Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN
CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Clinical Research Protocol

Canadian Journal of Kidney Health and Disease
Volume 11: 1–14

DOI: 10.1177/20543581241284030
journals.sagepub.com/home/cjk
Sage

Pregnancy Outcomes in Living Kidney Donors: Protocol of a Population-Based Cohort Study in Three Canadian Provinces

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Abstract

Background: A substantial proportion of living kidney donors are women of childbearing age. Some prior studies report a higher risk of gestational hypertension and pre-eclampsia in living kidney donors compared with nondonors. Further research is needed to better quantify the risk of adverse maternal, fetal/infant, and neonatal outcomes attributable to living kidney donation.

Objective: To determine the risk of hypertensive disorders of pregnancy, including gestational hypertension, pre-eclampsia, and eclampsia, and other maternal and fetal/infant outcomes in living kidney donors compared with a matched group of nondonors of similar baseline health.

Design and Setting: Protocol for a population-based, matched cohort study using Canadian administrative health care databases. The protocol will be run separately in 3 provinces, Ontario, Alberta, and British Columbia, and results will be combined statistically using meta-analysis.

Participants: The cohort will include women aged 18 to 48 years who donated a kidney between July 1992 and March 2022 and had at least one postdonation singleton pregnancy of ≥20 weeks gestation between January 1993 and February 2023. We expect to include at least 150 living kidney donors with over 200 postdonation pregnancies from Ontario and a similar number of donors and pregnancies across Alberta and British Columbia combined. Nondonors will include women from the general population with at least one pregnancy of ≥20 weeks gestation between January 1993 and February 2023. Nondonors will be randomly assigned cohort entry dates based on the distribution of nephrectomy dates in donors. The sample of nondonors will be restricted to those aged 18 to 48 years on their cohort entry dates with delivery dates at least 6 months after their assigned entry dates. A concern with donor and nondonor comparisons is that donors are healthier than the general population. To reduce this concern, we will also apply 30+ exclusion criteria to further restrict the nondonor group so that they have similar health measures at cohort entry as the donors. Donor and nondonor pregnancies will then be matched (1:4) on 5 potential confounders: delivery date, maternal age at delivery date, time between cohort entry and delivery date, neighborhood income quintile, and parity at delivery date.

Measurements: The primary outcome will be a composite of maternal gestational hypertension, preeclampsia, or eclampsia. Secondary maternal outcomes will include components of the primary outcome, early pre-eclampsia, severe maternal morbidity, cesarean section, postpartum hemorrhage, and gestational diabetes. Fetal/infant/neonatal outcomes will include premature birth/low birth weight, small for gestational age, neonatal intensive care unit admission, stillbirth, and neonatal death.

Methods: The primary unit of analysis will be the pregnancy. We will compute the risk ratio of the primary composite outcome in donors versus nondonors using a log-binomial mixed regression model with random effects to account for the correlation within women with multiple pregnancies and within matched sets of donors and nondonors. We will perform the statistical analyses within each province and then combine aggregated results using meta-analytic techniques to produce overall estimates of the study outcomes.

Limitations: Due to regulations that prevent individual-level records from being sent to other provinces, we cannot pool individual-level data from all 3 provinces.
Conclusion: Compared to prior studies, this study will better estimate the donation-attributable risk of adverse maternal, fetal/infant, and neonatal outcomes. Transplant centers can use the results to counsel female living donor candidates of childbearing age and to inform recommended practices for the follow-up and care of living kidney donors who become pregnant.

Abrege
Contexte: Une importante proportion des donneurs de rein vivants sont des femmes en âge de procréer. Quelques études antérieures rapportent un risque plus élevé d'hypertension gestationnelle et de prééclampsie chez les donneuses d'un rein par rapport aux non-donneuses. D'autres recherches sont nécessaires pour mieux quantifier le risque d'issues néonatales négatives attribuables au don de rein par un donneur vivant pour la mère et le fœtus/nouveau-né.
Objectif: Déterminer le risque de troubles hypertensifs pendant la grossesse, notamment l'hypertension gestationnelle, la prééclampsie et l'éclampsie, et d'autres résultats pour la mère et le fœtus/nouveau-né chez les donneuses d'un rein par rapport à un groupe apparié de non-donneuses avec caractéristiques de santé initiales similaires.
Cadre et conception de l'étude: Protocole pour une étude de cohorte avec populations appariées utilisant les bases de données administratives de santé canadiennes. Le protocole sera réalisé séparément dans trois provinces (Ontario, Alberta et Colombie-Britannique) et les résultats seront combinés statistiquement au moyen d'une méta-analyze.
Sujets: La cohorte sera constituée de femmes âgées de 18 à 48 ans ayant donné un rein entre juillet 1992 et mars 2022 et ayant vécu au moins une grossesse unique de plus de 20 semaines post-don entre janvier 1993 et février 2023. Nous prévoyons inclure au moins 150 donneuses de rein vivantes avec plus de 200 grossesses post-don en Ontario et des nombres similaires en combinant les donneuses et les grossesses pour l'Alberta et la Colombie-Britannique. Les non-donneuses seront des femmes de la population générale ayant eu au moins une grossesse de plus de 20 semaines entre janvier 1993 et février 2023. Les non-donneuses se verront attribuer au hasard une date d'entrée dans la cohorte en fonction des dates de néphrectomie chez les donneuses. L'échantillon des non-donneuses sera limité aux femmes âgées de 18 à 48 ans à la date de leur entrée dans la cohorte avec un accouchement prévu au moins 6 mois après la date d'entrée leur ayant été attribuée. Les donneuses sont généralement en meilleure santé que la population générale, ce qui entraîne une préoccupation quant à leur comparaison à des non-donneuses. Pour atténuer cette différence, plus de 30 critères d'exclusion seront appliqués aux non-donneuses afin qu'elles présentent des mesures de santé similaires à celles des donneuses à leur entrée dans la cohorte. Les grossesses des donneuses et non-donneuses seront ensuite appariées (1:4) selon 5 facteurs de confusion potentiels : date d'accouchement, âge maternel à l'accouchement, temps entre l'entrée dans la cohorte et l'accouchement, quintile de revenu du quartier de résidence et parité à la date d'accouchement.
Mesures: Le principal critère de jugement sera un composite d'hypertension gestationnelle maternelle, de prééclampsie ou d'éclampsie. Les résultats maternels secondaires comprendront des composantes du résultat primaire, la prééclampsie précoce, la morbidité maternelle grave, la césarienne, l'hémorragie post-partum et le diabète gestationnel. Les résultats fœtaux/néonataux comprendront les naissances prématurées ou de faible poids, un bébé petit pour l'âge gestationnel, l'admission en unité de soins intensifs néonataux, la mortinaissance et le décès néonatal.

