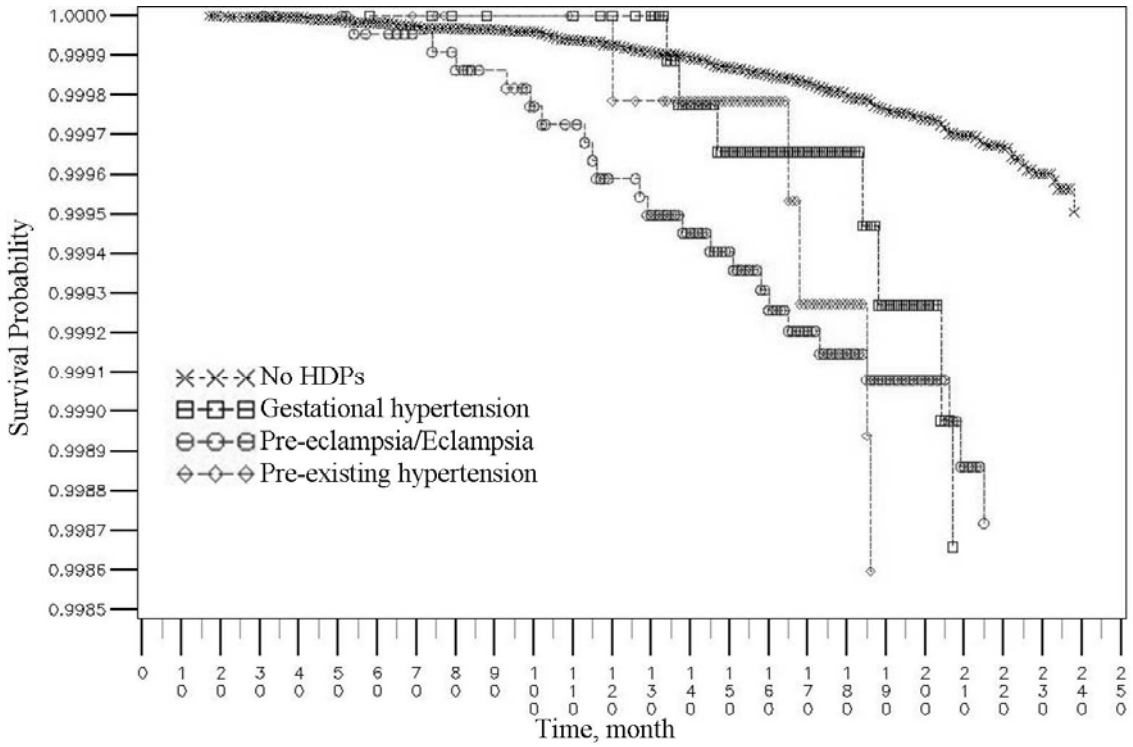
In the second stratum, 12.42% of the subsequent ESRD hospitalization could be attributed to previous HDPs complicated pregnancy (2.46% to gestational hypertension and 7.99% to pre-eclampsia). Approximately 5.61% of the subsequent ESRD hospitalization could be attributed to preterm delivery.

The Kaplan-Meier survival analysis exhibited that the proportion of non-ESRD hospitalization during the follow-up period was significantly different in women with and without HDPs (log-rank<0.001, Figure 5.5). During the follow-up period, the survival curve for non-HDPs women was always higher than the curves for women with pre-eclampsia or with gestational hypertension. The survival curve for women with pre-eclampsia declined more quickly than did the curve for women with gestational hypertension at early stage of follow-up period, but two curves were closer each other at the end of follow-up period, suggesting that women with previous pre-eclamptic pregnancy experience ESRD hospitalization earlier than women with gestational hypertension, but the overall risk of subsequent ESRD hospitalization showed no difference between these two groups in long term.

5.4.2.3 Diagnosis of interaction stratified Cox regression model

The PH assumption for Cox regression analysis can be assessed by several numerical or graphical approaches. One numerical method is to evaluate the interactions with time for each explanatory variable in the model. As shown in Table 5. 6 and Table 5.7, no variable was significant for time-dependence (p>0.01), suggesting that PH assumption

Figure 5.5 Estimated proportions of women without subsequent ESRD hospitalization for women in the stratum of multiple deliveries during the study period. Log-rank test, $p<0.001$.



was satisfied for this Cox regression analysis. Standardized Schoenfeld is a common graphical method used to check Cox model assumption. Figure 5.6 and Figure 5.7 shows that the plots of standardized Schoenfeld residuals against time for each explanatory variable (except the demographic variables) used in Cox regression model for the two strata. The Schoenfeld residuals are not defined for censored observations, and only represent the observations of those admitted to hospital for ESRD within the follow-up period. The dot line was a smoothing-spline fit to the plot. The standardized Schoenfeld residuals showed in plots were independent of time to ESRD hospitalization as they were randomly distributed without displaying a trend or systematic departures from a

Figure 5.6 Plots of standardized Schoenfeld residuals for the Cox regression analysis for the incidence of subsequent ESRD hospitalization with regards to gestational hypertension, pre-eclampsia, caesarean delivery, IUGR, deep vein thrombosis, cardiomyopathy, transfusion, and preterm delivery among women in the stratum of one-delivery during the study period

