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Financial Costs Incurred by Living Kidney Donors: Findings from a Canadian Multi-centre Prospective Cohort Study

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Abstract

This prospective cohort study across 12 Canadian transplant centres evaluated the costs incurred by 912 living kidney donors. Expenses and resources were captured to 3-months post-donation, and micro-costing was used to appraise the costs incurred by donors. Living kidney donors incurred average total costs of $4790, and direct and indirect costs of $2110 and $2679, respectively. 13.3% of donors incurred total costs exceeding $10,000, and 8.6% of donors incurred costs >25% of their annual household income. Costs incurred by spousal donors were not significantly different from either unrelated or closely related donors. Similarly, costs incurred by kidney paired donors were not significantly different from other donors. In multivariable analyses, living >100 km from the transplant evaluation centre and being employed were associated with higher total costs. In conclusion, many living kidney donors incur substantial costs associated with donation, and our findings can be used to improve the donation experience.

Keywords

Living kidney donation, kidney transplantation, cost analysis, prospective cohort study, micro-costing, reimbursement policy

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List of Abbreviations

LKD	=	Living Kidney Donor
ESKD	=	End-Stage Kidney Disease
GFR	=	Glomerular Filtration Rate
RRT	=	Renal Replacement Therapy
HD	=	Hemodialysis
PD	=	Peritoneal Dialysis
QALY	=	Quality Adjusted Life Years
KPD	=	Kidney Paired Donation
CI	=	Confidence Interval
CAD	=	Canadian Dollars
SD	=	Standard Deviation
KDOC	=	Kidney Donor Outcomes Cohort
USD	=	United States Dollars
LODERP	=	Living Organ Donor Expense Reimbursement Program
TGLN	=	Trillium Gift of Life Network
CCA	=	Complete-Case Analysis
MAR	=	Missing at Random
MI	=	Multiple Imputation

MICE	=	Multiple Imputation by Chained Equations
PMM	=	Predictive Mean Matching
ANOVA	=	Analysis of Variance
BC_a	=	Bias Corrected and Accelerated
GLM	=	Generalized Linear Models
AME	=	Average Marginal Effect
STROBE	=	STrengthening the Reporting of OBservational studies in Epidemiology
API	=	Application Programming Interface
OLS	=	Ordinary Least Squares
KDIGO	=	Kidney Disease: Improving Global Outcomes
LHSC	=	London Health Sciences Centre
CRF	=	Case Report Form

Chapter 1

1 Introduction

Over 40,000 Canadians live with end-stage kidney disease (ESKD), a number that has more than doubled in the last two decades.[2,3] Patients living with kidney failure have a 5-year survival rate of just 38%: comparable to rates for many advanced cancers.[4] Kidney transplantation is the preferred treatment for end-stage kidney disease and, compared to dialysis, results in increased long-term survival, improved quality of life, and reduced health care costs.[5-7] Unfortunately, supply has not met the demand; patients wait several years to receive a deceased donor kidney transplant, and 2-3% of patients die waiting each year.[8]

In response to the shortage of deceased donor kidneys, living donor kidney transplantation has emerged to fill in the gap, accounting for ~40% of kidney transplants in Canada today.[9,10] Compared to deceased donation, living kidney transplants offer ESKD patients the measurable benefits of decreased time on dialysis and better graft survival.[11,12] However, the number and rate of living donor kidney transplants has stagnated over the last decade despite growing waiting lists and the implementation of kidney paired donation programs across Canada.[9,13]

Living kidney donors incur financial costs throughout the donation process in the form of direct (travel, accommodation, parking, and medication) and indirect costs (lost income and lost productivity).[14,15] These financial costs may pose a barrier to donation for some candidates.[16] There is consensus within the transplant community that living kidney donation should be a financially neutral act and it is just that donor costs associated with transplantation be reimbursed.[17] These costs incurred by donors occur in the context of their gift improving the health of the recipient, and substantial healthcare savings in averted dialysis costs (every 100 living kidney donor transplants over a 5-year period save the healthcare system about $25 million).[2,18,19] Given this, many argue that the full extent of economic consequences to donors should be mitigated, including home and work productivity losses.[20] The burden of these out-of-pocket costs may dissuade donors; presently, socioeconomically disadvantaged patients with kidney failure are less likely to receive a living donor kidney than wealthier patients.[21] In response, Canada implemented its first programs to reimburse donors for their expenses in 2009; nevertheless, the policies that govern these programs lack evidence-based criteria and vary considerably across provinces.[22]

Many prior efforts to describe the economic costs and financial burden of living kidney donation have been limited by small sample sizes, the retrospective nature of the studies, and incomplete or inadequate cost-capturing.[15] There is an opportunity to better characterize the costs of living kidney donation from the perspective of the donor: a critical component of donor education and a truly informed consent process ensuring patients understand the economic consequences of donation. Given the gaps in the literature, there is a clear need to accurately quantify the costs of living kidney transplantation from the donor perspective in a rigorous prospective study.

1.1 Aim and Scope

The overarching aim of this research is to gain a holistic understanding of the economic costs incurred by Canadian living kidney donors. This understanding can be used to support informed consent, and to inform strategies that address the financial barriers to donation which includes an evidence-based reimbursement policy. This research uses a prospective design, with comprehensive cost-capturing instruments, and a sample size five times larger than the leading study in the field.

Chapter 2

2 Literature Review

2.1 End-Stage Kidney Disease

End-stage kidney disease (ESKD), or kidney failure, occurs as a result of reduction in renal function to a point where the kidneys are no longer able to sustain day-to-day life.[23] ESKD is the final and most severe stage of chronic kidney disease.[24,25] The 2012 Kidney Disease Improving Global Outcomes guidelines for evaluating and managing kidney disease defined ESKD as a reduction in glomerular filtration rate (GFR) to less than 15 mL/min/1.73 m^2 or dysfunction necessitating renal replacement therapy (dialysis or a kidney transplant).[25] GFR is a measure of kidney function describing the flow rate of filtered fluid through the kidney; a GFR is > 90 mL/min/1.73 m^2 is considered normal or healthy.[25,26] Diabetes as a cause of kidney disease is growing and accounts for nearly half of the primary diagnoses of Canadian patients with ESKD.[9]

In a report by the Canadian Organ Replacement Register, the burden of kidney failure is growing; the prevalence of ESKD has increased nearly 141% since 1993 and continues to climb.[3] By the end of 2013, over 40,000 Canadians were living with kidney failure, compared to less than 15,000 just 20 years earlier.[2,3] Between 1993 and 2001, the incidence of ESKD among older patients doubled, and though these rates have stabilized in recent years, there were 5431 Canadians newly diagnosed with ESKD in 2012, almost double the number diagnosed in 1993.[3]

For all patients with incident ESKD, the 5-year unadjusted survival rate is just 38%, similar to the survival rates for many advanced cancers.[4] In patients over the age of 65, the 5-year survival is only 18%.[27] In 2013, more than half of incident cases of ESKD in Canada were among patients aged 65 and older.[3] Beyond the poor mortality outcomes for kidney failure, patients have a markedly reduced health related quality of life.[28-30] In a prospective study of Canadian ESKD patients, half reported problems with pain, and of these patients, three-quarters reported that their pain was ineffectively managed.[31]

Treating kidney failure is resource intensive for both the healthcare system and for patients. In 2002, over 1.2% of total Canadian healthcare expenditures were devoted to caring for patients with ESKD, while only 0.092% of the population has kidney failure.[32,33] Beyond this, many patients experience restrictions in their professional and personal lives, placing a heavy financial burden on patients, their families, and the healthcare system.[34-36]

2.2 Renal Replacement Therapy

The treatment for end-stage kidney disease is renal replacement therapy (RRT), where the blood-filtering function of the kidneys is replaced by way of dialysis or a kidney transplant. The following sections will discuss the prevalent RRT modalities in Canada and their outcomes from the perspective of patients with kidney failure.

2.2.1 Dialysis

Dialysis is a type of renal replacement therapy involving the removal of wastes and excess water by diffusing solutes and filtering fluid across a semi-permeable membrane. There are two main types of dialysis: hemodialysis (HD) and peritoneal dialysis (PD).

Hemodialysis works by removing waste products and excess fluid from blood by circulating it outside the body through an external filter.[37] In Canada, hemodialysis is the most common form of RRT: 77% of patients starting renal replacement therapy for ESKD in 2013 initiated treatment on hemodialysis.[9] The 5-year survival rate for HD is 44.8%, however, survival varies across patient age and primary diagnosis.[9] Typically, patients receive hemodialysis 3-4 times a week for sessions of 3-5 hours in length. Transportation costs and productivity losses due to hemodialysis are a financial burden felt both by patients and their caregivers. A small Canadian randomized trial found that the overall patient-borne cost for in-centre hemodialysis is $3104 over a 6 month period, while the annual healthcare cost of treating a patient with HD ranges from $90,000 to $107,000 to the public insurer.[33,38]

In peritoneal dialysis (PD), a glucose solution is passed into the peritoneal cavity to facilitate the removal of waste and excess fluid; the peritoneal membrane acts as the semi-permeable membrane.[37] About 10% of Canadian ESKD patients are treated with peritoneal dialysis, and 19.4% initiated treatment on PD in 2013.[9] Some studies (but not others) have suggested that peritoneal dialysis is associated with a survival advantage compared with in-centre hemodialysis, and in Canada, the 5-year survival rate for PD is 54.5%.[9,39-41] However, uncertainty in the relative efficacy of the two dialysis modalities remains due to a lack of randomized trials comparing the two directly. Peritoneal dialysis is administered at home by the patient and offers more control and independence than hemodialysis. The overall healthcare cost of PD also appears to be appreciably less than that of HD, with the cost of treating a single patient at $56,000 per year.[33]

2.2.2 Transplantation

Kidney transplantation is the preferred renal replacement therapy for most patients with kidney failure. In 2013, 42.5% of Canadian patients living with ESKD had functioning kidney transplants and 3.9% of patients with kidney failure initiated therapy by way of transplant (referred to as a pre-emptive kidney transplant).[9]

Kidney transplantation is dependent on the availability of organs from either deceased donors or living donors. Donor kidneys and recipients are assessed for compatibility based on blood typing, serum crossmatch, and histocompatibility. Unfortunately, the number of patients waiting for a deceased donor kidney in Canada increased 13% from 2001 to 2012; by the end of 2013, there were 3277 Canadians on the waiting list for a kidney transplant.[8,9]

2.2.2.1 Deceased Donor Kidney Transplantation

Deceased donor kidneys come from two main sources: donors who are declared brain-dead or donors following a cardiac death. Historically, the deceased donor rate in Canada has varied between 12 and 14 per million population, much lower than countries with national donation programs, such as Spain.[42] Nonetheless, deceased donor kidneys accounted for 61% of kidney transplants in Canada between 2004 and 2013.[9]

Compared to dialysis, deceased donor kidney transplantation substantially improves quality of life and confers a significant long-term survival benefit (reducing the relative risk of death by 64% at one year).[5,6] Graft survival rates for patients receiving deceased donor kidneys are 94.8% at 1 year and 82.6% at 5 years after transplant.[9]

2.2.2.2 Living Donor Kidney Transplantation

Deceased donation has not met the demand for kidneys. Living kidney donation has evolved substantially since the first kidney transplant between identical twins in 1954.[43] Beyond the developments in transplant surgery techniques and immunosuppression, there is now a better understanding of best practices to evaluate living kidney donor candidates, and the outcomes of living kidney donors.[44]

Compared to deceased donation, living kidney transplantation offers substantial benefits to patients with ESKD, including decreased time on dialysis, and improved graft and recipient survival.[11,12] Graft survival rates for patients receiving living donor kidneys are 97.7% at 1 year and 89.2% at 5 years.[9] On average, patients receiving living donor kidneys live 10 to 15 years longer than patients on dialysis.[5]

The number of living donor kidney transplants has increased by 26% between 1998 and 2008, representing about 40% of kidney transplants in Canada today.[9,10] However, the number of living donor kidney transplants has stagnated since 2006, fluctuating between 435 and 477 donations each year.[9]

2.2.2.3 Costs of Kidney Transplantation

The healthcare costs of living kidney donation are similar to or lower than costs associated with deceased donation, and substantially lower than costs associated with dialysis.[19,45] The average cost of in-centre hemodialysis ranges from $95,000 to $107,000 per patient per year.[18,19] The average initial cost for a kidney transplant approximates $100,000 in the first year, and $20,000 in each subsequent year for follow-up and medication costs; over 5 years, each kidney transplant results in a healthcare savings of approximately $250,000 dollars compared to dialysis.[2,7,18,19] Phrased another way, every 100 kidney transplants result in a 5-year healthcare savings of $25 million in averted dialysis costs.

A cost-utility analysis of renal replacement therapies demonstrates that, in the first year compared to dialysis, transplantation results in a per-patient healthcare savings of $7119 and a net gain of 0.12 quality-adjust life-years (QALYs). Corresponding numbers in the second-year post-transplant are savings of $43,365 and a gain of 0.11 QALYs per patient.[7]

2.3 Living Kidney Donation in Canada

In Canada, there are 18 active adult kidney transplant programs across seven provinces. Between 2004 and 2013, these centres performed 4417 living donor kidney transplants (about 500 living kidney donor transplants a year).[9] The donors participating in these transplants include directed donors, non-directed donors, and donors participating in kidney paired donation. These three types of donors are described below.

Directed donors are those who specify the recipient to whom they intend to donate their kidney. In other words, they “direct” the donation. Directed donors may be genetically related (such as a child or sibling) or emotionally related (such as a spouse/partner or friend).

Non-directed donors are those who do not specify their recipient and instead donate based on compatibility to a recipient selected from the waiting list (which may include initiating a chain of donations through kidney paired donation). The policy of several transplant centres is for non-directed donors to remain anonymous throughout the donation process (i.e. they never meet their recipient).

An estimated one-third of willing directed donors are unable to proceed with donation due to incompatibility with their intended recipient.[46] To address this, Canadian Blood Services (CBS) established the national Kidney Paired Donation Program and the Canadian Transplant Registry in 2009.[13] Kidney paired donation (KPD) facilitates transplantation by matching incompatible donor-recipient pairs through *n*-way, domino chain, and paired exchanges.[13] By 2011, all provinces with transplant programs were fully participating. The KPD Program runs a matching algorithm against donor and ESKD patient records in the transplant registry in four month cycles. The algorithm identifies potential exchanges and scores matches on variables predictive of transplant success.[47] By the end of 2013, the program had facilitated 271 kidney transplants, with the number of donations per cycle growing each year.[13]

Donors participating in the KPD Program face a unique set of challenges throughout their donation process. Regulatory frameworks enacted by Health Canada necessitate donor travel to the recipient's location for transplant, and as a result, 53% of these kidney paired donors have been required to travel out-of-province for surgery.[13] This travel gives rise to a financial burden in the form of flights and accommodations, separates donors from loved ones at an inherently stressful time, and potentially exposes donors to language barriers in bilingual Canada.[48,49] For these reasons, CBS has emphasized the importance of identifying barriers to program registration to ensure the long-term success of KPD in Canada.[13]

The following sections serve as a critical review of living kidney donation from the perspective of the donor, with a focus on the economic consequences of donation.

2.3.1 Medical Outcomes of Living Kidney Donors

Living kidney donation is practiced under the principle that both short-term and long-term medical risks borne by donors are outweighed by expected benefits to the recipient and a psychological benefit of altruism to the donor.[50] However, understanding and quantifying these risks is paramount to guiding informed consent in donor registration and facilitating donor follow-up.

The most immediate risk encountered by donors is that of surgical mortality. In a study drawing from over 80,000 living kidney donations in the United States between 1994 and 2009, the 90-day surgical mortality was found to be 3.1 per 10,000 donors (95% CI: 2.0 to 4.6).[51] Other retrospective studies in Japan and Norway found similar results.[52,53]

Living kidney donors face a 25-40% reduction in glomerular filtration rate following nephrectomy.[54] There is uncertainty and debate as to whether this reduction results in long-term adverse outcomes, such as kidney and cardiovascular disease.[55-57] Much of the literature on the medical risks to living kidney donors make comparisons to the general population. However, donors are generally healthier as a group due to rigorous donation criteria and evaluation, thus understanding the risks to donors requires comparisons to non-donors with similar indicators of baseline good health.[21]

Several studies have reported a low incidence of ESKD in living kidney donors within 10 years post-nephrectomy, ranging from 0.2% to 0.5%.[58-60] However, a study in the United States compared 96,217 donors (median follow-up of 7.6 years) to healthy matched controls (median follow-up of 15 years) and found the cumulative incidence of ESKD was significantly higher in the living kidney donor group (30.8 per 10,000 people, 95% CI: 24.3 to 38.5) compared to healthy controls (3.9 cases per 10,000 people, 95% CI: 0.8 to 8.9).[61] A similar study by Mjøen *et al.* found that living kidney donors had a hazard ratio of 11.38 (95% CI: 4.7 to 29.63) for ESKD compared to healthy non-donors.[62]

When comparing outcomes of all-cause mortality and cardiovascular disease between living kidney donors and healthy non-donors, most studies report no differences in long-term survival or risk of developing cardiovascular disease.[51,63,64] One Norwegian study did report significantly higher mortality in kidney donors than in matched non-donors at 25 years (adjusted HR = 1.3; 95% CI: 1.11 to 1.52), however, the accrual periods for comparator groups differed and survival differences may reflect changes in care or mortality trends over time.[62]

A Canadian retrospective study examined pregnancy outcomes post-donation. They found that female living kidney donors who become pregnant post-donation were at a significantly higher risk of pre-eclampsia or gestational hypertension compared to healthy non-donor controls (11% vs. 5%; odds ratio 2.4; 95% CI: 1.2 to 5.0).[65]

No differences in risk of kidney stones requiring surgical intervention, fracture events, or gastrointestinal bleeding have been reported across several studies which compared living kidney donors to healthy matched non-donor controls.[66-68]

2.3.2 Psychosocial Outcomes of Living Kidney Donors

Psychosocial assessments are an essential component of kidney donor evaluation, screening, and informed consent. There is a need to identify and measure the potential harms and benefits of living kidney donation to donor psychological well-being.

A systematic review of clinical practice guidelines for the screening and follow-up of living kidney donors identified four major domains encompassing psychosocial assessments: informed voluntary consent, motivation, history of mental illness or substance abuse, and support and coping mechanisms.[69] However, the review also reported considerable variation between guidelines and highlighted a need for high-quality outcome data to guide the development of consistent and evidence-based recommendations.[69]A survey of 221 transplant professionals from 40 countries noted that living kidney donors receive inconsistent information regarding the psychosocial and financial costs of donation during the informed consent process.[70]

Clemens *et al.* performed a systematic review of studies capturing the post-donation psychosocial outcomes of living kidney donors, finding 51 studies assessing 5139 donors between 1969 and 2006.[50] Only 10 of the studies followed donors prospectively to assess psychosocial well-being, and 20 of the 41 retrospective studies did not report average times between donation and follow-up.[50] Across reports, only 71% of eligible participants responded, and only 29 studies compared the psychosocial health of living kidney donors to healthy non-donor controls.[50]

Despite the methodological limitations of the included studies, there was overall agreement in the literature: most donors reported either no change or an improvement in their post-donation psychosocial well-being.[50] The proportion of donors experiencing no symptoms of depression ranged from 77% to 95% across five studies.[71-75] Furthermore, a retrospective report by Tanrivedi *et al.* found that donors actually reported fewer depressive symptoms on the Beck Depression Inventory than non-donor controls.[76] Retrospective studies by Duque *et al*. and Corley *et al*. found that 81% and 95% of living kidney donors reported feeling happier post-donation.[77,78] And across 17 studies, kidney donors were found to have comparable or better quality of life scores compared to the general population.[50] However, not all donors experienced positive outcomes. The review noted that some donors experienced stress due to the financial burden of donation and some donors felt anxiety about their remaining kidney failing.[50] Clemens *et al.* argued that further studies with appropriate control groups were necessary to better guide donor screening guidelines.[50]

To partially address these concerns, an international multi-centre cohort study retrospectively assessed the quality of life of 203 living kidney donors compared to 104 non-donor controls.[79] The researchers found that, across three distinct and validated scales, there were no significant differences in quality of life between kidney donors and non-donors in both unadjusted and adjusted analyses.[79] The study also reported no differences between donors and non-donors in number of visits to mental health professionals or use of psychotropic medications.[79]

A Dutch study, which criticized previous reports for the use of inappropriate control groups due to their retrospective nature, prospectively followed 135 living kidney donors matched 1:1 to individuals from the general population based on gender and baseline mental health.[80] The authors found that kidney donors did not experience changes in psychological complaints and well-being from baseline to 6 months post-donation, and beyond this, there were no difference between donors and controls over the follow-up period.[80] The authors concluded that post-donation short-term positive or negative variations in kidney donor psychosocial health did not differ from changes observed in a comparable population of non-donors.[80]

The RELIVE Study mailed surveys to 6909 patients who donated kidneys across three U.S. transplant centres from 1963 through to 2005.[81] The questionnaires collected psychosocial outcomes relating to donor experience, psychological state, and relationship with the recipient: 2455 (36%) of donors responded.[81] The authors found that 95% of donors perceived their donation experience as positive overall, and 75% reported that donation had positively affected the donor-recipient relationship.[81] However, the study did caution that approximately 9% of donors reported at least one negative psychosocial outcome, though recipient graft failure was the only significant predictor of having ≥1 poor psychosocial outcome.[81]

Though these recent studies of donor emotional well-being and quality of life support the safety of living kidney donation, further large and comprehensive prospective studies are necessary to identify the factors associated with diminished psychosocial health and identify donors in need of additional education or support.

2.3.3 Economic Outcomes of Living Kidney Donors

Despite the measurable health benefits to recipients and cost savings to the healthcare system as a result of living donor kidney transplantation compared with dialysis, many living kidney donors face economic consequences during the donation process.[14] Surveys of donors and prospective donors have identified financial consequences to donation as potential disincentives and a source of concern when making the decision to donate.[82,83] Understanding and quantifying the financial burden of donation on living kidney donors is critical to guiding the informed consent process and developing reimbursement policies that are effective and just.

2.3.3.1 Financial Burden to Donors

Clarke *et al.* performed a systematic review of studies reporting costs associated with becoming a living kidney donor and found 35 studies from 12 countries that measured at least one cost relevant to donors.[15] The authors defined direct costs as those consuming resources (travel, accommodation, medications) and indirect costs as those related to productivity losses (lost income, dependent care, housework). This contrasts with the prevailing view in health economic literature which characterizes direct costs as those borne by the health sector and patients, and indirect costs as expenses which are external to the patient and include intangible costs to society as a whole.[84] This work focuses on the donor perspective, and as such we adopted the cost categories as defined by Clarke *et al.* to permit comparisons to the existing literature. In assessing study quality, the authors found that 30 of the 35 studies collected cost data retrospectively, with donor recall times ranging from 8 weeks to 9 years.[15] Only four of the studies assessed the costs incurred by donors as a primary objective, and none reported the cost definitions and criteria they employed to estimate total costs borne by donors.[85-88]

The proportion of living kidney donors incurring any costs during the donation process ranged from 9% to 45% in 10 studies from seven countries.[72,73,85,86,89-94] A retrospective study by Johnson *et al.* found that the overall costs to living kidney donors ranged from $0 to $28,906 with an average cost of $837 (2004 USD).[73] Another retrospective study by Smith *et al.* reported costs ranging from $0 to $13,788 (2004 USD).[85] Unfortunately, neither of the studies reported costs by expense type.

Donors incur out-of-pocket costs for travel and accommodation during evaluation and for surgery, yet only four studies considered these costs explicitly.[15] One study found that donors incurred an average of $1720 for travel and accommodation combined, with costs ranging from $76 to $12,579 (2004 USD).[87] A Canadian study reported that 53% of donors paid for transportation and parking during the donation process.[95] A multi-centre study in the United States found that 99% of donors experienced costs related to travel and 88% paid for accommodation during their donation experience.[96]

Indirect costs were also reported. Proportions of donors with lost earnings due to donation ranged from 14% to 30% across three studies.[73,87,95] Only two studies collected information on the value of income lost by donors during the donation process: a retrospective study by Lyons *et al.* reported an average loss of $3386 and a prospective study by Zuidema *et al.* found an average loss of $682 (2004 USD).[87,88] No study measured the value of indirect costs due to lost household productivity, however, two studies reported that 9-44% of donors faced costs related to caring for dependents.[95,96]

Clarke *et al.* argued that due to the retrospective nature of the studies, lengthy timeframes for recall, incomplete and undetailed cost data, and poor donor response rates, the estimated costs to donors remain uncertain and likely to be underestimated in the literature.[15] The authors argued that a detailed multi-centre prospective cohort study was necessary to comprehensively measure the costs borne by living kidney donors.[15]

Since then, three prospective studies have attempted to methodically describe the costs of donors: one in Canada and two in the United States.