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Méthodologie: La principale unité d'analyze sera la grossesse. Nous calculerons le rapport de risque du résultat composite primaire chez les donneuses comparativement aux non-donneuses à l'aide d'un modèle mixte de régression log-binomiale à effets aléatoires pour tenir compte de la corrélation chez les femmes avec grossesses multiples et au sein d'ensembles appariés de donneuses et de non-donneuses. Nous effectuerons des analyses statistiques dans chaque province, puis nous utiliserons des techniques méta-analytiques pour combiner les résultats agrégés et produire des estimations globales des résultats de l'étude.
Limites: En raison des règlements qui empêchent l'envoi de dossiers individuels à d'autres provinces, nous ne pouvons regrouper les données individuelles des sujets des trois provinces.
Conclusion: Cette étude permettra de mieux estimer le risque de résultats indésirables maternels, fœtaux et néonataux attribuable au don d'organe que les études précédentes. Les centers de transplantation pourront utiliser ces résultats pour conseiller les candidates au don vivant d'organe en âge de procréer et éclairer les recommandations de pratique pour le suivi et les soins des donneuses de rein vivantes qui deviennent enceintes.

Keywords
living kidney donation, hypertensive disorders of pregnancy, gestational hypertension, pre-eclampsia, pregnancy outcomes

Received May 6, 2024. Accepted for publication July 29, 2024.

Introduction

Compared with dialysis, a kidney transplant from a living donor (versus a deceased donor) is the preferred treatment for patients with kidney failure.[1-3] Each year, approximately 16 000 women globally become living kidney donors (~3500 in the United States), and more than half are of childbearing age (in the United States 65% of female donors are aged 18-49 years at the time of donation).[4,5] Young women contemplating kidney donation ask how becoming a donor will impact their future pregnancies.

The 2017 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for living kidney donors recommends women be counseled on the risks of hypertensive disorders of pregnancy such as gestational hypertension and pre-eclampsia in future pregnancies.[6,7] This recommendation is based on 3 prior retrospective cohort studies.[8-10] Garg et al,[8] using administrative health care databases from Ontario, Canada reported a 2.4-fold (95% confidence interval [CI]: 1.2–5.0) higher risk of pre-eclampsia and gestational hypertension in postdonation pregnancies (15/131 pregnancies) compared with matched nondonors (38/788 pregnancies). Ibrahim et al,[10] using survey data, reported a significantly higher risk of gestational hypertension after donation (28/490 pregnancies) than before donation (17/2723 pregnancies; $P < .0001$) and a higher risk of pre-eclampsia after donation (27/490 postdonation pregnancies vs 23/2723 predonation pregnancies; $P < .0001$). Reisaeter et al,[9] using information from the Norwegian national birth registry, reported a significantly higher risk of pre-eclampsia after donation (6/106) than before donation (16/620) after adjusting for maternal age, parity, and year of birth ($P = .026$).

More recent studies report no significant difference in hypertensive disorders of pregnancy among living donors compared with nondonors, although the accuracy and generalizability of this assertion has limitations.[11,12] One of these studies was conducted in a single center in South Korea,[11] and the other included only 59 primiparous donors from Utah and Idaho in the United States matched on age and race to 236 nondonors.[12] In a recent systematic review of evidence on the risk of pregnancy complications after living kidney donation, the certainty of evidence was rated as low for any donation-attributable risk of gestational hypertension and pre-eclampsia and very low for any donation-attributable risk of preterm delivery and low birth weight.[13] This rating was based on identifying a moderate-to-serious risk of bias in several studies and factors such as single-center study designs, small sample sizes, incomplete data reporting, and the potential for recall bias, survival bias, and response bias.[13] In addition, effect estimates were imprecise for several other maternal and fetal/infant outcomes, including gestational diabetes, cesarean section, preterm delivery, and low birth weight.[8-10,14]

Large, high-quality multicenter studies are needed to provide better estimates of the donation-attributable risk of pregnancy complications. Best estimates of treatment effects come from large, multicenter randomized trials; yet, it will never be possible to randomly allocate participants to donation and nondonation. Thus, estimates will come from observational cohort studies that compare groups of donors and nondonors on their outcomes. However, there are several concerns with such comparisons, which need to be carefully considered when designing a study. Given the selection process they undergo to become donors, donors are inherently healthier than the general population. They may receive more follow-up surveillance than nondonors in routine care, and as a result, have more outcome ascertainment. Those donating to a blood relative with kidney failure, especially a first-degree relative, may be more likely to have a genetic predisposition to kidney disease. Finally, while it would be ideal to conduct studies in a prospective fashion, in our experience, it is infeasible to recruit a sufficiently large number of donors and nondonors at the time of donation, and then

follow an adequate number longitudinally for many years for some to become pregnant.[15,16] Thus, at this time, feasible estimates of donation-attributable risks of adverse maternal and fetal/infant outcomes come from carefully designed multicenter retrospective cohort studies.

Here, we describe a protocol for a large, Canadian multicenter, retrospective cohort study designed to assess whether living kidney donors have a higher risk of gestational hypertension, pre-eclampsia, or eclampsia or other maternal and fetal/infant outcomes compared with nondonors of similar baseline health. To do this, we will separately analyze administrative health care databases in Ontario, Alberta, and British Columbia and then will statistically combine the results using meta-analysis. We used the Standardized Protocol Items Recommendations for Observational Studies 2023 checklist to guide the reporting of this protocol.[17]

Primary Objectives

1. To determine the risk of gestational hypertension, pre-eclampsia, and/or eclampsia in living kidney donors compared with nondonors of similar baseline health.
2. To determine the risk of other maternal, fetal/infant, and neonatal outcomes in living kidney donors compared with nondonors of similar baseline health.