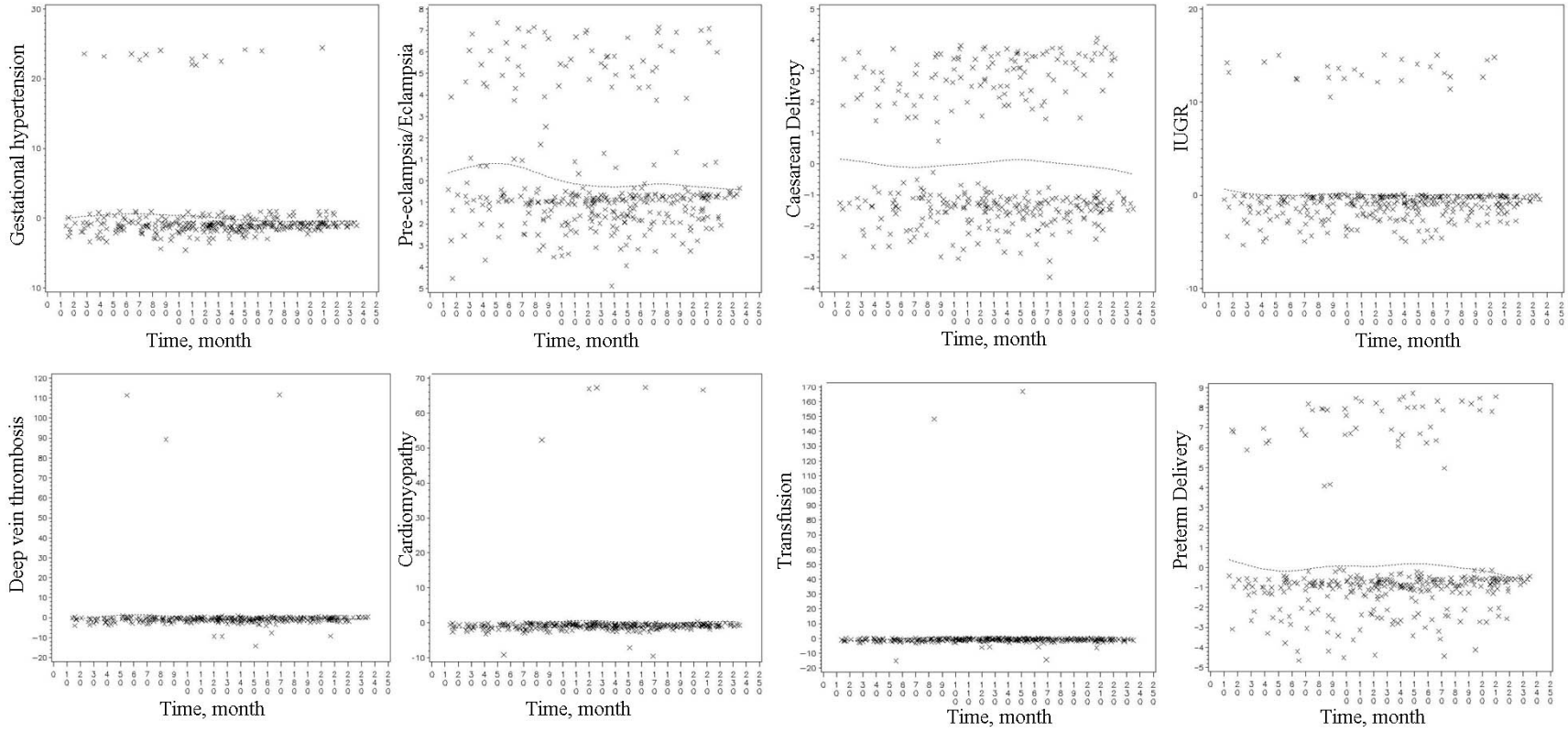
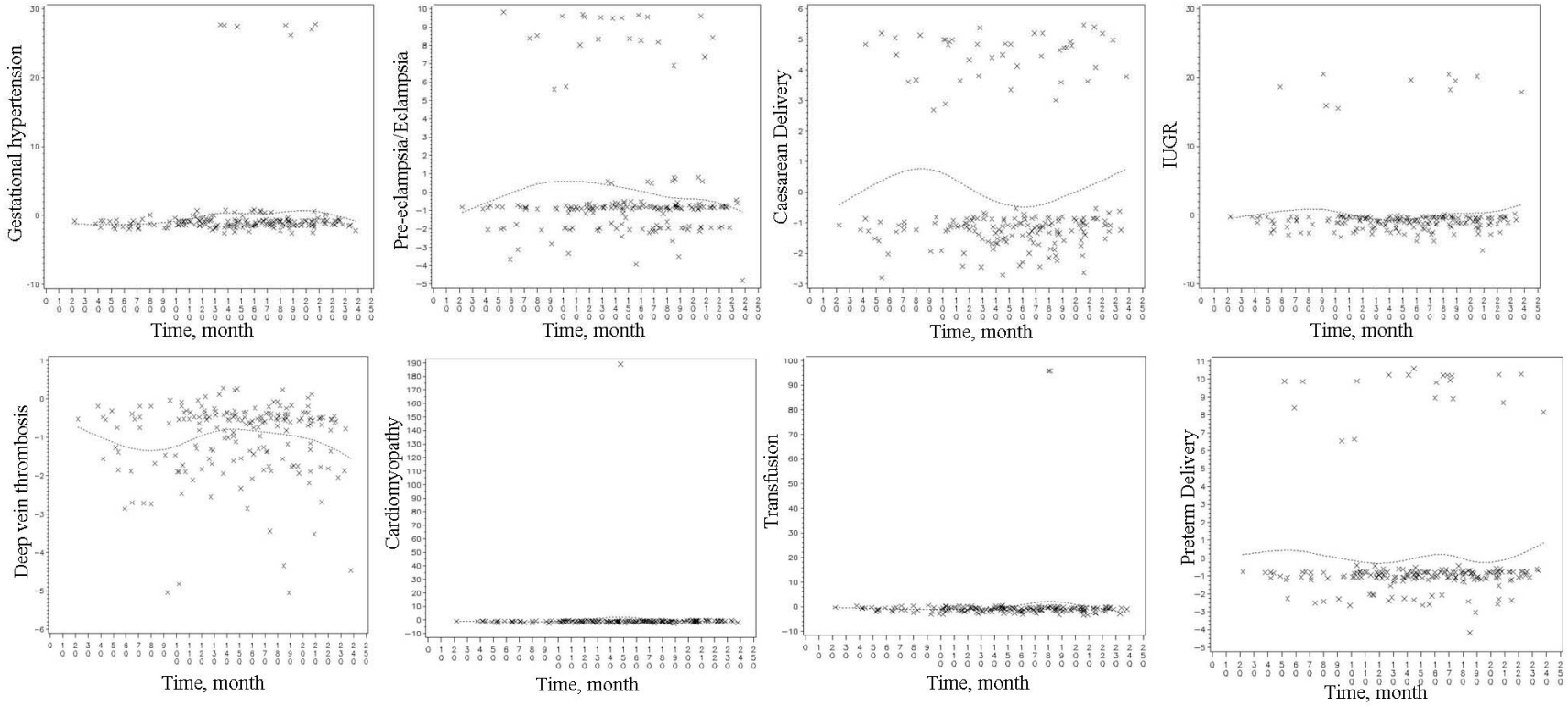


Figure 5.7 Plots of standardized Schoenfeld residuals for the Cox regression analysis for the incidence of subsequent ESRD hospitalization with regards to gestational hypertension, pre-eclampsia, caesarean delivery, IUGR, deep vein thrombosis, cardiomyopathy, transfusion, and preterm delivery among women in the stratum of multiple deliveries during the study period



horizontal line. In conclusion, the effects of tested explanatory variables did not violate the PH assumption in this Cox model.

Deviance residuals measure the difference between observed and expected hazard in Cox regression analysis, and are useful to evaluate model fitness and identify outliers. As shown in Figure 5.8 and Figure 5.9, deviance residuals in this study exhibited unsymmetrical distribution: the residuals representing censored observations clumped around zero and the residuals representing observations with ESRD hospitalization were showed as the positive residuals with the range from 3 to 5 standard deviations. This is because ESRD hospitalization occurs rarely in general population, and majority of observations in this study cohort became censored at the end of follow-up period. Therefore, heavy censoring distorted the expected normal approximation in present study. Normally, residuals are expected within ± 3 standard deviations for a good fitted model and observations with residual values beyond this range might be considered as outliers. ESRD is a very rare medical condition in general population. Among over one and half million subjects, only several hundreds women were admitted to hospital for ESRD during approximately twenty years of follow-up. The large standard deviation could be due to an extreme low incidence of ESRD hospitalization and complicated multiple residual risk factors, which might be not related to the index pregnancy. The main objective of this study was to describe and interpret the adverse effects of hypertensive disorders during pregnancy on the risk of subsequent ESRD hospitalization, but not to establish a prediction model. Therefore, the narrowly scattered values of deviance residuals in this longitudinal study were still at an acceptable level.

Figure 5.8 Plots of deviance residuals for the Cox regression analysis for the incidence of subsequent ESRD hospitalization with regards to gestational hypertension, pre-eclampsia, caesarean delivery, IUGR, deep vein thrombosis, cardiomyopathy, transfusion, and preterm delivery among women in the stratum of one-delivery during the study period

