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Risk of kidney stones in living kidney donors: A matched cohort study

Sonia Thomas, *The University of Western Ontario*

Supervisor: Dr. Amit X. Garg, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

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RISK OF KIDNEY STONES IN LIVING KIDNEY DONORS: A MATCHED COHORT
STUDY

(Thesis format: Monograph)

by

Sonia M. Thomas

Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

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Abstract

A kidney stone in a person with one kidney requires urgent attention which may result in surgical and/or hospital attention. We conducted a matched retrospective cohort study to determine if living kidney donors compared to healthy non-donors have a higher risk of: 1) kidney stones with surgical intervention, and 2) hospital encounters for kidney stones. We reviewed and linked information from pre-donation charts to Ontario healthcare databases. We selected healthy non-donors from the general population, matching ten non-donors to every donor, to generate a cohort of 2,019 donors and 20,190 non-donors. There was no difference in the rate of 1) kidney stones with surgical intervention comparing donors to non-donors (8.3 vs 9.7 events/10,000 person-years; rate ratio[RR] 0.85; 95% confidence interval[CI] 0.47-1.53), and 2) hospital encounters for kidney stones (12.1 vs 16.1 events/10,000 person-years; RR 0.75; 95% CI 0.45-1.24). These interim results are reassuring for the safety of living kidney donation.

Keywords

Administrative data, kidney stones, calculi, living kidney donor, health outcomes, retrospective cohort study, kidney transplantation

Co-Authorship Statement

The study presented here were designed and executed by Sonia Thomas. This includes but is not limited to study conception, data creation plan (DCP) production, design and manuscript production and editing. Regular feedback was provided by the supervisory committee as well as each of the co-authors (listed below).

Dr. Garg was the primary supervisor and was involved in all aspects of the work. I would also like to acknowledge the other co-authors and reviewers who helped edit the manuscript and grant that funded this work. The manuscript was published in the American Journal of Transplantation on September 18th 2013.

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Chapter 1: Introduction

1.1 Background & Overview

Every year, over 27,000 individuals worldwide choose to undergo living kidney donation to help someone in need (1). Knowledge of the long-term outcomes of living kidney donors is required to maintain public trust in the transplantation system, inform the choices of potential donors and recipients, and to guide the follow-up care necessary to maintain optimal long-term health.

One outcome that remains poorly understood in past living kidney donors is the subsequent development of kidney stones. In September 2012 we performed a detailed search of bibliographic databases (Pubmed, Google Scholar) and found only a few reports of living kidney donors being treated for kidney stones at the time of nephrectomy. However, these studies did not report the rate or long-term risk of kidney stones in this unique population. We expanded the search to include kidney stones in those with a solitary kidney for any reason and again found only literature discussing the management of the stone at the time of its occurrence.

In the general population, kidney stones are common with an estimated lifetime risk of 10-15% (2, 3). Most stones are small and pass through the urinary tract spontaneously within four weeks of initial symptoms. However, some stones may require surgical intervention including shockwave lithotripsy, ureteroscopy or percutaneous nephrolithotomy (3, 4). There is no reason to suspect that living kidney donors would have a higher risk of kidney stones than members of the general population. Yet, a kidney stone in an individual with a solitary kidney can potentially obstruct the ureter, leading to acute renal failure and may result in urgent hospital attention and even surgical

intervention (5). This is also a concern because kidney stones can result in a decline in renal function, and this risk may be even higher in donors compared to non-donors. We conducted this matched retrospective cohort study to determine if living kidney donors compared to healthy non-donors have a higher risk of: 1) kidney stones with surgical intervention, and 2) hospital encounters for kidney stones.

Chapter 2: Literature Review

2.1 Kidney failure

End-stage renal disease (ESRD) or kidney failure is the result of complications from reduced renal function, and is the most severe stage of chronic kidney disease (CKD) (6). The best measure of renal function used to assess the severity of kidney disease is called the glomerular filtration rate (GFR) (7). It represents an estimate of the amount of blood filtered by the glomeruli in the kidney per minute. The GFR of a healthy individual is typically around 90-120 mL/min per 1.73m² (8). ESRD is characterized by either a reduction in estimated glomerular filtration rate (GFR) to level below 15 mL/min per 1.73m², or by the requirement of renal replacement therapy to prevent increased morbidity and mortality (6).

The prevalence of end-stage renal disease or kidney failure is on the rise, with over one million individuals affected worldwide. This number continues to increase by 7% per year and in Canada alone the number of individuals living with end-stage renal disease has tripled over the past two decades (9, 10). Patients with ESRD require some form of renal replacement therapy in order to maintain life.

2.2 Renal Replacement Therapy

There are several different types of renal replacement therapy that can be used to treat patients with kidney failure. Dialysis involves the use of an artificial filtration system to clear the patient's blood of toxic waste products. There are two main forms of dialysis. The first and most common form of dialysis is hemodialysis, which involves taking blood out of the patient's body, filtering it through the dialysis machine and then pumping it

back into the patient (11). Typically a patient has to receive hemodialysis multiple times a week, with each treatment lasting 3-4 hours. The second form of dialysis is peritoneal dialysis, which allows the filtration to occur within the patient's body through the introduction of fluid within the peritoneum. Waste products are filtered from the blood across the peritoneum membrane, and the fluid is then flushed out of the peritoneal cavity (11). Though the majority of patients with kidney failure are treated with dialysis, it is not their best treatment option. Dialysis is associated with numerous complications, reduced survival, and poorer quality of life when compared with transplantation (11-14).

Compared to dialysis, transplantation is the preferred treatment option for end-stage renal disease resulting in 10 to 15 years longer survival (15). A systematic review of 110 studies comparing kidney transplantation to dialysis concluded that transplantation was associated with significantly reduced mortality, reduced cardiovascular complications and improved quality of life (16). As well, the magnitude of the improvement in health with transplantation was found to increase over time (16).

There are two types of transplantation – deceased donation or living donation. Deceased donation occurs after an individual dies as a result of brain death or cardiovascular collapse. In this case, the individual either registered or expressed their wish to become an organ donor prior to death (which is confirmed by family members of the deceased). Unfortunately the number of deceased donations has not been sufficient enough to meet the growing demand for organs. On the other hand, rates of living kidney donation are rising in an attempt to address this demand. Living kidney donation involves a living individual making the choice to donate one of their kidneys to someone in need.

2.3 Living kidney donation

The first successful living kidney donation was performed by Dr. Murray in 1954 between identical twins (17). Since then there have been significant advancements in transplant medicine and immunosuppression. Individuals who receive a kidney from a living donor have better outcomes with longer graft survival than those who receive a kidney from a deceased donor (18). The longer survival of a graft from a living kidney donor can be attributed to the fact that the kidney can be removed from the donor and transplanted into the recipient without delay. This minimizes the damage to the kidney due to ischemia, or loss of blood flow (19).

A decision analysis of treatment options for patients with end-stage renal disease and type I diabetes demonstrated that transplants from living kidney donors were associated with 10.29 quality-adjusted life-years (QALY), while deceased donor transplants and dialysis treatments were associated with 6.53 QALY and 4.52 QALY respectively (20).

Living kidney donation is also a more cost-effective treatment option for patients with end-stage renal disease. Dialysis is an expensive procedure, costing the healthcare system millions of dollars every year (21, 22). In Canada the cost for dialysis treatments is approximately \$60,000 per patient per year, while in comparison the cost of a one-time kidney transplant is approximately \$23,000 plus an additional \$6000 for annual transplant medications (10). If all 3000 individuals on the wait list for a kidney transplant received a kidney, it would save the healthcare system an estimated \$150 million dollars annually (23).

Rates of living kidney donation have been increasing worldwide to address the organ shortage, with over 27,000 individuals choosing to donate every year (1). Living donation is practiced under the framework that minimal medical risks faced by the donor are outweighed by better recipient health and possible psychological benefits of altruism to the donor (24). There is global consensus for a need to better understand the long-term risks faced by living kidney donors, a historically neglected area (25). For this reason, this topic has been the subject of active research. Better knowledge of the long-term outcomes of individuals who become living kidney donors maintains public trust in the transplantation system, informs the choices of potential donors and recipients, and guides follow-up care to maintain optimal long-term health. Recent high-quality studies have examined outcomes of mortality, cardiovascular events, end-stage renal disease, acute kidney injury with receipt of dialysis, and fragility fractures after kidney donation (26-28). Reassuringly, these studies did not find an increase in risk, adding to the evidence base supporting the safety of the practice among carefully selected donors. However, there are still other important outcomes which remain to be studied.

2.4 Kidney stones

Kidney stones or renal calculi are a common occurrence, with a prevalence of approximately 5.2% in North America and an estimated lifetime risk of 10-15% (3, 29). After the development of a kidney stone, the risk of a subsequent stone increases with a recurrence rate of 75% over 20 years (2, 3). Kidney stones result from an abnormal urinary composition, which cause the crystallization of stone-forming salts. Approximately 80% of stones are formed from calcium-based salts, while the remainder form from compounds like uric acid, cystine and struvite (30). Abnormalities in urinary

composition can be caused by both metabolic and environmental factors (2).

Environmental factors include hot climate (certain regions within the US are referred to as the 'stone belt' due to a higher prevalence of kidney stones because of climate), strenuous exercise, and diets rich in animal protein and salt. Metabolic factors include hypercalciuria (increased absorption of calcium in the intestine or decreased absorption in the kidney) and hypocitraturia (excess dietary acid) (2).

Epidemiological studies have identified several risk factors associated with the formation of kidney stones. Literature describes males having a 2-3 times higher risk of developing kidney stones than females (29, 31, 32). The peak incidence of kidney stones occurs during the age range of 40-50 years (29, 33-35).

2.5 Treating kidney stones

The majority of stones are small enough to pass through the urinary tract spontaneously without any intervention. This typically occurs within four weeks after the onset of symptoms (4). However, if the kidney stone does not resolve with expectant management, a urologist may choose to surgically intervene using shockwave lithotripsy, ureteroscopy or percutaneous nephrolithotomy (4). Surgical procedures are usually required when stones are 3 mm or greater in size (3, 4). Approximately 10-20% of kidney stones are treated surgically (32).

Extracorporeal shockwave lithotripsy is a procedure that involves targeting a shockwave from an external source, propagating through the patient's body to the kidney stone causing it to break into smaller fragments. These fragments are then removed or allowed to pass spontaneously (4, 36, 37).

Ureteroscopy requires the use of an endoscope to visualize the urinary tract and collecting system. Ureteroscopes enable the use of other instruments to allow for stone fragmentation and removal (4, 37).

Percutaneous nephrolithotomy is a procedure during which the surgeon makes a small incision in the patient's back to remove the kidney stone using a hollow tube and a probe (4). Sometimes a laser is used to fragment the kidney stone. The fragments are then removed using basket extraction or a suction device (4, 37).

2.6 Kidney stones in living kidney donors

In a patient with a solitary kidney, the development of a kidney stone is potentially more serious. If the kidney stone obstructs the ureter, this usually requires an emergency surgical intervention to prevent acute renal failure (5). Literature has also demonstrated that kidney stones can result in a decline in renal function (38, 39). In an individual with one kidney, the consequences of this could potentially be more severe as they do not have a second kidney to compensate for the reduced renal function.