Secondary Objective

3. To determine if the donation-attributable risk estimate of adverse maternal, fetal/infant, or neonatal outcomes differs between donors who do and do not donate to a first-degree relative with kidney failure.

Methods

Study Design and Setting

We will conduct a population-based, matched cohort study using linked administrative health care databases in 3 Canadian provinces: Ontario (15,500,632 residents), Alberta (4,703,772 residents), and British Columbia (5,437,722 residents); number of residents as of April 1, 2023.[18] This study protocol will be implemented separately in these 3 provinces, and the results will subsequently be combined statistically via meta-analysis. All Canadian residents have universal access to hospital care and physician services through a government-funded single-payer system within each province. This protocol describes the design elements and analysis that will be used for Ontario data. We will apply similar methods to data from Alberta and British Columbia. The accrual period of the Ontario cohort will be from July 1, 1992 until March 31, 2022, and the last day of follow-up will be March 31, 2023. The study timeline is shown in Figure 1. During the study period, there were a total of 9 transplant centers: 5 kidney transplant centers in Ontario, 2 in Alberta, and 2 in British Columbia. During this time, approximately 250 to 300 living kidney donations occurred per year in Ontario, 70 to 80 per year in Alberta, and 75 to 100 per year in British Columbia.[19]

Participant Selection

The cohort will include 2 groups of women: (1) living kidney donors with at least 1 postdonation singleton pregnancy of ≥20 weeks gestation and (2) nondonors with at least 1 singleton pregnancy of ≥20 weeks gestation in follow-up. Due to the rigorous health screening that donor candidates undergo to qualify for donation, donors tend to be healthier than the general population.[7,20] For this reason, we will endeavor to select a nondonor comparison group with good health at baseline similar to that of donors at the time of cohort entry (acknowledging that the nondonors chosen will not have the rigorous predonation testing that donors undergo). Details on the selection of each group are provided below along with the exclusion criteria (Figure 2 and Table 1) and the matching process.

Selection of living kidney donors. We will first select women who donated a kidney at an adult transplant center between July 1, 1992 and March 31, 2022 (dates may vary in Alberta and British Columbia depending on data availability). The donors' nephrectomy dates will be their cohort entry dates. We will restrict the sample to women aged 18 to 48 years on this date and select those who had at least one singleton pregnancy of at least 20 weeks' gestation with a delivery date at least 6 months after nephrectomy, between January 1, 1993 and February 17, 2023. We will restrict the last delivery date to February 17, 2023 to allow at least 6 weeks of postpartum observation time to assess study outcomes, as the last follow-up date is March 31, 2023. We will include all eligible singleton pregnancies that occurred during the accrual period, including in women with more than one pregnancy in follow-up. In the main analysis, pregnancies, rather than individual women will be the unit of analysis.

Exclusions. As part of data cleaning, we will exclude women who have invalid or missing identifiers, missing or invalid data on age or sex, a recorded date of death on or before cohort entry, or missing or invalid/inconsistent donation data (we expect to exclude only a very small number of women for these reasons). Additional exclusion criteria will include removing any transplant candidate or recipient miscoded as a donor (identified by predonation evidence of receiving dialysis or receipt of a kidney transplant), and evidence that a woman was not a permanent resident of the province (eg, coded as such, or no physician visits in the year before cohort entry or no more contact with the healthcare system in the absence of death in the months following donation). We will also exclude women with a precohort entry history of

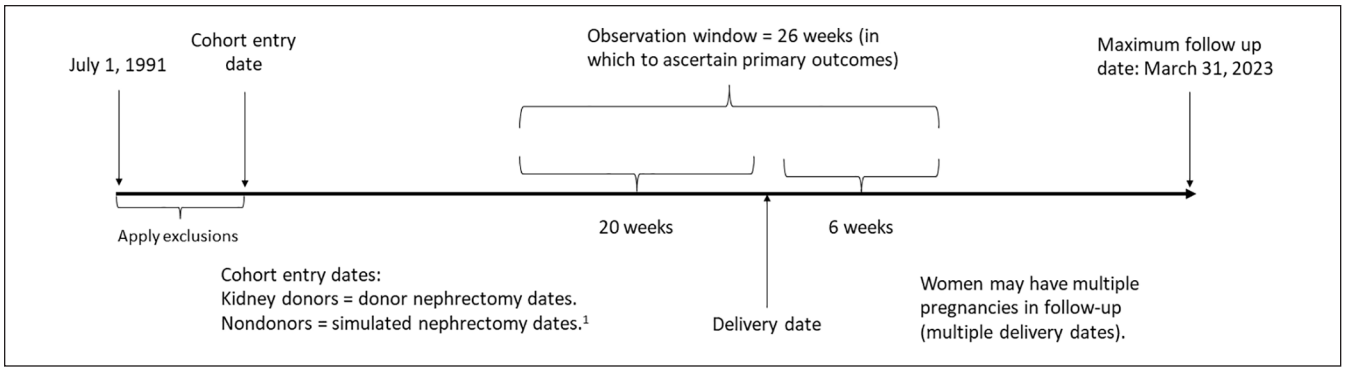

Figure 1. Study timeline outlining the accrual interval, the observation window for outcome ascertainment, and the maximum follow-up date.
[1]A cohort entry date will be randomly assigned according to the distribution of the time intervals between the donors' cohort entry dates and their delivery dates. We will randomly sample these time intervals with replacement using bootstrapping and subtract the selected time interval from the nondonor's delivery date; the resulting date will be their cohort entry date.