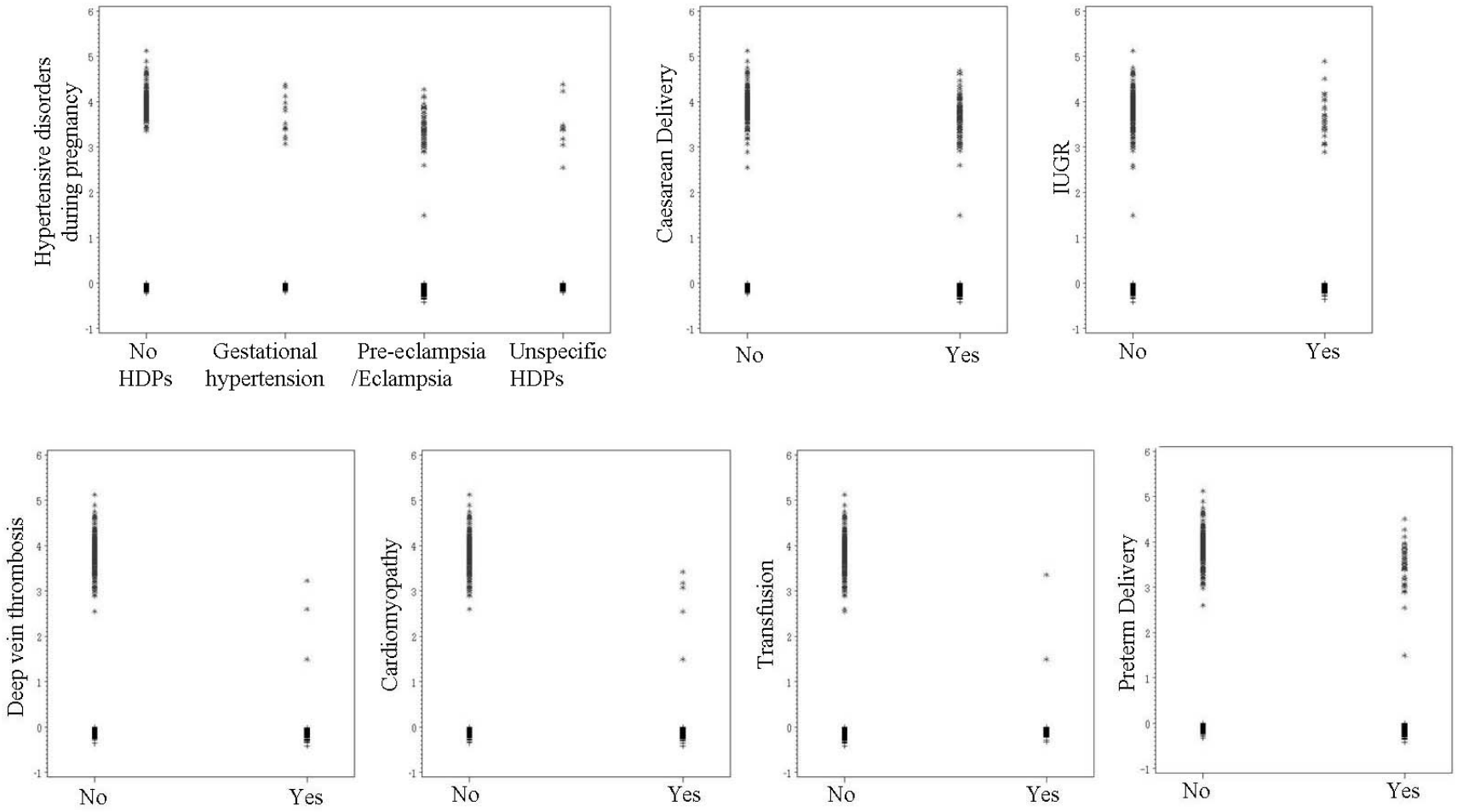
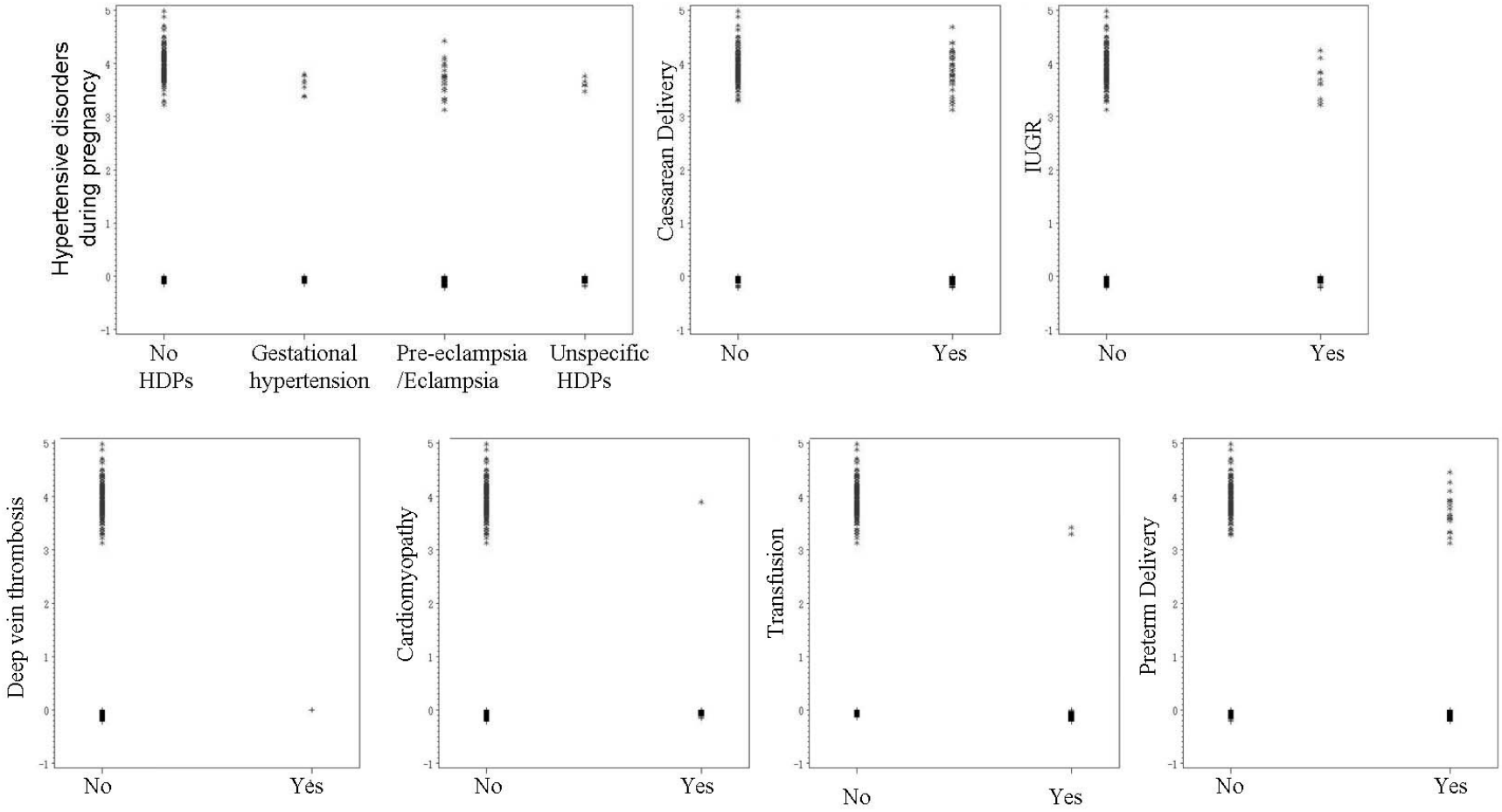


Figure 5.9 Plots of deviance residuals for the Cox regression analysis for the incidence of subsequent ESRD hospitalization with regards to gestational hypertension, pre-eclampsia, caesarean delivery, IUGR, deep vein thrombosis, cardiomyopathy, transfusion, and preterm delivery among women in the stratum of multiple deliveries during the study period



To evaluate the adequacy of the fitted model, deletion diagnostics was applied to calculate the disproportionate influence (dfbeta) from any observation on each estimated parameter. As compared with the estimated coefficients, the magnitudes of the largest dfbeta values were at acceptable level (Figure 5.10 and Figure 5.11). Removal of these potentially influential observations only altered the results slightly. Therefore, these observations were kept in the final regression model.

5.5 Assessment of potential interactions between various types of HDPs and other explanatory variables in relation to subsequent ESRD hospitalization

Three measures, RERI, AP and S, were applied to investigate the additive interactions between various types of HDPs and other significant explanatory variables identified from Cox regression analysis in relation to subsequent ESRD hospitalization. In this study, the interaction effect between two risk factors on subsequent ESRD hospitalization was considered as departure from additivity when all three measures indicated the same direction of significant departure. According to this criterion, positive interaction between pre-eclampsia and preterm delivery was identified in the first stratum where women had only one delivery within the study period (Table 5.8).

Among women with one-delivery during the study period, women without any types of HDPs and preterm delivery (n=898,527) was categorized into reference category and 0.024% (n=219) of these women who had ESRD hospitalization during the follow-up period. The category of preterm delivery consisted of 41,827 women who delivered a baby before 37 weeks of gestation without pre-eclampsia and 0.06% (n=27) of these women had ESRD hospitalization during the follow-up period. Women with pre-eclamptic pregnancy and full-term labor (n=25,423) were classified into the category of

Figure 5.10 Plots of dfbeta for the Cox regression analysis for the incidence of subsequent ESRD hospitalization with regards to gestational hypertension, pre-eclampsia, caesarean delivery, IUGR, deep vein thrombosis, cardiomyopathy, transfusion, and preterm delivery among women in the stratum of one-delivery during the study period