Klarenbach *et al*. followed a group of 100 living kidney donors across seven Canadian transplant centres between 2004 and 2008.[1] They prospectively collected data on costs and resources up to one year post-donation and comprehensively micro-costed the economic costs (2008 CAD). The authors reported that 96% of donors incurred costs due to donation, with 94% and 49% experiencing out-of-pocket expenses for travel and accommodation respectively.[1] Among those who incurred the expense, donors reported an average cost of $897 (SD $1048) for ground travel, $1480 (SD $1108) for air travel, $1759 (SD $2567) for non-hospital accommodation, and $1780 (SD $2504) for any direct costs.[1] One third of donors incurred costs >$3,000 throughout the donation process.[1] The authors reported the proportions of donors experiencing expenses, resource consumption, and monetary value of economic consequences by cost category. Regrettably, due to the small sample size, the study was unable to comprehensively collect cost data for donors participating in kidney paired donation, donors with air travel expenses, or the burden of expenses in important donor subgroups (e.g. spousal donors burdened with the loss of possibly two incomes). Canada is a geographically large country where 53% of donors participating in KPD travel outside of their province to donate; the inability to capture these important cost components of living kidney donation is an important limitation of the cost analysis performed by Klarenbach *et al*.[13]

Two studies by Rodrigue *et al.* reporting findings from the Kidney Donor Outcomes Cohort (KDOC) Study quantified costs faced by living kidney donors, the first study restricted cost-capturing to the pre-donation period, with the second confined to a post-donation window.[97,98] To quantify costs associated with donor evaluation during the pre-donation period, the authors recruited 194 living kidney donors (at the time of approval for surgery) and surveys were completed an average of 7 days before surgery.[97] They collected out-of-pocket expenses and resource use to measure evaluation-related direct and indirect costs (USD).[97] The study found that 96% of donors experienced direct costs during the pre-donation evaluation period, with 80% of donors reporting ground travel costs, 17% incurring costs for accommodation, and 14% facing air travel costs. For donors reporting the expense, the mean direct cost incurred during the evaluation period was $543 (SD $954), with the highest direct costs due to air travel (mean = $1265, SD = $999) and accommodation (mean = $649, SD = $862). The study found that almost one quarter of donors experienced total costs in excess of $1000 during the pre-donation period. For the second study, the authors prospectively followed 182 living kidney donors across six transplant centres in the United States until 12 months post-donation.[98] The study found that 92% of donors experienced direct costs as a result of donation, with 86% and 23% reporting expenses related to ground transportation and lodging, respectively.[98]

Among those who incurred the expense, donors reported an average cost of $388 (SD $462) for ground travel, $1375 (SD $1440) for air travel, $1176 (SD $1582) for lodging, and $1253 (SD $1951) for any direct costs.[98] One fifth of donors reported costs exceeding $5000, and financial burden (net financial loss divided by monthly household income) was significantly higher with greater travel distance, lower household income, and more unpaid work hours missed.[98] The authors reported costs and resource use for both donors and their caregivers separately by cost category. Though the largest reports of their type, Formica *et al.* noted that the cohort followed by Rodrigue *et al*. represents less than 3% of donations taking place in the United States during the reporting period, and the study recruited heavily from a fairly limited geographic area in the northeast of the country.[99] Beyond this, the study did not report on the burden of costs between important donor subgroups.

Wiseman *et al.* evaluated the financial burden faced by living kidney donors in a subjective manner, arguing that though previous work had sought to quantify the costs, little had been done to appreciate the subjective magnitude of burden imposed on donors by these costs.[100] From 2003 to 2015, the authors surveyed 1136 donors at 6 months post-donation to assess the severity of their financial burden due to donation on a scale of 0 to 10 (0 = no burden, 10 = extreme burden).[100] The study found that among the 796 donors (70%) who responded, 26% reported their financial burden as moderate (≥5), while 8% scored their burden as ≥8.[100] Interestingly, the authors found that even among those donors who reported no direct out-of-pocket costs, almost a quarter faced considerable financial burden.[100] Beyond the degree of burden, 35% of donors used savings and 14% borrowed money from loved ones to cover the expenses associated with donation.[100] The

RELIVE Study, a retrospective study measuring the outcomes of living kidney donors who donated from 1963 to 2005, found comparable results: the authors reported that 20% of donors judged the costs they encountered during donation to be burdensome.[81]

Unfortunately, the Wiseman *et al.* study is limited by a low response rate, a lengthy 6-month recall window, and a homogenous donor sample, which potentially limits the generalizability of their findings and underestimates the true severity of the financial burden faced by living kidney donors.

To date, the studies by Klarenbach *et al.* and Rodrigue *et al.* offer the most comprehensive glimpses into the costs borne by living kidney donors. However, due to small sample sizes, limited generalizability, and incomplete cost capturing, there is an opportunity for a large prospective cohort study to better estimate the total costs borne by donors, to appreciate the differences in costs between donor subgroups, and to identify factors associated with higher costs and greater financial burden among living kidney donors.

2.3.3.2 Reimbursement Ethics and Policy

Reimbursing living kidney donors for expenses incurred during evaluation, surgery and convalescence is justifiable and supported by a majority of transplant professionals and by the public at large.[101,102] Many have called for the need to remove financial disincentives from living kidney donation to ensure equity, barrier free access, and justice.[103-105] The overwhelming consensus for financial neutrality in living donation prompted the American Medical Association's Council on Ethics and Judicial Affairs to support reimbursement and differentiate it from for profit donation, which is illegal in most jurisdictions, including Canada.[106]

In Canada, facilitation of organ donation operates under a framework of altruism, and provincial legislations governing donation ban the exchange of “valuable consideration” for donated organs.[107,108] However, there is considerable debate on the complex ethics of valuable consideration and the policy prohibiting implementation of financial incentives to increase rates of organ donation.[109-113]

Canadian reimbursement initiatives began in earnest with the launch of the Living Organ Donor Expense Reimbursement Program (LODERP) in British Columbia in 2006.[114] By the end of 2011 all seven provinces with active kidney transplant programs had initiatives in place to reimburse donors for expenses encountered during the donation process. These programs are administered at the provincial level and facilitated by several organizations: Kidney Foundation of Canada (Alberta, British Columbia, Manitoba and Saskatchewan), Trillium Gift of Life Network (Ontario), Transplant Quebec (Quebec), and Legacy of Life (Nova Scotia).

Reimbursement administered by different organizations has resulted in marked variation in program implementation across provinces (Table 1). Though almost all programs provide the same total maximum amount reimbursed, the costs reimbursed by expense type vary even between programs facilitated by the same organization. The variation in program implementation across provinces has led many to argue for an evidence-based national reimbursement policy with a unified strategy to reimburse donors for their legitimate medical expenses and remove barriers to living kidney donation.[48]

Table 1. Overview and comparison of provincial reimbursement program expense ceilings by cost category for provinces with adult kidney transplant centres

Expense Type	Maximum Amount Reimbursed (Per Week/Day/Night), CAD Province						
	AB	BC	MB	NS	ON	QC	SK
Travel	$1500	$1500	$1500	$1500	$1500	$1500	$1500
Parking	$140 ($20/day)	$120 ($12/day)	$65	$65	$140 ($20/day)	$140 ($20/day)	$120 ($12/day)
Accommodation	$625 ($125/night)	$875 ($125/night)	$910 ($130/night)	$910 ($130/night)	$625 ($125/night)	$650 ($130/night)	$875 ($125/night)
Meals	$200 ($40/day)	$175 ($25/day)	$225 ($25/day)	$225 ($25/day)	$200 ($40/day)	$225 ($45/day)	$175 ($25/day)
Income	$3200 ($400/week)	$3200 ($400/week)	$2800 ($350/week)	$2800 ($350/week)	$3200 ($400/week)	$3200 ($400/week)	$3200 ($400/week)

2.3.3.3 Socioeconomic Barriers to Donation

Evidence suggests that household income is associated with access to living donor kidney transplantation: a study reporting on 133 potential donors found that recipients with higher incomes were more likely to receive a living donor kidney, versus a deceased donor kidney.[115] A study by Gill *et al.* reviewed 54,483 living donor kidney transplants in the United States between 2000 and 2009, and found that recipients share similar incomes to their donors.[116] Thiessen *et al.* surveyed a small group of potential donors who had opted out of donation and found that though the reasons for withdrawing from donor evaluation were numerous and varied, the perceived financial burden of the donation process was most frequently cited as the deciding factor.[117]

A study by Rodrigue *et al.* surveyed 456 end-stage kidney disease patients (including waitlisted transplant candidates, and recipients of both living and deceased donor kidneys) about attitudes surrounding the financial implications of donation from a donor's perspective.[118] Almost one-third of patients reported being told by a willing donor candidate that they were concerned about lost income associated with the donation process, and of those willing donor candidates who reported these concerns 64% did not complete the donor evaluation.[118] In the same study, the only significant predictor of a willing donor candidate expressing concern for lost income was lower patient household income.[118]

Another study suggests that the decline in living donation in the United States is in part due to decrements in median household income and economic pressures negatively influencing willingness to come forward as a living kidney donor.[119] Wiseman *et al.*

found the financial burden for donors undergoing surgery during the recent economic recession was higher than those donating pre-recession.[100] Changes in living donation in the past decade have varied between income groups: the disparity in living donation between low-income and high-income populations has widened in response to recent economic instability.[120]

Chapter 3

3 Objectives and Hypotheses

The overarching aim of this work is to conduct a comprehensive study of the costs of living kidney donation in Canada with the intention of describing, in detail, the costs borne by living kidney donors and identifying differences in expenses and financial burden between donor groups. This work will serve to inform donor reimbursement policy and generate recommendations with the aim of removing the financial disincentives associated with living kidney donation. The specific objectives and hypotheses are:

Objective 1: To describe, in detail, the costs incurred by living kidney donors in Canada. Specifically, to characterize the direct, indirect, and total costs borne by Canadian living kidney donors throughout the transplantation process by cost category and resource type using a micro-costing approach.

Objective 2: To identify differences in costs and financial burden between groups within the Canadian living kidney donor population. Specifically, to identify which donors face disproportionately higher costs, the cost categories that differ between groups, and the factors associated with increased financial burden.

Hypothesis 1: We expect that, due to the retrospective nature and lengthy timeframes for participant recall in previous work, the existing literature exceedingly underestimates the true financial costs borne by donors during living kidney donation. Due to small sample sizes, an incomplete collection of incurred costs, and a shifting landscape with the introduction of Kidney Paired Donation (KPD), we expect our cost estimates to be more accurate and, specifically, greater than those reported by Klarenbach *et al*. and Rodrigue *et al*. previously.[1,98]

Hypothesis 2: We expect that, due to differences in requirements for travel and associated flight and accommodation costs, kidney paired donors and non-directed donors will have higher *direct* and *total* costs than other types of donors. We expect that, due to increased costs associated with lost income, care of dependents, and lost home productivity, living kidney donors who donate to a spouse/partner will have significantly higher *indirect* and *total* costs than other donor-recipient relationship groups.

Chapter 4

4 Study Design and Methods

This chapter discusses the research design and methodology common to all analyses in the chapters that follow. It is intended to provide an overview of the methodological approach and assumptions linking the study data and findings into a cohesive work.

4.1 Living Kidney Donor Study

The Living Kidney Donor (LKD) Study is a CIHR-funded Canadian multi-centre prospective cohort study exploring the long-term outcomes of living kidney donation. The LKD Study recruited living kidney donors and non-donor controls from all twelve major transplant centres across Canada from June 2009 to December 2014 (ClinicalTrials.gov Identifier: NCT00319579). The study protocol was approved by The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects and all participants provided informed consent (Appendix A). The study protocol was guided by a Pilot Phase and participants recruited into the Pilot Phase were rolled over into Phase II of the study.

The LKD Study follows donor and control participants annually, with each participant completing surveys, blood pressure readings, and laboratory readings for a minimum of 5 years after donation. Informed consent was obtained to perform data linkages with healthcare record organizations and administrative databases to collect participant data and to facilitate long-term follow up of donors and non-donor controls.

The overarching objectives of the LKD study are to improve the practice of living kidney donation, with an emphasis on better understanding the long-term medical risks of donating a kidney, the psychological effects of becoming a kidney donor, and the economic consequences incurred by living kidney donors throughout the donation process. Given that randomization is not possible for the research objectives, the prospective cohort design provides the highest level of epidemiological evidence available to answer the research questions.[121]

The current work focuses on the financial burden involved in becoming a kidney donor and the costs of living kidney donation up to three months post-donation. Discussion of study methodology and the analyses in the chapters that follow are restricted to the outcomes of non-pilot kidney donors, as the results of the Pilot Phase have been published previously.[1]

4.1.1 Eligibility Criteria and Recruitment

All donors deemed eligible to donate a kidney by a nephrology team at one of the twelve Canadian transplant centres were eligible to participate in the study. Donors were ≥18 years of age, and could speak and read in English and/or French. All participants were enrolled in the study prior to donation. Recruiting from the twelve transplant centres, representing all the major living kidney donor centres in Canada, helped improve study generalizability and meet recruitment targets (Appendix B).

The specific recruitment process varied between participating transplant centres, as the living donor evaluation process differs at each centre. Nevertheless, the recruitment techniques across all centres included: introduction of the study to donors by members of the nephrology/transplant team, use of educational materials such as handouts, identification of participants with the assistance of hospital coordinators, meeting with donor candidates during hospital visits for their evaluation, providing donors with a study letter of information, and obtaining informed consent.

4.1.2 Data Collection

The LKD Study schedule is divided into four data collection periods: pre-donation, peri-operative period, three months post-donation, and annually post-donation (Figure 1, Part A). The pre-donation and post-surgery data collections were coordinated by the participant's local transplant centre; all subsequent post-donation data collection was completed by the central interviewing facility at the London Health Sciences Centre (LHSC).

Following participant recruitment and informed consent, trained research staff at each transplant centre provided donors with verbal and written instructions regarding study participation. During this recruitment visit, participants completed case report forms (CRF) and self-administered standardized surveys. Research staff also recorded participant pre-donation weight, height and blood pressure, and collected urine and blood specimens. Following surgery, local coordinators collected nephrologist, surgeon and psychosocial consult notes, results of testing during evaluation, surgical information, and discharge status from donor medical charts.

At three months post-donation, research staff at the central interviewing facility sent participants the study case report forms and standardized surveys by mail. Before study materials were mailed, participants were contacted to remind them of an upcoming data collection period and to verify mailing addresses.

Annually post-donation, participants are mailed a study kit containing the case report forms and standardized surveys, a home blood pressure machine for recording measurements, and a laboratory requisition for blood work.

Upon collection, de-identified consult notes, completed case report forms, and standardized surveys were entered and stored in a secure online database by local and central coordinators to ensure data quality and handling. Physical records were stored at the central interviewing facility.

4.1.3 Retention

Loss to follow-up is a critical barrier in prospective studies and often results in bias.[122] To minimize loss to follow-up the LKD Study employs a number of proven retention strategies and a systematic procedure for late or missing data collection (Appendix C).[123-125] Other strategies include repeated contact from both local transplant centres and the central facility, reminder calls and letters, logos on study materials to foster a study identity, tokens of appreciation sent alongside mailed study kits, and courier and home nurse services (Figure 1, Part B).

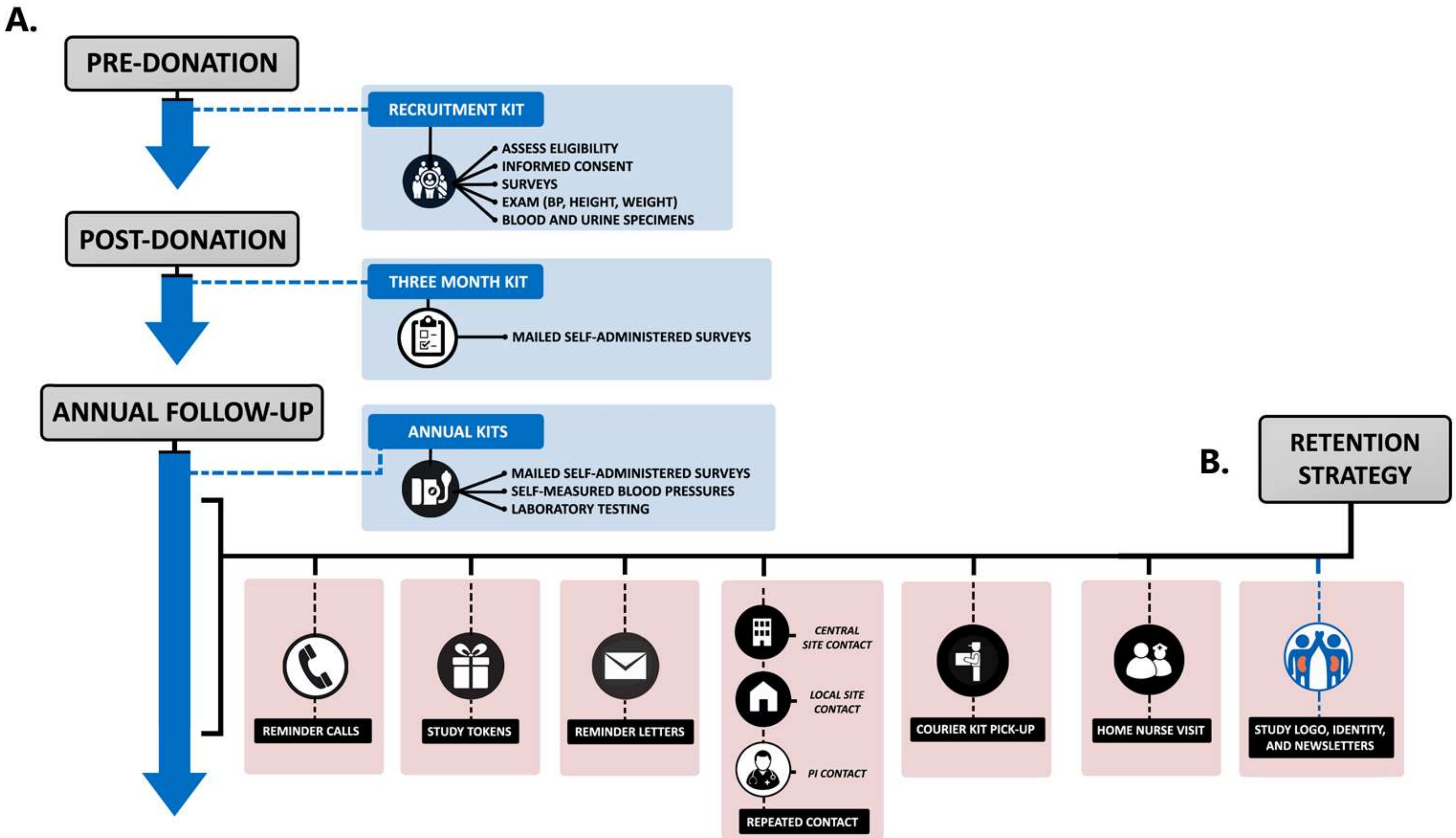


Figure 1. Data collection periods and retention strategies employed in the Living Kidney Donor Study

4.1.4 Outcome Measurement

The scope of this work focuses solely on the economic consequences of living kidney donation and the financial burden borne by donors to inform policies governing reimbursement in Canada. As such, medical and psychosocial outcomes, though important, have been omitted from our discussion of the study design and methods. The following sections will describe the identification, collection, and measurement of economic outcomes for living kidney donors.

4.1.4.1 Economic Outcomes

During the pilot phase, study investigators performed a systematic review of the existing literature on the economic costs of living kidney donation.[15] Guided by this review and through consultation with transplantation experts, a framework was developed of all costs incurred by donors during the pre-donation, donation, and post-donation time periods (visually represented in Figure 2). The framework defined two major types of expenses incurred by living kidney donors: direct costs (i.e. the consumption of resources) and indirect costs (i.e. lost productivity). This framework and detailed cost categories guided the data collection of the economic consequences to donors.

Donor economic outcomes were measured by mailed self-administered surveys at three months post-donation. The reasoning for this time frame is two-fold: 1) to best capture all costs (most economic consequences are experienced by donors within 3-months post-donation) and 2) to limit recall bias (a 90-day period for self-reported information on costs agrees well with actual records, and recollection of costs more than twelve months after they are incurred is likely to result in underestimates).[126,127]

Detailed cost-capturing methods and the data collection tools are presented in Appendix D.

4.2 Micro-Costing Methods

Costs incurred by donors were evaluated using the three-step micro-costing technique of i) identification, ii) measurement, and iii) valuation of resources (Figure 2).[128]

4.2.1 Resource Identification

Resources were identified through the economic outcomes framework as either direct or indirect costs, and the unit of each resource was defined. Direct costs included expenses for travel, accommodation, and medications. Indirect costs were associated with time and productivity losses including: lost income, home productivity, and caring for dependents.

4.2.2 Resource Measurement

The three-month economic case report form captures direct and indirect costs borne by donors in the form of both units of resources consumed and out-of-pocket expenses by category. Quantifying resource utilization in each cost category by collecting the number of units consumed (e.g. the number of nights spent in paid accommodation) allows for portability of the results, allowing for comparisons across jurisdictions.

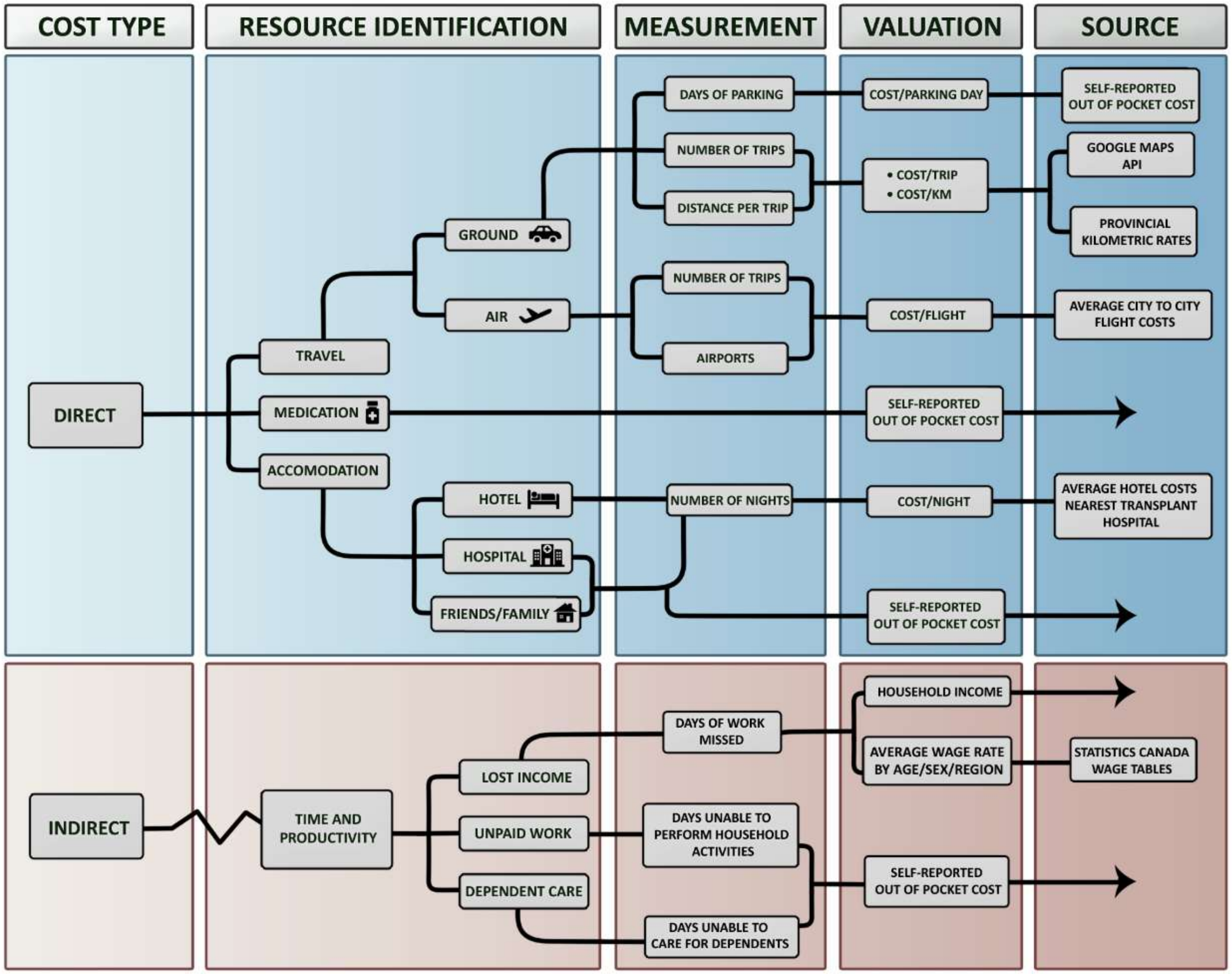


Figure 2. Micro-costing mechanism applied to measure the economic consequences of living kidney donation from the donor perspective.

4.2.3 Resource Valuation

To describe costs, resource units were assigned a value using conventional costing techniques and appropriate provincial or local rates and estimates (e.g. provincial age- and sex-specific average wage rates for unpaid days of work missed due to donation). For resources where no unit cost or rate was available (e.g. expenses associated with dependent care) donor reported out-of-pocket expenses were used instead.

4.2.4 Direct Costs

Direct costs were defined as the value of resources consumed during the pre-donation, donation, and post-donation periods. These costs included ground and air travel costs associated with donor evaluation, surgery and follow-up, accommodation costs during donor evaluation and surgery, and prescription medication costs (e.g. pain medications and antibiotics) post-donation. The direct cost for each donor was calculated as the sum of the above-mentioned cost categories.

4.2.4.1 Ground Travel Costs

In the 3-month post-donation economic assessment, donors reported the number of round-trips to see health professionals for living donor evaluation and the transplant centre where these evaluations took place. The driving distance between donors' homes and transplant centres was calculated using Google Maps application programming interface (API). The postal codes of donors and their respective centre were entered into the Google Maps API which produced the shortest driving distance between the locations. This driving distance was doubled to produce a round-trip distance-travelled, which was then multiplied by the reported number of round-trips to determine the donor's total driving distance during evaluation. The donor's total driving distance was then multiplied by the provincial kilometric rate for their province of residence to estimate the total costs of ground travel (Appendix E).[129]

Donors who flew to the transplant centre which they reported as the site of their evaluations were expected to have minimal ground travel costs; and for the purposes of this analysis had 0 kilometers inputted for their ground travel.

Donors were also asked to report the number of days and total out-of-pocket expenses for paid parking due to ground travel for evaluation, testing, and surgery.

4.2.4.2 Air Travel Costs

In the 3-month post-donation economic assessment, donors were asked if they travelled by airplane during the donation process. Donors who flew were asked to report the city of departure, the city of arrival, and the number of round-trip and/or one-way flights between these cities. Air travel rates were estimated using Google Flights between the cities of departure and arrival for either round-trip or one-way flights. The cost of air travel was estimated for the day of April 11, 2016, returning on April 12, 2016 (if round-trip). Rates between cities were obtained on February 27, 2016. Rates were chosen using Google Flights' price graph as follows: 1) lowest available economy-class flight regardless of time of departure or arrival, 2) direct flight, when available, and 3) use of Air Canada (Canada's most popular domestic airline), when available. Air travel rates included taxes and fees.

Air travel rates were then multiplied by the appropriate number of round-trip or one-way flights for each donor. The total air travel cost for each donor was the sum of the cost of flights during the donation process. Donors were also asked to report if air travel expenses were incurred by family/friends while accompanying them during the donation process (yes/no).

4.2.4.3 Accommodation Costs

All accommodation costs were captured in the 3-month post-donation economic assessment.