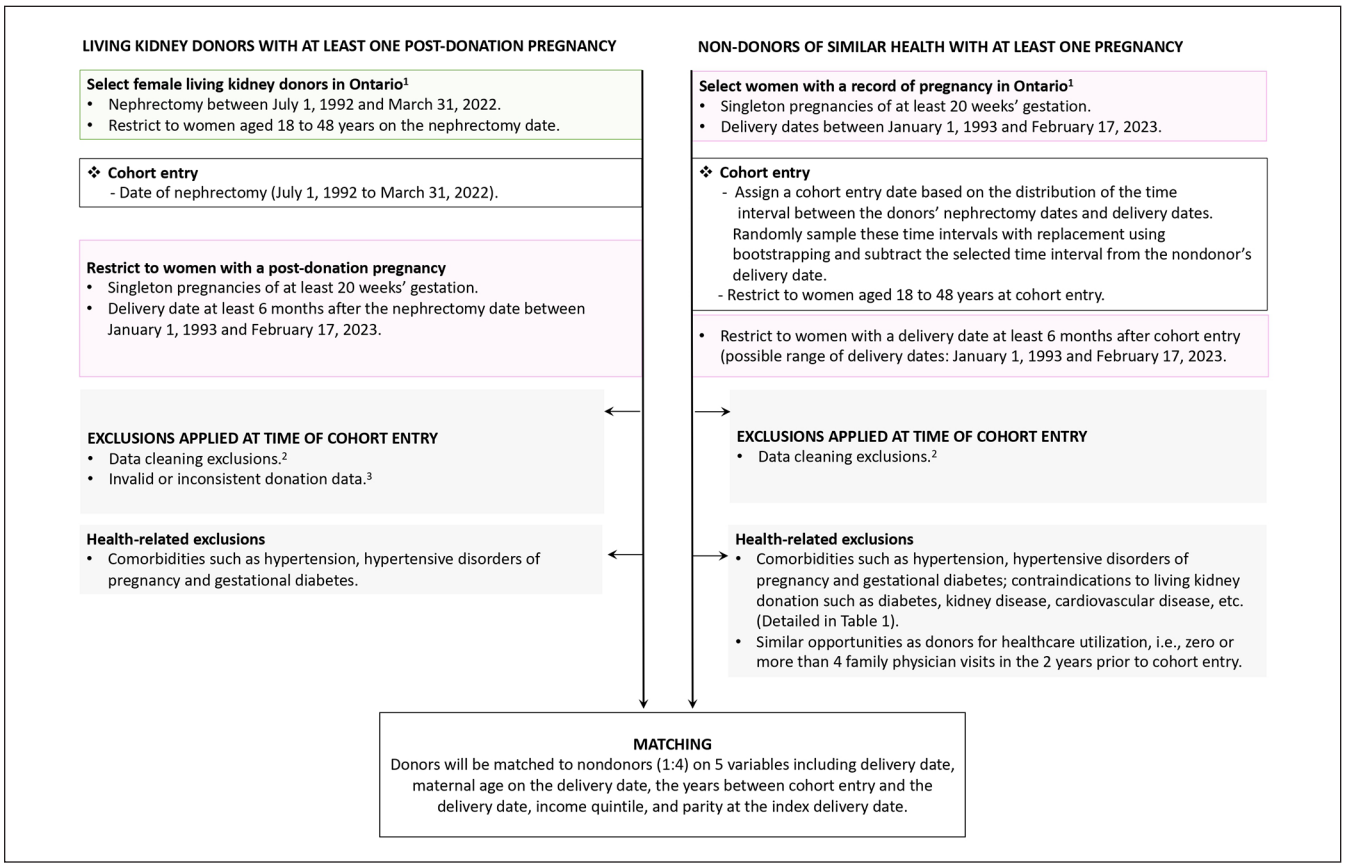

Figure 2. Inclusion and exclusion criteria for selecting donors and nondonors.
[1]As data availability permits, similar inclusion/exclusion criteria will be applied to Alberta and British Columbia.
[2]Examples of data cleaning exclusions: Missing or invalid key number, missing or invalid age (>105 years old), missing or invalid sex, death on or before the cohort entry date, not a permanent resident of the province.
[3]Kidney transplant recipient; listed as living kidney donor more than once; predonation evidence of receiving dialysis.

hypertension as well as pregnancies that were complicated by gestational hypertension, pre-eclampsia, eclampsia or gestational diabetes. Multifetal pregnancies will also be excluded.

Selection of nondonors. We will first select all female residents of the province with a record of a singleton pregnancy of at least 20 weeks gestation and a delivery date between January 1, 1993 and February 17, 2023 (dates may vary in

Table 1. Exclusion Criteria for Nondonors: Comorbidities and Other Contraindications to Living Kidney Donation Recorded on or Before the Cohort Entry Date.[a,b]

Hypertensive disorders of pregnancy
- Gestational hypertension, pre-eclampsia, or eclampsia in a previous pregnancy

Healthcare utilization
- Zero or more than 4 family physician visits in the 2 years prior to cohort entry
- 1 or more hospitalization for any mental illness in the last year
- 1 or more intensive care unit visit in the last year
- 1 or more hospitalization for a palliative care service in the last year
- 4 or more hospitalizations in the 1 year prior to index date 1
- Home oxygen therapy
- Residence at long-term care facility

Evidence of kidney disease
- Nephrology consultation and/or any kidney biopsy
- Evidence of 1 or more dialysis code recorded between July 1, 1991 to 4 months after cohort entry
- Evidence of previous partial or complete nephrectomy for any reason
- Listed as a kidney donor or recipient
- Acute kidney injury in the past 5 years
- Evidence of chronic kidney disease
- Polycystic kidney disease
- Evidence of genitourinary diseases
- Any prior evidence of dialysis

Comorbidities

Cardiovascular disease and risk factors
- Congestive heart failure
- Cardiovascular procedure (eg, coronary artery bypass graft surgery)
- Myocardial infarction
- Peripheral vascular disease
- Abdominal aneurysm repair or aortic bypass
- Ischemic stroke
- Hypertension
- Moderate or severe obstructive sleep apnea

Malignancy
- Any cancer diagnosis in the past 5 years

Hepatic Disorders
- Liver disease or cirrhosis

Endocrinologic Disorders
- Diabetes mellitus
- Gestational diabetes mellitus

Infectious Disorders
- Infective endocarditis
- Hepatitis B infection
- Human immunodeficiency virus

Rheumatologic Disorders
- Rheumatoid arthritis in the past 5 years
- Systemic autoimmune rheumatic diseases in the past 5 years

Other contraindications to living kidney donation or characteristics that would likely preclude donation
- Any prior solid organ transplant
- Dementia
- Alcoholism diagnosed in the past 5 years

Comorbidity Indices
- Charlson Comorbidity Index score $\geq$3 in the past 5 years[c]
- Adjusted Clinical Group score $>$20 in the past 5 years[d]

[a]In donors, the cohort entry date will be the date of nephrectomy; in nondonors the cohort entry date will be randomly assigned based on the distribution of nephrectomy dates and delivery dates in donors.
[b]Unless otherwise specified, the look-back period will be to 1991 (or more recently than 1991 depending on data availability).
[c]The Charlson Comorbidity Index utilizes 17 weighted comorbidity categories to predict 10-year survival. The comorbidities are based on International Classification of Diseases (ICD) diagnosis codes. (Reference: Charlson et al.[21]).
[d]The Adjusted Clinical Group (ACG) is a population/patient case mix adjustment system that was applied to score comorbidity. ACG generates a measurement of an individual's expected health services consumption. Ambulatory Diagnostic Groups (ADGs) are generated by categorization of ICD-9/ICD-9-CM codes into 32 groups. ADGs are based on chronicity, disability, clinical similarity, and likelihood to require specialty care. (Reference: The Johns Hopkins University Bloomberg School of Public Health, Health Services Research & Development Center[22]).