On review of the literature, no risk estimates of kidney stones in living kidney donors were found. Instead the majority of the literature described donor-gifted lithiasis (5, 40-45). This occurs when a stone is found in the donor kidney (either living or deceased) at the time of transplantation surgery. Normally the identified stone is removed immediately before transplantation into the recipient, or it is left as is if deemed small enough to not cause any complications to the recipient. However, all these studies only describe kidney stones which occurred prior to transplant, when the donor still had two kidneys.

While the risk of kidney stones in living kidney donors has not been reported in literature, there have been case reports and discussions of treatment for kidney stones in individuals with a solitary kidney for any reason (46-51). One study comparing solitary and bilateral kidney patients being treated with percutaneous nephrolithotomy described individuals with a solitary kidney as having undergone significantly more procedures to remove kidney stones prior to the study (46). However, all of these studies focused on the method of treatment and did not provide estimates of the risk of kidney stones in individuals with a solitary kidney for any reason.

2.7 Studying long-term outcomes of living kidney donors

There are four major challenges to obtaining reliable estimates of the long-term risks associated with becoming a living kidney donor:

- 1) Many donors do not reside close to a transplant centre, and their only purpose of visiting is to donate their kidney to the recipient. Beyond the first year after nephrectomy the majority of donors do not follow-up with the transplant centre. This makes it challenging to follow all donors for a given transplant centre over many years (where loss to follow-up can result in both selection biases and information biases).
- 2) People experience health events as they age, and so when we observe such events in donors during follow-up it is questioned whether such events occurred due to aging and were unrelated to the donation process, or whether they are a biological consequence of nephrectomy. The only reliable way to solve this issue is to also study a non-donor ‘control’ group, where the rate of events observed in follow-up

can be compared between donors and non-donors to establish any true risk attributable to donation.

- 3) Choosing the best type of non-donors to compare to the donors is central to any study of relative risks associated with donor nephrectomy (52). Donors go through a detailed selection process and are inherently healthier than the general population (53). Thus the ideal non-donor controls are those individuals who have a similar health state to donors at the time of nephrectomy.
- 4) It may take years for biological changes from donation to manifest. To achieve such a long follow-up in a prospective study requires years of waiting and is an expensive proposition.

The need for solutions to generate reliable information on long-term living donor outcomes was recently outlined in a State of the Art Conference with international opinion leaders (54). To address this need we are fortunate to have developed a unique cohort in Ontario, Canada. This cohort addresses the four challenges described above and its strengths are internationally recognized.

2.9 Health administrative data in Ontario

Ontario currently has approximately 13 million residents who have universal access to hospital and physician care (55). The province's administrative healthcare databases provide a rich data source unique to Canada, which is representative of the entire province. Using these databases allows us to address weaknesses faced by prospective studies by minimizing selection and information biases, allowing for large sample sizes

and long periods of follow-up, as well as minimizing any loss-to-follow up (only due to emigration out of the province, <0.5% per year).

In order to study the outcomes of living kidney donors, we manually reviewed the medical charts of over 2000 living kidney donors, and then linked this information to provincial healthcare databases housed at the Institute of Clinical Evaluative Sciences (ICES). We isolated the healthiest segment of the general population, providing us with a suitable non-donor comparison group.

We have successfully leveraged this cohort in the past to provide much needed information on the risk of cardiovascular events, acute kidney injury with receipt of dialysis and fragility fractures in living kidney donors (published in the British Medical Journal (BMJ), Nephrology Dialysis Transplantation (NDT) and American Journal of Kidney Diseases (AJKD) respectively) (26-28).

Chapter 3: Rationale

3.1 Rationale

We performed detailed searches of Pubmed, EMBASE and Google Scholar, and determined that there are no existing studies that evaluate the long-term risk of kidney stones in living kidney donors. When we expanded our search to include individuals with a solitary kidney for any reason, we still failed to find any description of the risk of these long-term outcomes (56).

We did find some information on the treatment of kidney stones in patients with a single kidney. Individuals with a solitary kidney treated with percutaneous nephrolithotomy had less favourable outcomes compared to those with two kidneys (46). Patients with a solitary kidney also underwent more procedures to remove kidney stones compared to those with two kidneys (46).

There is no reason to suspect that living kidney donors would have a higher risk of kidney stones than members of the general population. Yet, a kidney stone in an individual with a solitary kidney can potentially obstruct the ureter, leading to acute renal failure and may result in urgent hospital attention and even surgical intervention. This is also a concern because kidney stones can result in a decline in renal function, and this risk may be even higher in donors compared to non-donors (38, 39).

Given the current state of the literature, the study we conducted is novel and meets an information need.

3.2 Research Question & Hypothesis

We conducted this matched retrospective cohort study to determine if living kidney donors compared to healthy non-donors have a higher risk of: 1) kidney stones with surgical intervention, and 2) hospital encounters for kidney stones.

Hypothesis: We expected that living kidney donors may be at greater relative risk for kidney stones with a surgical intervention compared to a group of healthy non-donors (where kidney stones which develop in follow-up will be less likely to result in an intervention). However, the absolute increase in risk will be low when compared to the control group of non-donors.

Chapter 4: Methods

4.1 Study design

We conducted a matched retrospective cohort study using Ontario's administrative healthcare databases held at the Institute for Clinical Evaluative Sciences (ICES).

4.2 Data sources and data collection: Ontario healthcare databases

The following databases were used to ascertain our variables of interest:

The Trillium Gift of Life Network (TGLN) is Ontario's central organ and tissue donation agency with information on kidney donors and recipients in Ontario. We used the TGLN database to identify living kidney donors, the main exposure group in this study. During the years 2008 to 2010 we manually reviewed each of the medical charts of over 2000 living kidney donations which occurred between 1992 and 2009 at the five major transplant centres in Ontario. The five major transplant centres include London, Ottawa, Hamilton and the two centres in Toronto. I personally was responsible for reviewing all charts from the London, Ontario centre. The living donor information in the TGLN database is now complete, updated and accurate up to 2009.

The Canadian Institute for Health Information Discharge Abstract Database, Same Day Surgery, and National Ambulatory Care Reporting System (CIHI-DAD, SDS, NACRS) databases collect demographic, diagnostic, and procedural variables for inpatient, emergency department and outpatient visits. Diagnostic and inpatient procedural coding uses the 9th version of the Canadian Modified International Classification of Disease system (ICD-9 CA) prior to 2002 and the 10th version (ICD-10 CA) thereafter. We used the CIHI datasets to identify the occurrence of kidney stones with surgical intervention.

We also used the datasets to identify any comorbid conditions which acted as exclusion criteria for the non-donor controls (see codes in Table 1).

The Ontario Health Insurance Plan (OHIP) captures information on inpatient, outpatient, and laboratory services based on billing claims from Ontario physicians. In chart abstraction studies, agreement between abstracted OHIP codes and the actual codes the physicians recorded on the chart for the “most responsible” diagnosis was over 90% while agreement for procedural codes was over 88% (57). We used OHIP diagnostic codes to identify baseline conditions and both procedural and diagnostic codes to define our outcomes.

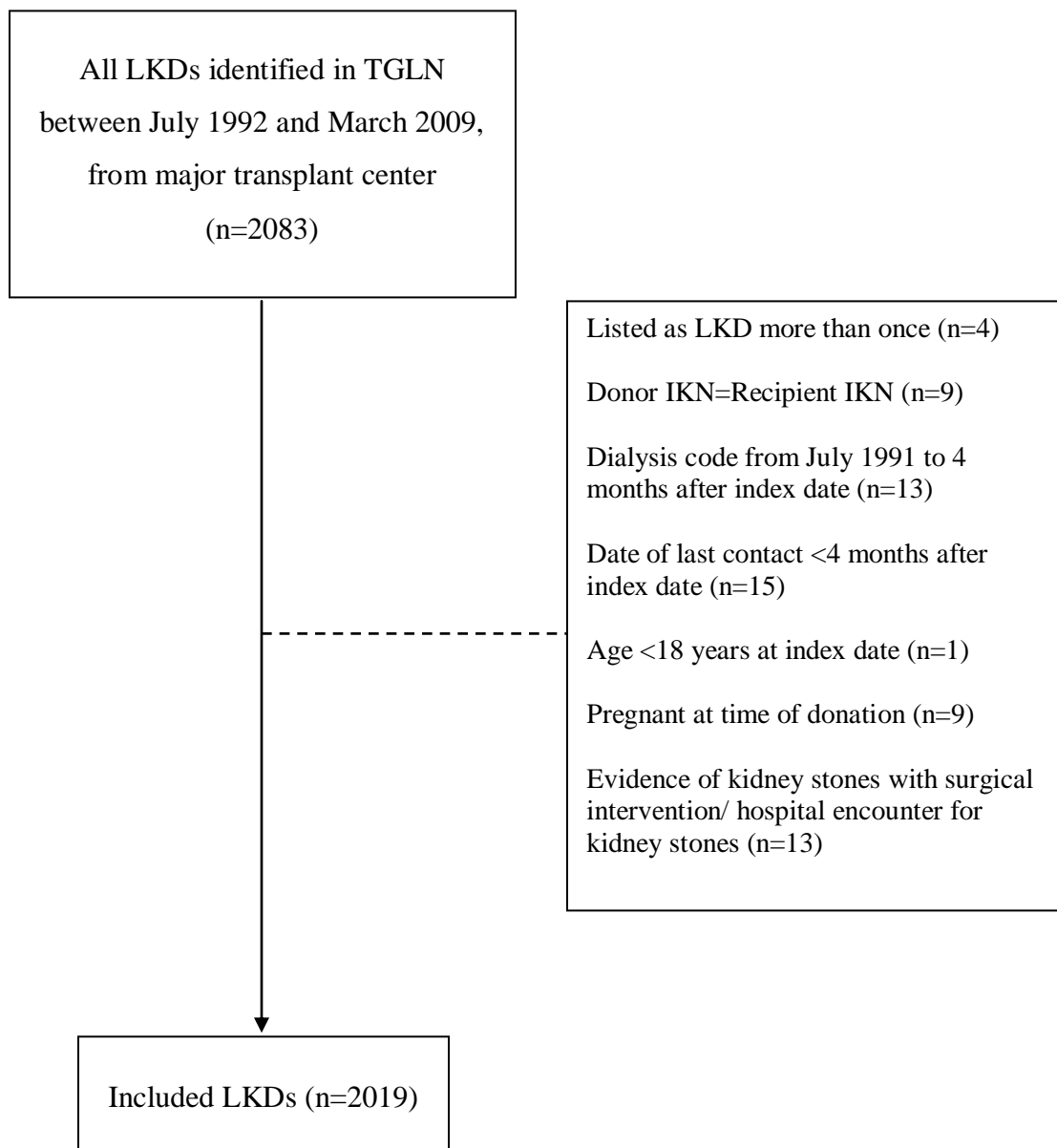
The Registered Persons Database (RPDB) captures demographic information on Ontario residents including their sex, date of birth, postal code and vital status. We used the RPDB to ascertain baseline demographics, exclusion criteria and potential confounders.