Donors reported the number of nights spent in paid accommodation during the evaluation and donation process. The three hotels nearest the hospital where each donor's surgery took place were identified using Google Maps "hotels nearby" function. Hotel rates were chosen using the following criteria: 1) single occupancy room, 2) lowest available rate, and 3) accommodation for the night of April 11, 2016. Rates for three hotels per hospital were obtained on February 27, 2016. Rates were averaged across the three hotels per hospital, and appropriate federal taxes, provincial taxes, and municipal destination marketing fees were applied (Appendix E). The average rates (with taxes) were multiplied by the number of nights in paid accommodation for each donor to determine the total cost of paid accommodation.

Donors were asked to report the number of nights and total out-of-pocket expenses related to staying with family and/or friends throughout the donation process.

Donors were asked to report the number of nights and total out-of-pocket expenses related to staying in hospital (e.g. cable, telephone etc.) for testing and/or surgery.

Total accommodation cost for each donor was the sum of the cost of paid accommodation, the total out-of-pocket expenses for staying with family and/or friends, and the total out-of-pocket expenses related to staying in hospital.

4.2.4.4 Medication Costs

In the 3-month economic assessment, donors were asked to estimate their total out-of-pocket costs for medications prescribed because of donating their kidney. Donors were not asked to report the type or duration of prescribed medications; therefore, self-reported out-of-pocket expenses were used as the estimate for medication costs.

4.2.5 Indirect Costs

Indirect costs were defined as the value of time sacrificed and productivity losses during the pre-donation, donation, and post-donation periods. These costs included lost income due to unpaid days of missed work, productivity losses associated with household and domestic activities, and productivity losses associated with caring for dependents. The indirect cost for each donor was calculated as the sum of the above-mentioned cost categories.

4.2.5.1 Lost Workforce Productivity

In the 3-month economic assessment, donors were asked to report the number of days or part days they were unable to work following donation (if they were employed) and the number of these days that were unpaid. The number of unpaid days away from work was multiplied by an 8-hour work-day. We then multiplied the number of hours of lost pay by the 2016 (age-, sex-, and province-specific) average wage rates from the Labour Force Survey to estimate lost workforce productivity due to donation (Appendix E).[130] We did not collect donor reported wage rates due to the invasiveness of the question and anticipated poor response rate. The human capital approach and use of average wage rates are suggested by the Canadian Agency for Drugs and Technologies in Health's guidelines for economic evaluations, have been used previously in the evaluation of the costs incurred by living kidney donors, and are frequently used in health economic evaluations to estimate workforce productivity.[1,130,131] In accordance with Drummond *et al.*'s recommendations based on equity concerns in estimating productivity losses, a sensitivity analysis using 2016 average provincial wage rates to value lost wages was performed: the results did not change (Appendix E).[84,132]

4.2.5.2 Lost Non-Workforce Productivity

All productivity losses were captured in the 3-month economic assessment. Our assessment did not include opportunity costs.

Donors were asked to report the number of days they were unable to perform household activities (e.g. housework, shopping etc.) and their total out-of-pocket expenses related to these productivity losses (e.g. cost of housekeeping) even if they were fully or partially reimbursed.

Donors were asked to report the number of days they were unable to care for dependents (e.g. children, spouse etc.) and their total out-of-pocket expenses related to these productivity losses (e.g. cost of a babysitter) even if they were fully or partially reimbursed.

4.2.6 Inflation

As donor reported out-of-pocket expenses for paid parking, staying with family and/or friends, hospital accommodation, prescription medication, and productivity losses were incurred by donors between the years 2009 and 2015, the total costs for these categories were standardized to the year 2016 using inflation rates (based on Canada's Consumer Price Index) according to each donor's year of surgery (Appendix E).[133] Lost wages were estimated using the year 2016 age-, sex- and province-specific average wage rates and ground travel was estimated using year 2016 provincial kilometric rates.

4.3 Study Characteristics

The purpose of this research is to describe the economic consequences of living kidney donation (the financial burden borne by donors). The primary analyses are driven by data collected during the 3-month post-donation assessment. The following section describes power and sample size considerations, follow-up of study participants, and characteristics of responders and non-responders.

4.3.1 Power and Sample Size

The primary outcome of the Living Kidney Donor Study is the risk of hypertension many years after donation between donors and controls. As such, power and sample size considerations for recruitment were calculated to detect a minimal clinically important effect in the outcome of hypertension. However, the 95% confidence intervals for the costing estimates do provide a plausible range of where the true parameter may lie. As shown in the results, most cost comparisons have an upper or lower bound with no more than a difference of $1000.

4.3.2 Participant Recruitment and Follow-Up

During the recruitment period, a total of 1042 living kidney donors were recruited into the study (Figure 3).

Of the 1042 donors recruited, 73 pilot donors and 57 donors who completed their evaluation or surgery outside of Canada were excluded from our analysis, leaving 912 eligible donors.

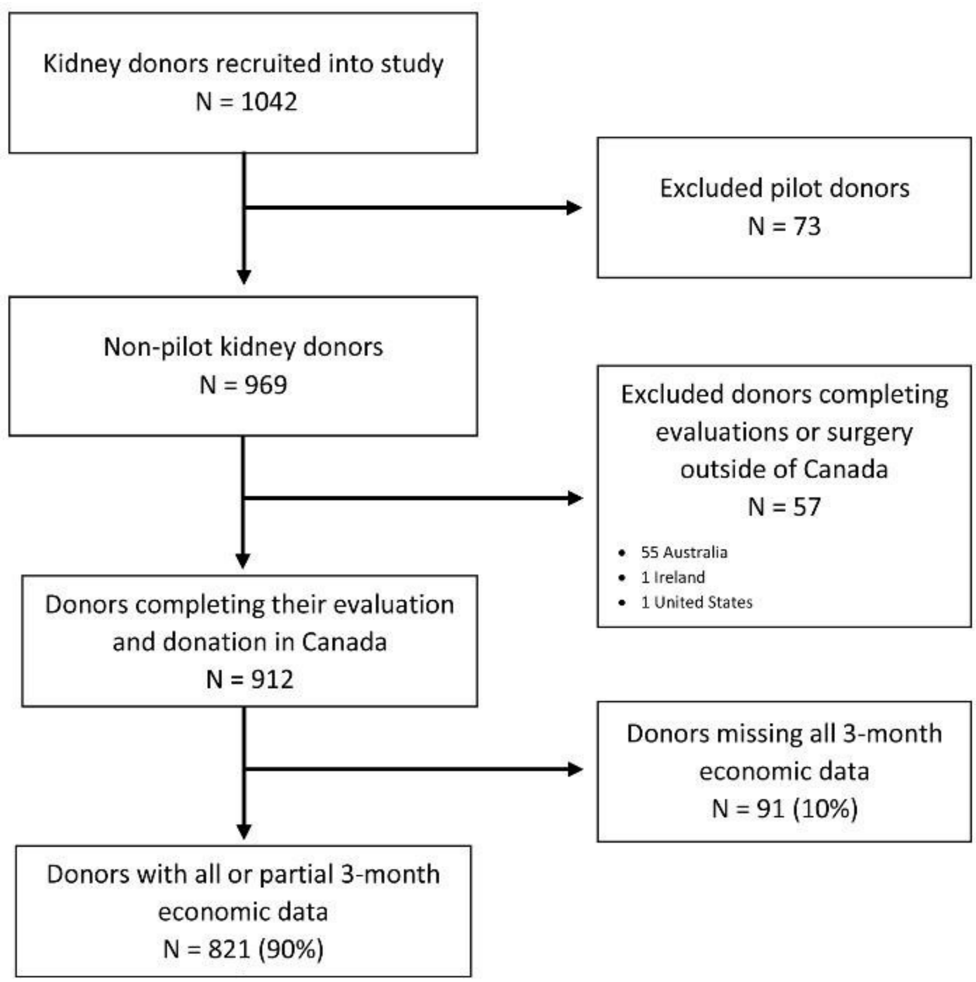


Figure 3 LKD study participant flow diagram for donors. Excluded pilot patient results are reported elsewhere.[1] Donors missing all 3-month economic data were included in multiple imputation analyses.

4.3.3 Participant Characteristics

We compared donors who provided some or all 3-month economic data (responders) to those who were missing all 3-month economic data (non-responders) across demographic variables collected during the recruitment assessment (Table 2). Differences between responders and non-responders were assessed using t-tests for means, Fisher's exact tests for proportions, and Wilcoxon rank-sum tests when the outcome distribution was skewed. For all comparisons, *p*-values < 0.05 were considered statistically significant.

Table 2. Baseline characteristic of donors who partially or fully completed the 3-month economic assessment compared to those donors missing all their 3-month data.

Baseline Characteristics	Donors reporting 3-month data (n = 821)	Donors missing all 3-month data (n = 91)	p-value
Age, years, mean (SD)[1]	47.7 (11.3)	40.9 (11.0)	*<0.001*
Women, n (%)	555 (68%)	54 (59%)	0.127
Distance from home to transplant centre where evaluated, kilometers, median (p25, p75)	58.9 (18.2, 195.0)	57.2 (23.3, 221.0)	0.500
Province of transplant centre, n (%)			0.641
Alberta	115 (14%)	18 (20%)	
British Columbia	251 (30%)	24 (26%)	
Manitoba	32 (4%)	5 (5%)	
Nova Scotia	38 (5%)	4 (4%)	
Ontario	344 (42%)	35 (38%)	
Quebec	41 (5%)	5 (5%)	
Donation type, n (%)			*0.039*
Non-directed	36 (4%)	1 (1%)	
Emotionally related	289 (35%)	27 (30%)	
Genetically related	385 (47%)	56 (62%)	
Paired	111 (14%)	7 (8%)	

Baseline Characteristics	Donors reporting 3-month data (n = 821)	Donors missing all 3-month data (n = 91)	p-value
Donor's relationship to recipient, n (%)			0.131
Parent	114 (14%)	14 (15%)	
Son/daughter	68 (8%)	10 (11%)	
Sibling	181 (22%)	30 (33%)	
Partner/spouse	129 (16%)	9 (10%)	
Friend/acquaintance	93 (11%)	11 (12%)	
Other (related)	38 (5%)	4 (4%)	
Other (unrelated)	51 (6%)	5 (5%)	
Don't know the recipient who received kidney	147 (18%)	8 (9%)	
Marital status, n (%)			*<0.001*
Currently married	543 (66%)	40 (44%)	
Common law/living with partner	110 (13%)	16 (18%)	
Never married	91 (11%)	16 (18%)	
Divorced	44 (5%)	8 (9%)	
Separated	22 (3%)	9 (10%)	
Widowed	11 (1%)	2 (2%)	
Employment status, n (%)			*<0.001*
Employed full-time	518 (63%)	60 (65%)	
Employed part-time	114 (14%)	9 (10%)	
Homemaker	35 (4%)	4 (4%)	
Student	7 (1%)	1 (1%)	
Temporary sick leave or disability	17 (2%)	5 (5%)	
Unemployed	29 (4%)	11 (12%)	
Retired	87 (11%)	1 (1%)	
Other	14 (2%)	1 (1%)	
Highest level of education completed, n (%)			*<0.001*
Primary school	15 (2%)	7 (8%)	
Secondary school	241 (29%)	47 (52%)	
Trade school	53 (6%)	8 (9%)	
College	215 (26%)	18 (20%)	
University	297 (36%)	11 (12%)	
Race, n (%)			*0.003*
White	720 (88%)	69 (76%)	
Non-white	101 (12%)	22 (24%)	

[1] age at time of surgery

There were no significant differences in between responders and non-responders on the following baseline characteristics: proportion of women, the province where transplant evaluation occurred, donor relationship to their recipient, and distance from home to transplant centre.

Responders were older than non-responders (mean 47.7 vs. 40.9 years; $p < 0.001$) and a higher proportion of responding donors were white (88% vs. 76%; $p = 0.003$). At recruitment, responders also significantly differed from non-responders in marital status ($p < 0.001$), employment status ($p < 0.001$), donation type ($p = 0.039$), and highest level of education completed ($p < 0.001$).

4.4 Data Quality and Handling

The following sections describe methods used to ensure data quality and handle missing data.

4.4.1 Data Screening and Cleaning

We systematically screened data for outlying, discrepant, and missing values to ensure data validity, consistency, and completeness. All variables included in the micro-costing approach were screened to ensure values fell within a plausible range. Database case report forms were checked against physical survey records to identify potential data entry and typographical errors (e.g. postal codes where a “0” is mistakenly inputted as “O”). Survey skip patterns were screened (for nested questions with conditional responses) to ensure reported values were consistent with previous answers. Multiple attempts were made to contact donors (by phone, mail, and email) to recover any missing data via structured interviews and to verify discrepant values. Alternate contacts were telephoned for updated donor contact information if information on record was no longer current. Any remaining missing values were abstracted from nephrologist, surgeon and psychosocial consult notes wherever possible. Statistical methods to deal with missing data are described in detail in the following section.

4.4.2 Missing Data

Of the living kidney donors eligible for analysis of economic outcomes, 90% completed the 3-month economic assessment (responders). Within the responder group, less than 2% of variables employed in our micro-costing approach for both direct and indirect costs were missing. Complete-case analysis (CCA) involves the listwise deletion of cases where any micro-costing variables are missing. CCA was available for direct costs and indirect costs in 96% and 95% of responders, respectively. Complete-case analysis was available for total costs (the sum of direct and indirect costs) in 93% of responders (Table 3).

Three mechanisms to missing data have been described: missing completely at random (MCAR) in which the missingness is unrelated to the value of any variables, missing at random (MAR) in which the missingness is dependent upon *observed* variables only, and not missing at random (NMAR) in which the missing values are related to *unobserved* variables.[134] Missing data in our study was assumed to be missing at random. Data MAR can be entirely accounted for by the observed variables (with complete information) and is not associated with unobserved values.[135] As complete-case analysis may result in biased estimates if the complete and missing cases systematically differ, multiple imputation (MI) was used to impute variables used in the micro-costing approach in both the incomplete cases and in the 10% of donors missing all three-month data (non-responders).[136] Multiple imputation has been used widely in cost-effectiveness research to impute missing or incomplete resource utilization and cost data.[137]

The multiple imputation approach implemented was informed by the pattern of missing data. Faria *et al.* recommends imputing at the resource level (rather than the total cost level) when different types of resources have different patterns of missingness.[138] In light of this recommendation, and in order to report costs and resource consumption across groups, variables in the micro-costing approach were imputed at the disaggregate rather than the aggregate level.[138] For example, if a donor was missing the number of ground trips to a transplant centre, we imputed this value, instead of imputing the cost of ground travel.

Table 3. Frequency of missing variables used in micro-costing by responder group.

Variable	Missingness, n (%)		
	Responders (n = 821)	Non-Responders (n = 91)	Total (n = 912)
Direct Costs			
Number of Trips	9 (1.1%)	91 (100%)	100 (11.0%)
Nights in Hotels	4 (0.5%)	91 (100%)	95 (10.4%)
Hospital Costs	12 (1.5%)	91 (100%)	103 (11.3%)
Friends/Family Accommodation Costs	8 (1.0%)	91 (100%)	99 (10.9%)
Parking Costs	13 (1.6%)	91 (100%)	104 (11.4%)
Medication Costs	13 (1.6%)	91 (100%)	104 (11.4%)
Indirect Costs			
Days Off Without Pay	16 (1.9%)	91 (100%)	107 (11.7%)
Unable to Care for Dependents Costs	27 (3.3%)	91 (100%)	118 (12.9%)
Unable to Perform Household Activities Costs	28 (3.4%)	91 (100%)	119 (13%)

There are two principal approaches to multivariate multiple imputation: joint modeling and multiple imputation by chained equations (MICE).[139] Joint modeling imputes all missing values concurrently, often using a multivariate normal distribution.[139-141] Multiple imputation by chained equations is a pragmatic method to deal with missing data occurring in several variables; the approach is based on a series of imputation models, one for each of the imputed variables.[140] There is no consensus recommendation in the literature for choice of approach. We opted to employ MICE due to its suitability for the missingness within our dataset and its flexibility for handling different types of variables and distributions because each uses its own model for imputation.[142] In our analyses, multiple imputation was performed in Stata 14.2 which allows for MICE using the `mi impute chained` command.[139,143]

Missing binary variables (e.g. did the donor travel by plane) in our dataset were modeled using logistic regression. Missing count variables (e.g. number of nights in paid accommodation) were modeled using Poisson regression. Ordinal variables (e.g. severity of post-operative complications) were modeled using ordered logit regression.

As out-of-pocket costs are non-normally distributed continuous variables (right-skewed), we used predictive mean matching (PMM) to impute donor reported expenses (e.g. cost of prescription medication). Predictive mean matching generates imputed values by sampling from observed values, and as such the underlying distribution of the imputed values matches closely with that of observed ones.[142,144] Each imputed value is randomly drawn from the observed values of a number of “nearest neighbours” (k) with predictive means similar to the missing observation (as determined by linear regression).[139] Based on a simulation study, Morris *et al.* advocate for drawing from a pool of $k = 10$ donors.[145]

Vroomen *et al.* demonstrated the validity of PMM in imputing missing cost data by generating incomplete datasets from a complete reference dataset, imputing missing costs, and comparing imputed values to the reference dataset.[146]

We followed Stata's guidelines in the building of imputation models; the reference manual recommended using as many predictors as possible in the model (the demographic and derived variables collected during the recruitment assessment), including any cluster identifiers in the model (i.e. location of donor evaluation), and inclusion of all variables used in later analyses (including dependent variables).[139] These variables were complete for non-responders. Models were evaluated separately for convergence and fit before being added to the MICE command.

White *et al.* argue that the number of imputations should be at least as many as the percentage of incomplete cases (in our analysis this is ~15), while the Stata documentation recommends generating 20 imputations to reduce sampling error.[139,142] To be conservative, we used 20 imputations. Stata automatically combines multiply-imputed datasets according to Rubin's rules during analysis and when generating estimates using the command `mi estimate`.[147] According to Rubin's rules, estimates are calculated for each imputed dataset and the overall point estimate is the mean of these values, while the standard errors are combinations of within-imputation and between-imputation variance.[147]

Diagnostics of the multiply-imputed data were performed using the Stata command `midiagplots` which allows for efficient comparisons of the distributions of imputed and observed values to identify problems with the imputation model (Appendix F).

4.5 Statistical Analyses

The following sections will describe, in detail, the statistical methods and analyses performed in this work.

Analyses were conducted on both multiple-imputed and complete-case datasets and estimates for each were reported (Appendix H). Descriptive statistics for incurred costs and resource use were reported separately for i) donors who reported the outcome and ii) all donors. Statistical tests were two-tailed using a significance level of 0.05 and analyses were conducted using Stata Release 14.2 (StataCorp LP, College Station, TX).

4.5.1 Univariate Cost Analysis

Univariate analysis of costs incurred by living kidney donors was conducted between pre-specified groups of donors to identify differences in economic outcomes. The primary analyses compared direct, indirect, and total costs between *donation-type* groups: non-directed donors and kidney paired donors vs. all other donors, and *relationship-type* groups (among donors not participating in non-directed or kidney paired donations): spousal donors vs. closely-related donors (sibling, parent, child) and unrelated donors (friends, acquaintances, other).

The distribution of cost data is generally right skewed, as costs cannot be negative and patients with complicated cases may face substantially higher costs and use more resources.[148,149] In light of this, median costs are routinely used to describe cost data. However, in economic evaluations, the arithmetic mean is of chief interest because of its utility to policy and decision makers.[149-151] Stata's `sktest` for normality was used to assess skewness and kurtosis of cost distributions.[143] Due to the skewed nature of our cost data and in effort to report our findings pragmatically, incurred expenses were reported as means (standard deviation) and medians (25^{th} percentile, 75th percentile). Costs were compared to the common maximum provincial reimbursement amount of $5500 and the proportion of donors incurring costs greater than this limit was reported. Resource consumption and counts were reported as medians (25^{th} to 75th percentiles).

4.5.1.1 Bootstrapping

There are several approaches to conduct univariate analyses of costs with skewed distributions. Parametric methods such as the t-test and ANOVA are common in the literature, however, there are no precise thresholds for the minimum sample sizes and maximum skewness necessary to ensure the reliability of these tests.[149,152] Non-parametric tests such as the Wilcoxon rank-sum have found utility as alternatives to parametric methods, but they merely describe differences in the cost distributions and medians between groups and not necessarily the arithmetic mean.[149,151,153] Logarithmic transformation of cost data has been commonly employed in healthcare cost research to approximate normality and conduct parametric tests on transformed scales, however, concerns about zero costs, inferences on the geometric rather than the arithmetic mean, and retransformation with smearing factors make these methods unwieldly.[149]

To compare costs between groups, we calculated arithmetic means and mean differences, and employed non-parametric bootstrapping to build confidence intervals (CIs) for these measures. The non-parametric bootstrap technique avoids assumptions of the distribution and many of the problems encountered with other parametric and non-parametric tests of costs.[149] Point estimates of the arithmetic mean and mean differences are calculated directly from the cost data and bootstrapping provides measures of variability, including 95% confidence intervals.[149] In brief, the bootstrapping approach takes repeated random draws of the observed data (samples of the same size with replacement) and generates a series of resamples. The statistic of interest (in our case the arithmetic mean and difference in mean cost) can be calculated from each resample, and the distribution of this statistic from the resamples can be used to calculate 95% confidence intervals.[149,154,155] Efron and Tibshirani recommend that at least 1000 resamples are necessary to obtain bootstrap confidence intervals, and thus 1000 repetitions were conducted.[155,156] Bias-corrected and accelerated (BC_a) bootstrap confidence intervals perform better than standard percentile approaches and correct for skewness; we reported the arithmetic means and mean differences of costs between groups with BC_a 95% confidence intervals.[154,157,158]

4.5.2 Multivariable Cost Analysis

Multivariable analysis was used to obtain adjusted comparisons of direct, indirect, and total incurred expenses between donation-type groups and relationship-type groups.

Secondary analyses were conducted to describe the direct, indirect, and total costs incurred by donors across sociodemographic variables, including sex, age at time of nephrectomy (18-34 years vs. 35-54 years vs. 65+ years), distance from transplant center, race (white vs. non-white), income, employment status (employed vs. unemployed vs. retired vs. other), and province of transplant centre.

Trends in counts (e.g. number of visits) and skewed continuous variables (e.g. costs) across groups were evaluated using Stata's `nptrend` command: a non-parametric test for trends across ordered groups. The test functions as an extension of the Wilcoxon rank-sum test and is intended for scenarios where a variable is measured across more than two groups.[159]

4.5.2.1 Generalized Linear Models

Using multivariable models to analyze costs does not avoid the same distributional issues of heavily skewed cost data encountered in univariate analyses. Ordinary least squares (OLS) regressions of untransformed and transformed costs, though the most common approaches to cost analysis, face problems with violations of the assumptions of homoscedasticity and normally distributed error terms, and problems with retransformation.[149,152]

Generalized linear models (GLM) have become increasingly used as an alternative to OLS models to analyze costs.[149] GLMs have emerged because of the flexibility they offer in allowing mean and variance to be directly specified, and because they avoid distributional problems in cost analysis, as mean and variance can be modelled on the original scales.[149,160] To employ GLMs in cost analysis we determine a *link function* and a *family* based on the data. The link function describes how the mean on the original scale is related to the linear combination of the coefficients and regressors in the model, and so does not face issues of retransformation.[149,160] The log link has been used widely in healthcare cost literature as it predicts the log of the mean, and thus, exponentiation of the predictions from the GLM to arrive at the arithmetic means does not require smearing factors.[149] Specification of a distributional family reflecting the mean-variance relationship allows for heteroscedasticity to be modelled.[160] For example, the gamma family specifies the variance as being proportional to the square of the mean.[160]

Misspecification of the link function and family may affect model fit, and result in inefficient and biased parameter estimates.[160] For our multivariable analysis, the choice of link function was guided by the Stata program `glmdiag` which performs the Pregibon linktest, Pearson's correlation test, and the modified Hosmer-Lemeshow test.[161-163] Specification of the distributional family was informed by the modified Park test.[164] Candidate families assessed included: Gaussian (constant variance), gamma (variance proportional to square of the mean), Poisson (variance proportional to the mean), and inverse Gaussian (variance proportional to cube of the mean).[149] The results of model diagnostic and goodness of fit tests are reported in Appendix G. Following these diagnostic tests for link function and family, we employed a GLM with a log link and gamma distribution to elicit adjusted comparisons of donor expenses between groups, a specification commonly used in health economic literature to model costs.[160]

Deviance residuals were assessed using normal plots to judge goodness of fit for our model.[160,165] The Stata program `collin`, which provides variance inflation factors, tolerance, and condition index, was used to detect multicollinearity across covariates.[143,166]

4.5.2.2 Average Marginal Effects

Glick *et al.* cautioned that, with multiplicative models such as GLM, non-linear retransformations when estimating costs can introduce covariate imbalances.[149] To overcome this problem, the authors recommend estimating differences between groups as incremental costs using the technique of recycled predictions.[149] Recycled predictions generate an identical covariate structure for each group by treating each observation as if they were in one group, predicting costs, and then treating each observation as if they were in the comparison group, and again predicting the cost for each.[149,167] Differences in the costs between individual observations reflect the marginal effect of being in the comparison group; the average of these individual effects results in an average marginal effect (AME) comparing costs between groups while holding all other covariates constant.[167] Stata performs recycled predictions using the `margins` and `mimrgns` commands.[143]

To report the results of the multivariable analysis, we performed pairwise recycled predictions between referent and comparator groups to calculate the adjusted AMEs (as differences in indirect, direct, and total costs between demographic groups, donation-type groups, and relationship-type groups), along with their 95% confidence intervals and *p*-values.

4.5.2.3 Covariate Selection

The analyses were adjusted for a set of covariates identified using a theory driven approach relying on previous literature and clinical judgement. Analyses were adjusted for age, sex, post-operative complications, income, and transplant centre.

Age and sex are well characterized determinants of healthcare expenditures and resource utilization.[168,169] Beyond this, previous reports characterizing patient direct medical expenses and identifying predictors of cost have adjusted for age and sex in multivariable analyses.[170,171] To be consistent with the literature we included donor sex and age at the time of surgery as covariates in our model.