Alberta and British Columbia depending on data availability). All eligible pregnancies for a given woman within the accrual period will be selected, including for women with more than one pregnancy in follow-up.

We will randomly assign each woman a cohort entry date according to the distribution of the time intervals between the donors' cohort entry dates and their delivery dates. We will randomly sample these time intervals with replacement using bootstrapping and subtract the selected time interval from the nondonor's delivery date; the resulting date will be their cohort entry date. We will then restrict this sample to women (nondonors) who were aged 18 to 48 years at cohort entry.

Exclusions. We will apply the same data cleaning steps as described above for donors. We will also apply a set of 39 health-related exclusion (restriction) criteria, which are listed in Table 1, aiming to create a cohort of nondonors who have a similar health status as donors at cohort entry. The criteria were chosen based on published guidelines on contraindications to kidney donation,[7,20] risk factors for chronic kidney disease, clinician input, and an analysis of predonation characteristics of 4146 living kidney donors who donated in Ontario between 1992 and 2021. We also analyzed 80+ characteristics and identified those that occurred in $<0.5\%$ of donors. For example, to ensure that nondonors had the same opportunity as donors to obtain health care services from physicians and were also permanent residents of the province, we will restrict the sample of nondonors to women who visited a physician at least once during the previous 2 years. We will also remove anyone with a prior history of kidney transplantation, dialysis, or nephrectomy. While some of these variables, such as living in a long-term care home, may not be explicitly stated contraindications to kidney donation, clinicians would consider them to be preclusions to donation. These exclusion criteria captured recent acute illnesses requiring intensive care unit visit or ≥ 4 hospitalizations in the last year, indicators of poor baseline health such as home oxygen therapy, evidence of kidney disease, cardiovascular disease, hypertension or gestational hypertension/pre-eclampsia/eclampsia, cancer, liver disease, diabetes or gestational diabetes, infections, rheumatologic disorders, and substance use disorders. In addition to these health-related exclusion criteria, we will also exclude nondonors with multifetal pregnancies. After applying these exclusions, we expect to remove approximately 75% of women in the general population from being selected as matched nondonors. To align with our planned analyses where the unit of analysis will be at the pregnancy-level, donor pregnancies will then be matched (1:4) to nondonor pregnancies as described below.

Matching. Each donor pregnancy will be matched without replacement to 4 nondonor pregnancies on the following 5 potential confounders[23-26] (the rationale is provided in brackets):

1. The date of the woman's delivery (to account for era effects).
2. A woman's age on her delivery date (because older age is associated with a higher risk of hypertensive disorders of pregnancy).
3. The time between cohort entry and the delivery date (to account for era effects).
4. Neighborhood income quintile (because lower income is associated with a higher risk of hypertensive disorders of pregnancy).
5. The number of births of at least 20 weeks' gestation between July 1, 1991 and the delivery date of the index pregnancy, excluding the index pregnancy (because nulliparity is a risk factor for preeclampsia [note: pregnancy data are not available in Ontario data sources before July 1991]).[24]

Variables

Baseline characteristics. The characteristics of women at the time of cohort entry and the characteristics of pregnancies after cohort entry will be summarized for each group (Supplemental eTable 1). Where possible, we will use validated algorithms to define the characteristics. Baseline characteristics will be presented for each province separately and pooled together.

Exposure. The exposure in this study is living kidney donation. The referent group will be the nondonor group in the main analyses.

Outcomes. Women will be followed for pregnancies and their associated study outcomes from cohort entry until death, emigration from the province, or the end of the observation period (March 31, 2023).

Primary outcome. The primary composite outcome is a diagnosis of gestational hypertension, pre-eclampsia, and/or eclampsia between 20 weeks gestation and 6 weeks after birth as recorded in a health care database. The codes to be used to ascertain this outcome and their operating characteristics are published elsewhere.[8] Each component of the composite outcome (gestational hypertension, pre-eclampsia, and eclampsia) will also be reported individually as secondary outcomes (to comply with privacy regulations for minimizing the chance of identification of a study participant, if there are too few eclampsia events to report separately, the number will be combined with preeclampsia events). The follow-up period for the primary outcome will be from 20 weeks before each delivery date until 6 weeks afterwards as postpartum pre-eclampsia can occur up to 6 weeks after

delivery;[27,28] this also aligns with World Health Organization's definition of the postnatal period.[29] In the general population, 3% to 9% of pregnancies are affected by gestational hypertension, with preeclampsia occurring in 1% to 4% of pregnancies.[30-32]

Secondary outcomes. The secondary maternal outcomes are early hypertensive disorders of pregnancy (diagnosed at <34 weeks gestation), severe maternal morbidity (SMM; examined as a count variable by number of SMM indicators, median [interquartile range, IQR]; a higher number indicates greater morbidity), cesarean section, postpartum hemorrhage, and gestational diabetes.

Early (<34 weeks gestation) versus late (≥34 weeks gestation) pre-eclampsia may be phenotypes of different mechanisms that result in uteroplacental circulatory dysfunction and thus impact fetal/infant outcomes.[33-35] Severe maternal morbidity will be estimated using a validated indicator that incorporates 40 indicators of maternal morbidity and mortality (including acute renal failure) that are captured in provincial administrative health care databases between 20 weeks gestation and 42 days after delivery.[36] As the definition of SMM relies on the use of International classification of Diseases: 10th Revision (ICD-10) codes, which first came into use in Ontario on April 1, 2002, SMM will only be assessed in pregnancies of ≥20 weeks gestation with a delivery on or after this date.