4.3 Cohort selection

Kidney donors undergo a complete medical evaluation to ensure they are in excellent health prior to donation. In this study the date of nephrectomy was used as the date of cohort entry, and is also referred to as their index date. The accrual period was from July 1st, 1992 to March 31st, 2012. To select a similar group of healthy non-donor controls, we first randomly assigned an index date to all adults in the population of Ontario, following the distribution of index dates in living kidney donors. For the control population we excluded all individuals who have evidence of a medical condition prior to their index date which would preclude them from becoming a living kidney donor (such as diabetes, hypertension or kidney disease). From the remaining controls we then

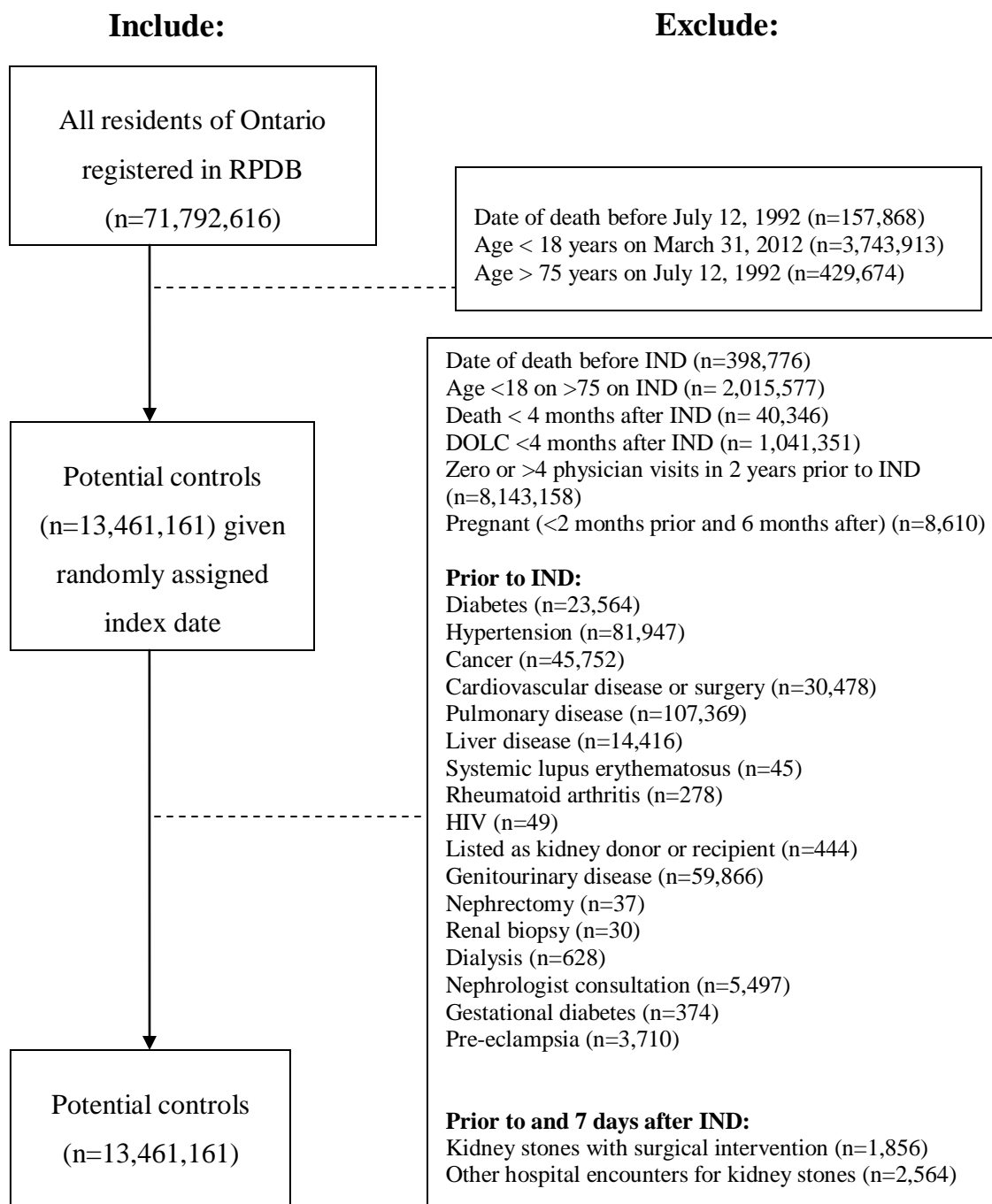
utilized a technique of matching, such that each donor was matched to ten non-donor controls based on index date (± 6 months), age (± 2 years), sex, neighbourhood income quintile, and residential status (rural, urban). This process of: i) restricting the non-donor control sample to the healthiest segment of the population, and ii) matching donors and non-donors on key characteristics, represents our primary strategies to minimize confounding. Typically studies have demonstrated a limited increase in precision when the ratio of controls to cases is increased beyond four (58-60). However, given that our study was conducted using administrative data from the entire province of Ontario, it was feasible for us to obtain additional matched controls resulting in a slight increase in precision.

We followed our donors and non-donor controls for outcomes of interest until March 31st, 2012 (last date of follow-up). We have successfully used a similar technique to report the risk of cardiovascular events, acute kidney injury with dialysis and fracture outcomes in donors and non-donor controls (26-28).

Figure 1: Cohort selection flowchart for living kidney donors

LKD: Living Kidney Donor

IKN: ICES Key Number

Figure 2: Cohort selection flowchart for healthy non-donors

RPDB: Registered Persons Database

IND: Index date

DOLC: Date of Last Contact

4.4 Study Population

Donors were those individuals who donated a kidney at one of the five major adult transplant centers in Ontario.

Our exclusion criteria for donors included the following:

- 1) Evidence of kidney stones prior to index date (to ensure we capture only de novo events in follow-up: also the number of donors with a prior history of kidney stones is uncommon in our setting, and we cannot meaningfully look at this small group of patients).

As mentioned above, non-donor controls must be in good health to ensure they are comparable to living kidney donors who undergo rigorous medical assessment in order to qualify for donation. To create an appropriate non-donor control group with similar health status to our donor group, we excluded all individuals from the general population with evidence of a contraindication to donation including the following:

- 1) Any of the following conditions: Diabetes, hypertension, cancer, cardiovascular disease (including any heart disease, stroke or peripheral vascular disease), pulmonary disease, liver disease, systemic lupus erythematosus, rheumatoid arthritis, HIV, gestational diabetes, pre-eclampsia, kidney stones or any genitourinary disease renal disease (including a history of nephrectomy, kidney transplant, kidney biopsy, or dialysis) (53).
- 2) Pregnant at the time of index date (ineligible to donate a kidney at that time).

- 3) Evidence of kidney stones with surgical intervention prior to the index date (as this same exclusion criteria is being used in our donor cohort).

4.5 Outcome: Kidney stones with surgical intervention

Our primary outcome was the evidence of kidney stones with surgical intervention following the index date until March 31st, 2012 (see Appendix 2 for codes). These codes have not been formally validated but are expected to have high sensitivity and specificity similar to other fee for service codes (61). The codes were also chosen based on clinical expertise and an understanding of urology billing practices.

All participants were followed up from index date until: i) death, ii) emigration from the province, or iii) the end of study period (March 31, 2012). Of the individuals who reached the end of the study (March 31, 2012), those whose most recent healthcare encounter was more than three years before the end of study (March 31, 2012) were classified as having emigrated from the province. These individuals were censored at one year following their last healthcare encounter.

Outcomes include recurrent events (participants can have more than one occurrence of a kidney stone with surgical intervention during follow-up, but such interventions must be separated by at least 90 days to ensure it is an intervention for a new stone or reoccurrence of a stone).

4.6 Data Analysis

Descriptive Statistics and Baseline Characteristics: We described the continuous baseline characteristics as means with standard deviations for normally distributed data or as

medians with interquartile ranges for skewed data. We presented categorical variables as proportions. We assessed the differences between donors and non-donors using standardized differences (62). Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation, where a value greater than 10% is interpreted as a meaningful difference between the groups (62). Our data sources and variables of interest were complete. In previous studies missing data has been < 1% (26-28).

Primary analyses: We used a negative binomial model stratified on matched sets to estimate the rate ratio and 95% confidence interval. This model also accounts for the possibility of a person having more than one stone event in follow-up (defined by events separated by at least 90 days). We repeated the primary analysis in three pre-specified subgroups defined by age (<40 vs \geq 40 at index date), sex and index date (1992 to 2001 [median follow-up 13.3 years, interquartile range (IQR) 11.4 to 15.8] vs. 2002 to 2009 [median follow-up 5.9 years, IQR 4.3 to 7.8]).

Additional analyses: We examined whether rate ratios differed among subgroups using a series of pair-wise standard z-tests. We repeated the primary analysis using Kaplan-Meier estimates stratified on matched sets to examine the first stone event in follow-up for both the primary and secondary outcomes. We examined the characteristics associated with stone events separately in donors and non-donors using negative binomial regression models. All analyses were performed at ICES with SAS software version 9.2 (SAS Institute, Cary, NC).

Table 1 provides sample size calculations based on $\alpha = 5\%$, $1 - \beta = 80\%$, an incidence of 2.5% in non-donors, a 1:10 ratio of kidney donors to non-donors, and a continuity correction for the difference in proportions. Based on these calculations, we only required 1515 donors and 15150 non-donors to detect an odds ratio of 1.5 over a median follow-up of 11 years, should an association exist. These are numbers well below our attained sample.

Table 1. Sample size calculations

Presented are the number of individuals required in each group to detect a defined difference in the rate ratio should it in truth exist.

Rate Ratio to be detected		
1.50	1.75	
1515	696	Living kidney donors
15150	6960	Non-donor controls

Assumptions: The proportion of non-donor controls who will develop a kidney stone over a median follow-up of 6 years is 2.5%. $\alpha = 0.05$, $1-\beta = 0.8$, a ratio of kidney donors to non-donor controls of 1:10. To simplify the calculations these analyses disregard the matching used to generate the sets and only consider the development of the first kidney stone in follow up. A continuity correction was used for the difference in proportions.

Chapter 5: Results

5.1 Baseline characteristics

Table 2 shows the baseline characteristics of the selected 2,019 donors and 20,190 matched non-donors. Donors and non-donors had similar baseline characteristics. The median age at index date was 43 years (interquartile range 34 to 50) and median age at last follow-up was 52 years (interquartile range 44 to 60). Approximately 60% of the donor and non-donor cohorts were female, and 13% had a rural residency status. Approximately 62% of donors are first degree relatives of the recipient, with roughly 35% donating to a sibling, 14% donating to a parent, and 13% donating to their child. The remaining living kidney donors donated to their spouse (20%), another relative (6%) or to an unrelated individual (12%). Donors had a median of 11 physician visits in the year prior to the index data, compared to a median of 1 physician visit in non-donors. This difference is expected, given the thorough medical work-up which is a necessary part of the donor evaluation process.

Table 2.

Baseline characteristics of donors and healthy non-donors at the time of cohort entry.