Donor complications are associated with lengthier hospital stays, a higher probability of hospital readmission, greater use of post-discharge medications, and increased healthcare costs.[172-174] In light of this, donor complications may result in prolonged time off work, increased number of visits to healthcare professionals, and medication costs covered by the donor. A study by Wiseman *et al.* found that operative outcomes had a significant impact on financial burden.[100] As a result, we included donors' Clavien-Dindo classification as a covariate in our model to adjust for post-operative complications. The Clavien-Dindo system is a tool that ranks surgical complications based on the therapeutic intervention necessary to correct the complication.[175] Clavien-Dindo grades were abstracted from donor surgical notes and discharge summaries.

A report by Sanmartin *et al.* found that, from 1998 to 2009, out-of-pocket healthcare expenditures increased for all Canadian households, but the increases were greater among Canadians in the lower income quintiles.[176] The authors argued that this cost burden can result in a reduced use of healthcare services.[176] Therefore, self-reported household income of donors was included in our multivariable model.

Our prospective cohort study recruited donors from 12 transplant centres across Canada and variations in donor selection criteria, evaluation, and follow-up cannot be ruled out. To account for potential variation in practice patterns between centres and generate robust standard errors that allow for intragroup correlation, we specified the transplant centre of donor evaluation as the cluster variable used in Stata's variance estimator for multivariable analyses.[143]

4.6 STROBE Statement and Checklist

This work, including its reporting, adheres to the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) initiative, statement and checklist for cohort studies. (Appendix I).[177]

Chapter 5

5 Results

5.1 Descriptive Statistics

This section reports the demographic characteristics and economic outcomes of our cohort of Canadian living kidney donors. Specifically, it describes the direct, indirect, and total costs incurred and resources consumed by donors throughout the living donation process by cost category and resource type. Differences in demographic characteristics between groups were assessed using analysis of variance for means, and Fisher's exact tests for proportions. For all comparisons, p-values < 0.05 were considered statistically significant.

5.1.1 Demographic Characteristics

The demographic characteristics of study participants are presented in Table 4. Most living kidney donors enrolled in the study (n = 912) were recruited at transplant centres in two provinces: British Columbia (30%) and Ontario (42%). The average age at the time of donation was 47.0 years, and most donors were women (67%) and white (87%). Donors underwent transplant surgery between 2009 and 2015, and at the time of surgery, 64% were married, 77% were employed, and 60% lived less than 100 km from their transplant centre. Most donors had completed university as their highest level of education (34%), followed closely by secondary school (32%) and college (26%).

Among the 668 donors reporting income, 35% had an annual household income greater than \$100,000 (CAD). In relation to their recipients, donors were most commonly siblings (23%), followed by spouses/partners (15%), parents (14%), friends (11%), and sons/daughters (9%) of their recipients. In total, 17% of all donors participated in either kidney paired (13%) or non-directed (4%) donations, and as such did not know the recipient who received their kidney.

5.1.1.1 Donation-Type Groups

Donor characteristics were generally similar across donation-type groups; exceptions include differences in racial makeup (proportion of white donors: *non-directed* = 100% vs. *kidney paired* = 86% vs. *all others* = 85%, $p = 0.02$) and age: *kidney paired donors* were significantly older than *all other donors* at the time of surgery (49.9 years vs. 46.5 years, $p = 0.01$).

5.1.1.2 Relationship-Type Groups

Although donors across relationship-type groups were mostly similar with respect to demographic characteristics, there were significant differences across the three groups in the proportion of female donors (*spousal* = 81% vs. *closely related* = 63% vs. *unrelated* = 66%, $p < 0.001$) and in donor racial makeup (proportion of white donors: *spousal* = 88% vs. *closely related* = 82% vs. *unrelated* = 92%, $p = 0.004$). Additionally, at the time of surgery, *spousal donors* were significantly older than both *closely related* and *unrelated* donor groups (49.6 years vs. 46.0 years and 45.4 years respectively, $p = 0.001$).

Table 4. Demographic characteristics of living kidney donors.

Variable	All donors (N = 912)	Donation-type group (N = 912)			Relationship-type group (N = 757)[2]		
		Non-directed donors (n = 37)	Kidney paired donors (n = 118)	All other donors (n = 757)	Spousal donors (n = 138)	Closely related donors (n = 417)	Unrelated donors (n = 202)
Age at donation, years, mean (SD)	47.0 (11.5)	47.6 (12.9)	49.9 (10.7)	46.5 (11.4)	49.6 (10.7)	46.0 (11.9)	45.4 (10.6)
Female, n (%)	609 (67%)	24 (65%)	78 (66%)	507 (67%)	112 (81%)	261 (63%)	134 (66%)
Race, n (%)							
White	789 (87%)	37 (100%)	101 (86%)	651 (86%)	121 (88%)	344 (82%)	186 (92%)
Year of surgery, n (%)							
2009	3 (0%)	0 (0%)	0 (0%)	3 (0%)	1 (1%)	0 (0%)	2 (1%)
2010	132 (14%)	3 (8%)	10 (9%)	119 (16%)	20 (14%)	72 (17%)	27 (13%)
2011	180 (20%)	5 (14%)	15 (13%)	160 (21%)	26 (19%)	85 (20%)	49 (24%)
2012	209 (23%)	8 (22%)	21 (18%)	180 (24%)	31 (22%)	103 (25%)	46 (23%)
2013	222 (24%)	11 (30%)	45 (38%)	166 (22%)	32 (23%)	91 (22%)	43 (21%)
2014	165 (18%)	10 (27%)	27 (23%)	128 (17%)	28 (20%)	65 (16%)	35 (17%)
2015	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)
Marital status, n (%)							
Married	583 (64%)	20 (54%)	86 (73%)	477 (63%)	120 (87%)	249 (60%)	108 (53%)
Common-law/living with partner	126 (14%)	7 (19%)	17 (14%)	102 (13%)	18 (13%)	52 (12%)	32 (16%)
Separated or divorced	83 (9%)	4 (11%)	6 (5%)	73 (10%)	0 (0%)	42 (10%)	31 (15%)
Never married	107 (12%)	6 (16%)	8 (7%)	93 (12%)	0 (0%)	65 (16%)	28 (14%)
Widowed	13 (1%)	0 (0%)	1 (1%)	12 (2%)	0 (0%)	9 (2%)	3 (1%)
Donor evaluation <100 km of home, n (%)	546 (60%)	21 (57%)	67 (57%)	458 (61%)	85 (62%)	255 (61%)	118 (58%)

Variable	All donors (N = 912)	Donation-type group (N = 912): Non-directed donors (n = 37)	Kidney paired donors (n = 118)	All other donors (n = 757)	Relationship-type group (N = 757)[2]: Spousal donors (n = 138)	Closely related donors (n = 417)	Unrelated donors (n = 202)
Employment status, n (%)							
Employed (full-time)	578 (63%)	18 (49%)	79 (67%)	481 (64%)	70 (51%)	275 (66%)	136 (67%)
Employed (part-time)	123 (13%)	10 (27%)	16 (14%)	123 (13%)	25 (18%)	46 (11%)	26 (13%)
Retired	87 (10%)	2 (5%)	13 (11%)	72 (10%)	21 (15%)	38 (9%)	13 (6%)
Other	124 (14%)	7 (19%)	20 (17%)	107 (14%)	22 (16%)	58 (14%)	27 (13%)
Education level, n (%)							
Primary School	22 (2%)	0 (0%)	3 (3%)	19 (3%)	3 (2%)	11 (3%)	5 (2%)
Secondary school	288 (32%)	10 (27%)	27 (23%)	251 (33%)	41 (30%)	139 (33%)	71 (35%)
Trade school	61 (7%)	1 (3%)	8 (7%)	52 (7%)	12 (9%)	25 (6%)	15 (7%)
College	233 (26%)	8 (22%)	30 (25%)	195 (26%)	41 (30%)	101 (24%)	53 (26%)
University	308 (34%)	18 (49%)	40 (42%)	240 (32%)	41 (30%)	141 (34%)	58 (29%)
Annual household income, n (%)[1]							
<$10,000	11 of 668 (2%)	2 of 29 (7%)	1 of 96 (1%)	8 of 543 (1%)	1 of 96 (1%)	4 of 296 (1%)	3 of 151 (2%)
$10,000 to $20,000	26 of 668 (4%)	2 of 29 (7%)	3 of 96 (3%)	21 of 543 (4%)	3 of 96 (3%)	11 of 296 (4%)	7 of 151 (5%)
$20,000 to $30,000	35 of 668 (5%)	3 of 29 (10%)	7 of 96 (7%)	25 of 543 (5%)	6 of 96 (6%)	11 of 296 (94%)	8 of 151 (5%)
$30,000 to $40,000	46 of 668 (7%)	3 of 29 (10%)	2 of 96 (2%)	41 of 543 (8%)	11 of 96 (11%)	21 of 296 (7%)	9 of 151 (6%)
$40,000 to $50,000	42 of 668 (6%)	3 of 29 (10%)	2 of 96 (2%)	37 of 543 (7%)	7 of 96 (7%)	20 of 296 (7%)	10 of 151 (7%)
$50,000 to $60,000	40 of 668 (6%)	2 of 29 (7%)	8 of 96 (8%)	30 of 543 (6%)	6 of 96 (6%)	16 of 296 (5%)	8 of 151 (5.3%)
$60,000 to $70,000	65 of 668 (10%)	2 of 29 (7%)	6 of 96 (6%)	57 of 543 (11%)	12 of 96 (13%)	31 of 296 (10%)	14 of 151 (9%)
$70,000 to $80,000	60 of 668 (9%)	1 of 29 (3%)	15 of 96 (16%)	44 of 543 (8%)	6 of 96 (6%)	26 of 296 (9%)	12 of 151 (8%)
$80,000 to $90,000	57 of 668 (9%)	2 of 29 (7%)	6 of 96 (6%)	49 of 543 (9%)	8 of 96 (8%)	29 of 296 (10%)	12 of 151 (8%)
$90,000 to $100,000	51 of 668 (8%)	1 of 29 (3%)	5 of 96 (5%)	45 of 543 (8%)	8 of 96 (8%)	24 of 296 (8%)	13 of 151 (9%)
>$100,000	235 of 668 (35%)	8 of 29 (28%)	41 of 96 (43%)	186 of 543 (34%)	28 of 96 (29%)	103 of 296 (35%)	55 of 151 (36%)
Annual household income, median (IQR), (CAD 2016)[3]	$81,659 (48,449-114,730)	$62,271 (36,253- 105,937)	$91,598 (63,127-114,730)	$81,376 (47,867-114,631)	$76,607 (47,580-113,047)	$82,608 (50,923-114,532)	$85,203 (47,688-114,730)

Variable	All donors (N = 912)	Donation-type group (N = 912)			Relationship-type group (N = 757)[2]		
		Non-directed donors (n = 37)	Kidney paired donors (n = 118)	All other donors (n = 757)	Spousal donors (n = 138)	Closely related donors (n = 417)	Unrelated donors (n = 202)
Province of transplant centre, n (%)							
Alberta	132 (15%)	5 (14%)	14 (12%)	115 (15%)	10 (7%)	70 (17%)	35 (17%)
British Columbia	274 (30%)	13 (35%)	47 (48%)	204 (27%)	41 (30%)	106 (25%)	57 (28%)
Manitoba	37 (4%)	0 (0%)	2 (2%)	35 (5%)	2 (1%)	27 (6%)	6 (3%)
Nova Scotia	42 (5%)	1 (3%)	4 (3%)	37 (5%)	4 (3%)	27 (6%)	6 (3%)
Ontario	379 (42%)	18 (48%)	38 (32%)	323 (43%)	67 (49%)	164 (39%)	92 (46%)
Quebec	46 (5%)	0 (0%)	3 (3%)	43 (6%)	14 (10%)	23 (6%)	6 (3%)
Relationship to recipient, n (%)							
Sibling	211 (23%)	0 (0%)	0 (0%)	211 (28%)	0 (0%)	211 (51%)	0 (0%)
Parent	128 (14%)	0 (0%)	0 (0%)	128 (17%)	0 (0%)	128 (31%)	0 (0%)
Son/daughter	78 (9%)	0 (0%)	0 (0%)	78 (10%)	0 (0%)	78 (19%)	0 (0%)
Spouse/partner	138 (15%)	0 (0%)	0 (0%)	138 (18%)	138 (100%)	0 (0%)	0 (0%)
Friend	104 (11%)	0 (0%)	0 (0%)	104 (14%)	0 (0%)	0 (0%)	104 (51%)
Don't know recipient	155 (17%)	37 (100%)	118 (100%)	0 (%)	0 (0%)	0 (0%)	0 (0%)
Other	98 (11%)	0 (0%)	0 (0%)	98 (13%)	0 (0%)	0 (0%)	98 (49%)

[1] Annual household income was an optional response and thus only available for 668 donors. Responses for all other variables were complete.
[2] Among donors not participating in non-directed or kidney paired donations.
[3] Median (IQR) income available from all donors: derived from mid-point of imputed categorical values inflated to 2016 Canadian dollars (i.e. $15,000 when the donor reported an income level of $10,000 to $20,000). An income of $110,000 was used for donors reporting household incomes >$100,000, and $5000 was used for donors reporting <$10,000.

5.1.2 Costs Incurred and Resources Consumed

All costs are reported in 2016 Canadian dollars (CAD) as means (standard deviation) and medians (25th percentile-75th percentile).

For all donors, the mean total cost (sum of direct and indirect costs) was $4790 (6122), and median total cost was $2616 (1073-6120). The mean direct cost incurred (from the beginning of donor evaluation up to three months post-donation) was $2110 (2505), and the median direct cost was $1302 (581-2674) (Table 5). The mean indirect cost incurred by all donors was $2679 (5478), and median indirect cost was $22 (0-2770).

Table 5. Direct, indirect, and total incurred costs (CAD), for all donors, including those incurring no expenses (n = 912).

Cost type	Costs incurred, all donors (CAD)	
	Mean (SD)	Median (25th-75th percentile)
Direct	2110 (2505)	1302 (581-2674)
Indirect	2679 (5478)	22 (0-2770)
Total	4790 (6122)	2616 (1073-6120)

Approximately 23% of living kidney donors incurred less than $1000 in total costs throughout the donation process (Figure 4). However, about 28% of donors experienced costs >$5500, which is the most common maximum amount of reimbursement offered by provincial programs. Beyond this, 13.3% of donors experienced total costs over $10,000 and 8.6% of donors incurred total costs greater than 25% of their household income.

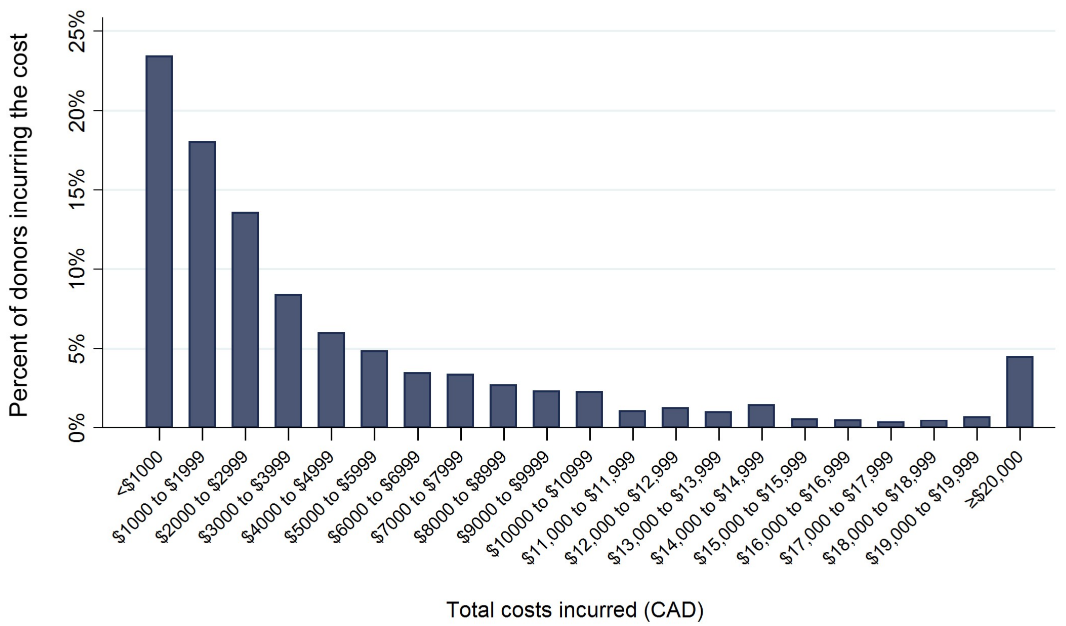


Figure 4. Relative frequency of total costs incurred by living kidney donors (n = 912).

5.1.2.1 Direct Costs and Resources

Among donors incurring direct costs, the greatest cost was for ground travel, followed by non-hospital paid accommodation (Table 6). Incurred expenses most frequently reported by donors were for ground travel (90%), parking (90%), and medications (77%).

Donors reported a median of 10 return trips to transplant centres to see health professionals. Air travel was reported by 21% of donors with a median of 1 return flight. Among donors reporting air travel, 71% had friends and/or family who incurred flight costs while accompanying them throughout the donation process. Approximately 45% of donors reported costs for non-hospital paid accommodation, and stayed a median of 4 nights. Additionally, 38% of donors reported that friends and/or family incurred accommodation costs while accompanying them during their kidney donation.

Among those reporting the outcome or consuming the resource, the mean costs per donor were $1113 for ground travel, $1063 for non-hospital paid accommodation, $781 for accommodation with family or friends, $294 for hospital accommodation, $138 for parking, and $69 for pain medications or antibiotics post-surgery. For donors who flew during the evaluation and donation process, the average cost of air travel was $639.

For all donors (including those reporting no out-of-pocket expenses for any cost category), the average costs per donor were $999 for ground travel, $474 for non-hospital paid accommodation, $203 for accommodation with family or friends, $137 for air travel, $133 for hospital accommodation, $122 for parking, and $43 for medications.

Table 6. Direct costs (2016 CAD) incurred and resource use from 3-month economic assessment.

Cost category	Description	Donors reporting resource, n (%)[2]	Resource use[3]		Costs for donors reporting expense (CAD)		Costs for all donors, n = 912 (CAD)	
			Units	Median (IQR)	Average (SD)	Median (IQR)	Average (SD)	Median (IQR)
Travel	Ground travel	818 (90%)	# Return trips	10 (7-15)	1113 (1623)	513 (194-1261)	999 (1574)	407 (129-1146)
	Air travel	195 (21%)	# Return trips	1 (1-2)	639 (462)	561 (327-757)	137 (338)	0 (0-0)
	Parking[1]	824 (90%)	# Days of paid parking	7 (4-11)	138 (292)	104 (55-165)	122 (278)	90 (42-158)
Accommodation	Family and friends[1]	287 (31%)	# Nights	6 (3-12)	781 (1497)	319 (160-774)	203 (835)	0 (0-42)
	Non-hospital paid	407 (45%)	# Nights	4 (2-8)	1063 (1711)	618 (227-1249)	474 (1258)	0 (0-540)
	Hospital[1]	414 (45%)	# Nights	4 (3-5)	294 (522)	105 (48-341)	133 (381)	0 (0-101)
Medication	Post-donation pain medication or antibiotics after hospital discharge[1]	700 (77%)	Drugs taken (yes/no)	n/a	69 (211)	33 (21-63)	43 (170)	16 (0-45)

[1] Self-reported costs (not micro- costed).

[2] Number of donors reporting resource use (even if no out-of-pocket expenses were incurred).

[3] In donors reporting the outcome; medications provided in hospital are covered through universal health care. Some outpatient drugs are also covered through universal healthcare plans for segments of the population (e.g. in the province of Ontario, Canada those 65 years and older have universal drug benefits).

5.1.2.2 Indirect Costs and Resources

Across all donors, 707 (78%) reported that they were unable to go to work for a median of 35 days following surgery (Table 7). Lost income for donors who were unable to work, including time off *with or without* loss of pay (i.e. use of sick days or vacation time), was an average of $8702 per donor. Moreover, 39% of all donors reported that time away from work resulted in lost wages, with a median of 20 days unpaid. Among donors who reported unpaid time off work, the average loss of wages was $6322 per donor.

Across all donors, 740 (81%) were unable to perform household activities for a median of 15 days post-surgery, and 516 (57%) were unable to care for dependents for a median of 14 days post-surgery. Among donors reporting productivity losses, household and dependent out-of-pocket costs incurred were an average of $736 and $977 per donor, respectively.

For all 912 donors (including those reporting no productivity losses), the mean costs per donor were $6762 for inability to work, $2470 for lost wages, $112 for lost household productivity, and $97 for caring for dependents.

Table 7. Indirect costs (2016 CAD) incurred and resource use, up to 3-month economic assessment.

Cost category	Description	Donors reporting resource, n (%)[4]	Number of days[5]	Costs for donors reporting expense (CAD)		Costs for all donors, n = 912 (CAD)	
			Median (IQR)	Average (SD)	Median (IQR)	Average (SD)	Median (IQR)
Lost income*	Unable to work if employed[1]	707 (78%)	35 (15-60)	8702 (6709)	7488 (3391-12,447)	6762 (6935)	5572 (597-11,119)
	Unpaid time off work[2]	356 (39%)	20 (9-42)	6322 (6779)	4055 (1881-8956)	2470 (5239)	0 (0-2579)
Lost productivity	Unable to perform household activities[3]	740 (81%)	15 (10-30)	736 (2881)	320 (204-531)	112 (1149)	0 (0-0)
	Unable to care for dependants[3]	516 (57%)	14 (7-25)	977 (2159)	344 (172-657)	97 (740)	0 (0-0)

* Time valued at provincial average wage rate: assuming 8-hour work day
[1] With *or without* loss of pay.
[2] Included in calculation of total cost.
[3] Self-reported costs (not micro-costed).
[4] Number of donors reporting resource use (even if no out-of-pocket expenses were incurred).
[5] In donors reporting the outcome.

5.2 Univariate Analysis of Costs

This section describes differences in direct, indirect, and total costs borne by donors contrasting donation-type and relationship-type groups within the Canadian living kidney donor population. Costs are reported in 2016 Canadian dollars as means and mean differences with 95% confidence intervals.

5.2.1 Costs Incurred by Donation-Type Groups

For the period beginning with donor evaluation and ending at 3 months post-surgery, *non-directed donors* (n = 37) incurred average direct, indirect, and total costs of $2095, $2550, and $4645, respectively (Table 8). *Kidney paired donors* (n = 118) incurred average direct, indirect, and total costs of $2394, $2045, and $4439, respectively. The mean direct, indirect, and total expenses incurred by *all other donors* (n = 757) were $2067, $2785, and $4852, respectively.

There were no significant differences in the mean direct, indirect, and total costs incurred by either *non-directed donors* or *kidney paired donors,* as compared to *all other donors.* The mean differences in total costs experienced by *non-directed donors* and *kidney paired donors* relative to the total costs incurred by *all other donors* were -$207 (-2167 to 1753) and -$413 (-1537 to 712), respectively (Figure 5). For *non-directed donors*, the mean differences in direct and indirect costs incurred compared to *all other donors* were $28 (804 to 859) and -$235 (-1482 to 1951), respectively. For *kidney paired donors*, the mean differences in direct and indirect costs relative to *all other donors* were $327 (-237 to 890) and -$740 (-1595 to 116), respectively.

Table 8. Unadjusted direct, indirect, and total costs (2016 CAD) incurred by living kidney donors, by donation-type group (n = 912).

	All Other Donors		Non-Directed Donors		Kidney Paired Donors		All Other Donors	Non-Directed Donors	Kidney Paired Donors
Cost type	Mean (95% CI)[1]	MD (95% CI)[2]	Mean (95% CI)[1]	MD (95% CI)[2]	Mean (95% CI)[1]	MD (95% CI)[2]	Median (IQR)	Median (IQR)	Median (IQR)
Direct	2067 (1879 to 2255)	*ref*	2095 (1266 to 2923)	28 (-804 to 859)	2394 (2040 to 2748)	327 (-237 to 890)	1221 (551-2550)	1984 (702-2639)	2060 (1022-3263)
Indirect	2785 (2372 to 3197)	*ref*	2550 (810 to 4290)	-235 (-1482 to 1951)	2045 (1366 to 2724)	-740 (-1595 to 116)	40 (0-2832)	104 (0-2499)	3 (0-2359)
Total	4852 (4396 to 5307)	*ref*	4645 (2694 to 6595)	-207 (-2167 to 1753)	4439 (3607 to 5271)	-413 (-1537 to 712)	2520 (1016-6230)	2695 (1191-4477)	2970 (1639-5933)

[1] Bootstrapped mean and 95% confidence interval.
[2] MD = mean difference, as marginal effect from univariate generalized linear model.

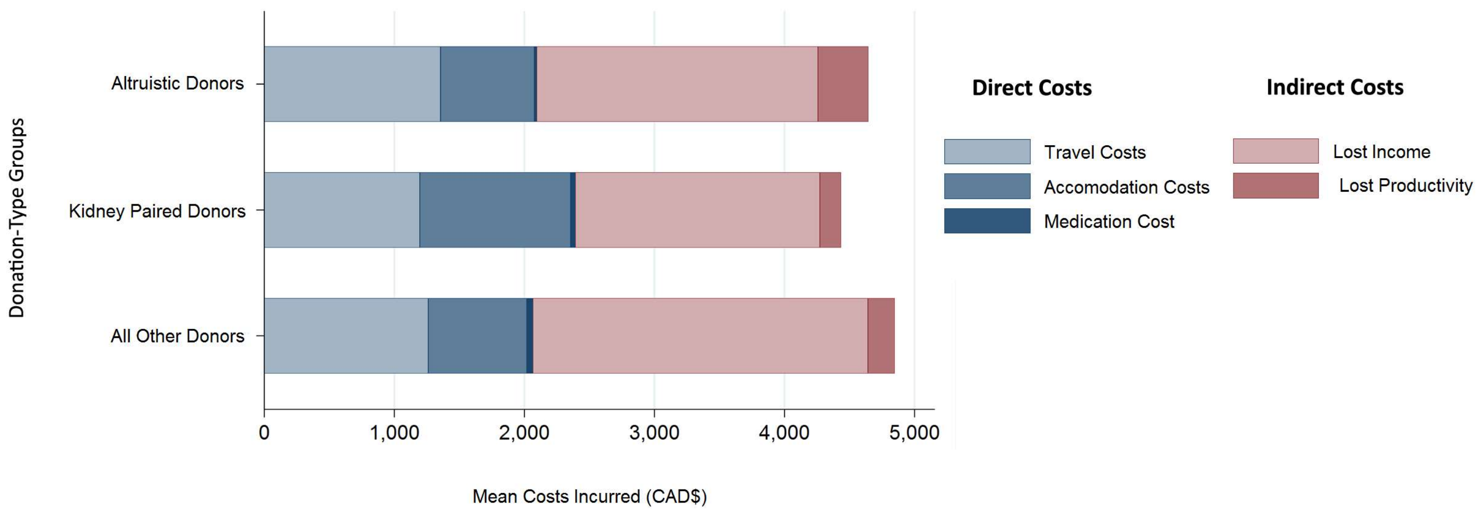


Figure 5. Mean direct and indirect costs by cost category and donation-type group.