We will also examine infant outcomes, including a composite outcome of premature birth (gestational age <37 weeks) and low birth weight (defined as <2.5 kg), small for gestational age (defined as a birth weight below the 10th percentile relative to the reference population of live births of the same sex and gestational age), neonatal intensive care unit admission, stillbirth (defined as a fetal death at ≥20 weeks' gestation), and neonatal death (death between 0 and 27 days after delivery).

Effect modifiers. All donor candidates of childbearing age demonstrate excellent predonation measures of kidney function as adults (high clearance, no albuminuria, normal blood pressure), which makes the chance they carry a serious genetic predisposition to kidney disease less likely. Nonetheless, it remains possible that women who have a family history of kidney failure may have a genetic predisposition to kidney disease and thereby a higher risk of hypertensive disorders of pregnancy compared to women without such a family history.[8] The effect of a donor being a first-degree genetic relative of her recipient (versus all other types of relationships including a spouse or friend) on the primary outcome will be examined in 2 ways in the Ontario cohort (as these data are not available in Alberta and British Columbia databases). First, a first-degree genetic relationship between the donor and her recipient will be examined as an effect modifier of the primary outcome, where matched nondonors will follow the grouping of their donor. Second, we will restrict the analysis to donors only and compare the outcomes in donors who are first-degree genetic relatives of their recipients to donors who are not first-degree genetic relatives of their recipients. The baseline characteristics of the 2 donor groups will be balanced using propensity score weighting, and we will produce a weighted risk estimate of the primary outcome (with donors who are not first-degree relatives of the recipient serving as the referent group).

We will also explore additional subgroup analyses of the primary outcome (where some of these risks may interact synergistically with donation and be amplified): (1) parity (nulliparous vs parous at the index delivery date, because the risk may be higher in a first pregnancy),[37] (2) time from cohort entry to the delivery date of the pregnancy (because the risk in donors may be higher in the first 2 years after nephrectomy), (3) maternal age at delivery (because the risk may be higher in older women).[29,30]

Data Sources, Ethical Considerations, and Data Linkage

All data for this study will come from linked provincial administrative health care databases in Ontario, Alberta, and British Columbia. The databases contain linked health-related data generated from the health care encounters in each province. Descriptions of the key databases we will use for each province are provided below and in Supplemental eTables 2 to 4, respectively.

Data for residents of Ontario will be obtained from administrative databases housed at ICES; the use of ICES data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require research ethics board approval. Data for residents of Alberta will be obtained from Alberta Health Services (AHS) and Alberta Health (AH), which are provincial integrated health systems that deliver health services to residents of Alberta and adjacent regions in Saskatchewan, British Columbia, and Northwest Territories.[38] Data for residents of British Columbia will be obtained from Population Data BC. We have received approval from the University of Calgary Research Ethics Board (REB22-1819) to conduct the study using administrative databases of AHS and Population Data BC. The conduct and reporting of the study will follow recommended guidelines for observational studies conducted using routinely collected health data.[39] The Data Access Support Hub (DASH), supported through Health Data Research Network Canada, will facilitate and coordinate multijurisdictional data access across the provinces.[40]

We will have access to individual-level data within Ontario and British Columbia. However, individual-level data from British Columbia will not be transferable to databases outside the province. Within each province, individual-level data will be linked across databases using unique encoded identifiers. As described in the Statistical Analysis

section, the aggregate-level results (for example, the frequencies of each baseline characteristic, the relative risks of the primary outcome, the component endpoints and secondary outcomes) will be combined using meta-analytic techniques to produce overall effect estimates.

Ontario data sources. Information on living kidney donors will be obtained from the Trillium Gift of Life Network (TGLN). Trillium Gift of Life Network manages the provincial organ and tissue donor registry in Ontario. Our team previously verified the accuracy of these data by manually reviewing the perioperative records of 5 Ontario adult transplant centers between 1992 and 2010.[8] Hospital birth records will be obtained from the ICES-derived MOMBABY database, which is linked to the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and contains information on maternal and newborn outcomes. Demographic characteristics and vital statistics will be obtained from the Registered Persons Database. Information on hospital admissions, diagnoses, and health care visits will be obtained from CIHI-DAD, the CIHI National Ambulatory Care Reporting System (NACRS), and the Ontario Health Insurance Plan database.

Alberta data sources. Information on living kidney donors will be obtained from CIHI-DAD using a validated algorithm that identifies living donor nephrectomies.[41] Hospital birth records and information on maternal and newborn outcomes will be obtained from the Alberta Perinatal Health Program and CIHI-DAD databases. Demographic characteristics and vital statistics will be obtained from the Alberta Vital Statistics and Provincial Registry databases. Information on hospital admissions, diagnoses, and health care visits will be obtained from CIHI-DAD, CIHI-NACRS, and the Alberta Practitioner Claims database.

British Columbia data sources. Information on living kidney donors will be obtained from CIHI-DAD using a validated algorithm that identifies living donor nephrectomies.[41] Hospital birth records and information on maternal and newborn outcomes will be obtained from the BC Perinatal Data Registry. Demographic characteristics and vital statistics will be obtained from Population Data BC's Consolidation File/ Central Demographics database. Information on hospital admissions, diagnoses, and health care visits will be obtained from CIHI-DAD, CIHI-NACRS, and Population Data BC's Medical Services Plan database.

Potential Biases

Restriction and matching will be used to reduce the influence of confounding. The risk of bias will be assessed using the ROBINS-I tool (Risk of Bias in nonrandomized studies of interventions),[42] which includes 7 domains: confounding, sample selection, intervention classification (or in this case, exposure), deviations from the interventions (or in this case, exposure), missing data, outcome measurement, and result reporting. Two independent reviewers will assess the risk of bias of the final study and report the results.

Assessment of Study Quality

Based on the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies,[43] we anticipate a 9/9 rating (highest quality) of the reporting of our study findings in the domains of cohort selection, comparability of exposed to control groups, and outcomes (Supplemental eTable 5).

Missing Data

Loss to follow-up in administrative databases is minimal, with the only reason for loss to follow-up being emigration from the province (eg, $<0.5\%$ of Ontarians emigrate every year).[44]

Statistical Analysis

The analyses will be performed separately within each province, and the results will be combined using meta-analytic techniques as described below.