	Donors <u>n = 2,019</u>	Non-donors <u>n = 20,190</u>
Age, years	43 (34 – 50)	43 (34 – 50)
Women	1,213 (60%)	12,130 (60%)
Rural town	270 (13%)	2700 (13%)
Income quintile		
Lowest	308 (15%)	3,080 (15%)
Middle	423 (21%)	4,230 (21%)
Highest	463 (23%)	4,630 (23%)
Physician visits in prior year*	11 (8 – 15)	1 (0 – 2)
Year of cohort entry		
1992 – 1997	391 (19%)	3915 (19%)
1998 – 2003	729 (36%)	7285 (36%)
2004 – 2009	899 (45%)	8990 (45%)

Data presented as median (interquartile range) or as number (percent). The time of cohort entry is also referred to as the index date. This was the date of nephrectomy in donors and was randomly assigned to non-donors to establish the time follow-up began.

*Indicates a standardized difference between donors and non-donors greater than 10%. As expected, donors had more physician visits in the year prior to index date compared to non-donors, as such visits are a necessary part of the donor evaluation process.

The median length of follow-up was 8.4 years (8.8 years in donors, 8.4 years in non-donors, maximum 19.7 years). A total of 856 donors and 8,128 non-donors had over 10 years of follow-up. The median age at the time of last follow-up for the entire cohort was 52 years (interquartile range 44 to 60). Of the 22,209 individuals (2,019 donors, 20,190 non-donors), 20,084 (90.4%) reached the end-of-study follow-up (March 31, 2012), 1,499 (6.7%) were censored at emigration from the province, 480 (2.2%) were censored at the time of death and the remainder received at least one intervention for kidney stones. Total person years of follow-up were 204,199 (19,118 donors, 185,081 non-donors).

5. 2 Outcomes

The main outcomes are presented in Table 3 and Figures 3a and 3b. There were 195 events of kidney stones with surgical intervention (16 in donors, 179 in non-donors). The rate of this event was no different in donors compared to non-donors (8.3 vs 9.7 events per 10,000 person-years; rate ratio, 0.85; 95% confidence interval (CI) 0.47-1.53). There were a total of 323 events of hospital encounters for kidney stones (23 in donors, 300 in non-donors) recorded in our data sources. The rate of this event was no different in donors compared to non-donors (12.1 vs 16.1 events per 10,000 person-years; rate ratio 0.75; 95% CI 0.45-1.24). The results for both outcomes were the same when we assessed the time to first event (kidney stone with surgical intervention: hazard ratio 1.04, 95% CI 0.60 – 1.80; hospital encounter for kidney stone: hazard ratio 0.81, 95% CI 0.51 – 1.30; see figures 3a and 3b for Kaplan-Meier curves).

Table 3. Primary and secondary outcome events among donors and non-donors.

	Kidney stones with surgical intervention		Hospital encounter for kidney stones	
	Donors (n=2,019)	Non-donors (n=20,190)	Donors (n=2,019)	Non-donors (n=20,190)
Median follow-up, years (IQR)	8.8 (5.6 – 12.9)	8.4 (5.3 – 12.6)	8.8 (5.6 – 12.9)	8.4 (5.3 – 12.6)
Range follow-up, years (min, max)	0.55, 19.7	0.34, 19.7	0.55, 19.7	0.34, 19.7
Total follow-up, person-years	19118	185080	19118	185080
No. (%) of events:				
0	2,005 (99%)	20,058 (99%)	2,000 (99%)	19,965 (99%)
1	12 (0.6%)	105 (0.5%)	15 (0.7%)	182 (0.9%)
2	≤5*	12 (0.1%)	≤5*	23 (0.1%)
≥3	≤5*	15 (0.1%)	≤5*	20 (0.1%)
No. of events per 10,000 person years	8.3	9.7	12.1	16.1
Model based rate ratio †	0.85 (0.47 – 1.53)	1.00 (reference)	0.75 (0.45 – 1.24)	1.00 (reference)

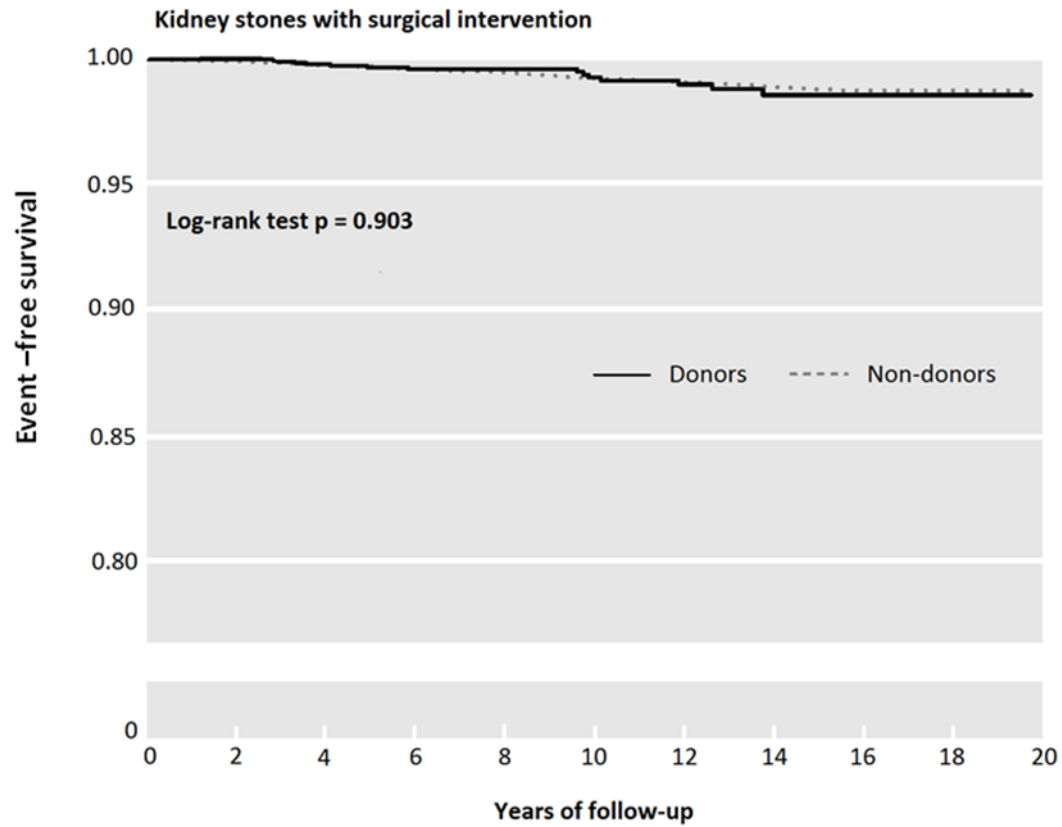
Data presented as number (percentage) or value (95% confidence interval) unless otherwise specified.

IQR (interquartile range)

*cell counts less than or equal to 5 have been suppressed for reasons of privacy.

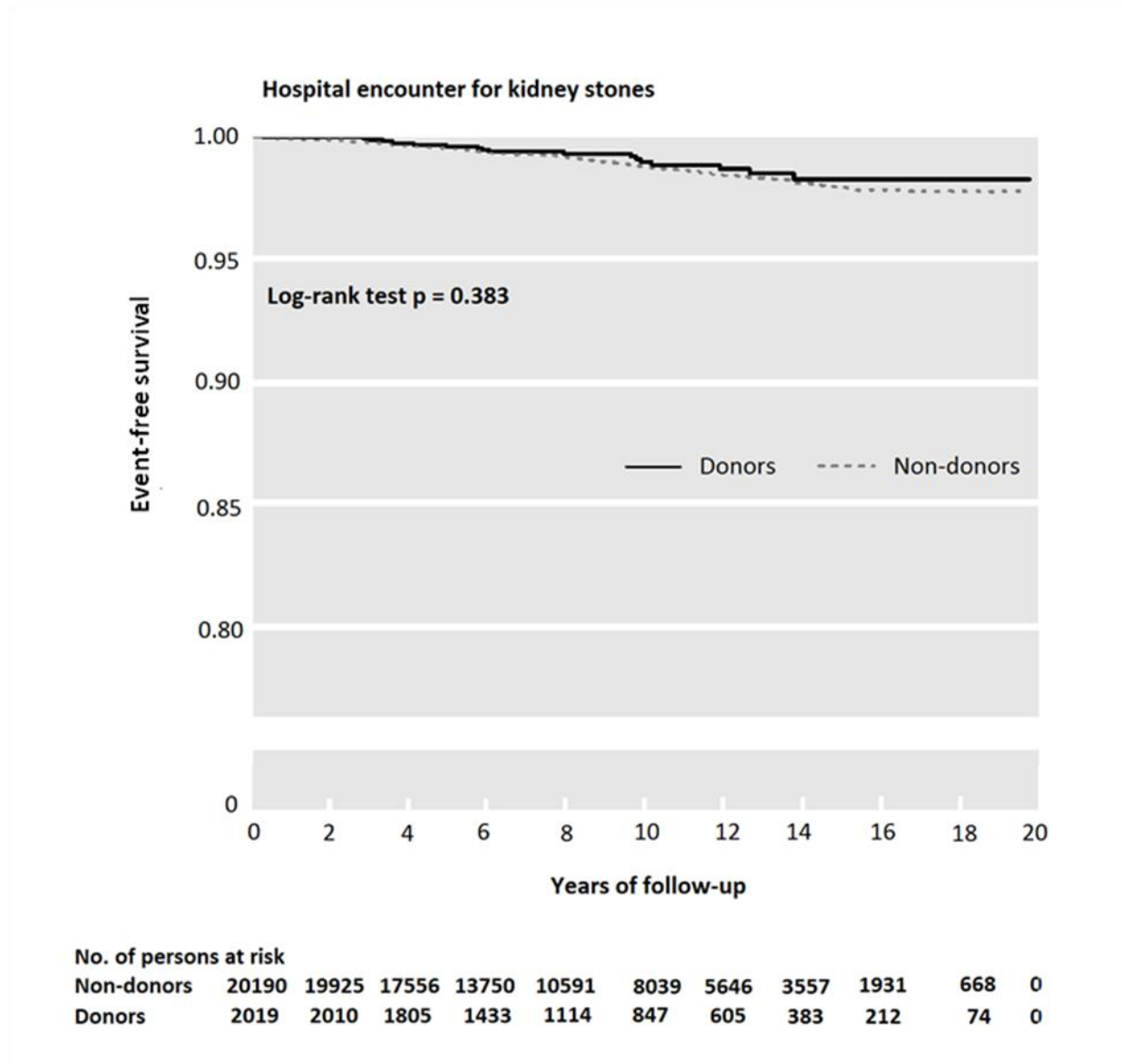
†p-values=0.58 and 0.27, respectively.

Figure 3a. Kaplan-Meier curve of time to first kidney stone with surgical intervention.