5.2.2 Costs Incurred by Relationship-Type Groups

As of three months post-donation, *spousal donors* (n = 138) incurred average direct, indirect, and total costs of $2379, $2947, and $5326, respectively (Table 9). *Closely related donors* (n = 417) incurred average direct, indirect, and total costs of $1984, $2963, and $4947, respectively. And finally, the mean direct, indirect, and total expenses incurred by *unrelated donors* (n = 202) were $2026, $2305, and $4330, respectively.

There were no significant differences in the mean direct, indirect, and total costs incurred by either *closely related donors* or *unrelated donors,* as compared to *spousal donors.* For *closely related donors*, the mean difference in total costs relative to *spousal donors* was -$379 (-1693 to 935). For *unrelated donors,* the mean difference in total costs compared to *spousal donors* was -$996 (-2393 to 402).

The mean differences in direct costs incurred by *closely related donors* and *unrelated donors* compared to those incurred by *spousal donors* were -$395 (-943 to 153) and -$353 (-955 to 249), respectively (Figure 6). Mean differences in indirect costs compared to *spousal donors* were $16 (-1146 to 1178) for *closely related donors*, and -$642 (-1842 to 557) for *unrelated donors*.

Table 9. Unadjusted direct, indirect, and total costs (2016 CAD) incurred by living kidney donors, by relationship-type group (n = 757)[3].

	Spousal Donors		Closely Related Donors		Unrelated Donors		Spousal Donors	Closely Related Donors	Unrelated Donors
Cost type	Mean (95% CI)[1]	MD (95% CI)[2]	Mean (95% CI)[1]	MD (95% CI)[2]	Mean (95% CI)[1]	MD (95% CI)[2]	Median (IQR)	Median (IQR)	Median (IQR)
Direct	2379 (1815 to 2943)	*ref*	1984 (1750 to 2217)	-395 (-943 to 153)	2026 (1670 to 2381)	-353 (-955 to 249)	1289 (562-2471)	1193 (554-2574)	1214 (509-2473)
Indirect	2947 (1751 to 4143)	*ref*	2963 (2423 to 3503)	16 (-1146 to 1178)	2305 (1669 to 2941)	-642 (-1842 to 557)	139 (0-3034)	25 (0-2931)	15 (0-2668)
Total	5326 (3985 to 6667)	*ref*	4947 (4350 to 5544)	-379 (-1693 to 935)	4330 (3593 to 5068)	-996 (-2393 to 402)	2190 (1097-6480)	2629 (963-6159)	2493 (1043-6204)

[1] Bootstrapped mean and 95% confidence interval.
[2] MD = mean difference, as marginal effect from univariate generalized linear model.
[3] Among donors not participating in non-directed or kidney paired donations.

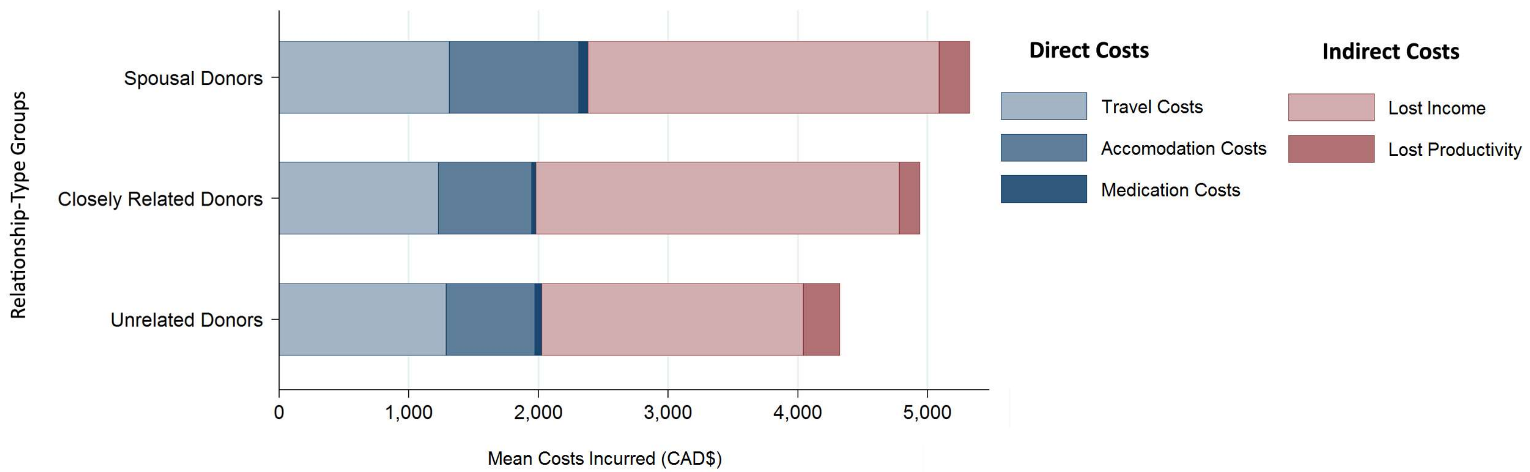


Figure 6. Mean direct and indirect costs by cost category and relationship-type group.

5.3 Multivariable Analyses of Costs

This section describes the adjusted average marginal effects of donation-type, relationship-type, and demographic characteristics on mean direct, indirect, and total costs incurred by living kidney donors during the donation process. Marginal effects are reported as mean differences and 95% confidence intervals in costs (in 2016 Canadian dollars) compared to a reference category. Average marginal costs are adjusted for age, sex, income level, Clavien-Dindo grade, and transplant centre.

5.3.1 Primary Analysis

In adjusted analyses, the mean direct costs experienced by either *non-directed donors* or *kidney paired donors* were not significantly different compared to the direct costs incurred by *all other donors* (Table 10). The mean differences in direct costs borne by *non-directed donors* and *kidney paired donors* relative to *all other donors* were $119 (-644 to 882) and $321 (-54 to 695), respectively. Adjusted mean indirect and total costs incurred by either *non-directed donors* or *kidney paired donors* were not significantly different than those experienced by *all other donors*. Mean differences in indirect and total costs, compared to *all other donors,* were respectively -$351 (-1742 to 1040) and -$434 (-1632 to 765) for *non-directed donors*. For *kidney paired donors,* mean differences in indirect and total costs relative to *all other donors* were -$252 (-958 to 453) and $120 (-786 to 1026), respectively.

The mean indirect out-of-pocket expenses incurred by *spousal donors* were not significantly different compared to either *closely related donors* or *unrelated donors.* In adjusted analyses, mean differences in indirect costs experienced by *closely related donors* and *unrelated donors* relative to *spousal donors* were $50 (-1243 to 1343) and -$856 (-1834 to 122), respectively. Mean differences in direct and total costs incurred by *closely related donors* and *unrelated donors* compared to the referent group of *spousal donors* were not significant. Mean differences in direct and total costs, compared to *spousal donors,* were respectively -$235 (-660 to 190) and -$332 (-1565 to 901) for *closely related donors*. For *unrelated donors*, mean differences in direct and total costs relative to *spousal donors* were -$122 (-851 to 606) and -$1034 (-2136 to 67), respectively.

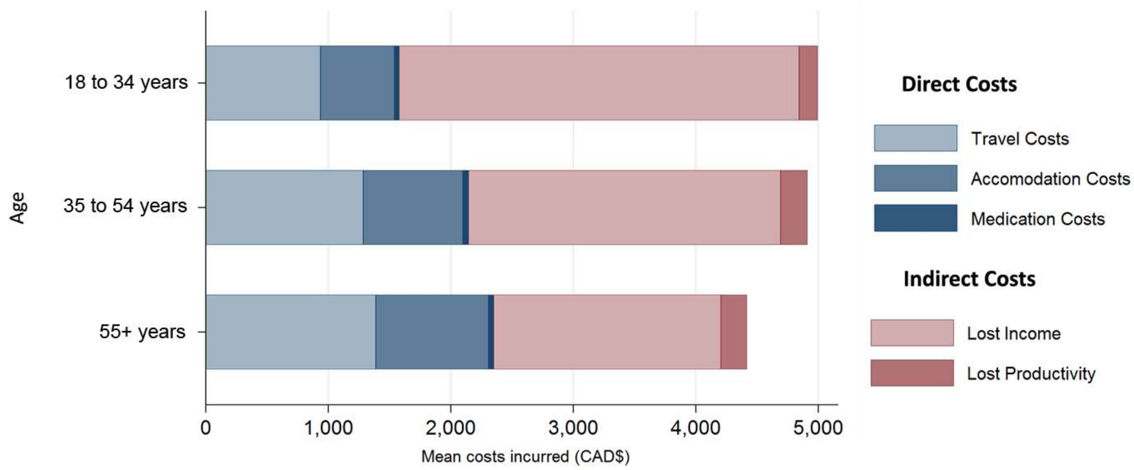
5.3.2 Secondary Analyses

In adjusted analyses, donors who lived further from the transplant centre in which they were evaluated (≥100 km) experienced significantly higher direct and total costs, as compared to donors who lived closer (<100 km); mean differences in indirect costs between these two groups was non-significant.

Though older and younger donors did not significantly differ in total costs incurred, there were significant differences in indirect and direct costs between the groups (Figure 7). In multivariable analyses, donors in the 35 to 54 year-old and 55+ year-old age groups experienced significantly higher mean *direct* costs compared to the referent 18 to 34 year-old donor group (Table 10). Donors 55 years of age and older faced significantly lower mean *indirect* costs compared to 18 to 34 year-old donors (mean difference = -$1543 [-2622 to -465], $p = 0.005$). The mean differences in *total* costs compared to 18 to 24 year-old donors were not significant for any age group.

There was a significant trend of an increasing number of trips to transplant centres for evaluation ($p = 0.03$) and higher travel costs ($p < 0.001$), as well as greater number of nights in paid accommodation ($p < 0.001$) and higher accommodation costs across older age groups ($p = 0.004$). Conversely, the number of days off work ($p < 0.001$) and lost wages significantly decreased across older age groups ($p < 0.001$).

Figure 7. The mean direct and indirect costs incurred by donors by age category.



In adjusted analyses, the mean costs incurred by male donors and female donors did not differ significantly; mean differences in direct and indirect costs for female donors relative to male donors were -\$75 (-381 to 231) and -\$506 (-152 to 1164), respectively. The indirect and total costs experienced by employed donors were significantly higher than both unemployed donors and retired donors. Mean differences in indirect and total costs incurred, compared to employed donors, were respectively -\$1838 (-2580 to -1096, $p < 0.001$) and -\$2433 (-3369 to -1497, $p < 0.001$) for unemployed donors, and -\$2614 (-3214 to -2014, $p < 0.001$) and -\$2482 (-3262 to -1702, $p < 0.001$) for retired donors. Compared to donor households making less than \$20,000 in annual income, the average marginal effect of household income (across all levels of income ≥\$20,000) on donor direct, indirect, and total costs was non-significant.

Compared to those donating in Ontario, donors who donated their kidneys in Alberta and Manitoba experienced significantly lower mean direct costs. Mean differences in direct expenses compared to Ontarian donors were -\$594 (-1001 to -187, $p = 0.004$) in Alberta and -\$1032 (-1711 to -354, $p = 0.003$) in Manitoba. Indirect and total costs of donating in any province did not differ significantly compared to donating in Ontario.

Table 10. Adjusted[1] average marginal effects of demographic variables on direct, indirect, and total costs (2016 CAD) incurred by living kidney donors (n = 912).

Variable	Direct costs (CAD)		Indirect costs (CAD)		Total costs (CAD)	
	Marginal effect (95% CI)	*p*	Marginal effect (95% CI)	*p*	Marginal effect (95% CI)	*p*
Donation-type						
All other donors	*ref*		*ref*		*ref*	
Non-directed donors	119 (-644 to 882)	0.76	-351 (-1742 to 1040)	0.62	-434 (-1632 to 765)	0.48
Kidney paired donors	321 (-54 to 695)	0.09	-252 (-958 to 453)	0.48	120 (-786 to 1026)	0.80
Relationship-type[2]						
Spousal donors	*ref*		*ref*		*ref*	
Closely related donors	-235 (-660 to 190)	0.28	50 (-1243 to 1343)	0.94	-332 (-1565 to 901)	0.60
Unrelated donors	-122 (-851 to 606)	0.74	-856 (-1834 to 122)	0.09	-1034 (-2136 to 67)	0.07
Distance from centre						
<100 km	*ref*		*ref*		*ref*	
≥100 km	2645 (2229 to 3060)	<0.001	-235 (-896 to 425)	0.49	2583 (1813 to 3353)	<0.001
Sex						
Male	*ref*		*ref*		*ref*	
Female	-75 (-381 to 231)	0.63	-506 (-152 to 1164)	0.13	-566 (-10 to 1142)	0.054
Age (years)						
<35	*ref*		*ref*		*ref*	
35 to 54	570 (115 to 1025)	0.01	-762 (-1939 to 415)	0.20	-70 (-1392 to 1252)	0.92
55+	712 (141 to 1283)	0.01	-1543 (-2622 to -465)	0.005	-597 (-1786 to 593)	0.33
Race						
White	*ref*		*ref*		*ref*	
Non-White	-234 (-673 to 205)	0.30	-390 (-1553 to 772)	0.51	-403 (-1641 to 835)	0.52

Variable	Direct costs (CAD)		Indirect costs (CAD)		Total costs (CAD)	
	Marginal effect (95% CI)	*p*	Marginal effect (95% CI)	*p*	Marginal effect (95% CI)	*p*
Income (CAD)						
<$20,000	*ref*		*ref*		*ref*	
$20,000 to $40,000	759 (-144 to 1663)	0.10	617 (-1990 to 3224)	0.64	1569 (-1099 to 4237)	0.25
$40,000 to $60,000	742 (-129 to 1613)	0.09	-915 (-3070 to 1241)	0.40	14 (-2217 to 2244)	0.99
$60,000 to $80,000	752 (-113 to 1618)	0.09	-585 (-3048 to 1877)	0.64	329 (-2038 to 2697)	0.79
$80,000 to $100,000	319 (-502 to 1141)	0.44	-1544 (-4050 to 961)	0.23	-993 (-3625 to 1639)	0.46
>$100,000	346 (-481 to 1173)	0.41	-1894 (-4011 to 223)	0.08	-1391 (-3451 to 669)	0.18
Employment status						
Employed	*ref*		*ref*		*ref*	
Unemployed	-551 (-1114 to 11)	0.06	-1838 (-2580 to -1096)	<0.001	-2433 (-3369 to -1497)	<0.001
Retired	-190 (-542 to 162)	0.29	-2614 (-3214 to -2014)	<0.001	-2482 (-3262 to -1702)	<0.001
Other	112 (-706 to 931)	0.79	-204 (-2054 to 1646)	0.83	-218 (-2178 to 1742)	0.83
Province of transplant centre						
Ontario	*ref*		*ref*		*ref*	
Alberta	-594 (-1001 to -187)	0.004	764 (-586 to 2114)	0.27	212 (-1086 to 1510)	0.75
British Columbia	77 (-317 to 471)	0.70	-45 (-911 to 820)	0.92	177 (-747 to 1100)	0.71
Manitoba	-1032 (-1711 to -354)	0.003	480 (-1652 to 2612)	0.66	-355 (-2407 to 1698)	0.74
Nova Scotia	312 (-454 to 1078)	0.42	-405 (-1997 to 1187)	0.62	0 (-1740 to 1739)	1.00
Quebec	106 (-743 to 956)	0.81	375 (-1503 to 2253)	0.70	421 (-1625 to 2466)	0.69

[1] Adjusted for age, sex, income, Clavien-Dindo grade, and transplant centre.
[2] Among donors not participating in non-directed or kidney paired donations (n = 757).

Chapter 6

6 Discussion and Conclusion

The following sections will discuss the findings of this work in the context of the research questions and hypotheses, draw comparisons to the existing body of evidence, evaluate the broader societal implications of the results, assess the work's strengths and weaknesses, and project the necessary next steps and future directions within the field of living kidney donor outcomes.

6.1 Overview

An overarching goal of this work was to comprehensively characterize the resources and costs of living kidney donation at a granular level. To our knowledge, our study is the largest of its kind to prospectively capture the economic outcomes of donors and the first to evaluate whether some types/groups of donors experience higher costs than others. Furthermore, our inclusion of kidney paired donors, who face unique donation circumstances, and a larger sample size, increase the generalizability and accuracy of our estimates.

Given the consensus within the transplant community and among the general public that living kidney donors should not be disadvantaged by their gift of life, removing significant financial hardship is paramount to upholding a just healthcare system.[102,104,178,179] Our finding that donors experience an average total cost of $4790 (median = $2616) throughout the donation process adds to the growing body of evidence that living kidney donors experience substantial financial losses due to donation. We anticipated that our large sample size and a comprehensive micro-costing approach would offer a more accurate estimate of donor expenses, and more specifically, that our estimates would exceed those within the existing literature. Our cohort of 912 living kidney donors incurred an average direct cost of $2110 during donation, higher than estimates of $1780 (2008 CAD) and $1157 (USD) from previous studies.[1,98] We found that 18% and 30% of donors experience costs exceeding $8000 and $5000, respectively: greater than estimates previously reported by Klarenbach *et al.* (15% of donors with >$8000 total costs; 2008 CAD) and Rodrigue *et al*. (20% of donors with >$5000 total costs; USD).[1,98] Beyond this, 13.3% of donors experienced costs in excess of $10,000 and 8.6% of donors incurred costs >25% of their annual household income. Importantly, 28% of donors incurred total costs exceeding the upper limit of reimbursement offered in Canada, leaving them with little recourse to shoulder the additional financial burden. With growing transplant waitlists and stagnating rates of donation, the high costs we observed demonstrate a need to limit the impact of financial disincentives on living kidney donation.[9]

To our knowledge, our study is the first to explore important potential donor subgroup differences. The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors highlighted the need to study approaches to reduce financial disincentives to living donation, "with particular attention to impact on current disparities in living donor kidney transplantation".[44] Dew *et al.* noted gaps in the available evidence regarding the financial outcomes of donors related to their recipients compared to unrelated donors.[180] Our comparisons of costs incurred between donation-type and relationship-type groups revealed that there are no meaningful differences in the economic outcomes of these donors. The finding is reassuring given the increasingly critical role kidney paired donation has assumed in offering life-extending treatment to patients with end-stage kidney disease. Kidney paired donation has been responsible for over 500 transplants in Canada since 2009, at a time during which rates of donation have plateaued, demonstrating the vital role these donors play in meeting the growing demand for kidneys. The finding that Canadian kidney paired donors do not face higher costs than other donors is encouraging for the continued success of the program, particularly in the potential inclusion of directed compatible donor-recipient pairs.[110] Spousal donors are responsible for about 15% of transplants in Canada, and given the potential additional financial burden of both the donor and recipient undergoing major surgery, it is encouraging that this sizeable group of donors does not shoulder significantly greater indirect and total costs related to loss of income or home productivity, as previously hypothesized. The findings of our study help contribute to the body of evidence supporting improved management of the financial consequences of living donation and the continued growth of kidney paired donation in Canada.

In our secondary analyses, we explored associations between demographic characteristics and incurred costs, the first time this analysis has been undertaken within a Canadian group of donors. Our findings that living >100 km from transplant evaluation centre and being employed are significantly associated with incurred total costs may guide informed consent practices and prepare donors for the burden of costs they may encounter during the evaluation and donation process. Rodrigue *et al.* also found that longer distance to transplant program was significantly correlated to financial loss.[98] Our results lend support to previous work in Australia describing distinct differences between the financial outcomes of donors living in urban centres as compared to rural donors; the study's authors argue that these differences in costs reflect a "rural disadvantage".[181]

Though total costs did not vary across age groups, the drivers of costs differed between younger and older living kidney donors. Our finding that older donors incurred higher direct costs possibly reflects additional testing and evaluation in this population due to comorbidities, and indeed older donors did take more trips to their transplant evaluation centre and incurred higher travel and accommodation costs. Younger donors, on the other hand, encountered higher indirect costs than older donors, which reflects differences in employment and increased number of unpaid days off work and lost wages for younger donors. Recognizing these important differences in direct and indirect costs incurred by donors will enable transplant programs to better prepare donor candidates for the financial losses they may encounter during donation.

6.2 Implications

In recent years, the rate of living kidney donation in Canada has plateaued despite an ever increasing demand.[9] In the U.S. these rates have decreased, a finding that has been linked to recent economic decline, and beyond this, evidence suggests that the disparity in rates of living donation between low-income and high-income groups has widened over this same period.[116,119] A survey of transplant candidates revealed substantial concern and reluctance about living kidney donation due to the financial consequences encountered by donors.[182]

A report from Israel demonstrated that the implementation of legislation which reduced financial disincentives substantially increased the rates of living kidney donation.[183] There is longstanding consensus within the transplant community that donating one's kidney should be a financially neutral act.[104] A report by Hays *et al.* offered an operational definition and a framework for financial neutrality that included medical costs, travel costs, accommodation costs, and lost wages.[20] The authors further argued that financial costs affect donor decision making and that achieving financial neutrality would serve to increase living donation rates.[20]

A consensus conference on best practices in living kidney donation developed a set of recommendations on reducing financial barriers to donation.[184] In their report, the authors argue for a standardized system of reimbursement, legislation that protects employed donors, development of a financial toolkit , and collection of granular data on costs incurred by donors.[184] Rudow *et al.* reiterated these practical recommendations by arguing that cost-effective reimbursement is possible by leveraging the cost savings associated with living donation.[185]

Our findings work to advance several of these recommendations, particularly in offering the granular cost data that allows for the implementation of evidence-based patient advocacy and education initiatives. This work offers the most comprehensive and granular understanding of the costs incurred by donors, and the demographic factors associated with these costs, to date. Our findings support the development of equation models (to estimate the costs donor candidates may encounter), and a financial toolkit (which may be used by transplant programs to communicate the financial risks of donation and refer donors to appropriate resources and services): addressing key evidence gaps behind consensus recommendations offered by Tushla *et al*. in their report.[184] Beyond this, understanding and quantifying the economic outcomes of living donation is paramount to guiding donor informed consent.

Rudow *et al.* argue that expansions of living kidney donation must be implemented with knowledge of the risks involved; our finding that kidney paired donors do not face financial disadvantages compared to other donors ensures that this group of Canadian donors is protected.[185]

There is substantial variation in the restrictions and upper limits to reimbursement offered by provincial programs across Canada. The comprehensive understanding of these costs by type and magnitude will inform and guide policy governing reimbursement. With 28% of donors encountering costs in excess of the maximum amount offered by most programs, it is time to consider a national and comprehensive reimbursement strategy in Canada.

6.3 Strengths

A major strength of this report is the multi-centre prospective cohort study design, with 90% complete follow-up and rigourous statistical methods which accounted for any missing data (a modern defensible approach to imputation). The statistical analyses were done with special attention paid the characteristically right-skewed nature of cost data, and the primary comparisons related to donor relationship type and donation-type were prespecified to avoid inflating type 1 errors due to multiple testing. Our study captured the outcomes on 37% of living kidney donors who completed their donation within

Canada during our recruitment window (from 2009 to 2014). By collecting data for 912 donors across 12 transplant centres coast-to-coast, we circumvent the major criticisms of previous work for sampling a small, geographically limited, and homogenous group of donors that is unrepresentative of the larger population.[99]

This group of 912 donors represents a sample size over five times larger than the next leading study in its field, allowing for assessment of important subgroup differences in financial outcomes. Our sample of donors is the first to include donors participating in kidney paired donation, a program which began in 2009 in Canada and for which there is a paucity of outcome data in the literature.

Our pre-specified study protocol and cost-capturing instruments were informed by a pilot study, allowing for granular, comprehensive, and complete data collection.[1] We achieved 90% follow-up for the 3-month economics assessment, and our group of non-responders demographically corresponds to non-responders in previous reports: younger, non-white, un-married, and unemployed.[100]

6.4 Limitations

Some limitations of this work include the generalizability of the findings to other health care systems, potential underestimation of the true cost borne by donors, incomplete income data collection, and restricting the scope of cost capturing to living kidney donors who completed donation.

First, as Canada has a single payer universal health care system, these costs may not reflect the entire spectrum of costs that may arise in other settings. For example, medical costs were not considered during data collection, whereas these costs may be substantial in non-universal healthcare settings, particularly considering recommendations for long-term monitoring of living kidney donors for adverse outcomes.[186] There is broad consensus among transplant professionals that living donors should be provided insurance for long-term follow-up of medical issues related to donation.[186]

Second, post-hospital discharge prescription drug coverage varies across provinces; some donors would qualify for provincial universal outpatient drug coverage. As such, the reported medication costs may not reflect the true outpatient prescription drug cost. Beyond this, some donors reported that the transplant centre in which they completed their evaluation was within a city they reported as an air travel destination. To avoid unreasonable cost estimates for these patients, we assumed that their ground travel was local (e.g. hotel to hospital), and assumed no ground travel costs. Lastly, a three month window for cost collection may not capture expenses incurred by donors encountering long-term complications necessitating services such as physiotherapy or extended home care. These assumptions serve to underestimate the true direct costs experienced by these groups of donors.

Another limitation was the completeness of income data: reporting of income was optional and data was only available for ~73% of donors, and as such, complete-case analyses adjusted for income were restricted to this group of donors. We used donor postal codes and corresponding dissemination areas (by way of the Postal Code Conversion File provided by Statistics Canada) to obtain donor neighbourhood median household income and the Canadian Marginalization Index using 2006 census data; we performed sensitivity analyses by adding these variables to our model to impute missing donor household income: our primary results did not change.[187,188]

Lastly, cost capturing was restricted to only those living kidney donors who completed donation. Donor candidates who were evaluated but never donated encounter important financial consequences during testing and evaluation (e.g. time away from work for testing).