Baseline characteristics of women (at the time of cohort entry) will be summarized using frequencies and proportions, means and standard deviations (SD), and medians and IQR, as appropriate. Generalized linear models with generalized estimating equations that account for correlation structure will be applied to compare baseline characteristics between donors and nondonor controls at cohort entry.

Pregnancy will be the unit of analysis for study outcomes. The risk ratio of the primary composite outcome in donor pregnancies versus nondonor pregnancies will be derived using a log-binomial mixed regression model with random effects for women and matched sets to account for the correlation within women with multiple pregnancies and within matched sets of donors and nondonors; P value statistical significance testing will be reported for meta-analytic results of the primary outcome. The component endpoints of the composite as well as other secondary outcomes will be analyzed using similar methods as described for the primary outcome. As SMM will be modeled as a count variable, a Poisson distribution will be used in the model instead of log-binomial. All secondary and other outcomes will be reported with 95% confidence intervals without adjustments for multiple testing and without P value reporting.

Meta-analysis of provincial results. We will conduct a random effects meta-analysis to quantitatively summarize effect estimates across the provinces. We will first examine province-level statistical heterogeneity for each outcome using (1) Cochran's Q (chi-squared test) and (2) the I^2 statistic (where an $I^2 > 50\%$ would indicate substantial variability in effect

sizes across provinces). In the absence of substantial heterogeneity, we will use meta-analytic techniques to combine the results from all 3 provinces using a random effects model. We will use the Paule-Mandel method to calculate the pooled risk ratios and 95% confidence intervals;[45] this method is expected to provide the least-biased estimate of between-province variance in a meta-analysis of 2 to 4 effect estimates without increasing type I error rates and with reasonable power.[46,47]

Subgroup analyses. We will first determine the within-subgroup effect size, then compare the pooled effect estimates across the subgroups to examine for significant between-subgroup interaction using fixed-effects models.[48]

Additional analysis. We will conduct additional analyses of the composite primary outcome in the cohorts as follows. (1) We will extend the observation window from 26 to 32 weeks to align with our previous study,[8] and ascertain outcomes between 20 weeks' gestation and 12 weeks postpartum. (2) We will restrict the Ontario cohort to women who donated a kidney between June 1, 2013 to March 31, 2022 (to exclude donors who were in our previous study)[8] and combine the effect estimate of the primary outcome with those of the other 2 provinces via meta-analysis. This allows us to examine the outcomes of interest in a cohort not captured in the previous study.[8] (3) We will assess whether the gestational age at which hypertensive disorders of pregnancy are diagnosed in donors differs from that of nondonors (using a linear mixed-effects model). (4) Given that donors may be monitored more closely for hypertensive disorders of pregnancy (due to knowledge of such potential complications after donation), we will examine the potential for surveillance bias by comparing the frequencies of antenatal visits, urinalyses (test for proteinuria), and antenatal ultrasounds between donors and nondonor controls (all health care encounters are recorded in provincial administrative health care databases). We expect both groups will receive a similar amount of high surveillance (standard pregnancy care in Canada), with no meaningful difference observed in this testing between the 2 groups. (5) Finally, we will conduct an e-value analysis to quantify the magnitude of unmeasured confounding required to nullify any observed association.[49]

Sample Size

In the absence of a closed-form formula and given the complexities of estimating power for a study with 2 different sources of correlation (ie, correlation between multiple pregnancies within the same woman and within matched sets of donors and nondonors), we have estimated the sample size assuming independence. Even after the correlation is accounted for in our primary analyses, there will be sufficient statistical power to detect a reasonable risk of the association if it in truth exists. We expect that the correlation induced by matching will increase the statistical power, whereas the correlation present within women with multiple pregnancies will decrease the power. Based on the results of prior studies,[8] in the absence of any correlation, and assuming all donors came from a single province, we estimate that 230 donor pregnancies and 920 nondonor pregnancies will provide at least 80% statistical power to detect a risk ratio of 2.0 for the primary outcome. This estimate assumes a 2-sided alpha of 0.05 and that 4.8% of the nondonors will experience hypertensive disorders of pregnancy (this percentage was observed in our prior work).[8] Across the 3 provinces, we expect to include at least 230 donor pregnancies.

Discussion

Female living kidney donor candidates of childbearing age should be informed of the potential risk of kidney donation on pregnancy outcomes. The existing literature provides mixed guidance on the risk of adverse maternal, fetal/infant, and neonatal outcomes after kidney donation.

We designed this study to generate better estimates of risk and to address the limitations of prior studies.[13] We have also applied our experiences gained from a previous study that examined pregnancy outcomes after living kidney donation.[8] First, we learned from our experiences in conducting a prospective cohort study of living kidney donors that it was infeasible to recruit a sufficiently large number of donors who later became pregnant in follow up.[16] Multicenter retrospective cohort studies provide the most feasible way to ascertain donation-attributable risks of adverse maternal and fetal/infant outcomes. Second, our multijurisdictional study increases the sample size and the databases capture donor outcomes over 20 years of follow up. Third, a common challenge of previous donor outcome studies is the identification of an adequate control group.[13] We will use several strategies to identify a comparison group of nondonors who would otherwise satisfy the criteria for kidney donation. We utilized guidelines of living kidney donor evaluation;[20,50] a data-driven approach of health characteristics that occurred in $<0.5\%$ of living kidney donors; risk factors for chronic kidney disease; and clinician inputs regarding medical conditions, such as home oxygen therapy, which influence clinician's decisions on a patient's suitability for donation. After restricting the nondonor pool in this way, we will match remaining nondonors to donors on potential confounders. Fourth, we are examining a series of important maternal and fetal/infant outcomes; some outcomes (such as SMM) will be reported for the first time in this literature. Fifth, we have observed shifts in living kidney donor eligibility with acceptance of donor candidates with comorbidities, such as hypertension, older age, and vascular multiplicity in recent years.[51,52] Moreover, clinical criteria for donor acceptance also varied across transplant centers as well as practitioner deviation from center policies regarding donor criteria.[51,53] Revisiting clinically important outcomes in contemporary

cohorts is needed due to shifts in donor eligibility criteria and variable practices of donor acceptance.