No. of persons at risk		0	2	4	6	8	10	12	14	16	18	20
Non-donors	20190	19942	17582	13788	10627	8076	5681	3588	1954	675	0	0
Donors	2019	2011	1807	1435	1117	849	606	384	213	74	0	0

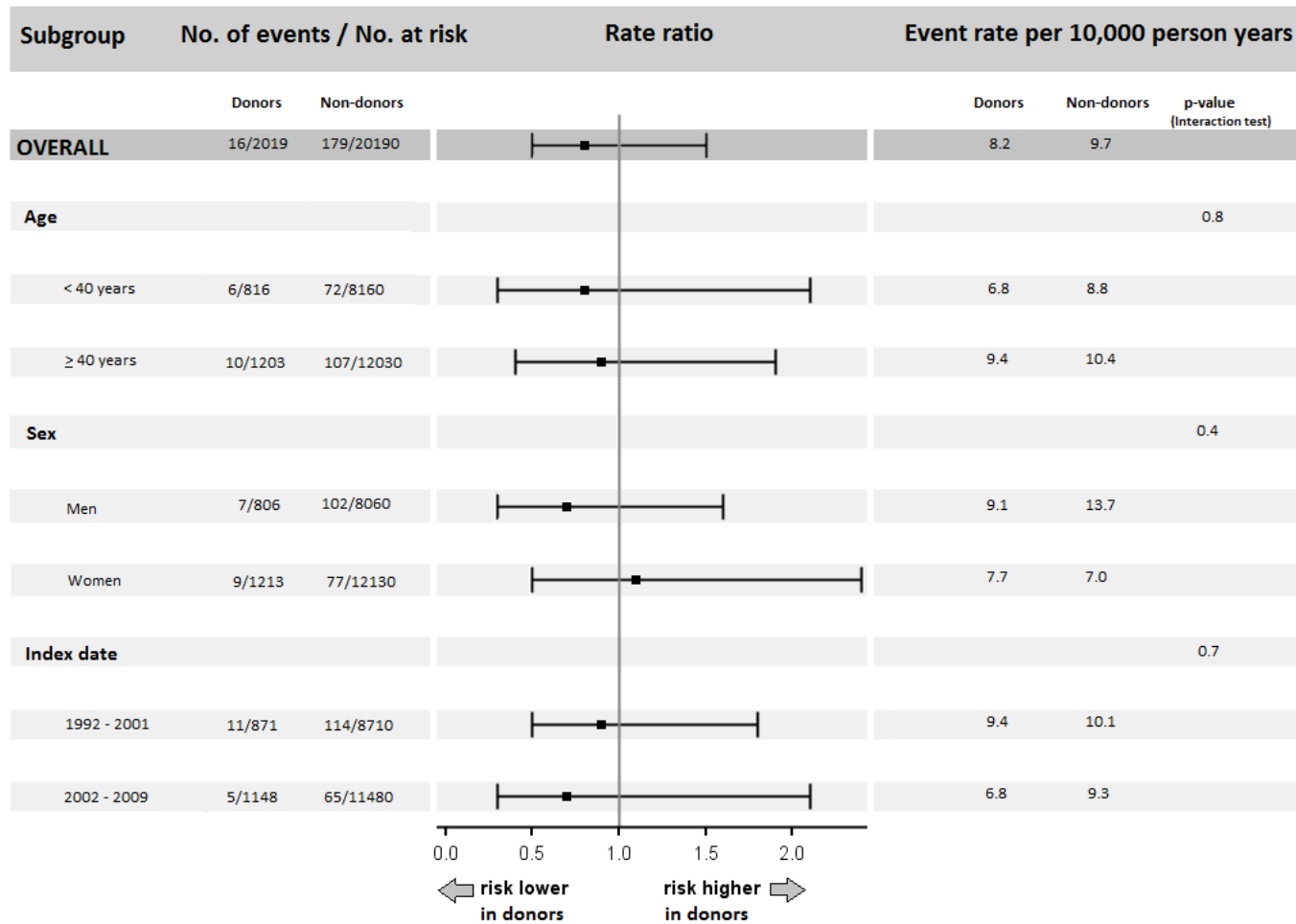
Figure 3b. Kaplan-Meier curve of time to first hospital encounter for a kidney stone.



Subgroup analyses are shown in Figures 4a and 4b. Older age at study enrolment, sex, and earlier date of enrolment (longer follow-up) did not influence the association between living kidney donation and risk of kidney stones with surgical intervention (p value for interaction ranged from 0.40 – 0.80). Subgroup results were similar for the secondary outcome of hospital encounters of kidney stones, with one exception: the rate ratio between living donation and outcome was lower in men compared to women. In the subgroup of men donors had a lower (not higher) risk of the outcome than non-donors.

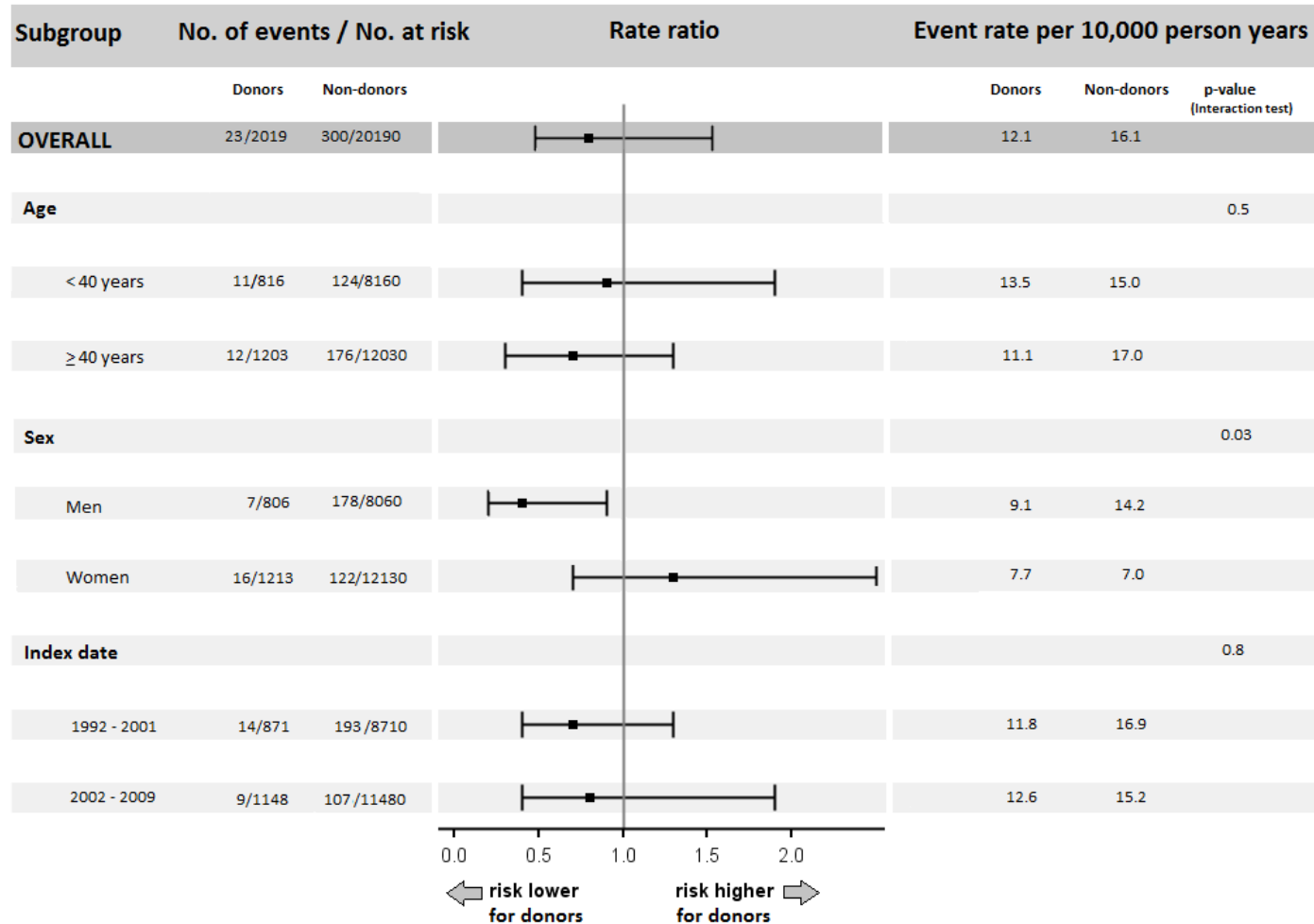
When donors and non-donors were examined separately, the 95% confidence intervals of risk factor rate ratios were more precise in non-donors (expected as there were 10 times as many non-donors as donors). In donors, no significant associations were observed between various risk factors (age, sex, rural residence, income quintile, and year of index date) and the primary or secondary outcomes (Table 4). In non-donors, older age and male sex were associated with an increased risk of kidney stones with surgical intervention and hospital encounters for kidney stones.

Figure 4a. Influence of age, sex, & index date (length of follow-up) on primary outcome of kidney stones with surgical intervention.



*Individuals with index date of 1992-2001 had median follow up of 13.3 years, interquartile range (IQR) 11.7 to 16.0; individuals with index date of 2002-2009 had median follow-up of 5.9 years, IQR 4.3 to 7.8.

Figure 4b. Influence of age, sex, & index date (length of follow-up) on secondary outcome of hospital encounters for kidney stones.



*Individuals with index date of 1992-2001 had median follow up of 13.3 years, interquartile range (IQR) 11.7 to 16.0; individuals with index date of 2002-2009 had median follow-up of 5.9 years, IQR 4.3 to 7.8.

Table 4. Risk factors for kidney stones in donor and non-donors when each group was analyzed separately.

	Donors	Non-donors
Kidney stones with surgical intervention		
Older age (per 5 years)	1.15 (0.90 – 1.50)	1.12 (1.02 – 1.23)
Women (vs. men)	0.92 (0.30 – 2.85)	0.49 (0.34 – 0.73)
Rural residence (vs. urban residence)	2.49 (0.29 – 21.65)	1.04 (0.59 – 1.84)
Higher income quintile	0.87 (0.59 – 1.29)	0.95 (0.82 – 1.10)
More recent year of index date	0.97 (0.85 – 1.11)	0.99 (0.94 – 1.04)
Hospital encounters for kidney stones		
Older age (per 5 years)	1.02 (0.82 – 1.26)	1.08 (1.01 – 1.15)
Women (vs. men)	1.60 (0.56 – 4.58)	0.46 (0.34 – 0.61)
Rural residence (vs. urban residence)	1.74 (0.33 – 9.06)	1.08 (0.70 – 1.67)
Higher income quintile	1.00 (0.70 – 1.43)	0.92 (0.82 – 1.02)
More recent year of index date	1.01 (0.91 – 1.13)	0.98 (0.95 – 1.02)

Separate negative binomial models were created for donors and non-donors. Presented are the rate ratios and 95% confidence intervals.

Chapter 6: Discussion

6.1 Overview of findings

We hypothesized that a donor with one kidney might receive surgical intervention for a stone more frequently than a non-donor with two kidneys presenting with a stone. Similarly, we expected that donors with stones might be more likely to present to hospital. However, our findings do not support these hypotheses. In this study, we determined that the rates of 1) kidney stones with surgical intervention, and 2) hospital encounters for kidney stones, were not significantly different between donors and non-donors. The majority of living kidney donors (99.3%) did not experience a kidney stone intervention or hospital encounter over a median follow-up of 8.8 years (maximum follow-up 19.7 years). There was also no evidence that donation increased the risk of either kidney stone event when examined in subgroups defined by age, sex, or index date (length of follow-up). The Kaplan-Meier curves after 10 years of follow-up did not suggest any higher risk of stone events in donors compared to non-donors.