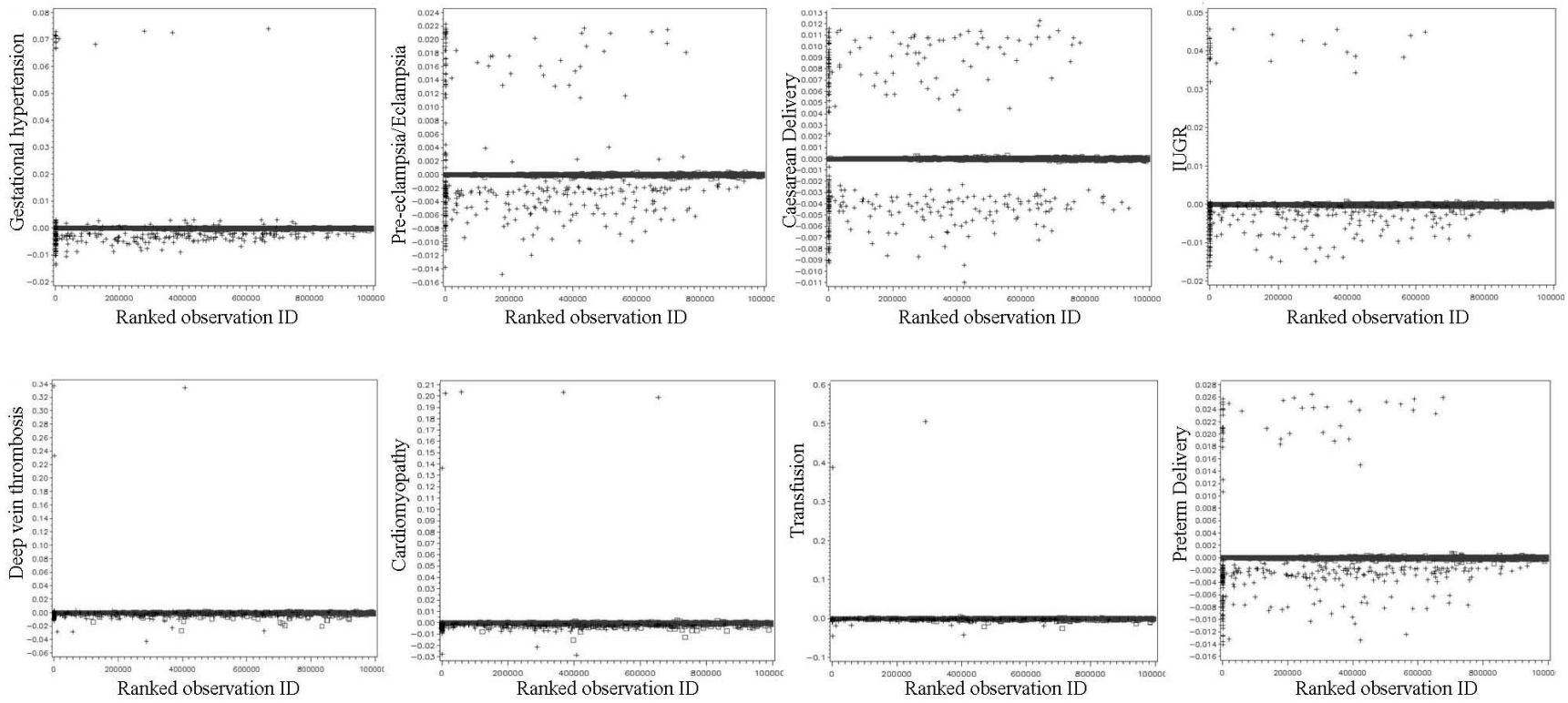


Figure 5.11 Plots of dfbeta for the Cox regression analysis for the incidence of subsequent ESRD hospitalization with regards to gestational hypertension, pre-eclampsia, caesarean delivery, IUGR, deep vein thrombosis, cardiomyopathy, transfusion, and preterm delivery among women in the stratum of multiple deliveries during the study period

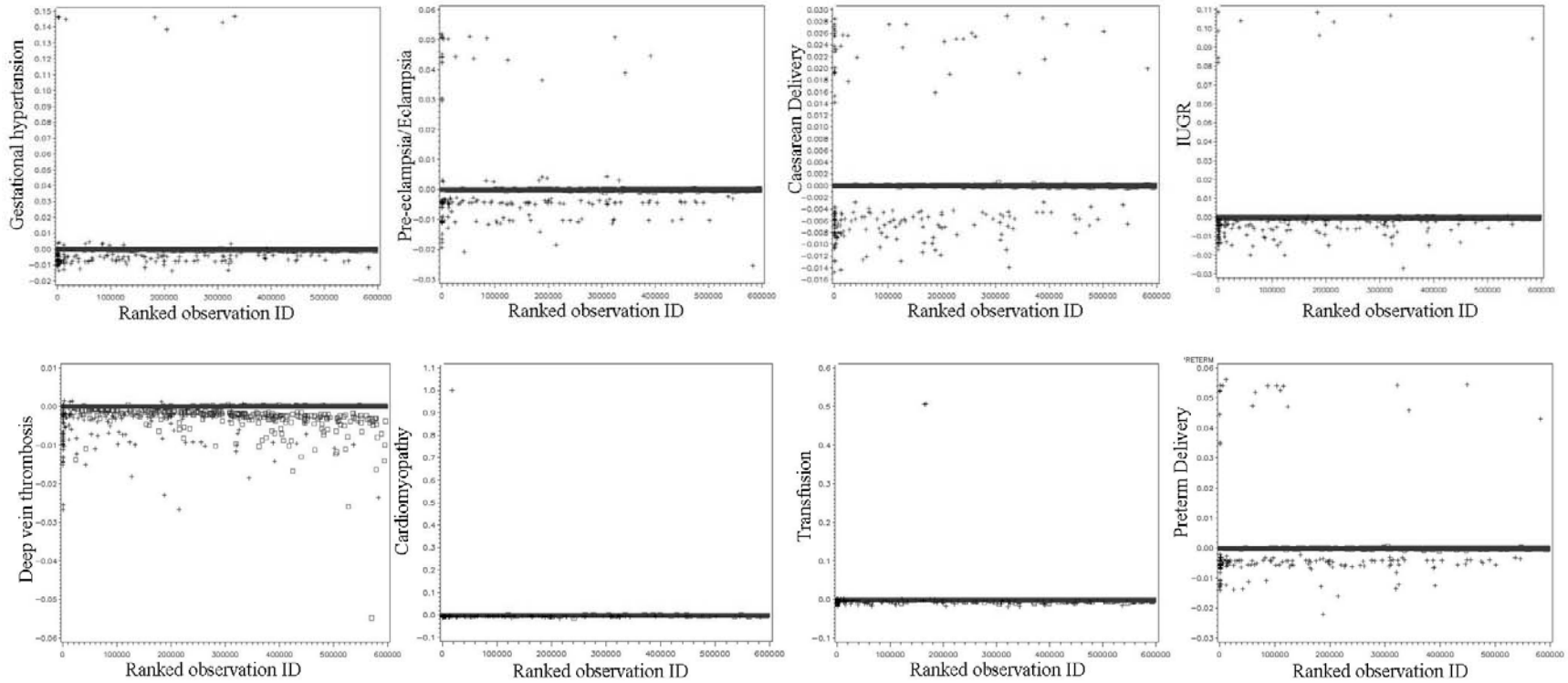


Table 5.8. Additive interaction between pre-eclampsia and preterm delivery in relation to subsequent ESRD hospitalization among women with one-delivery only during the study period

Exposure	ESRD, n	Adjusted hazard ratio (95% CI)
Null (n=898,527)	219	1.00
Preterm delivery (n=41,827)	27	2.13 (1.37-3.30)
Pre-eclampsia (n=25,423)	40	5.40 (3.83-7.61)
Pre-eclampsia & preterm delivery (n=4,244)	20	14.22 (8.70-23.26)

Measure	Estimate (95% CI)
RERI	7.70 (0.77-14.62)
AP	0.54 (0.29-0.79)
S	2.39 (1.32-4.35)

pre-eclampsia, and 40 of these women (0.15%) had ESRD hospitalization after the pregnancy. There were 4 244 women with both pre-eclamptic pregnancy and preterm delivery, and 0.47% (n=20) of them had ESRD hospitalization during follow-up period. Compared with the risk of subsequent ESRD hospitalization in the reference group, the adjusted hazard ratios for women with preterm delivery only and women with pre-eclampsia only were 2.13 (95% CI: 1.37-3.30) and 5.40 (95% CI: 3.83-7.61), respectively. For women with both preterm delivery and pre-eclampsia, the adjusted hazard ratio dramatically rose to 14.22 (95% CI: 8.70-23.26).

The three measures of additive interactions, RERI, AP and S, were 7.70 (95% CI: 0.77-14.62), 0.54 (95% CI: 0.29-0.79) and 2.40 (95% CI: 1.32-4.35), demonstrating a positive interaction on an additive scale, meaning that the combined effect of preterm delivery and pre-eclampsia was greater than the addition of the separate effects of these two factors.

5.6 Cox PH regression analysis for the incidence of non-diabetes-related ESRD hospitalization associated with HDPs during index pregnancy

Diabetes mellitus is an important risk factor for renal disease and ESRD[91,92]. Due to an association of HDPs complicated pregnancy with diabetes mellitus developed after pregnancy, diabetes mellitus could perform as an important confounder for the positive association between HDPs and the risk of having an ESRD later in life. Unfortunately, the information about diabetes mellitus was not fully available from the DAD. Therefore, diabetes mellitus developed after index pregnancy could not be adjusted in Cox regression analysis. To examine whether the estimates for the association of HDPs with the risk of later ESRD hospitalization was affected by diabetes mellitus, diabetes-related ESRD cases were removed.