6.5 Future Directions

Living kidney donation is practiced under the tenet that potential risks borne by the donor are offset by the psychological benefits of altruism.[50] With the financial consequences of donation comprehensively evaluated, there is a pressing need to characterize the potential impact of costs on the psychosocial and quality of life outcomes of donors to determine if increased costs undermine this principle. Beyond this, the identification of gaps in reimbursement in Canada, through comparisons of costs incurred with reimbursement received, is necessary to appreciate donor net financial loss and the additional cost to the healthcare system to implement a comprehensive national program. Lastly, comprehensive and targeted characterization of both modifiable and non-modifiable drivers of costs incurred by donors would allow transplant programs to mitigate these financial risks and to better prepare and educate donor candidates they evaluate.

There is considerable debate within the transplant community on the ethics of incentivizing living kidney donation to increase donation rates.[102,104,178,189] Proponents of incentives argue that current legislation prohibiting compensation for donation are not rooted in evidence and propose that pilot studies are the next critical step to evaluate potential compensation of donors.[178] On the other hand, critics of incentivizing living donation liken the practice to paying for organs, and instead argue for removal of disincentives as a priority.[104]

6.6 Conclusion

In this report, we offer compelling evidence that many living kidney donors incur considerable financial costs while providing the gift of life to patients with end-stage kidney disease. Each living kidney donation saves the health care system about $250,000 over a five-year period, yet at the same time a substantial number of donors face costs in excess of reimbursement limits and are left to cope with significant financial loss. There is a pressing need to remove barriers to donation by leveraging these cost savings to develop a cost-effective national and comprehensive reimbursement program. Removing financial disincentives would not only ensure a just and equitable system, but may serve to increase rates of living donation. The results of this work can be used to guide the development of policies and programs that safeguard donors from unfair financial risk and work to meet the growing demand for kidney transplants.

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Appendices

Appendix A: LKD Study protocol approval by The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects

Western

Office of Research Ethics

The University of Western Ontario

[redacted]

Website: www.uwo.ca/research/ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. A.X. Garg
Review Number: **15974E** **Review Level:** Expedited
Review Date: June 09, 2009

Protocol Title: Long-term Effects of Becoming a Living Kidney Donor Study
Department and Institution: Nephrology, London Health Sciences Centre
Sponsor: CIHR-CANADIAN INSTITUTE OF HEALTH RESEARCH
Ethics Approval Date: June 09, 2009 **Expiry Date:** December 31, 2015
Documents Reviewed and Approved: UWO Protocol, Patient Letter of Information and Consent for Donors and Non-Donors (dated April 27, 2009), Patient Letter of Information and Consent for Donors and Non-Donors (3 Months) (dated April 27, 2009), Patient Letter of Information and Consent for Kidney Transplant Recipient (dated April 27, 2009), Genetic Sub-study Letter of Information and Consent (dated March 31, 2009), Sub-Study: Pregnancy Outcomes in Living Kidney Donors Patient Letter of Information and Consent (dated March 26, 2009), Pregnancy Sub-study Friendly Reminder Postcard. Release of Medical Information Form. Retention Cards.
Documents Received for Information: Protocol - February 9, 2009

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

[redacted]

Chair of HSREB: Dr. Joseph Gilbert

Ethics Officer to Contact for Further Information

☐ Janice Sutherland ☐ Elizabeth Wambolt ☑ Grace Kelly ☐ Denise Grafton

[redacted] [redacted] [redacted] [redacted]

This is an official document. Please retain the original in your files.

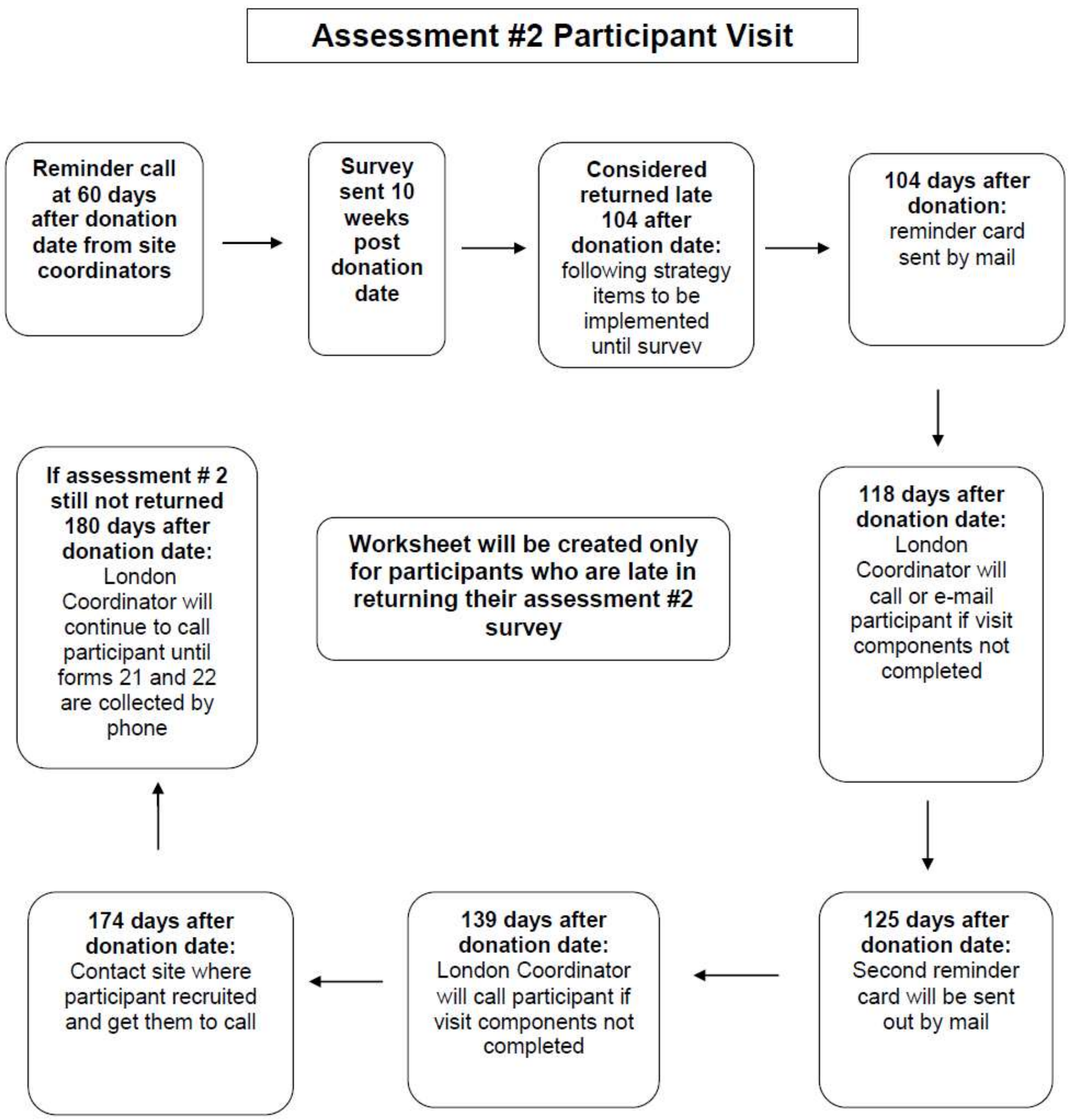
cc: ORE File
LHRI

Appendix B: The twelve major transplant centres across Canada participating in the Living Kidney Donor Study

Table 11. The major transplant centres participating in the LKD Study and their donor recruitment numbers.

Study Centre ID	Kidney Transplant Centre	City	Donors Recruited
001	London Health Sciences Centre	London, ON	77
002	St. Paul's Hospital	Vancouver, BC	180
003	The Ottawa Hospital	Ottawa, ON	91
005	Queen Elizabeth II Hospital	Halifax, NS	27
006	St. Michael's Hospital	Toronto, ON	74
007	St. Joseph's Hospital	Hamilton, ON	27
008	Health Sciences Centre	Winnipeg, MB	37
009	University of Alberta	Edmonton, AB	90
017	Toronto General Hospital	Toronto, ON	111
018	Foothills Medical Centre	Calgary, AB	45
019	Vancouver General Hospital	Vancouver, BC	94
020	Montreal General Hospital	Montreal, QC	46

Appendix C: LKD Study retention flowchart and worksheets for missing and late 3 month assessments.



Assessment # 2 Participant Follow-up Worksheet

Participant Study ID: ____________________ Nephrectomy Date: ______________

Participant Name: ____________________

Participant Mailing Address: ____

____

Participant Home #: ____________________

Participant Work #: ____________________

Participant Cell #: ____________________

Participant E-mail Address: __________________________

Items	Completed (x)	Date (day/month/year)	Signature	Comments
2 month reminder call				
Survey sent				
Reminder card #1				
Reminder call #1				
Reminder card #2				
Reminder call #2				
Survey sent again				
Site contacted to call participant				
Follow-up with site about contacting participant				
Forms 21 and 22 information collected				

Appendix D: Economic case report forms for 3-month and one-year assessments

LKD STUDY 3 - ☐☐☐ - ☐☐☐ - 1 Participant Initials: ☐☐☐ Assessment #: 0 2 Form #: 2 1

Centre ID Participant ID F M L

THREE MONTH ECONOMIC ASSESSMENT FORM

If a transplant program ever tested your blood to determine if you could be a kidney donor, please answer the following questions.

In the next set of questions, we are trying to measure financial and time burdens related to being a kidney donor. These include overnight stay, travel, medical expenses, and inability to do your usual activities. For these questions, we are interested in the total time period from when you first considered being a kidney donor up to now. Please include all costs, even costs that were completely paid or partly paid back to you. For costs, provide amounts in your country's currency.

Section 1 – Economic/Financial Cost and Reimbursement

1.) Estimate the number of trips (1 trip equals going to see someone and returning home) to health professionals (nephrologist, social worker, surgeon, etc.) and to have lab work done for living donor evaluation.

→ ☐☐☐ trip(s)

2.) Please state the name and city of the transplant centre where most of your donor evaluation occurred:

Name of Transplant Centre: ____________________

City: ____________________

Consider your total overnight stay expenses because of appointments, tests or hospital stays:

3.) In total, how many nights did you stay with family and friends?

→ ☐☐☐ night(s)

4.) Estimate your total out-of-pocket costs to date for staying with family or friends (if never stayed with family or friends, enter $0). Include all costs even those that were completely or partially paid back to you.

→ $☐☐☐☐☐

5.) In total, how many nights have you stayed in a place where you had to pay for accommodation such as a hotel/motel or bed and breakfast?

→ ☐☐☐ night(s)

6.) Estimate your total out-of-pocket costs to date for places where you had to pay accommodation (If never stayed in such accommodation, enter $0). Include all costs, even those that were completely or partially paid back to you.

→ $☐☐☐☐☐

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7.) Did a friend or family member incur costs as a result of staying in paid accommodation while you were in the hospital for transplant surgery?

☐ No ☐ Yes ☐ Not Applicable, I did not have transplant surgery

8.) Estimate the number of days you stayed in hospital for tests or for surgery (If you never stayed in hospital, enter 0 days).

→ ☐☐☐ day(s)

9.) Estimate your total out-of-pocket costs for hospital accommodation, such as expenses for cable, private room or telephone. Include all costs, even those that were completely or partially paid back to you (If you never stayed in the hospital enter $0).

→ $☐☐☐☐☐

Air Travel

10.) Did you travel by an airplane at least once for flights that you took in the process of donating your kidney (tests, appointments and hospital stays)?

☐ No ☐ Yes

City of Departure	City of Arrival	Number of Round trips	Number of One-way trips
e.g. Los Angeles, CA	Toronto, ON	2	0

11.) Did a friend/partner/spouse incur costs on at least one occasion as a result of travelling by plane to accompany you from home to the transplant centre?

☐ No ☐ Yes

12.) Please, select all methods of transportation you used to get from home to airport and from airport to the transplant centre:

☐ Own vehicle
☐ Rental car
☐ Taxi
☐ Bus
☐ Train
☐ Other (specify) ____________________

13.) Estimate your total out-of-pocket costs for your flights. Include all costs, even those that were completely or partially paid back to you.

$☐☐☐☐☐

Ground travel from home to transplant centre

The next set of questions pertain to ground travel from home to transplant centre where you did not travel all or part of the distance by airplane:

14.) Estimate the number of **return ground trips** (to and from your home to transplant centre) in your **own vehicle**.

→ [ ][ ][ ] trip(s)

15.) Estimate the number of **return ground trips** (to and from your home to transplant centre) by **rental car**.

→ [ ][ ][ ] trip(s)

16.) Estimate the number of **return ground trips** (to and from your home to transplant centre) by **taxi**.

→ [ ][ ][ ] trip(s)

17.) Estimate the number of **return ground trips** (to and from your home to transplant centre) by **bus**.

→ [ ][ ][ ] trip(s)

18.) Estimate the number of **return ground trips** (to and from your home to transplant centre) by **train**.

→ [ ][ ][ ] trip(s)

19.) Estimate your total out-of-pocket costs for ground travel. Do not include costs incurred traveling to and from an airport. Include all costs, even those that were completely or partially paid back to you.

→ $[ ][ ][ ][ ][ ]

20.) Estimate the number of days or part-days where you paid for parking due to tests or appointments related to donation.

→ [ ][ ][ ].[ ] day(s)

21.) Estimate your total out-of-pocket costs for parking. Include all costs, even those that were completely or partially paid back to you.

→ $[ ][ ][ ][ ][ ]

Medication Expenses

Consider medication expenses that you paid out-of-pocket, even those that were completely or partially paid back to you:

22.) As a result of donating a kidney, did you take any prescription pain medication or antibiotics after you left the hospital? If you did not donate a kidney answer "Not Applicable".

☐ Not Applicable, I did not have transplant surgery

☐ No ☐ Yes to medication

→ 23.) Did the province or state pay for some of the costs for these medications?

☐ No ☐ Yes

→ 24.) Did your private insurance pay for some of the costs for these medications?

☐ No ☐ Yes

→ 25.) Did you pay for some of the costs for these medications?

☐ No ☐ Yes

→ 26.) Estimate your total out-of-pocket costs for these medications. Include all costs that were completely or partially paid back to you.

→ $☐☐☐☐☐

Activities

Consider the time from when you were evaluated to be a kidney donor until now. How many days were you unable to perform the following activities due to appointments, tests, travel, or any other reason related to being a potential donor?

27.) Unable to perform household activities such as housework, childcare or shopping?

→ ☐☐☐.☐ day(s)

28.) Unable to care for dependents (children, parents, grandparents, spouse)?

→ ☐☐☐.☐ day(s)

29.) Unable to work if you were employed.

☐ No ☐ Yes

→ 30.) How many days were you unable to work? ☐☐☐.☐ day(s)

→ 31.) How many of these days were:

i.) Covered as sick days by your employer:
☐☐☐.☐ day(s)

ii.) Taken as vacation time from your employer:
☐☐☐.☐ day(s)

iii.) Other days off with pay:
☐☐☐.☐ day(s)

iv.) Days without pay (applies if self-employed):
☐☐☐.☐ day(s)

Estimate your total out of pocket expenses for the following (Include all costs that were completely or partially paid back to you):

32.) Unable to perform **household activities**: $☐☐☐☐☐

33.) Unable to **take care of your dependants**: $☐☐☐☐☐

34.) Unable to **go to work**: $☐☐☐☐☐☐

Person completing form (please print): ______________________ ________
last name first initial

Appendix E: Costing rates used in the valuation of resources

Table 12. 2016 kilometric travel rates for provinces and territories

Province	Kilometric Rate (2016 CAD/km)
Newfoundland	0.530
Prince Edward Island	0.475
Nova Scotia	0.485
New Brunswick	0.485
Quebec	0.495
Ontario	0.540
Manitoba	0.470
Saskatchewan	0.455
Alberta	0.435
British Columbia	0.475
Yukon	0.590
Northwest Territories	0.580
Nunavut	0.575

From: http://www.cra-arc.gc.ca/travelcosts/

Table 13. Individual and average hotel rates with applicable taxes (2016 CAD).[a]

Surgery Hospital	City	Hotels	Hotel Cost (CAD/night)	Average Hotel Cost (CAD/night)
Foothills Medical Centre	Calgary, AB	Hotel Alma	91.84	109.39
		Ramada Limited Calgary Northwest	104.16	
		Best Western Village Park Inn	132.16	
Hôpital Maisonneuve-Rosemont	Montreal, QC	Le Chablis	118.48	126.37
		Hotel University Montreal	140.99	
		Days Inn Montreal East	119.66	
Health Sciences Centre	Winnipeg, MB	Canad Inns Destination Centre – Health Sciences Centre	140.42	106.20
		Econo Lodge	89.68	
		Hotel Royal Plaza	88.50	
Hôtel-Dieu de Québec	Quebec City, QC	Fairmont Le Château Frontenac	199.42	148.68
		Hôtel de Vieux-Québec	158.12	
		Hotel Champlain Vieux-Quebec	88.5	
University Hospital	London, ON	Guest House on the Mount	66.67	115.64
		The Windermere Manor	158.20	
		Ivey Spencer Leadership Centre	122.04	
Montreal General Hospital	Montreal, QC	Chateau Versailles Hotel Montreal	143.35	133.09
		Le Méridien Versailles	176.53	
		Le Saint-Malo Hotel	79.38	

Hôpital Notre Dame	Montreal, QC	Hotel Dorion	73.45	120.05
		Hotel Chateau de L'Argoat	136.25	
		Kutuma Hotel & Suites	150.46	
The Ottawa Hospital	Ottawa, ON	Best Western PLUS Ottawa City Centre	151.96	121.41
		Travelodge Ottawa West	120.64	
		Richmond Plaza Motel	91.64	
QEII Health Sciences Centre	Halifax, NS	Atlantica Hotel Halifax	153.27	175.11
		Courtyard Halifax Downtown	209.43	
		The Lord Nelson Hotel & Suites	162.63	
Royal Victoria Hospital	Montreal, QC	Le Chabrol	112.55	125.58
		La Tour Belvedere	99.52	
		Residence Inn Montreal Westmount	164.68	
St. Joseph's Healthcare Hamilton	Hamilton, ON	Homewood Suites by Hilton	170.63	158.58
		Staybridge Suites Hamilton – Downtown	159.33	
		Sheraton Hamilton Hotel	145.77	
St. Michael's Hospital	Toronto, ON	Bond Place Hotel	117.16	172.07
		Chelsea Hotel	183.28	
		The Grand Hotel & Suites	215.76	
St. Paul's Hospital	Vancouver, BC	Ramada Vancouver Downtown	103.24	149.64
		Wedgewood Hotel & Spa Vancouver	184.44	
		The Fairmont Hotel Vancouver	161.24	

Toronto General Hospital	Toronto, ON	DoubleTree by Hilton Hotel Toronto Downtown	222.71	206.09
		Chelsea Hotel	183.28	
		BeSixFifty Hotel	212.28	
University of Alberta Hospital	Edmonton, AB	Campus Tower Suite Hotel	220.64	207.57
		Varscona Hotel on Whyte	184.80	
		Mettera Hotel on Whyte	217.28	
Vancouver General Hospital	Vancouver. BC	Holiday Inn Vancouver – Centre (Broadway)	160.08	188.31
		Granville Island Hotel	287.68	
		Executive Hotel Vintage Park Vancouver	117.16	
St. Paul's Hospital	Saskatoon, SK	Super 8 Saskatoon	123.20	160.53
		Holiday Inn Saskatoon	152.32	
		Hilton Garden Inn	206.08	

[a] Discussion of prices in section 4.2.4.3.

Table 14. Applicable taxes on accommodations in each province**.**

Province/City	Applicable Taxes and Fees
Alberta	= 12% (5% GST + 4% levy + 3% DMF)
British Columbia	= 16% (5% GST + 8% PST (for accommodation) + 3% DMF)
Manitoba	= 18% (5% GST + 8% PST + 5% DMF)
Nova Scotia	= 17% (15% HST + 2% DMF)
Saskatchewan	= 12% (5% GST + 5% PST + 2% DMF)
Ontario	
Toronto	16% (13% HST + 3% DMF)
Ottawa	16% (13% HST + 3% DMF)
Hamilton	13% (13% HST)
London	13% (13% HST)
Quebec	
Montreal	= 18.475% (5% GST + 9.975 PST + 3.5% DMF)
Quebec City	= 17.975% (5% GST + 9.975 PST + 3% DMF)

GST = federal goods and services tax, PST = provincial sales tax, HST = harmonized sales tax, DMF = tourism levies or destination marketing fees

Table 15. Average age-, sex-, and province-specific wage rates (2016 CAD).

Province[1]	Sex	Age group	Average wage rate (2016 CAD)
Newfoundland and Labrador	Males	15 to 24 years	14.95
		25 to 54 years	28.95
		55 years and over	26.44
	Females	15 to 24 years	14.08
		25 to 54 years	24.02
		55 years and over	20.44
Prince Edward Island	Males	15 to 24 years	13.47
		25 to 54 years	23.29
		55 years and over	22.59
	Females	15 to 24 years	12.92
		25 to 54 years	22.63
		55 years and over	21.32
Nova Scotia	Males	15 to 24 years	13.86
		25 to 54 years	25.53
		55 years and over	25.40
	Females	15 to 24 years	13.72
		25 to 54 years	23.53
		55 years and over	22.62
New Brunswick	Males	15 to 24 years	13.50
		25 to 54 years	24.58
		55 years and over	23.46
	Females	15 to 24 years	13.27
		25 to 54 years	22.88
		55 years and over	19.99
Quebec	Males	15 to 24 years	14.95
		25 to 54 years	27.72
		55 years and over	26.49
	Females	15 to 24 years	13.89
		25 to 54 years	24.97
		55 years and over	22.18

Ontario	Males	15 to 24 years	14.78
		25 to 54 years	30.28
		55 years and over	30.29
	Females	15 to 24 years	13.91
		25 to 54 years	26.37
		55 years and over	26.00
Manitoba	Males	15 to 24 years	14.94
		25 to 54 years	26.44
		55 years and over	26.91
	Females	15 to 24 years	14.15
		25 to 54 years	23.86
		55 years and over	24.84
Saskatchewan	Males	15 to 24 years	17.61
		25 to 54 years	30.91
		55 years and over	31.85
	Females	15 to 24 years	15.76
		25 to 54 years	26.40
		55 years and over	26.34
Alberta	Males	15 to 24 years	18.08
		25 to 54 years	35.14
		55 years and over	34.93
	Females	15 to 24 years	16.32
		25 to 54 years	28.17
		55 years and over	29.12
British Columbia	Males	15 to 24 years	15.81
		25 to 54 years	30.00
		55 years and over	29.30
	Females	15 to 24 years	14.11
		25 to 54 years	24.89
		55 years and over	24.19

[1] Territory age- and sex-specific wage rates were unavailable from the Labour Force Survey, average territory-specific wage rate was used instead, see table 16.

http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=2820074

Table 16. Average provincial wage rates (2016 CAD).

Province	Average wage rate (2016 CAD)
Newfoundland	24.90
Prince Edward Island	20.43
Nova Scotia	21.55
New Brunswick	21.51
Quebec	23.06
Ontario	23.68
Manitoba	22.72
Saskatchewan	25.60
Alberta	26.52
British Columbia	23.85
Yukon	26.55
Northwest Territories	31.28
Nunavut	30.74

http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/labr80-eng.htm

Table 17. Sensitivity analysis of direct, indirect, and total costs incurred (2016 CAD), for all donors (n = 912) using 2016 provincial wage rates.

Cost type	Costs incurred, all donors (CAD)	
	Mean (SD)	Median (25^{th}-75^{th} percentile)
Direct	2110 (2505)	1302 (581-2674)
Indirect	2424 (4882)	22 (0-2617)
Total	4535 (5573)	2565 (1066-5916)

Table 18. Inflation rates used to standardize costs to the year 2016 using Canada's Consumer Price Index.

Year of Surgery	Inflation Rate
2009	10.9%
2010	9.3%
2011	6.6%
2012	5.2%
2013	4.3%
2014	2.5%
2015	1.4%

http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ46a-eng.htm

Appendix F: Multiple imputation diagnostics

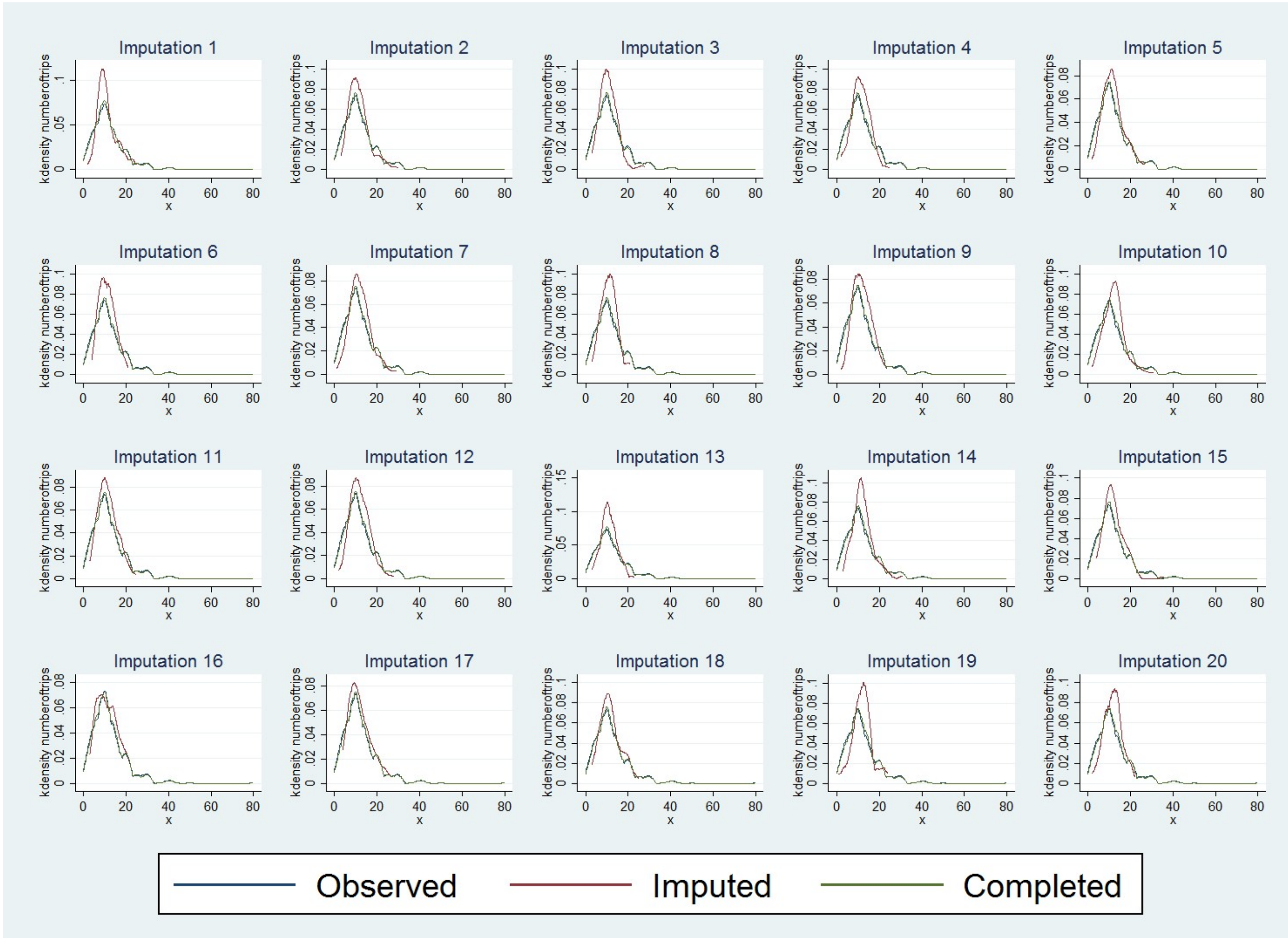

Figure 8. Distribution of imputed, observed, and completed values for "Number of Trips" across all 20 imputation sets. 100 of 912 values were imputed.