When non-donors were examined using a separate negative binomial model, both older age, and male sex were associated with an increased risk of kidney stones with surgical intervention, and hospitalization for kidney stones. This finding is consistent with previous literature, which has established age and male sex as known risk factors for kidney stones (29, 31). We did not find this to be the case within the donor cohort when analyzed separately, though we did expect these risk factors to behave similarly.

However, this can be explained by the limited number of kidney stone events within the donor cohort, preventing us from reliably assessing these risk factors in the separate analysis.

Overall, these findings are reassuring towards the practice of living kidney donation. It demonstrates the effectiveness of the thorough screening that donors undergo prior to donation.

6.2 Strengths

Our study has a number of strengths. To our knowledge this is the first study to report on a donor's long-term risk of kidney stones after living kidney donation. The universal healthcare benefits available to all Ontario residents allowed us to efficiently study all living donation activity in the largest province of Canada, minimizing both information and selection biases. We ensured the accuracy of donor data captured in the Trillium Gift of Life database through the manual review of over 2000 pre-donation medical charts at the five major transplant centres in Ontario. We addressed potential confounders by matching donors and non-donors on risk factors associated with kidney stone events such as older age and male sex (29, 31). Loss to follow-up, which is a concern in most long-term donor studies, was minimal in our study with less than 7% censored in follow-up at the time of emigration from the province.

6.3 Limitations

Our study does have some limitations. The retrospective nature of the study prevented us from controlling the assessment of the exposure and outcome, meaning we relied on administrative data collected for non-research purposes. The use of administrative data limited us with regards to: the types of data and variables that were available to us, how we ascertained our outcomes, and our inclusion and exclusion criteria for the selection of the donor and healthy non-donor cohorts.

Our administrative data sources also prevented us from addressing some potential confounders. We had no baseline or follow-up information in our data sources on dietary risk factors for stones such as water intake, salt consumption and calcium supplementation (2, 63). We did not take other known risk factors for kidney stones including race and Body Mass Index (BMI) into account because they could not be accurately ascertained using our data sources. However, given that 75% of the Ontario population is Caucasian, we expect our results to generalize well to Caucasian donors but not to other races. Previous literature has observed a higher prevalence of kidney stones in American Caucasians when compared to African Americans and Hispanics in the United States (64). Additionally, given Ontario's relatively uniform climate, the observed rates would not be comparable to regions within the kidney stone belt which are typically higher because of elevated temperatures.

Unlike the donors, most non-donors did not have routine imaging to rule out the presence of baseline asymptomatic kidney stones. Residual confounding, which is inherent to any observational study, may affect the association between living kidney donation and the outcome of interest seen in our study.

We relied on clinical expertise and knowledge of billing practices to define our outcomes, as the codes were either not validated or partially validated. There are no reliable codes to detect kidney stones that do not present to hospital attention. Also, codes to detect kidney stones presenting to hospital are insensitive and underestimate the true incidence of the event.(65) However, this is not the case for kidney stones requiring surgical intervention and we do not anticipate coding inaccuracies in stones presenting to hospital were differential between donors and non-donors (i.e. estimates of relative risk are valid).

6.4 Future Directions

While these findings are reassuring for the practice of living kidney donation, it is possible that the risk may take longer to manifest. In order to fully understand the long-term risk of kidney stones with surgical intervention in living kidney donors, we will continue to follow our cohort in order to obtain several additional decades of follow-up.

While living kidney donation is the preferred treatment option for individuals living with renal failure, the supply still does not meet the growing demand for organs. In order to address this discrepancy, efforts are being made to increase the number of living donations through the acceptance of expanded criteria donors. Expanded criteria donors are donors who may not meet the strict donation criteria, but are deemed sufficiently healthy enough to donate. Having a history of kidney stones was once a contraindication to becoming a living kidney donor. However, this criterion has become more relaxed in recent years. Our study does not provide evidence regarding the safety of this practice, as we assessed the de novo formation of kidney stones. Additionally these results should not be used to justify expansion of donor eligibility to those with risk factors for stones, such as obesity or a prior history of stones (3, 31, 66). Rather, this is only the first step in understanding the risk to expanded criteria donors. We have simply established that the baseline risk of kidney stone events in donors selected using the strict standard criteria is no different than in healthy non-donors. Further studies, following donors with a history of kidney stones, are needed to establish whether it is safe for such individuals to become donors.

In addition, future studies can assess the risk of any kidney stone event, not simply those requiring hospital encounters or surgical intervention. This would first require the validation of the ICD-9 and ICD-10 codes for diagnosis of kidney stones in order to accurately assess the risk of these events using administrative healthcare databases. However, a prospective cohort study would be the optimal method to ascertain a living kidney donor's risk of developing kidney stones post-donation. This would allow additional important confounders like diet, race, BMI, and family history of kidney stones to be addressed (32, 66, 67). Imaging could be performed on participants to identify the formation of asymptomatic kidney stones as well.

6.5 Conclusion

Through this study we have determined that the risks of 1) kidney stones with surgical intervention, and 2) hospital encounters for kidney stones are no different between living kidney donors and matched healthy non-donors. As we continue to follow this study cohort, these interim findings are reassuring to the safety of the practice of living kidney donation.

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Appendix A: Checklist of recommendations for reporting of observational studies using the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

	Item No	Recommendation	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	introduction
Methods			
Study design	4	Present key elements of study design early in the paper	methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	methods
		(b) For matched studies, give matching criteria and number of exposed and unexposed	methods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	methods
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	methods
Bias	9	Describe any efforts to address potential sources of bias	methods
Study size	10	Explain how the study size was arrived at	methods

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	methods
		(b) Describe any methods used to examine subgroups and interactions	methods
		(c) Explain how missing data were addressed	not applicable
		(d) If applicable, explain how loss to follow-up was addressed	not applicable
		(e) Describe any sensitivity analyses	not applicable
(Continued on next page)			
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods, results
		(b) Give reasons for non-participation at each stage	methods
		(c) Consider use of a flow diagram	methods
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	table 1
		(b) Indicate number of participants with missing data for each variable of interest	not applicable
		(c) Summarise follow-up time (e.g. average and total amount)	table 2
Outcome data	15	Report numbers of outcome events or summary measures over time	results, table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	results, table 2
		(b) Report category boundaries when continuous variables were categorized	table 1

		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	not applicable
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Results, table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	acknowledgements


Appendix B: Kidney stone codes

KIDNEY STONE WITH SURGICAL INTERVENTION		
OHIP fee codes	CCI	CCP
Z630 (Extracorporeal shock wave lithotripsy)	<u>Stone Destruction</u> 1pe59 (renal pelvic, ureteropelvic junction)	67.03 (percutaneous nephrostomy without fragmentation)
E773 (Stent with stone)		
Z629 (perinephrium percutaneous nephrostomy)	1pg59 (ureter, ureterovesical junction)	67.04 (percutaneous nephrostomy with fragmentation)
Z623 (Kidney, perinephrium insertion of stent)	1pm59 (urinary stoma, cystomy, nephrostomy, ureterostomy)	
J046 (Diagnostic radiology, percutaneous nephrostomy)		68.95 (ureteroscopy)
Z624 (Kidney perinephrium dilation of tract)	1pv59 (surgically created urinary tract)	71.96 (ultrasonic stone fragmentation)
Z627 (Kidney-removal of renal calculi)		
E759 (Disintegrated by US. add to removal renal calculi)	<u>Stone Extraction</u> 1pe57 (renal pelvic, ureteropelvic junction)	
E772 (Percut rem. staghorn calc. renal pelvis, add)	1pg57 (ureter, ureterovesical junction)	
Z628 (Ureteroscopy/cystoscopy above intramural ureter)		
E760 (Ureter-removal of stone add cysto & ureteroscopy)	1pm57 (urinary stoma, cystomy, nephrostomy, ureterostomy)	
E761 (Ureter-if disintegrat.by US add to cysto & ureterosc.)		
Z627 (Kidney-removal of renal calculi)	1pv57 (surgically created urinary tract)	
S430 (Kidney-litholapaxy-staghorn calculus,incl. X-ray)		
S405 (Nephrolithotomy)		
S408 (Pyelolithotomy)		

<p>S445 (ureterotomy removal of calculus upper 2/3)</p> <p>S446 (ureterotomy removal of calculus lower 1/3)</p>		
NON-SURGICAL HOSPITAL ENCOUNTERS FOR KIDNEY STONES		
<p>ICD-9: 592, 592.0, 592.1, 592.9</p> <p>ICD-10: N20</p>		




CCI: Canadian Classification of Health Interventions; CCP: Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures

Appendix C: Data Creation Plan

Risk of kidney stones with surgical intervention in living kidney donors	
Study number	2013 0906 010 000
Research program	Kidney, Dialysis, Transplantation (KDT)
Contacts	Sonia Thomas Anjie Huang Amit Garg Ngan Lam Danielle Nash Blayne Welk Ramesh Prasad Krista Lentine
Updates by	Sonia Thomas
PIA approved?	Yes
DCP update history	Version 1: October 29, 2012 (ST) Version 2: November 13, 2012 (ST, after meeting with AG) Version 3: November 16, 2012 (ST) Version 4: November 19, 2012 (after call with AH, AG) Version 5: November 28, 2012 (ST) Version 6: December 17, 2012 (ST)
Research question	To examine the long-term risk of kidney stones with intervention following living kidney donation. The study will include all living kidney donors in the province of Ontario who donated a kidney between July 1, 1992 and March 31, 2009. We will compare the risk of kidney stones with intervention in LKD to healthy non-donor controls.
Study design	Retrospective cohort study
List of datasets used	<ol style="list-style-type: none"> 1. Trillium Gift of Life Network (TGLN) [July 1992 – March 2009]  TGLN data dictionary.doc 2. Ontario Diabetes Database (ODD) [July 1991 – March 2009] 3. Ontario Hypertension Database (OHD) [July 1991 – March 2009] 4. CIHI-DAD and CIHI-SDS [July 1991 – March 2012] <u>Source</u> <input checked="" type="checkbox"/> All