In the first stratum of one-delivery during the study period, 52 women with hospital admission of diabetes-related ESRD were removed from the study population and 278 ESRD cases remained. Compared with the non-HDPs women, the women with gestational hypertension or with pre-eclampsia still had a significantly higher risk on the subsequent ESRD hospitalization with a hazard ratio of 3.71 (95% CI: 2.11-6.54) and 5.45 (95% CI: 3.91-7.62), respectively (Table 5.9). Caesarean delivery, IUGR, preterm delivery, and cardiomyopathy during pregnancy were also significantly associated with an increased risk ESRD hospitalization with hazard ratios being 1.58 (95% CI: 1.22-2.04),

Table 5.9 Cox PH regression analysis for the incidence of non-diabetes-related ESRD hospitalization associated with HDPs during index pregnancy among women who had only one delivery during the study period

Variables	β	SE[a]	Adjusted hazard ratio (95% CIs)	ESRD,n	PAF for ESRD (%)
HDPs					
Gestational Hypertension	1.3115	0.2887	3.71 (2.10-6.54)	13	3.42
Pre-eclampsia/Eclampsia	1.6962	0.1704	5.45 (3.91-7.62)	48	14.1
Unspecified HDPs	1.7967	0.3249	6.03 (3.19-11.40)	10	3
No HDPs[b]	0		1.00	207	
Age (years)					
15-19	0.1059	0.2712	1.11 (0.65-1.89)		
20-24	0.3437	0.1792	1.41 (0.99-2.00)		
30-34	0.0890	0.1599	1.09 (0.80-1.50)		
35-39	-0.1277	0.2038	0.88 (0.59-1.31)		
40-45	0.0398	0.3552	1.04 (0.52-2.09)		
25-29[b]	0				
Region					
Atlantic	-0.3158	0.2169	0.73 (0.48-1.12)		
Prairie	-0.8235	0.1925	0.44 (0.30-0.64)		
Pacific	0.0721	0.1546	1.08 (0.79-1.46)		
Territory	-0.8259	1.0044	0.44 (0.06-3.14)		
Ontario[b]	0				
Period					
1995/1996-1996/1997	-0.1028	0.1702	0.90 (0.65-1.26)		
1997/1998-1998/1999	0.2444	0.1816	1.28 (0.90-1.82)		
1999/2000- 2000/2001	0.1145	0.1969	1.12 (0.76-1.65)		
2001/2002- 2002/2003	-0.6337	0.2556	0.53 (0.32-0.88)		
1993/1994- 1994/1995[b]	0				
Caesarean delivery	0.4563	0.1319	1.58 (1.22-2.04)	95	12.52
IUGR	0.8278	0.2242	2.29 (1.48-3.55)	24	4.86
Deep vein thrombosis	1.8692	0.7136	6.48 (1.60-26.25)	2	0.61
Cardiomyopathy	1.4106	0.5059	4.10 (1.52-11.05)	4	1.09
Transfusion	0.8300	1.0036	2.29 (0.32-16.40)	1	0.2
Preterm delivery	0.7314	0.1899	2.08 (1.43-3.02)	35	6.53

[a] SE, Standard error;
[b] Reference group.

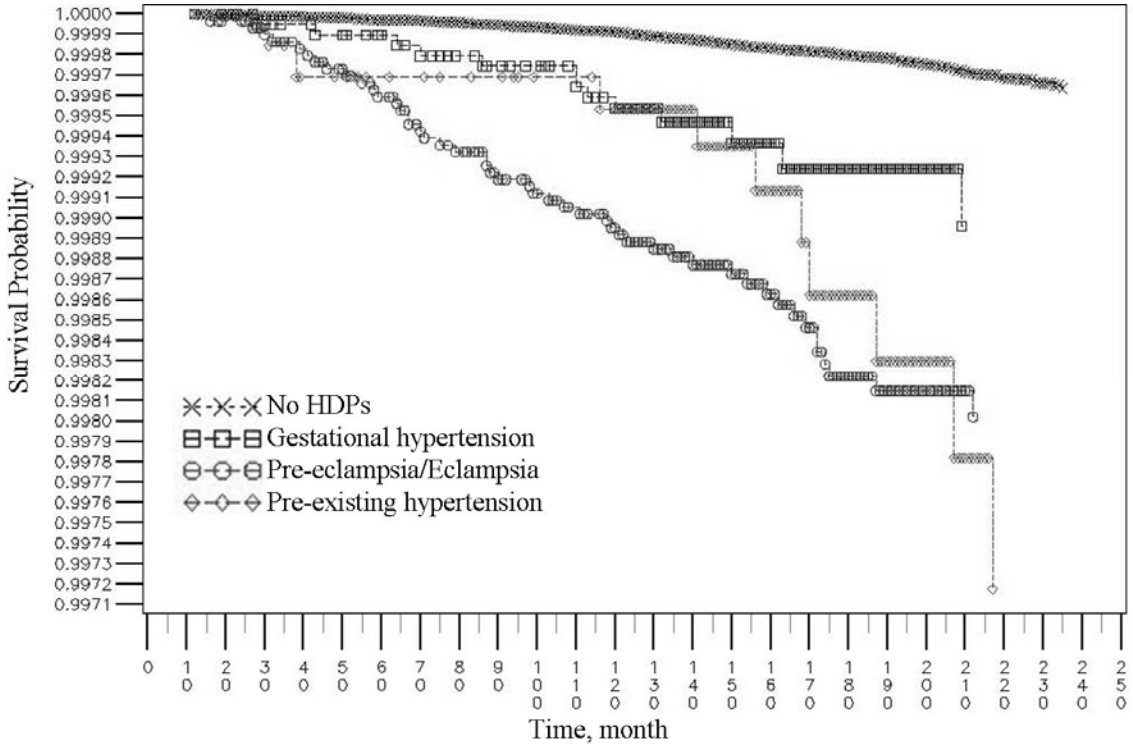
2.29 (95% CI: 1.48-3.55), 2.08 (95% CI: 1.43-3.02) and 4.10 (95% CI: 1.52-11.05), respectively.

In this stratum, 20.52% of the subsequent non-diabetes-related ESRD hospitalization was attributed to HDPs during the index pregnancy. PAFs were 3.42% for gestational hypertension and 14.10% for pre-eclampsia, respectively. Approximately 4.86% and 6.35% of the subsequent non-diabetes-related ESRD could be attributed to IUGR and preterm delivery, respectively.

Kaplan-Meier survival plot clearly showed that the survival curves for women with and without HDPs significantly separated each other (log-rank, $p<0.001$, Figure 5.12). Women with gestational hypertension or with pre-eclampsia had lower overall proportions of ESRD hospitalization during the follow-up period as compared with those without HDPs,

There were 159 non-diabetes-related ESRD cases were reported in the second stratum of women who had two or more deliveries during the study period. The cohort with pre-eclampsia showed a significant association with the risk of subsequent non-diabetes-related ESRD hospitalization (hazard ratio: 2.60; 95% CI: 1.53-4.44), while the association became nonsignificant with gestational hypertension (hazard ratio: 2.39; 95% CI: 0.98-5.86) (Table 5.10). Women with blood transfusion and with preterm delivery during index pregnancy had a risk of non-diabetes-related ESRD hospitalization 8.09 times (95% CI: 1.99-32.88) and 2.02 times (95% CI: 1.19-3.42), respectively, higher than those without such a condition. Subsequent non-diabetes-related ESRD hospitalization after index pregnancy was not significantly associated with a history of caesarean delivery, IUGR, deep vein thrombosis and cardiomyopathy during pregnancy.

Figure 5.12 Estimated proportions of women without subsequent non-diabetic ESRD hospitalization among women in the stratum with one-delivery during the study period. Log-rank test, $p<0.001$.



In the second stratum, the exclusion of diabetes-related ESRD cases reduced the percent of subsequent non-diabetes-related ESRD hospitalization attributed to HDPs to 8.27% (from 12.42%); 1.54% and 5.21% were attributed to gestational hypertension and pre-eclampsia, respectively (Table 5.10). In addition, approximately 3.40% and 5.07% of the subsequent non-diabetes-related ESRD hospitalization could be attributed to IUGR and preterm delivery, respectively.