We expect to follow more than 200 donors and 800 nondonors for pregnancy outcomes over a 20-year period. Attrition bias from differential loss to follow-up will be minimal, as study data will come from administrative health care databases, where the only reason for loss to follow-up is emigration from the home province. While some studies suggest that hypertensive disorders of pregnancy are a complication of kidney donation, it remains possible donors may be more vigilantly followed in their postdonation pregnancies with greater ascertainment of this outcome. We will investigate the potential for surveillance bias by comparing the frequencies of antenatal physician visits and diagnostic tests between donors and nondonors. We expect the pregnancies of donors and nondonors will have a similarly high level of health surveillance, as all Canadians have access to universal health care benefits, and screening for early markers of pre-eclampsia is recommended by Canadian guidelines.[54] Study outcomes will be defined in donors and nondonors based on mandatory hospital reporting during the pregnancy and on physician fee-for-service claims, which are less susceptible to recall or reporting bias than survey-based self-report measures obtained in the years after the pregnancy.[13] Measurement errors will be minimized by using validated diagnostic and procedural codes where possible; these codes are entered into administrative databases in real-time over a 20-year period by individuals unaware of our study.[36,41,55]

This study has some limitations. First, measurements of blood pressure, body mass index, and medication use during pregnancy are not available in our data sources. Second, accurate patient-reported racial information will not be available, although 60% to 80% of Ontario, Alberta, and British Columbia citizens are White, which will be similar in donors. Hypertension after kidney donation is more common among Black donors than White donors.[56] The APOL-1 G1 allele has been associated with approximately a 2-fold risk of early onset pre-eclampsia in women of African ancestry.[57] Whether the same is true during pregnancies in Black donors will not be addressed in this study (3.5% of Canadian citizens are Black).[58] Third, physicians use clinical judgment when applying accepted diagnostic criteria for gestational hypertension and pre-eclampsia, and not all diagnoses have the same medical significance. Fourth, due to provincial regulations, we will be unable to combine individual-level data across all 3 provinces to determine an overall effect estimate. Instead, we will use a random effects model and combine the results using the Paule-Mandel tau^2 estimator, which is recommended for combining 2 to 4 effect estimates from different data sources.[46] Fifth, administrative health care codes will not be perfect measures of study variables. However, previous validation studies have demonstrated that most codes are highly specific and moderately sensitive and will provide generalizable estimates for Canadian residents.[59] While misclassification of certain variables is possible due to coding errors, we have purposefully selected variables that can be defined using validated codes and algorithms.[59] Sixth, our study did not account for the use of medications such as aspirin for pre-eclampsia prophylaxis. This is because administrative databases do not include nonprescription medications, and our study cohort would not meet eligibility criteria for the Ontario Drug Benefits captured in administrative databases. Seventh, we did not examine the long-term impact of kidney donation on maternal health following postdonation pregnancies. Eighth, women with multifetal gestations will be excluded from our study due to their distinct risk profiles for hypertensive disorders of pregnancy and other clinically important outcomes compared to those with singleton pregnancies. This exclusion is unlikely to alter our study results as we expect multifetal gestations to occur in $<2\%$ of pregnancies in this cohort.[8] Finally, as with all observational studies, there is the possibility of residual confounding, which is a distortion in effect estimates despite the care we have taken in designing this study; as mentioned, selected nondonors will never have all the predonation testing that donors undergo to confirm good baseline health. As described, we will perform an analysis to quantify the strength of unmeasured confounding that would be needed to nullify any observed association.[49]

Conclusion

The findings from this population-based cohort study of living kidney donors will meaningfully contribute to the evidence base of the impact of kidney donation on subsequent pregnancy outcomes. We intend for the study results to be integrated into clinical guidelines for counseling of living kidney donor candidates and inform clinical practice for maternal care in pregnancies after living kidney donation.

Acknowledgments

The authors are grateful for the assistance and guidance of Erik Youngson and James King, from Alberta Health Services and the Alberta SPOR SUPPORT Unit (which is funded by the Canadian Institute of Health Research, Alberta Innovates, and the University Hospital Foundation) to access relevant data in Alberta databases and data analyses. Furthermore, the authors thank Tim Choi, lead of Data Partnerships of Population Data BC, for his assistance in navigating access to data in British Columbia databases. SM is supported by a Tier II Canada Research Chair. KLL is supported by the Mid-America Transplant/Jane A. Beckman Endowed Chair in Transplantation and serve as scientific director of the Scientific Registry of Transplant Recipients (SRTR) Living Donor Collective.

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This document used data adapted from the Statistics Canada Postal CodeOM Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from ©Canada Post Corporation and Statistics Canada. Parts of this

material are based on data and/or information compiled and provided by: MOH and CIHI. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. The author(s) acknowledge that the data used in this study were provided by the Trillium Gift of Life Network (Ontario Health), [2021], Toronto Ontario. The researcher's interpretations and statements in this publication are those of the researcher only and not those of Trillium Gift of Life Network (Ontario Health). These datasets were linked using unique encoded identifiers and analyzed at ICES.

Declaration of Conflicting Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AXG received an investigator-initiated grant from Astellas which featured as partnership funds in research funded by the Canadian Institutes of Health Research. KLL is volunteer chair of the American Society of Transplantation (AST) Living Donor Community of Practice, and a member of the American Society of Nephrology (ASN) Policy and Advocacy Committee, the National Kidney Foundation (NKF) Transplant Advisory Committee, and the National Living Donor Assistance Center Advisory Group. The other authors declare no conflicts of interest. The results presented in this paper have not been published previously in whole or part.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study is supported by the London Health Sciences Center Academic Realignment grant. CW received salary support from the PSI Foundation Research Trainee Award and KRESCENT post-doctoral fellowship award. AXG is supported by the Dr. Adam Linton Chair in Kidney Health Analytics. The authors thank the Data Access Support Hub for coordinating and facilitating data access in Alberta and British Columbia.

Data Availability Statement

The Ontario dataset of this study will be held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification. The Alberta data from the present study are held securely in coded form within Alberta Health Services and Alberta Health. Legal data-sharing agreements between Alberta Strategy for Patient Oriented Research Support Unit (AbSPORU) and the data providers (Alberta Health Services, Alberta Health) prohibit AbSPORU from making the data set publicly available.

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Supplemental Material

Supplemental material for this article is available online.

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