	<p><u>Institution types</u> <input checked="" type="checkbox"/> All</p> <p>5. NACRS [July 2000 – March 2012] <u>Source</u> <input checked="" type="checkbox"/> ED <u>Include planned visits</u> <input checked="" type="checkbox"/> Yes</p> <p>6. Ontario Health Insurance Plan (OHIP) [July 1991 – March 2012] <u>Code Types</u> <input checked="" type="checkbox"/> Feecodes</p> <p>[see Appendices A, B, C, D, E embedded in exclusion criteria section for codes]</p> <p>7. Registered Persons Database (RPDB) [July 1991 – March 2012]</p>
Defining the cohort	
Index date	Date of kidney donation in TGLN (LIVING_DONORS_ENC.TX_DATE)
Inclusion criteria	<p><i>Retrospective cohort study comparing 2 groups:</i></p> <p><u>Exposed:</u> Individuals who have undergone living kidney donation and meet the following requirements:</p> <ul style="list-style-type: none"> - Donated between July 1, 1992 and March 31, 2009 with a valid IKN (LIVING_DONORS_ENC.valikn = 'V') - Donation at a study eligible transplant center (LIVING_DONORS_ENC.TX_HOSP_OTTAWA HOSPITAL GENERAL CAMPUS; OTTAWA HOSPITAL CIVIC CAMPUS; ST JOSEPH'S HEALTHCARE SYSTEM – HAMILTON, ST MICHAEL'S HOSPITAL – [Toronto], TORONTO GENERAL HOSPITAL, UNIVERSITY HOSPITAL – [London]). In other words the hospitals excluded from the analysis are: KINGSTON GENERAL HOSPITAL, THE HOSPITAL FOR SICK CHILDREN) <p><u>Non-exposed:</u> Individuals from the general population matched to the exposed group (Medically eligible to donate a kidney, see “Exclusion Criteria”)</p>
Cohort size	Anticipate approximately 2000 living kidney donors and 20,000 matched non-donor controls (1:10 match ratio)
Exclusion criteria	
Exclusion criteria for DONORS (in order) (See Table 1)	<p><i>Data cleaning steps</i></p> <p><u>Exclude if:</u></p> <p>1) Missing DOB in RPDB (expect this will be close to 0)</p>

- 2) Missing gender in RPDB (expect this will be close to 0)
 - 3) Listed as living kidney donor more than once in TGLN dataset
 - 4) Donor id = recip id or don_ikn=recip_ikn;
this is either in i) Trillium sources OR ii) when linked to RPDB (note: appreciate this will remove the rare donor who develops ESRD and then requires a transplant; guarding against possibility out-of-province donor, etc. received services under recipient OHIP number).
 - 5) ≥ 1 dialysis code from Appendix A (CIHI or OHIP code) from July 1st, 1991 to 4 months after index date (rationale: this is being done to exclude any recipient who has been miscoded as a living kidney donor; appreciate this will remove any donor who required dialysis within 4 months of donation – a very rare event).
-
- Appendix A - dialysis codes.txt
- 6) Missing date of nephrectomy (missing LIVING_DONORS_ENC.TX_DATE; expect this to be 0 as this was used to construct dataset)
 - 7) Date of death in RPDB is before index date
 - 8) Date of death in RPDB < 4 months AFTER index date (rationale: this is being done to exclude any deceased kidney donor who has been miscoded as a living kidney donor. Appreciate this exclusion will result in “immortal time” for anyone left in the analysis (i.e. no chance of death between index date and four months after donation; rate of death is so exceedingly rare this is not an issue).
 - 9) Date of Last Contact (DOLC) is < 4 months AFTER index date (rationale: this is being done to exclude any out of province living kidney donors; by convention it would also result in the exclusion of any deaths in 4 months after donation, but this exclusion is being applied after the death exclusion above. By applying this exclusion we are restricting the analysis to those individuals who have ≥ 1 Ontario health care contact ≥ 4 months after donation).
 - 10) Age <18 at index date
 - 11) Age > 75 at index date
 - 12) Pregnant at the time of index date (defined by evidence of ≥ 1 birth code, in 2 months prior to index date to 6 months after index date; birth codes presented in Appendix B)

	<div style="text-align: center;">  Appendix B - birth codes.txt </div> <p>13) Evidence of kidney stones with surgical intervention prior to the index date and 7 days after index date (codes presented in Appendix D)</p> <div style="text-align: center;">  Appendix D - kidney stone with surgical int </div> <p>14) Evidence of other hospital encounters for kidney stones prior to the index date and 7 days after index date (codes presented in Appendix E)</p> <div style="text-align: center;">  Appendix E - kidney stone diagnostic code </div>
<p>Exclusion criteria for CONTROLS (in order) (See Table 1a and 1b)</p>	<p>See <i>Appendix C</i> for control exclusion criteria codes, and “Outline of Analysis Plan” section for description of method to select control subjects.</p> <p><i>Data cleaning steps</i></p> <p><u>Exclude if:</u></p> <ol style="list-style-type: none"> 1) Invalid IKN 2) Missing gender in RPDB 3) Missing date of birth in RPDB 4) Date of death in RPDB before July 12, 1992 (1st date of transplant in TGLN database) 5) Age <18 on March 31, 2009 6) Age >75 on January 1, 1992 <p>*ASSIGN INDEX DATE*</p> <p><u>Exclude if any of the following:</u> (from July 1991, up to but not including the index date)</p> <ol style="list-style-type: none"> 7) Date of death in RPDB is before randomly assigned index date 8) Date of death in RPDB is less than 4 months AFTER index date (rationale: same exclusion as kidney donors). 9) Age <18 on index date 10) Age >75 on index date 11) Date of Last Contact (DOLC) is less than 4 months AFTER index date (rationale: same exclusion as kidney donors). 12) Zero or > 4 physician visits in 2 years prior to index date (No matter how many physicians an individual sees on a given day, or the amount of codes that a physician bills for on a given day, this is still only counted as one visit. Physician visits defined by spec variable in the OHIP data – any spec that corresponds to a ‘physician’ (column C, physician “yes” in excel sheet attached).



specialty codes.xls

Exclude if any of the following (from July 1991, up to and including the index date):

- 13) Diabetes (if date of onset of condition in ODD is before or equal to index date)
- 14) Hypertension (if date of onset of condition in OHD is before or equal to index date)
- 15) Cancer
- 16) Cardiovascular disease
- 17) Any prior cardiovascular procedure
- 18) Pulmonary disease
- 19) Liver disease
- 20) Systemic lupus erythematosus
- 21) Rheumatoid arthritis
- 22) HIV
- 23) Listed in TGLN as a kidney donor or recipient (control_ikn=don_ikn OR receipt_ikn from July 1991 to index date)
- 24) Genitourinary disease
- 25) Nephrectomy
- 26) Any prior renal biopsy
- 27) Exclude if ≥ 1 dialysis code from Appendix A (CIHI or OHIP code) from July 1st, 1991 to 4 months after index date



Appendix A - dialysis codes.txt

28) Exclude if have ever seen a nephrologist in consultation:

A consultation is identified by OHIP code A135, billed by a nephrologist on either an outpatient or inpatient visit, where a nephrologist is defined as a physician who had both a) **and** b) anytime during the study accrual window [window is July 1,1991 to March 31,2009].

- a. billed an **A135 code** ≥ 50 times during the accrual period (can be same patient)
- b. billed renal dialysis code ≥ 50 times during accrual period [any **OHIP fee code** in Appendix A under category “Hemodialysis”, “Peritoneal Dialysis” or “Other”, but not “Continuous Renal Replacement Therapy”; note: can be same patient]



Appendix A - dialysis codes.txt

Ensures that controls are extremely healthy in regards to renal function, specifically.

Exclude if any of the following:

29) Pregnant at the time of index date (defined by evidence of ≥ 1 birth code, in 2 months prior to index date to 6 months after index date; birth codes presented in Appendix B)



Appendix B - birth codes.txt

30) Gestational diabetes prior to index date

31) Pre-eclampsia prior to index date



Appendix C - control exclusion criteria.txt

32) Evidence of kidney stones with surgical intervention prior to the index date and 7 days after index date:



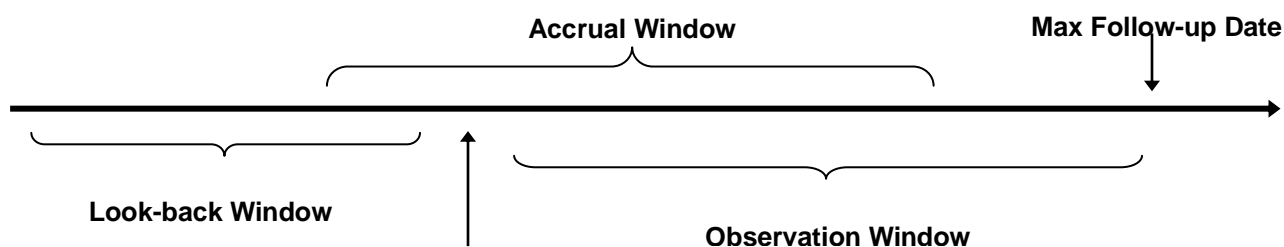
Appendix D - kidney stone with surgical int

33) Evidence of other hospital encounter for kidney stones prior to index date and 7 days after index date



Appendix E - kidney stone diagnostic code

Time frame definitions




Index date	Donors: Date of donation in TGLN (TX_DATE) Controls: Matched to donors (see “Matching Variables” section)
Accrual window	July 1, 1992 to March 31, 2009
Look-back window	Variable look-back window to July 1991 for all subjects to ascertain exclusion criteria
Max follow-up	March 31, 2012 for all subjects
Observation	Observation window terminates when the first of the following censoring






window termination	<p>events occurs:</p> <ol style="list-style-type: none"> 1. March 31, 2012 (end of the study) 2. Emigration: For patients who haven't died prior to end of study (March 31, 2012), if time between Date of Last Contact (DOLC, ICES variable) and end of study (March 31, 2012) is >3 years, censor at 1 year after DOLC 3. Death
---------------------------	---

Variable definitions

Exposure	Living kidney donation, defined by entry in TGLN as a donor.
-----------------	--

<p>Baseline Characteristics (see Table 2a and 2b)</p>	<p>Observed at time of index date: Record mean, median, categorical number (%) for the following variables in Table 2a:</p> <ol style="list-style-type: none"> 1. Year of index date (report as calendar year) 2. Age at index date 3. Gender (Female, N (%)) 4. Income quintile, for missing impute as 3 (median income) for purposes of matching 5. Residency status, rural or urban (Report only categorical number, (%)); for 'missing', code this as urban <p>Look back 1 year from index date:</p> <ol style="list-style-type: none"> 6. Health care use [Physicians and non-physicians should be defined using OHIP billing – spec data] <u>Non-physician health care professional visits</u> (defined below; if multiple codes on a single day only count once (%). <i>No difference is expected in the numbers for donors and controls.</i> <u>Physician visits</u> (divided into categories, any spec that corresponds to a 'physician' (column C, physician "yes" in previously attached excel sheet; if more than one physician visit on a single day only count once) by the number of visits) (%). Donors are expected to have more physician visits than controls. <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>Code</th> <th>Non-Physician Visits (definition for current study)</th> </tr> </thead> <tbody> <tr> <td>49</td> <td>DENTAL SURGERY (dentistry)</td> </tr> <tr> <td>50</td> <td>ORAL SURGERY (dentistry)</td> </tr> <tr> <td>51</td> <td>ORTHODONTICS (dentistry)</td> </tr> <tr> <td>53</td> <td>PERIODONTICS (dentistry)</td> </tr> <tr> <td>54</td> <td>ORAL PATHOLOGY (dentistry)</td> </tr> <tr> <td>55</td> <td>ENDODONTICS (dentistry)</td> </tr> <tr> <td>56</td> <td>OPTOMETRISTS</td> </tr> <tr> <td>58</td> <td>CHIROPODISTS</td> </tr> </tbody> </table>	Code	Non-Physician Visits (definition for current study)	49	DENTAL SURGERY (dentistry)	50	ORAL SURGERY (dentistry)	51	ORTHODONTICS (dentistry)	53	PERIODONTICS (dentistry)	54	ORAL PATHOLOGY (dentistry)	55	ENDODONTICS (dentistry)	56	OPTOMETRISTS	58	CHIROPODISTS
Code	Non-Physician Visits (definition for current study)																		
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55	ENDODONTICS (dentistry)																		
56	OPTOMETRISTS																		
58	CHIROPODISTS																		