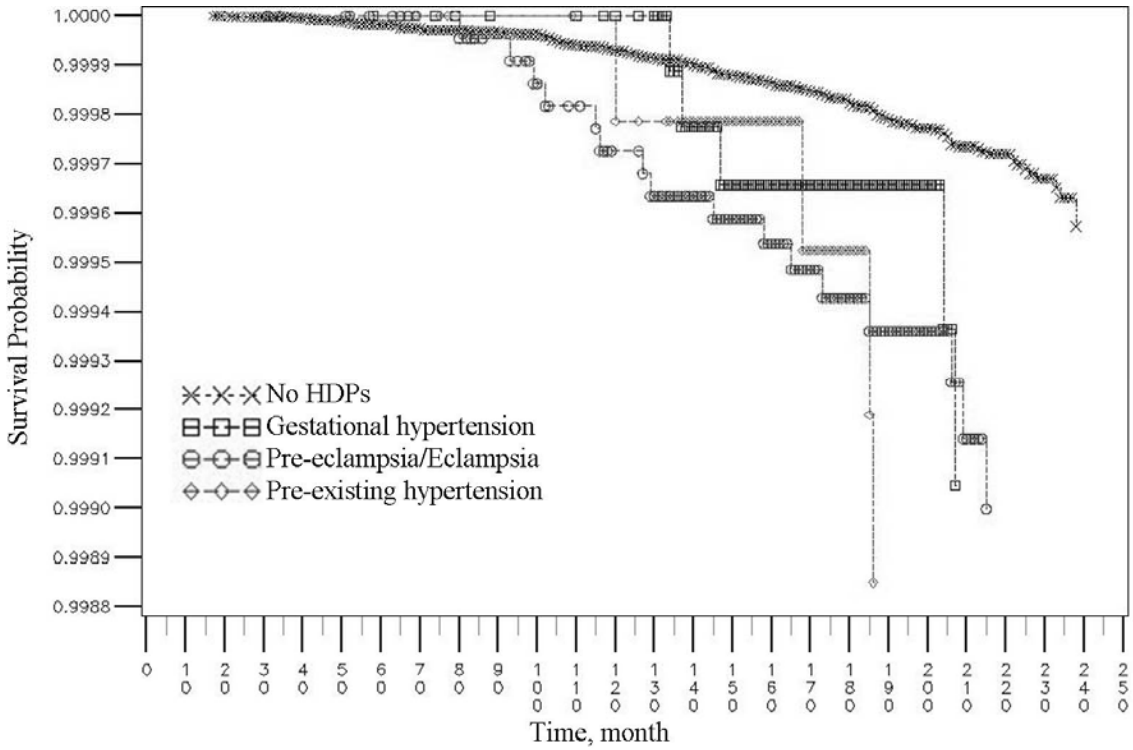
Kaplan-Meier survival plot showed that the overall proportion of subsequent non-diabetes-related ESRD hospitalization in women with pre-eclampsia was obviously lower than the proportions from other cohorts (Figure 5.13). At the end of follow-up period, the

Table 5.10 Cox PH regression analysis for the incidence of non-diabetes-related ESRD hospitalization associated with HDPs during index pregnancy among women who had multiple deliveries during the study period

Variables	β	SE[a]	Adjusted hazard ratio (95% CI)	ESRD, n	PAF for ESRD (%)
HDPs					
Gestational hypertension	0.8716	0.4575	2.39 (0.98-5.86)	5	1.54
Pre-eclampsia/Eclampsia	0.9569	0.2721	2.60 (1.53-4.44)	16	5.21
Unspecified HDPs	1.2726	0.5084	3.57 (1.32-9.67)	4	1.52
No HDPs[b]	0		1.00	134	
Age (years)					
15-19	-0.0874	0.2978	0.92 (0.51-1.64)		
20-24	0.2026	0.1947	1.23 (0.84-1.79)		
30-34	-0.4027	0.2314	0.67 (0.43-1.05)		
35-39	-0.1296	0.3768	0.88 (0.42-1.84)		
40-45	1.3629	0.7192	3.91 (0.95-16.00)		
25-29[b]	0		1.00		
Region					
Atlantic	-0.3629	0.3507	0.70 (0.35-1.38)		
Prairie	0.1790	0.2239	1.20 (0.77-1.86)		
Pacific	-0.1334	0.2218	0.88 (0.57-1.35)		
Territory	0.5251	1.0075	1.69 (0.24-12.18)		
Ontario[b]	0		1.00		
Period					
1995/1996-1996/1997	-0.1782	0.1979	0.84 (0.57-1.23)		
1997/1998-1998/1999	-0.1450	0.2397	0.87 (0.54-1.38)		
1999/2000- 2000/2001	-0.4122	0.3530	0.66 (0.33-1.32)		
2001/2002- 2002/2003	-11.592	303.0486	0 (0-8.34E+252)		
1993/1994- 1994/1995[b]	0		1.00		
Caesarean delivery	0.2657	0.1921	1.30 (0.90-1.90)	37	5.43
IUGR	0.7774	0.3349	2.18 (1.13-4.19)	10	3.40
Deep vein thrombosis	N/A	N/A	N/A	0	N/A
Cardiomyopathy	N/A	N/A	N/A	0	N/A
Transfusion	2.0912	0.7151	8.09 (1.99-32.88)	2	1.1
Preterm delivery	0.70161	0.2691	2.02 (1.19-3.42)	16	5.07

[a] SE, Standard error;
[b] Reference group.

Figure 5.13 Estimated proportions of women without subsequent non-diabetic ESRD hospitalization among women in the stratum of multiple deliveries during the study period. Log-rank test, $p<0.001$.



proportions for women with gestational hypertension and with pre-eclampsia were similar.

The PH assumption for above Cox regression analyses was checked by Schoenfeld residual against time, and no systematic pattern were observed, indicating the PH assumption was valid in this analysis. Cox regression model was fitted to show the association between HDPs and subsequent non-diabetes-related ESRD.

Chapter 6 Discussion

6.1 Summary of findings

Several large cohort studies have shown that pre-eclamptic pregnancy increased the risk of ischemic heart disease, hypertension, stroke, and death from cardiovascular causes in late life[93,94]. In our present population-based study, an increased risk of subsequent ESRD hospitalization was found among Canadian women who had a history of HDPs complicated pregnancy. Our study excluded women with diabetes mellitus, kidney disease and other diseases related to later ESRD, and mainly reflected the risk among otherwise healthy women. We also identified that preterm delivery additively interacted with pre-eclampsia, and was another important clinical indicator for the later ESRD. Moreover, our study also demonstrated that the adverse effect of HDPs on the risk of subsequent ESRD hospitalization was independent of the diabetes mellitus developed after pregnancy. These conclusions were made based on the analytic results after adjustment of demographic factors, some comorbid diseases and potential pregnancy-related confounders, including maternal age, delivery year and region.

Our present study demonstrated that the highest risk of subsequent ESRD hospitalization was found in women with pre-eclampsia superimposed on pre-existing hypertension, followed by those with pre-existing hypertension, with pre-eclampsia and with gestational hypertension. The median time from index delivery to ESRD hospitalization in women with pre-eclampsia superimposed on pre-existing hypertension was substantially shorter and was over four years earlier than that for women without HDPs. Our findings were consistent with those from another population-based study conduced in Taiwan[63], in which a similar risk pattern was reported among East Asian

women with various types of HDPs. The major difference between these two studies is that our results were derived from a study population in which women could experience multiple HDPs complicated pregnancies, whereas those women were excluded from analysis in the study from Taiwan[63]. An exclusion of women with multiple HDPs complicated pregnancies could clearly demonstrate the effect of a single HDP on the development of ESRD, while inclusion of these women reflected the adverse effects of HDPs on subsequent ESRD among the population in natural status.

Our study revealed that the incidence of subsequent ESRD hospitalization among Canadian pregnant women was significantly higher than the incidence reported from the study of Taiwanese women (1.7 vs. 0.26 per 100,000 person-years for women without HDPs and 9.90 vs. 3.88 per 100,000 person-years for women with HDPs). The higher incidence of subsequent ESRD hospitalization in our study could be partially attributable to our longer follow-up period (median, 193 months; IQR 159-219 months). ESRD is defined as the last stage of chronic kidney disease with a slow progress. Normally, the renal function of patient with chronic kidney disease gradually decreases over 5-20 years before disease develop into the end stage. In our study, the median time from index pregnancy to ESRD hospitalization ranged from 7.96 years to 12.17 years depending on whether women had a history of HDPs during the index pregnancy or not. Missing significant number of ESRD cases due to insufficient follow-up period (median: 108 months; IQR: 106-120 months) could lead to the low incidence of subsequent ESRD in the Taiwan study[63]. Our reported incidences of subsequent ESRD hospitalization were close to the rates from another long follow-up (318± 90months) study of Norwegian

women, which found an incidence of 14.5 per 100,000 person-years and 3.3 per 100,000 person-years in cohorts with and without pre-eclampsia, respectively.