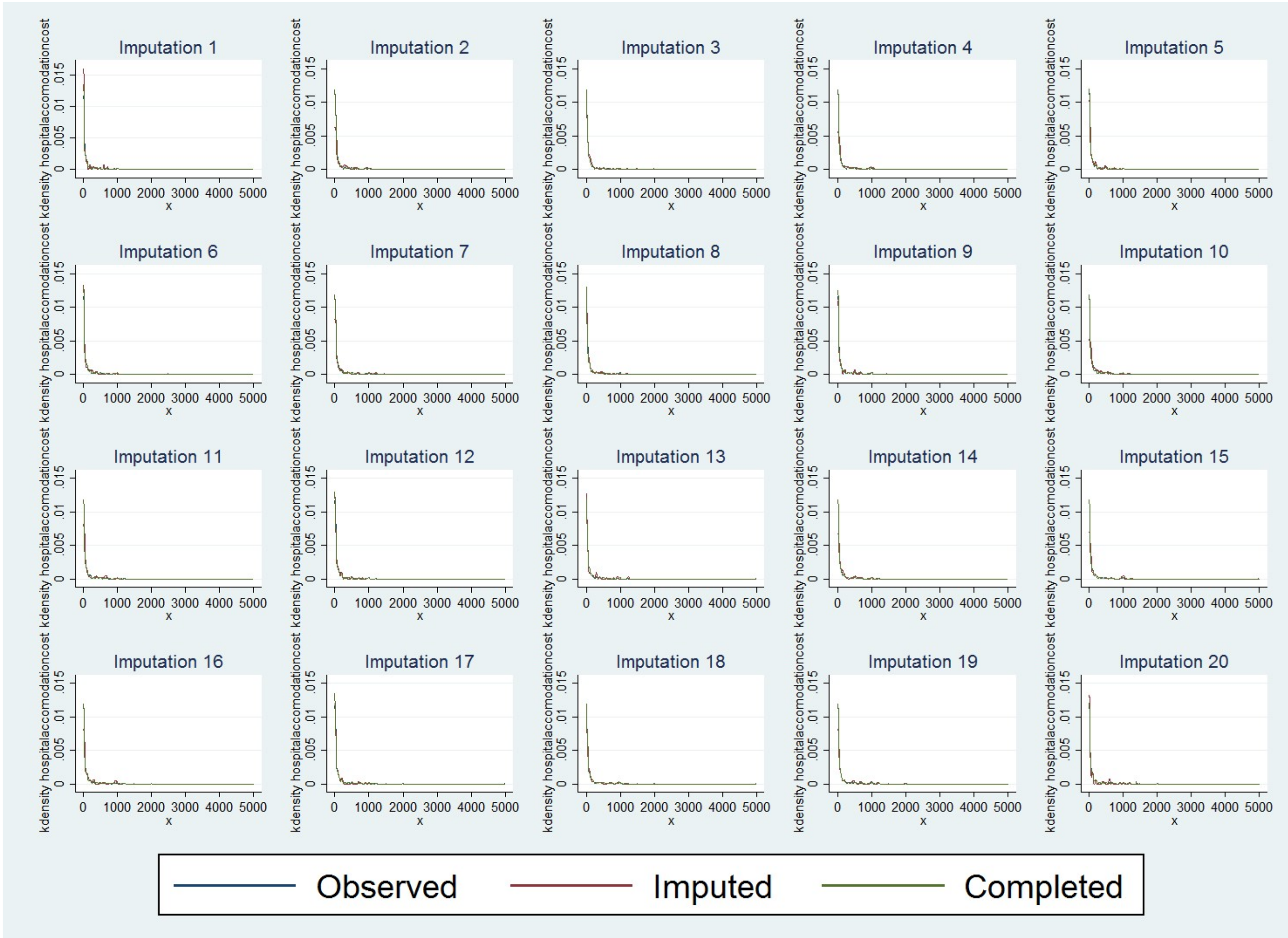

Figure 9. Distribution of imputed, observed, and completed values for "Hospital Accommodation Cost" across all 20 imputation sets. 103 of 912 values were imputed.

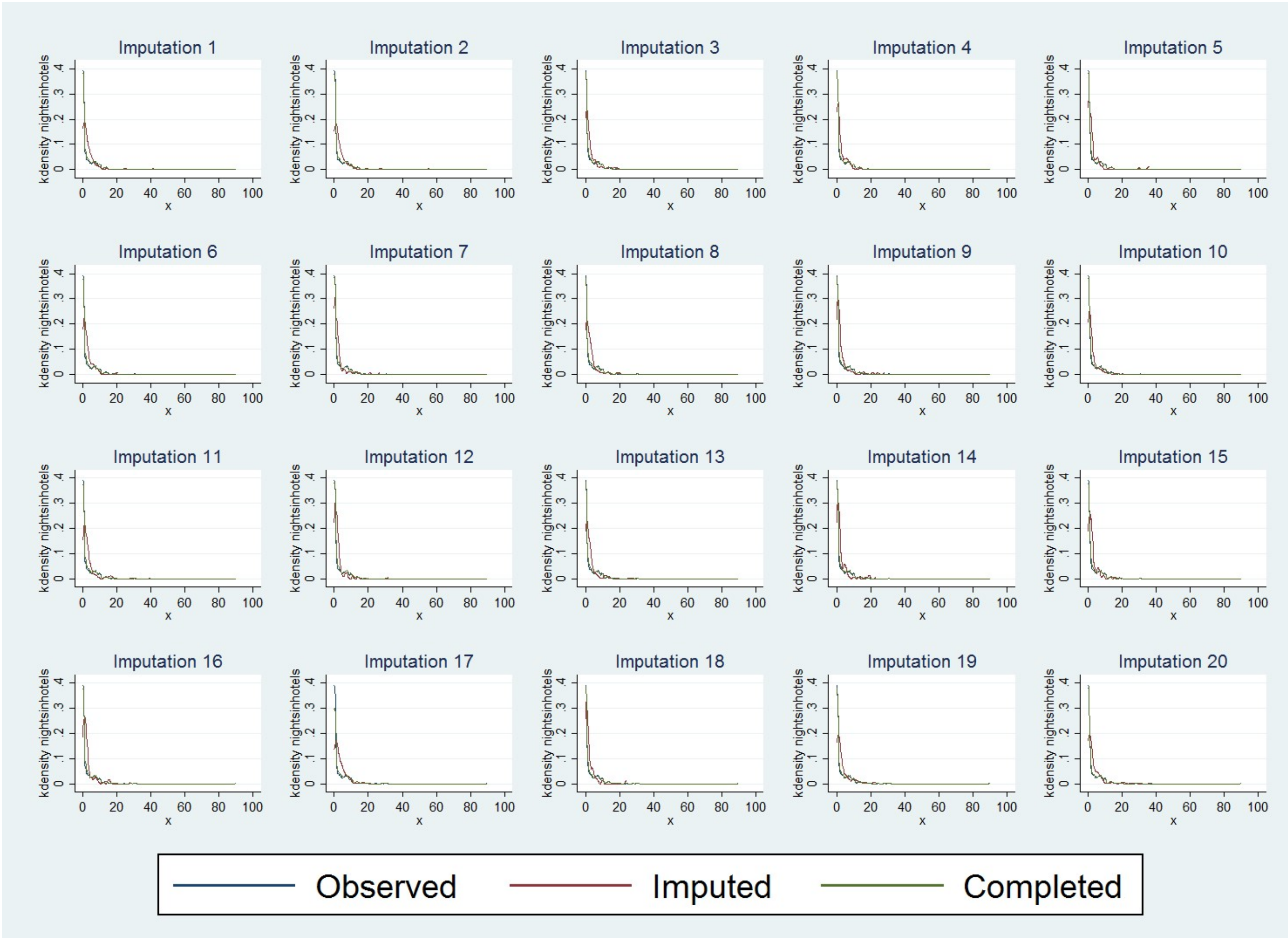

Figure 10. Distribution of imputed, observed, and completed values for "Nights in Hotels" across all 20 imputation sets. 95 of 912 values were imputed.

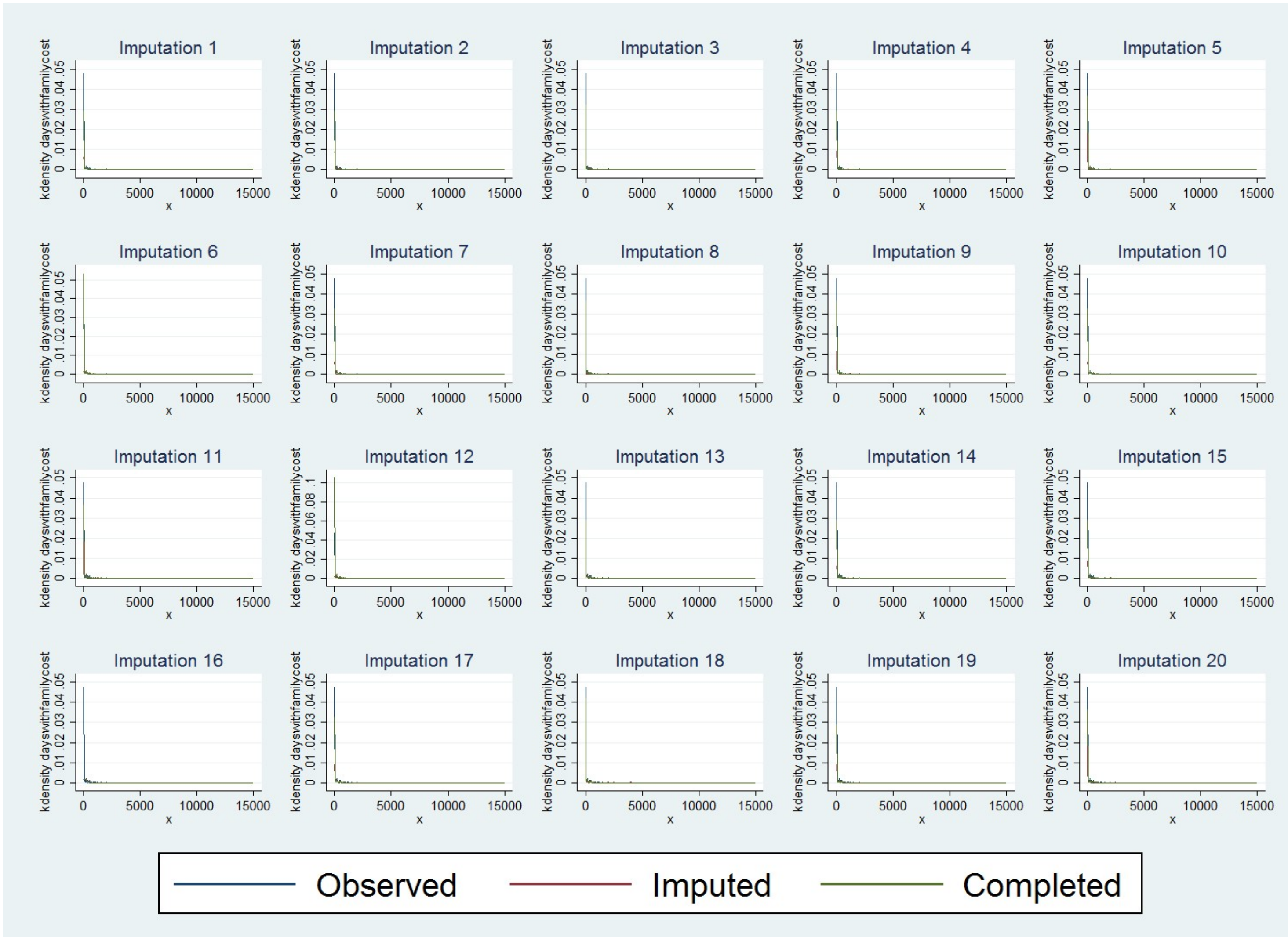

Figure 11. Distribution of imputed, observed, and completed values for "Friends/Family Accommodation Costs" across all 20 imputation sets. 99 of 912 values were imputed.

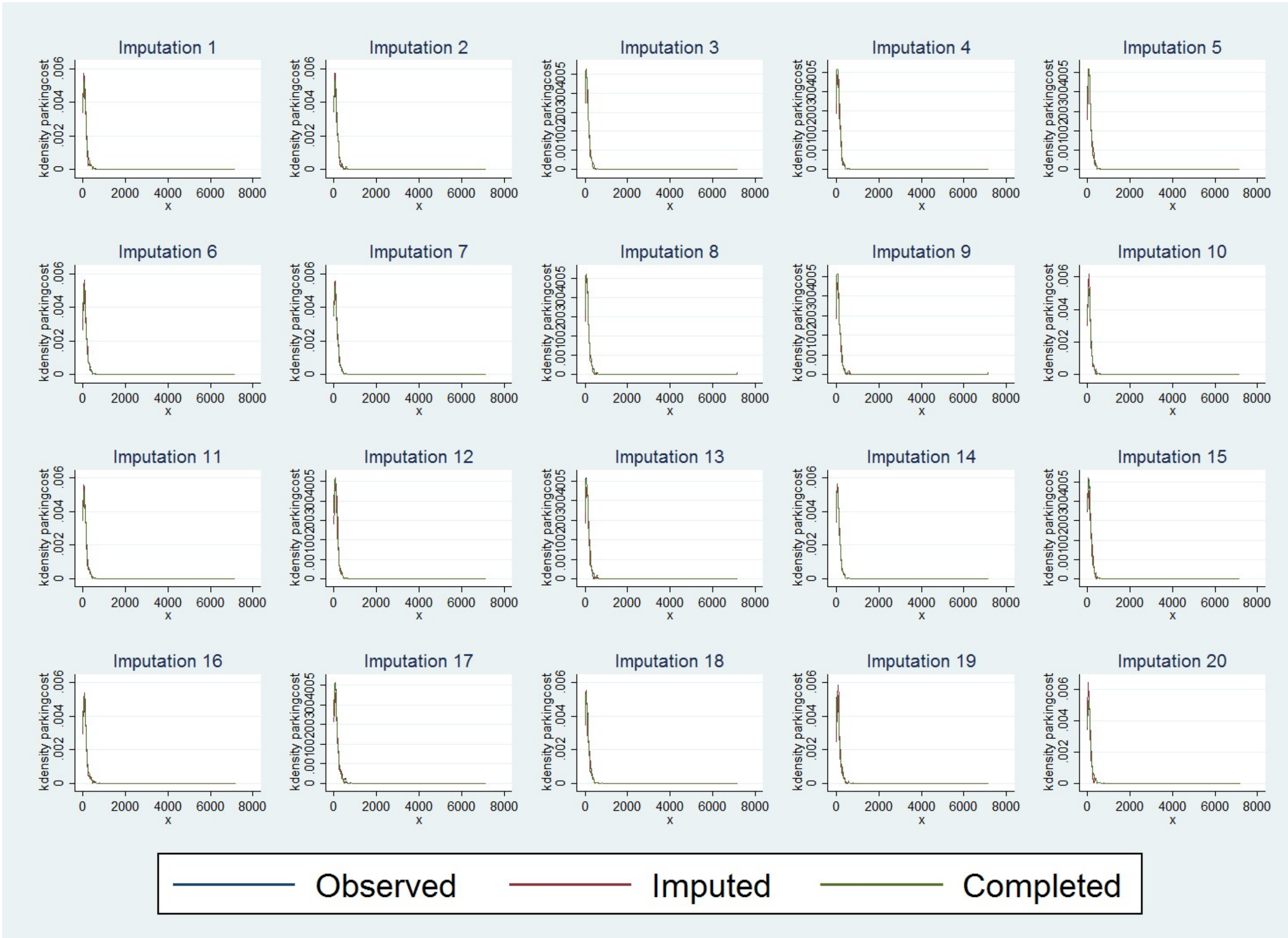

Figure 12. Distribution of imputed, observed, and completed values for "Parking Costs" across all 20 imputation sets. 104 of 912 values were imputed.

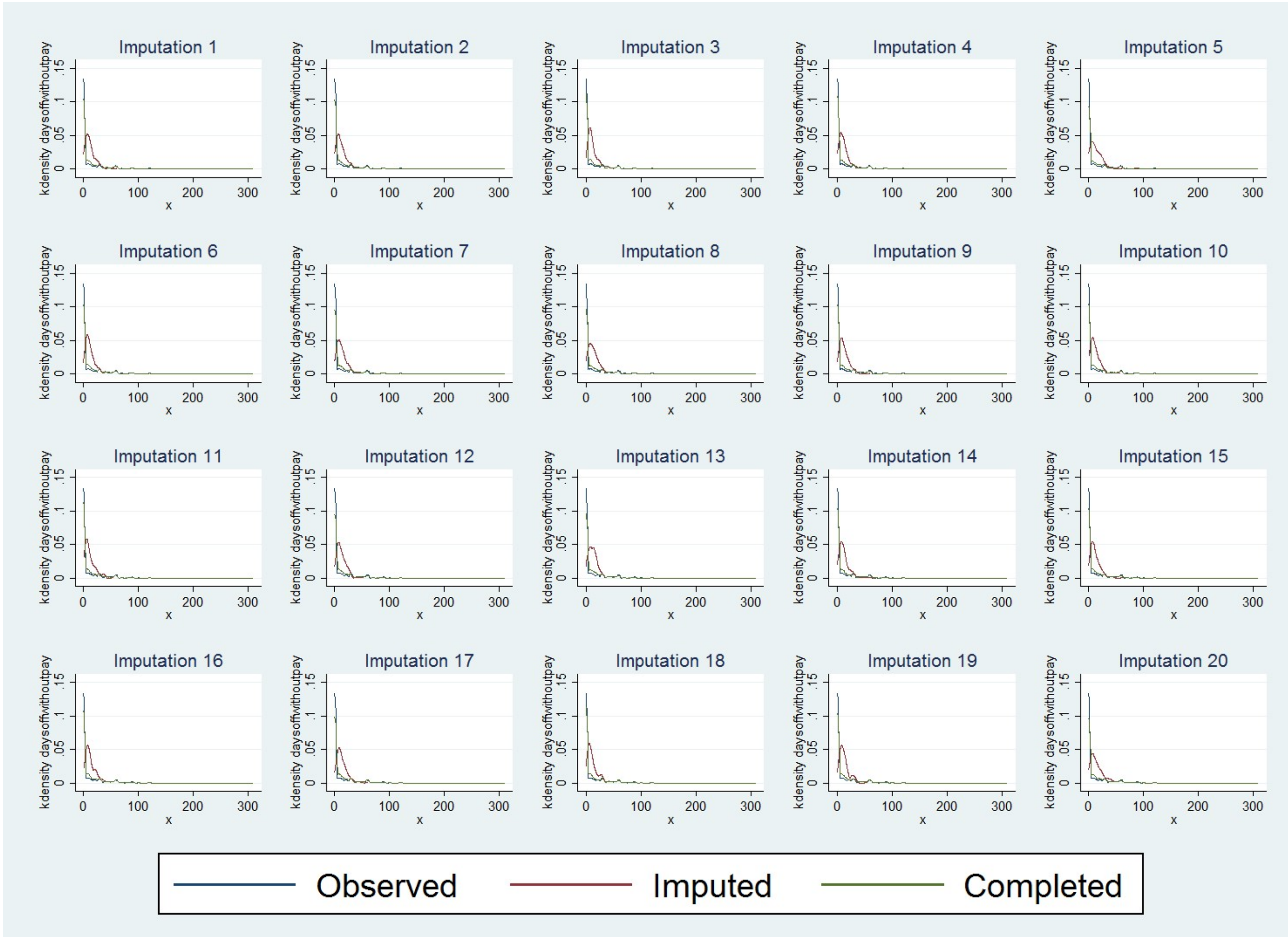

Figure 13. Distribution of imputed, observed, and completed values for "Days Off Without Pay" across all 20 imputation sets. 107 of 912 values were imputed.

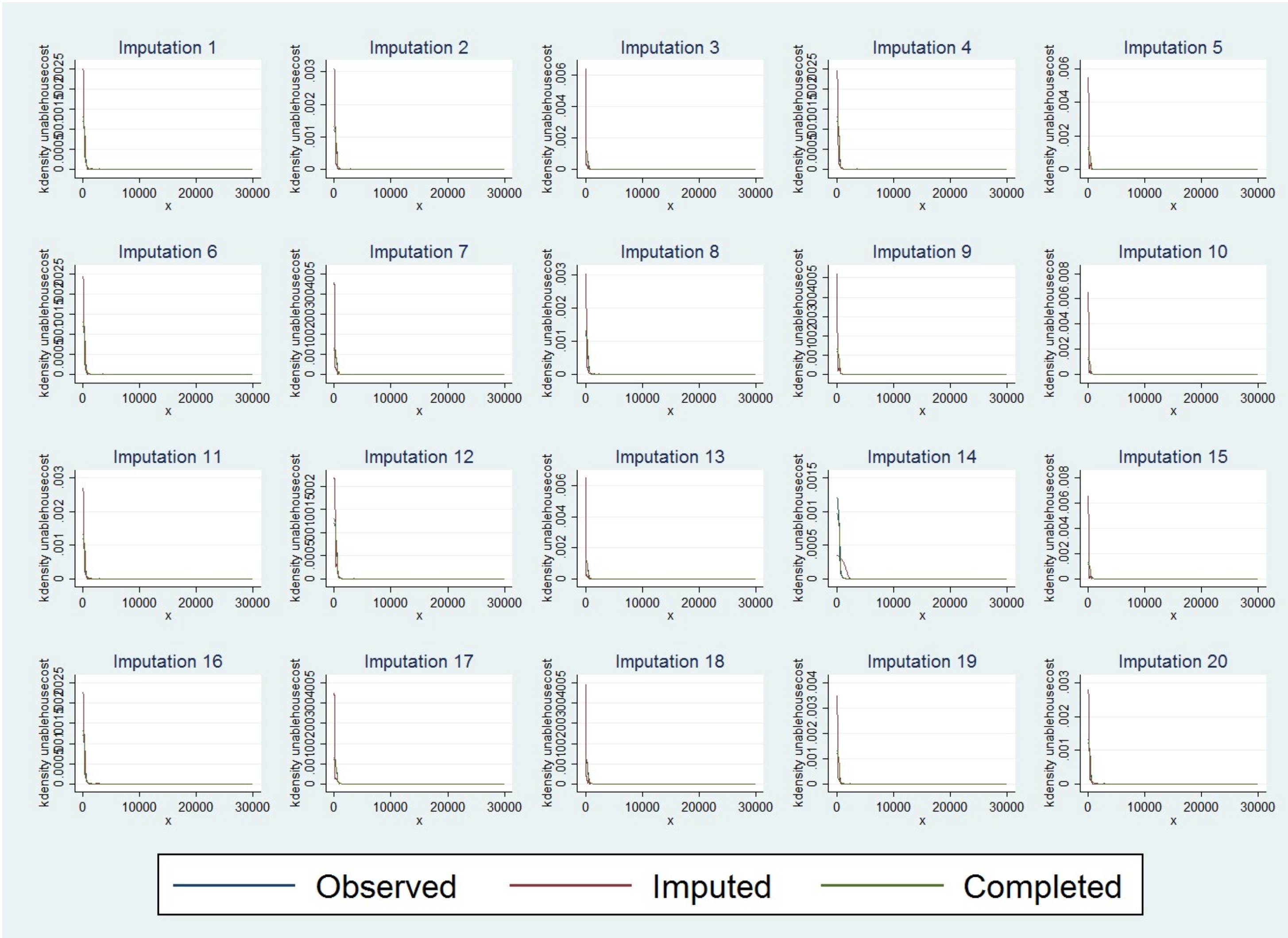

Figure 14 Distribution of imputed, observed, and completed values for "Unable to Perform Household Activities Costs" across all 20 imputation sets. 119 of 912 values were imputed.