	<table border="1" data-bbox="607 191 1446 396"> <tr> <td>59</td> <td>CHIROPRACTOR</td> </tr> <tr> <td>70</td> <td>ORAL RADIOLOGY (dentistry)</td> </tr> <tr> <td>71</td> <td>PROSTHODONTICS (dentistry)</td> </tr> <tr> <td>80</td> <td>PHYSIOTHERAPY (HOME)</td> </tr> <tr> <td>81</td> <td>PHYSIOTHERAPY (HOME/OFFICE)</td> </tr> </table> <p>Observed at end of follow-up:</p> <p>7. Age at last follow-up</p> <p>Donor characteristics only (Table 2b: These data come from TGLN database):</p> <p>8. Donor relationship to recipient (<i>TGLN variable Relationship</i>)</p> <p>9. Method of nephrectomy (<i>TGLN variable D_SURG_TYPE</i>)</p>	59	CHIROPRACTOR	70	ORAL RADIOLOGY (dentistry)	71	PROSTHODONTICS (dentistry)	80	PHYSIOTHERAPY (HOME)	81	PHYSIOTHERAPY (HOME/OFFICE)
59	CHIROPRACTOR										
70	ORAL RADIOLOGY (dentistry)										
71	PROSTHODONTICS (dentistry)										
80	PHYSIOTHERAPY (HOME)										
81	PHYSIOTHERAPY (HOME/OFFICE)										
<p>Matching Variables</p>	<p>Match 10 non-donor controls to each donor based on the following five (5) variables, in order:</p> <ol style="list-style-type: none"> 1. Index date (± 6 months) 2. Gender 3. Age (± 2 years) 4. Income quintile (same quintile; if ‘missing’, value is ‘3’) 5. Residential status (same status, rural or urban; if ‘missing’, code as ‘urban’) <p>NB: If not possible to find 10 controls who meet all criteria, choose the maximum number of controls who do meet all the criteria. Report number of controls achieved in Table 3.</p> <p>Assign a unique “Group ID” value to each matched group (1 donor, 10 controls)</p>										
<p>Primary outcome</p>	<p>Evidence of kidney stone with surgical intervention following the index date until March 31, 2012 (see Appendix D for codes, use CIHI-DAD, CIHI-SDS, NACRS-ED).</p>  <p>Appendix D- kidney stone with surgical int</p> <p>Note: Participants can have more than one occurrence of a kidney stone with surgical intervention during follow-up, but such interventions must be separated by at least 90 days to ensure it is for a new stone or reoccurrence of a stone.</p>										

<p>Secondary outcomes</p>	<p>1. Evidence of hospital encounter for kidney stones following the index date until March 31, 2012 (Appendix D and E together, use CIHI-DAD, CIHI-SDS and NACRS-ED)</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  Appendix D - kidney stone with surgical int </div> <div style="text-align: center;">  Appendix E - kidney stone diagnostic code </div> </div> <p>2. Time to first kidney stone with surgical intervention following the index date until March 31, 2012</p> <div style="text-align: center;">  Appendix D - kidney stone with surgical int </div> <p>3. Time to first hospital encounter for a kidney stone following the index date until March 31, 2012</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  Appendix D - kidney stone with surgical int </div> <div style="text-align: center;">  Appendix E - kidney stone diagnostic code </div> </div>
<p>Outline of analysis plan</p>	
<p>Steps to Identify Controls Matched to Donors</p>	<ol style="list-style-type: none"> 1. Restrict controls to individuals in the RPDB who have a valid IKN, date of birth, gender and meet first step of inclusion criteria. 2. Randomly assign an index date (July 1, 1992 – March 31, 2009) to all eligible individuals in the RPDB. Assign these index dates to match the distribution in the LKD cohort (TGLN dataset) based on the minimum, maximum, 25th, 50th and 75th percentile of the index dates in the LKD cohort. NB: Match the index date distribution after applying inclusion and exclusion criteria to the LKD cohort. 3. Apply exclusion criteria to individuals from the RPDB to determine eligible controls. 4. Match 10 controls to each donor (see “Matching Variables” section). 5. Each individual from the RPDB may serve as a control for no more than one donor. <p>Record level of matching achieved in Table 3.</p>
<p>Exploratory and</p>	<p>- Apply exclusion criteria and identify number of donors and controls lost (see Tables 1a and 1b).</p>


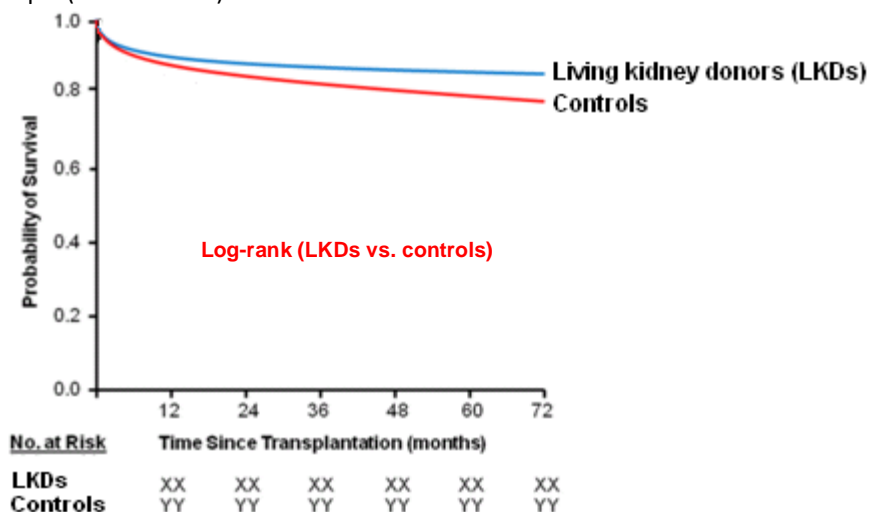
<p>Descriptive Analyses</p>	<ul style="list-style-type: none"> - Provide the frequencies and descriptive characteristics for all baseline characteristics for both donors and controls (Table 2a and 2b). ▪ Report standardized differences; to calculate standardized difference see below <div style="display: flex; align-items: flex-start;"> <div style="margin-right: 20px;">  <p>Statistics in Medicine (PS Matching diagnosis)</p> </div> <div> <p>3.2. Standardized differences for comparing means and prevalences between groups</p> <p>For continuous variables, the standardized difference is defined as</p> $d = \frac{(\bar{x}_{\text{treatment}} - \bar{x}_{\text{control}})}{\sqrt{\frac{s_{\text{treatment}}^2 + s_{\text{control}}^2}{2}}} \quad (1)$ <p>where $\bar{x}_{\text{treatment}}$ and \bar{x}_{control} denote the sample mean of the covariate in treated and untreated subjects, respectively, while $s_{\text{treatment}}^2$ and s_{control}^2 denote the sample variance of the covariate in treated and untreated subjects, respectively. For dichotomous variables, the standardized difference is defined as</p> $d = \frac{(\hat{p}_{\text{treatment}} - \hat{p}_{\text{control}})}{\sqrt{\frac{\hat{p}_{\text{treatment}}(1 - \hat{p}_{\text{treatment}}) + \hat{p}_{\text{control}}(1 - \hat{p}_{\text{control}})}{2}}} \quad (2)$ </div> </div> <ul style="list-style-type: none"> ▪ Report % of missing data for each variable (should be no missing data), impute value of “3” for missing income (matching characteristic), impute ‘urban’ value for missing urban/rural and discuss with team any other values with high level of missingness. - Report length of follow-up (max, min, mean, median and total person years) and distribution of censoring events (categorical number) in Table 4. As well report the number of persons who reached a maximal given year of follow-up (Table 5). - Report distribution of primary outcome events (categorical number) in Table 6.
<p>Primary analysis</p>	<ul style="list-style-type: none"> - Compare group differences using a negative binomial regression model to account for sources of statistical non-independence (multiple kidney stone events in a given individual, as well as the correlational structure within each matched set) - Report results in Table 7.
<p>Secondary analysis</p>	<ul style="list-style-type: none"> - Plot Kaplan-Meier (K-M) survival graphs for donors and controls (see Table 9a and 9b) ▪ Compare group differences using two-sided log-rank test. This test needs to account for the ‘correlation’ within group_id (see Figure 1 below). In this analysis patients are censored for death, emigration and end of the follow-up period (March 31, 2012). ▪ To account for the correlation, the log rank test is stratified by the match (group_id). This means the log rank statistic is calculated within matched sets (group_id), and then is combined to get an overall statistic. It is NOT weighted by the number of matched controls per matched donor (the way Cox proportional hazard regression would be in this situation).

Figure 1. K-M survival curves for primary outcome time-to-first event (kidney stone with surgical intervention) analysis

Patients censored for death, emigration and end of the follow-up period (March 31, 2012). Survival here refers to event free survival.

Example (fictional data):



Subgroup analyses

Perform subgroup analyses for primary outcome only using interaction terms. Report results in **Table 8**.

***Note:** Organize the subgroup according to the **donor characteristic with their associated matched controls**, and report the associative measure and upper and lower confidence interval to 3 decimal points. We will then compute each interaction term separately with summary measures using the method of Bland and Altman.


- Gender
- Age, <40 vs. ≥ 40 at index date
- Index date, from July 1992 to December 2001 vs. January 2002 to March 2009

- Sets defined by the ‘donor characteristic’; non-donors in set follow donors.
- Produce estimates of point estimate and 95% confidence interval for each stratum.
- We will calculate test of interaction based on the output of point estimate, lower CI, and upper CI (Bland and Altman technique, embedded article below, double click icon to access).



interaction altman
and bland bmj article.

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Curriculum Vitae

Name: Sonia Mary Thomas

Post-secondary Education and Degrees: The University of Western Ontario
London, Ontario, Canada
2006-2011 B.Sc. Physiology & Psychology (Double Major)

The University of Western Ontario
London, Ontario, Canada
2011 - 2013 M.Sc. Epidemiology & Biostatistics

Honours and Awards: Western Graduate Research Scholarship
2011 – 2013

Health Innovation Challenge (health policy, group category)
2012

Related Work Experience Research Assistant
Kidney Clinical Research Unit
2007-2011

Publications:

Thomas SM, Lam NN, Welk BK, Nguan C, Huang A, Nash DM, Prasad GVR, Knoll GA, Koval JJ, Lentine KL, Kim SJ, Lok CE, Garg AX. Risk of kidney stones with surgical intervention in living kidney donors. *American Journal of Transplantation*, 2013 Nov; 13(11): 2935-2944.

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