Cox PH regression analysis was used to evaluate the risk of ESRD later in life in women with a history of HDPs-complicated index pregnancy and reduce confounding. Because of lack of information on details of pre-existing hypertension in DAD database, this chronic medical condition was excluded from the study population. Therefore, the study was focused on the adverse influence of gestational hypertension and pre-eclampsia on the risk of subsequent ESRD hospitalization. Unlike other published studies, we found that the hazard ratio of subsequent ESRD hospitalization between women with pre-eclampsia and without significantly changed over time. The same phenomenon was also observed among women with different number of delivery during the study period. Therefore, PH assumption for Cox regression was invalided. The long follow-up period and large number of observations in this study cohort may contribute to the increased statistical power to identify the interaction of hazard ratio with time. To validate the PH assumption, the study population was stratified into two strata according to delivery number and the risks were analyzed and reported separately. In both strata of women with one-delivery and women with two or more deliveries, gestational hypertension or pre-eclampsia were identified as risk factors for subsequent ESRD hospitalization. Our results confirmed the previous published finding that HDPs complicated pregnancy was positively associated with subsequent ESRD[63-65].

In our present study, the risk of subsequent ESRD hospitalization in women with pre-eclampsia was 1.6-fold higher than the risk in women with gestational hypertension in the stratum where women had only one delivery, but this difference was smaller in the

stratum where women had more than one pregnancy during the study period. The reduced difference could attribute to the 40% decreased risk in women with pre-eclampsia in the second stratum. The reduced risk might be resulted from some factors that were related to the multiple factors, such as healthier status and less maternal complications, or the decision for subsequent pregnancy, but might be not the number of deliveries per se.

ESRD is a rare medical condition in general population. Our study estimated that gestational hypertension and pre-eclampsia should be attributed to future ESRD. The contributions of these two hypertensive disorders to ESRD were quantitatively estimated using PAF and 10 to 20% of ESRD cases should be avoided when these two disorders were eliminated. The PAF values suggest that hypertensive disorders during pregnancy, especially pre-eclampsia, have an important impact on the development of ESRD.

HDPs may be associated with direct renal damage during pregnancy. Although pathophysiology remains unclear, the pathogenesis of hypertensive disorders during pregnancy includes utero-placental insufficiency and fetal ischemia[95]. Once hypoperfusion of placenta, released antiangiogenic factors cause systemic endothelial cell dysfunction[96,97]. This impairs the kidney function as glomerular endotheliosis has been observed among women with previous HDPs[98,99]. Endotheliosis contributes to proteinuria which is a possible mediator of further renal damage[100]. Although proteinuria and HDPs are resolved after delivery, the injured function of kidney may be not recovered for a long period of time. A systematic meta-analysis reported that women with pre-eclampsia were associated with a higher risk of subsequent microalbuminuria[20]. The occurrence of microalbuminuria persists for at least five years after delivery in almost 40% of women

with pre-eclamptic pregnancy, while only 2% in those without pre-eclampsia[62,101]. Microalbuminuria is regarded as the first step in the development of clinical renal disease[102]. Although women with gestational hypertension usually had less adverse outcomes, endothelial dysfunction was also observed among these women[103]. Thus, like pre-eclampsia, temporary hypertension during pregnancy could affect renal function. In addition, gestational hypertension was also considered as a latent form of essential hypertension, a common risk factor for progression of chronic renal disease[50,104].

The presence of subclinical or undetected renal disease before the index pregnancy may be another possible mechanism for HDPs associated with an increased risk of an ESRD later in life. Pregestational renal disease was associated with the increased risk for developing pre-eclampsia during pregnancy[105]. Epidemiological study revealed that microalbuminuria and pre-eclampsia shared some similar risk factors[106]. Therefore, women who had microalbuminuria before pregnancy were associated with an increased risk for pre-eclampsia as well as renal disease later in life. It is also possible that elevated blood pressure during pregnancy may also exacerbate pregestational subclinical renal disease as chronic renal disease normally has a long asymptomatic period. The striking short median time from pregnancy to ESRD in the cohort with hypertensive gestation supports this finding.

Diabetes mellitus is a major risk factor for chronic kidney diseases, accounting for 26.9% of incident cases in 1996 and 53.8% in 2009 in Canada[107]. Libby et al. conducted a cohort study and reported that women with previous pre-eclampsia had an increased risk of developing type 2 diabetes mellitus with an adjusted odds ratio of 1.37 (95% CI: 1.12 to 1.75)[108]. Another study found an adjusted hazard ratio of 1.83 (95% CI: 1.26 to 2.62)

for diabetes mellitus associated with pre-eclampsia[18]. Diabetes mellitus may mediate the association between gestational hypertension and ESRD[64]. Diabetes mellitus developed after HDPs complicated pregnancy might confound our study results and must be taken into consideration. Because the detailed information on diabetes mellitus was not fully collected from the DAD database, we conducted a sensitivity analysis by removing diabetes-related ESRD from analysis. In women who had only one delivery during the study period, the adjusted hazard ratios of subsequent ESRD with gestational hypertension or pre-eclampsia changed slightly after diabetes-related ESRD cases were removed. However, in women who had multiple deliveries during study period, the corresponding adjusted hazard ratio reduced by 18% in women with pre-eclampsia and became nonsignificant in women with gestational hypertension. Women with multiple deliveries might have a healthier status in comparison with women who had only one delivery during the study period and had lower effects of HDPs on subsequent non-diabetes-related ESRD. Another possible reason is the reduced statistical power after removing diabetes-related ESRD cases.

In this study, we found that preterm delivery was associated with a high risk of subsequent ESRD with or without HDPs. This finding was consistent with the result from a Norwegian study[68]. Both pre-eclampsia and preterm delivery elevated the risks of future ischaemic heart disease and death due to cardiovascular causes[94,109]. Moreover, we found a positive additive interaction between preterm delivery and pre-eclampsia on ESRD hospitalization among women who had only one pregnancy during the study period. Preterm delivery is associated with pre-eclampsia[110,111]. Pre-eclampsia, along with preterm delivery could represent an early-onset of pre-eclampsia or sever pre-eclampsia

which usually have much worse adverse consequence[112,113], and may explain the significantly increased risk of an ESRD hospitalization in women with both pre-eclampsia and preterm delivery.

We also found that among women with one-delivery within the study period, those with IUGR during pregnancy had a higher risk of subsequent ESRD than women without such a medical condition. A previous study found that low birth weight for gestational age was associated with ESRD in adulthood[114]. IUGR refers to a condition in which a fetus is unable to achieve its genetically determined potential size. The high risk for later ESRD among women with IUGR in absence of pre-eclampsia, suggests that placental dysfunction without pre-eclampsia may be an important risk factor. IUGR is a common adverse outcome of pre-eclamptic pregnancy, especially severe and early-onset pre-eclampsia[16]. We examined the interaction between IUGR and pre-eclampsia or gestational hypertension in relation to subsequent ESRD, and found no significant departure from additivity, suggesting that IUGR may be independently associated with kidney damage.

Not only HDPs, caesarean delivery was also associated with an elevated risk of developing ESRD among women with one-delivery during the study period in present study. This significant association might be resulted from some factors that were related to the decision of delivery method rather than caesarean delivery itself. Wu et al. reported that Caesarean delivery was found as a risk factor for ESRD in univariate analysis, but became nonsignificant after adjustment for potential confounding[63]. In Taiwan, over 77% of women in the cohort with HDPs delivered with a caesarean section, while the corresponding proportion is 33% in out study.

Further, deep vein thrombosis and cardiomyopathy during the pregnancy was also associated with an elevated risk of subsequent ESRD among women who had only one delivery during the study period.

6.2 Strengths of the study

This is the first large nationwide retrospective population based cohort study aimed to examine the relationship between HDPs and subsequent ESRD hospitalization in Canada. There are several important advantages associated with the properties of the database. First, the hospital discharge database used in this study included up to 98% of all hospital delivery and hospitalization in Canada (excluding Quebec). Due to a low rate of home delivery and universal health care coverage in Canada, the losses to follow-up were almost negligible[115]. Second, the study included over 1.5 million women with a great statistical power and high generalizability. Third, the administrative hospital database used in the study collects detail information on comorbid conditions. In addition to a principal diagnosis, the DAD database contained up to 15 secondary diagnoses and 10 procedures which allow for documenting medical conditions in detail for every hospitalizations. Forth, compared with others studies[63,64], the follow-up period in our study was relatively long, which is important for a study of uncommon outcomes.

6.3 Limitations of the study

Our study has several limitations. Because gestational hypertension was defined as a temporary elevated blood pressure, which developed after 20 weeks of gestation, vasodilatation during early gestation could mask the pre-existing hypertension. Therefore, classification of HDPs based only on obstetrical delivery hospitalization discharge codes might have misclassified pre-existing hypertension into gestational hypertension and

increased the risk of subsequent ESRD hospitalization in the cohort with gestational hypertension.

The hospital administrative database used in present study did include the information on ethnicity, marital and social status, educational levels, dietary habits, body mass index, onset date of pre-eclampsia and laboratory measures (such as real blood pressure levels, glomerular filtration rate and proteinuria). Thus, these important variables could not be taken into account in our analysis. In addition, some medical conditions, such as hypertension, diabetes mellitus and obesity, developed during the follow-up period were not recorded on time in this national hospital discharge database.

In the present study, women with pre-existing renal disease were excluded from study population. Subclinical kidney disease might have been unreported or undetected for some women, though previous studies had the similar situation[63,65]. Nevertheless, even if this were the case, the dramatically increased risk still indicated that HDPs, especially pre-eclampsia, would be an important clinical indicator for developing ESRD later in life among these women.

Another limitation is that due to the lack of information on the history of delivery, we were unable to determine whether the index pregnancy in present study was primiparous or not. Therefore, this study cannot answer the question whether there is a risk difference for women with various times of HDPs with regards to subsequent ESRD hospitalization.

6.4 Impact of study findings

This present cohort study showed that hypertensive disorders during pregnancy increased the risk of subsequent ESRD hospitalization with reduced asymptomatic period among Canadian pregnant women. In clinical practice, a history of HDPs may indicate an

increased risk of chronic kidney disease and ESRD in the future. Physicians should pay attention to these women with a high risk of chronic renal disease. Pregnant women with any type of HDPs, especially with pre-existing hypertension or combination of pre-eclampsia and preterm delivery, should be informed of the potential risk about renal disease in late life. Close surveillance for microalbuminuria and regular medical checkups may be needed for these women. Although chronic kidney disease is generally progressive and irreversible, preventive strategies, such as lifestyle intervention, can slow down its progression. Our study had provided evidence and insight into maternal renal health that may be helpful in renal disease screening and prevention.

6.5 Future work

Our present study has provided valuable information on the associations between ESRD and earlier HDPs complicated pregnancy. Due to the properties of hospital administrative database used in this study, some important risk factors for ESRD, such as hypertension and diabetes mellitus which develops after pregnancy, were not available. We also had access to information on socioeconomic status, obesity, smoking, lifestyle, and genetic background that could be involved in the development of ESRD, and confound the associations of interest. These data need to be collected and assessed in future studies.

6.6 Conclusions

In summary, Canadian women with HDPs were at increased lifetime risk of ESRD. The increased risk of subsequent ESRD associated with pre-eclampsia could not be explained by diabetes mellitus developed after pregnancy and this associated risk tended to be stronger than gestational hypertension associated with ESRD hospitalization. In this

cohort study, we found that preterm delivery was another clinical maker for the risk of subsequent ESRD. The risk almost doubles among women with preterm delivery, and markedly higher if women also experienced pre-eclampsia during the index pregnancy. Although the absolute risk of ESRD is low, women with HDPs should have regular checkups for renal function.

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Appendix A Strategy and syntax for literature review

Search Strategy and syntax for databases through PubMed/Medline

1. (hypertension, pregnancy-induced/ OR preeclampsia/ OR eclampsia/);
2. (renal replacement therapy/ OR end-stage renal disease/);
3. ((cohort study/ OR follow-up study/ OR longitudinal study/ OR prospective study/ OR retrospective study/ OR case-control study/ OR epidemiologic methods/ OR odds ratio/ OR causality/) OR (relative risk*[tiab] OR population-base*[tiab]));
4. 1 AND 2 AND 3;

Search Strategy and syntax for databases through OvidSP:

1. (exp hypertension, pregnancy-induced/ OR exp pre-eclampsia/ OR exp eclampsia/);
2. (exp renal replacement therapy/ OR exp kidney failure, chronic/ OR exp end-stage renal disease/);
3. (exp cohort studies/ OR exp follow-up studies/ OR exp longitudinal studies/ OR exp prospective studies/ OR exp retrospective studies/ OR exp case-control studies/ OR exp epidemiologic methods/ OR exp odds ratio/ OR exp causality/);
4. (relative risk* OR population-base*).ti,ab.;
5. 3 OR 4;
6. 1 AND 2 AND 5;

Appendix B Algorithm for identifying obstetrical delivery records:

For records using ICD-9 coding system:

1. Any diagnostic code starting with V27 or 650;
2. Any diagnostic code between 640 and 676.9 with the 5th digit of 1 or 2.

For records using ICD-10 coding system:

1. Any diagnostic code staring with Z37;
2. Any diagnostic code between O10 and O99.8 with the 5th and 6th digits of 01 or 02.

Appendix C List of ICD-9 and ICD-10 diagnosis codes used in the study

Medical conditions	ICD-9 codes	ICD-10 codes
Gestational hypertension	642.3	O13
Pre-eclampsia/Eclampsia	642.4, 642.5, 642.6	O14,O15,O13003,
Pre-existing hypertension	642.0, 642.2, 401-405	O10 (except O10.2), I10, I11, I12, I13, I15
Pre-eclampsia imposed pre-existing hypertension	642.7, (642.4, 642.5, 642.6, 642.7) and (642.0, 642.1, 642.2, 401-405)	O11
Unspecified maternal hypertension	642.9	O16
Chronic renal disease	585	N18
Renal disease	580, 581, 582, 583, 585, 587, 588, 5996, 403, 404, 6462, 2503,	E102, E112, E132, I12, I13, N00, N01,N03, N04, N05, N07, N08, N138, N139, N14,N150, N18, N25, N26, N290, E142,O121
Kidney transplantation	V420 CCP code: 675.9	
Dialysis	V451, V560, V561, V568 CCP code: 512.7, 514.2, 514.3, 519.5, 669.8	
ESRD		N180, N185, N0835, E1022, E1122, E1322, E1422
Diabetes-related ESRD	ESRD with Diabetes Milletus	N0835, E1022, E1122, E1322, E1422
Diabetes	250, 648.0	E10,E11, E13, E14, O240-O243
Gestational diabetes	648.8	O244
Rheumatoid arthritis	714.0	M05, M06
Systemic lupus erythematosus	710.0	M32
Thrombotic microangiopathy	446.6	M311
Hemolytic uremia syndrome	283.11	D592-D594
Multiple gestation	651, 6526, V272, V273, V274, V275, V276, V277	O30, O318, O3250, Z372-Z377
Caesarean delivery	CCP codes: 860-861, 868, 869	CCI codes:5MD60

Medical induced delivery	CCP codes: 855	CCI codes: 5AC30ALI2, 5AC30CAI2, 5AC30GUI2, 5AC30HAI2, 5AC30YA12, 5AC30YBI2, 5AC30ZZI2
Surgical induced delivery	CCP codes: 8501	5AC30AP
Hysterectomy	802, 803	CCI codes: 5MD60KE, 5ME60RC, 5MD60CB, 5MD60RD, 1RM87LAGX, 1RM89LA (without 1PL74, 1RS80, 1RS74)
Blood transfusion	130.1, 130.3, 130.4	1LZ19HMU1, 1LZ19HMU9, 1LZ19HHU9, 1LZ19HHU1
Grand multiparity	659.4, V233	Z354
Preterm delivery	644.1	O60
Intrauterine growth restriction	656.5	O365
Intrauterine fetal death	646.5, V271, V273, V274, V276, V277	O364, Z371, Z373. Z374, Z376, Z377
Fetal distress	656.3	O68, O363
Placenta previa	641.0, 641.1	O44
Placenta abruption	641.2	O45
Placental disorders	656.0, 656.7	O43
Malpresentation	652	O32
Uterine rupture	665.0, 665.1	O710, O711
Premature rupture of membranes	658.1	O42
Oligohydramnios	658.0	O410
Polyhydramnios	657	O40
Prolonged pregnancy	645	O48
Postpartum hemorrhage	666	O72
Obesity	278.0	E66
Acute rheumatic Fever	390-392	I00-I02
Chronic rheumatic heart disease	393-398	I05-I09
Coagulation defects	286	D65-D68
Deep venous thrombosis	451.1, 451.2, 415.1, 671.3, 671.4, 673	I801-I803, I26, O223, O871, O88

Hyperlipidemia	272.0, 272.1, 272.2, 272.4	E780-E782, E784, E785, H036
Disorders of thyroid gland	240-246, 648.1	E00-E07, E350,E890, O905, O992
Major puerperal infection	670, 672	O850, O864, O868
Sepsis	038, 659.3, 670	A34, A40, A41, A427, O753, O85, O868
Ischemic heart disease	410-414	I20-I25, I513
Heart failure	428	I50
Cardiomyopathy	420-429	I30-I52
Cerebrovascular disease	430-438	I60-I69, G45, G464-G466