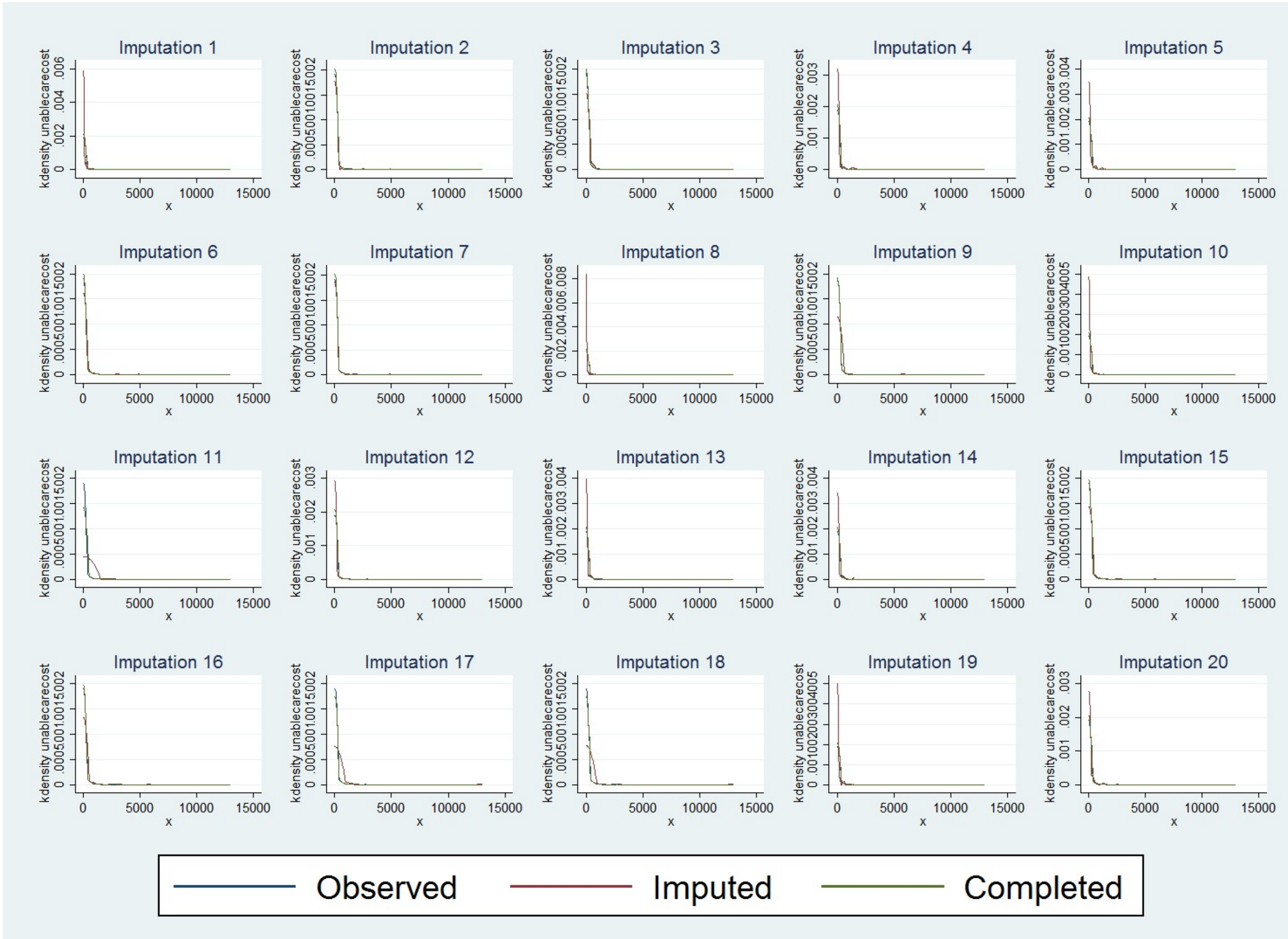

Figure 15. Distribution of imputed, observed, and completed values for "Unable to Care for Dependents Costs" across all 20 imputation sets. 118 of 912 values were imputed.

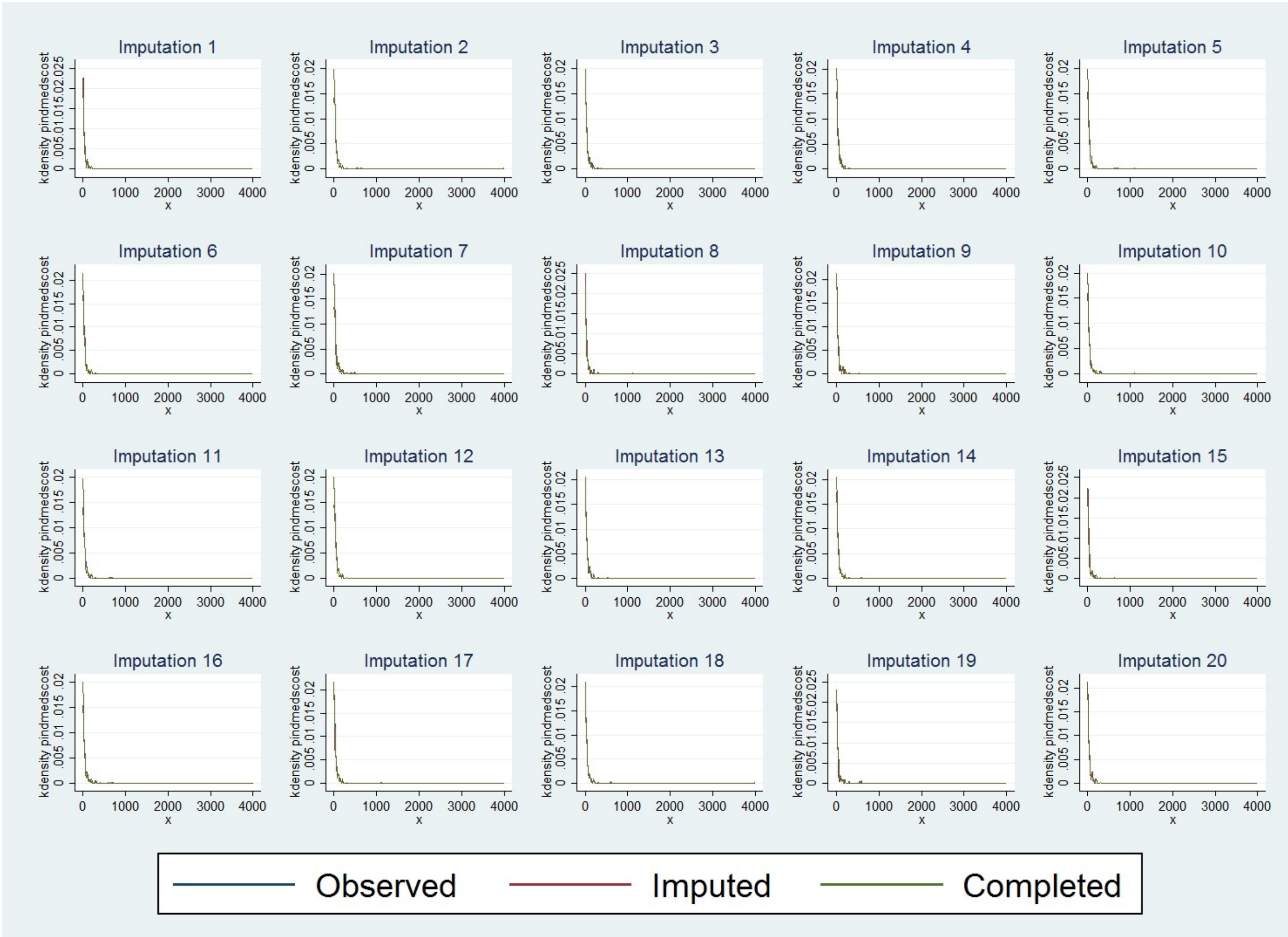

Figure 16. Distribution of imputed, observed, and completed values for "Medication Costs" across all 20 imputation sets. 104 of 912 values were imputed.

Appendix G: GLM – model diagnostics and goodness of fit

a)

```
glmdiag

FITTED MODEL:  Link = Log ; Family =  Gamma

Results, Modified Park Test (for Family)

   Coefficient:   2.355146

   Family, Chi2, and p-value in descending order of likelihood

     Family                               Chi2         P-value

     Gamma:                             0.6320          0.4266
     Inverse Gaussian or Wald:          2.0837          0.1489
     Poisson:                           9.2019          0.0024
     Gaussian NLLS:                    27.7933          0.0000

Results of tests of GLM Log  link

     Pearson Correlation Test:                          0.6684
     Pregibon Link Test:                                0.8874
     Modified Hosmer and Lemeshow:                      0.6124
```

b)

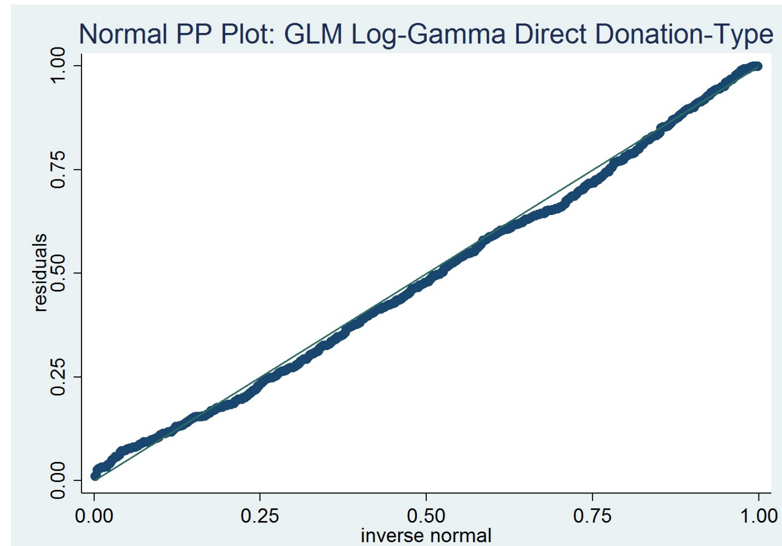

Figure 17. a) GLM diagnostic output b) Normal probability plot assessing deviance residuals for models estimating effect of donation-type groups on direct costs.

a)

```
glmdiag


FITTED MODEL:  Link = Log ; Family =  Gamma

Results, Modified Park Test (for Family)

   Coefficient:   1.433472

   Family, Chi2, and p-value in descending order of likelihood

     Family                               Chi2         P-value

     Poisson:                           1.0210          0.3123
     Gamma:                             1.7440          0.1866
     Gaussian NLLS:                    11.1658          0.0008
     Inverse Gaussian or Wald:         13.3349          0.0003

Results of tests of GLM Log  link

     Pearson Correlation Test:                          0.3781
     Pregibon Link Test:                                0.3400
     Modified Hosmer and Lemeshow:                      0.8733
```

b)

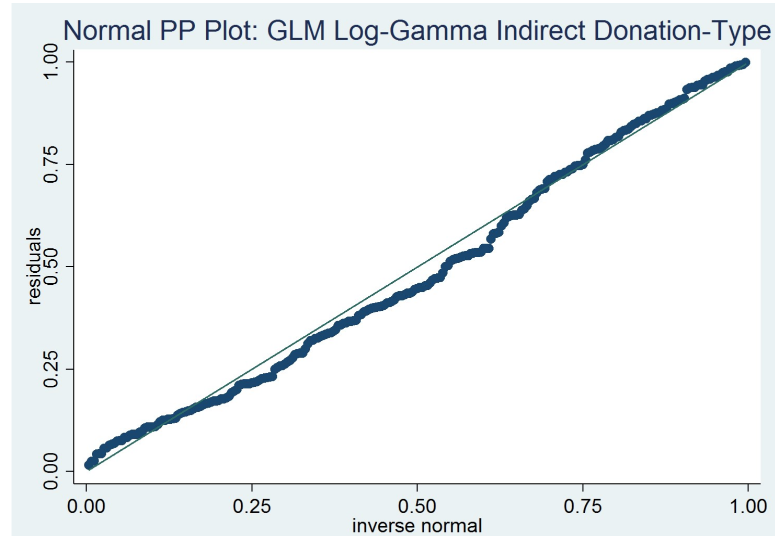

Figure 18. a) GLM diagnostic output b) Normal probability plot assessing deviance residuals for models estimating effect of donation-type groups on indirect costs.

a)

```
glmdiag

FITTED MODEL:  Link = Log ; Family =  Gamma

Results, Modified Park Test (for Family)

   Coefficient:   2.034903

   Family, Chi2, and p-value in descending order of likelihood

     Family                                  Chi2         P-value

     Gamma:                                0.0049          0.9440
     Inverse Gaussian or Wald:             3.7731          0.0521
     Poisson:                              4.3386          0.0373
     Gaussian NLLS:                       16.7741          0.0000

Results of tests of GLM Log  link

     Pearson Correlation Test:                             0.9323
     Pregibon Link Test:                                   0.7301
     Modified Hosmer and Lemeshow:                         0.7432
```

b)

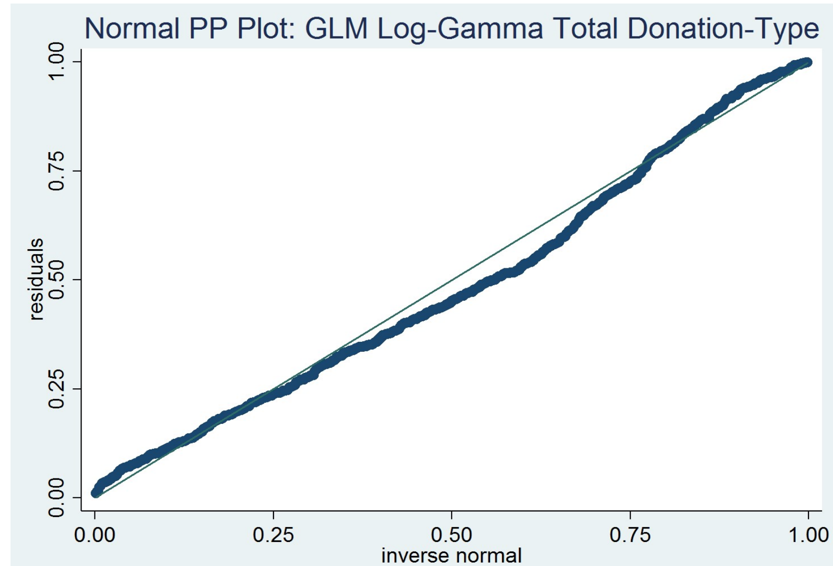

Figure 19. a) GLM diagnostic output b) Normal probability plot assessing deviance residuals for models estimating effect of donation-type groups on total costs.

a)

```
glmdiag

FITTED MODEL:  Link = Log ; Family =  Gamma

Results, Modified Park Test (for Family)

   Coefficient:   2.628664

   Family, Chi2, and p-value in descending order of likelihood

     Family                                Chi2         P-value

     Inverse Gaussian or Wald:           0.8909          0.3452
     Gamma:                              2.5535          0.1100
     Poisson:                           17.1382          0.0000
     Gaussian NLLS:                     44.6450          0.0000

Results of tests of GLM Log  link

     Pearson Correlation Test:                           0.6786
     Pregibon Link Test:                                 0.7508
     Modified Hosmer and Lemeshow:                       0.9355
```

b)

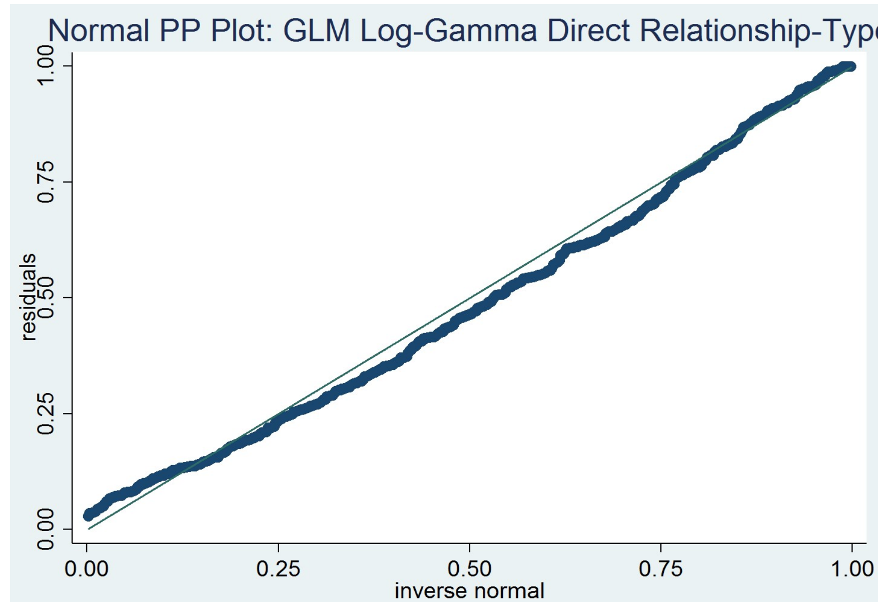

Figure 20. a) GLM diagnostic output b) Normal probability plot assessing deviance residuals for models estimating effect of relationship-type groups on direct costs.

a)

```
glmdiag

FITTED MODEL:  Link = Log ; Family =  Gamma

Results, Modified Park Test (for Family)

   Coefficient:   1.433862

   Family, Chi2, and p-value in descending order of likelihood

     Family                                  Chi2         P-value

     Poisson:                              1.9834          0.1590
     Gamma:                                3.3772          0.0661
     Gaussian NLLS:                       21.6636          0.0000
     Inverse Gaussian or Wald:            25.8450          0.0000

Results of tests of GLM Log  link

     Pearson Correlation Test:                            0.1101
     Pregibon Link Test:                                  0.2319
     Modified Hosmer and Lemeshow:                        0.1570
```

b)

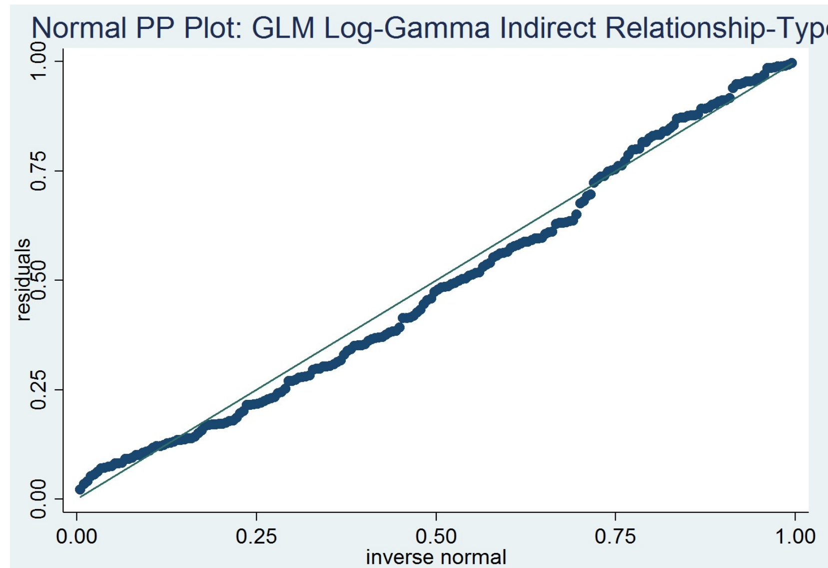

Figure 21. a) GLM diagnostic output b) Normal probability plot assessing deviance residuals for models estimating effect of relationship-type groups on indirect costs.

a)

```
glmdiag


FITTED MODEL:  Link = Log ; Family =  Gamma

Results, Modified Park Test (for Family)

   Coefficient:   1.914324

   Family, Chi2, and p-value in descending order of likelihood

     Family                                   Chi2          P-value

     Gamma:                                 0.0603           0.8059
     Poisson:                               6.8730           0.0088
     Inverse Gaussian or Wald:              9.6905           0.0019
     Gaussian NLLS:                        30.1285           0.0000

Results of tests of GLM Log  link

     Pearson Correlation Test:                               0.6892
     Pregibon Link Test:                                     0.6816
     Modified Hosmer and Lemeshow:                           0.7898
```

b)

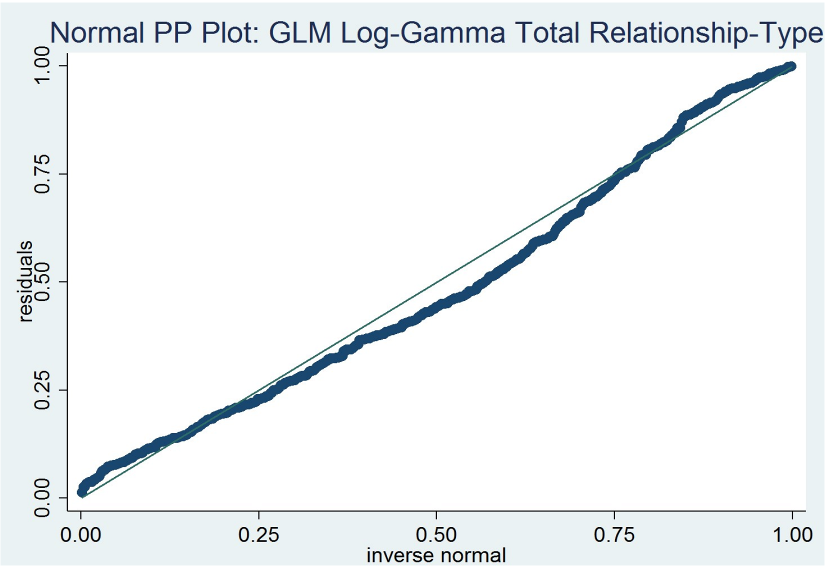

Figure 22. a) GLM diagnostic output b) Normal probability plot assessing deviance residuals for models estimating effect of relationship-type groups on total costs.

Appendix H: Complete-case analyses

Table 19. Complete-case analysis of direct resource use for all donors, from 3-month economic assessment (2016 CAD).

Cost category	Description	Donors reporting resource, n (%)[2]	Resource use[3]		Costs for donors reporting expense (CAD)		Costs for all donors, n = 912 (CAD)	
			Units	Median (IQR)	Average (SD)	Median (IQR)	Average (SD)	Median (IQR)
Travel	Ground travel	726 (89%)	# Return trips	10 (7-15)	1070 (1584)	500 (190-1192)	957 (1534)	402 (127-1116)
	Air travel	173 (21%)	# Return trips	1 (1-2)	637 (458)	562 (324-744)	134 (334)	0 (0-0)
	Parking[1]	716 (89%)	# Days of paid parking	7 (4-11)	139 (296)	104 (55-164)	122 (281)	89 (42-158)
Accommodation	Family and friends[1]	287 (35%)	# Nights	6 (3-12)	766 (1439)	315 (158-765)	197 (802)	0 (0-31)
	Non-hospital paid	339 (41%)	# Nights	5 (2-8)	1150 (1818)	748 (299-1347)	477 (1300)	0 (0-565)
	Hospital[1]	368 (45%)	# Nights	4 (3-5)	295 (530)	105 (47-336)	134 (386)	0 (0-103)
Medication	Pain medication or antibiotics[1]	629 (77%)	Drugs taken (yes/no)	n/a	69 (213)	33 (21-63)	43 (171)	16 (0-46)

[1] Self-reported costs (not micro-costed).
[2] Denominator varies with participant response rate for each variable (Table 3); among donors reporting resource use (even if no out-of-pocket expenses were incurred).
[3] In donors reporting the outcome.

Table 20. Complete-case analysis of indirect resource use for all donors, from 3-month economic assessment (2016 CAD).

Cost category	Description	Donors reporting resource, n (%)[2]	Number of days[3]	Costs in donors reporting expense (CAD)		Costs for all donors, n = 912 (CAD)	
			Median (IQR)	Average (SD)	Median (IQR)	Average (SD)	Median (IQR)
Lost income	Unable to work if employed	634 (78%)	35 (15-60)	7827 (7439)	5974 (2481-11,748)	2441 (5511)	0 (0-2110)
	Unpaid time off work	251 (31%)	30 (10-56)				
Lost productivity	Unable to perform household activities[1]	641 (79%)	16 (10-30)	762 (3009)	320 (205-532)	116 (1203)	0 (0-0)
	Unable to care for dependants[1]	411 (51%)	15 (9-30)	981 (2194)	328 (158-631)	95 (739)	0 (0-0)

[1] Self-reported costs (not micro-costed).
[2] Denominator varies with participant response rate for each variable (Table 3); among donors reporting resource use (even if no out-of-pocket expenses were incurred).
[3] In donors reporting the outcome.

Table 21. Complete-case direct, indirect, and total incurred costs, all donors (2016 CAD).

Cost type	Costs incurred (CAD)	
	Mean (SD)	Median (IQR)
Direct (n = 785)	2064 (2531)	1255 (543-2603)
Indirect (n = 780)	2595 (5652)	0 (0-2368)
Total (n = 757)	4443 (5782)	2252 (891-5581)

Table 22. Complete-case unadjusted direct, indirect, and total costs (2016 CAD) incurred by living kidney donors, by donation-type group.

	All Other Donors		Non-Directed Donors		Kidney Paired Donors		All Other Donors	Non-Directed Donors	Kidney Paired Donors
Cost type	Mean (95% CI)[1]	MD (95% CI)[2]	Mean (95% CI)[1]	MD (95% CI)[2]	Mean (95% CI)[1]	MD (95% CI)[2]	Median (IQR)	Median (IQR)	Median (IQR)
Direct[3]	2013 (1833 to 2247)	*ref*	2140 (1550 to 3636)	126 (-776 to 1030)	2345 (2030 to 2710)	331 (-257 to 919)	1175 (489-2505)	2139 (690-2709)	2073 (1020-3241)
Indirect[3]	2686 (2250 to 3173)	*ref*	2579 (1292 to 5360)	-107 (-2004 to 1790)	2044 (1424 to 2994)	-642 (-1598 to 314)	0 (0-2411)	0 (0-2619)	0 (0-2080)
Total[3]	4728 (4249 to 5286)	*ref*	4778 (3081 to 7665)	50 (-2177 to 2278)	4457 (3681 to 5625)	-271 (-1542 to 1001)	2152 (859-5886)	2678 (1008-4772)	2914 (1578-5869)

[1] Bootstrapped mean and 95% confidence interval.
[2] MD = mean difference, as marginal effect from univariate generalized linear model.
[3] Number of donors varies by response rate (Table 20); Direct (Others = 644, Non-Directed = 35, Paired = 105); Indirect (Others = 640, Non-Directed = 35, Paired = 105); Total (Others = 621, Non-Directed = 34, Paired = 102).

Table 23. Complete-case unadjusted direct, indirect, and total costs (2016 CAD) incurred by living kidney donors, by relationship-type group.

	Spousal Donors		Closely Related Donors		Unrelated Donors		Spousal Donors	Closely Related Donors	Unrelated Donors
Cost type	Mean (95% CI)[1]	MD (95% CI)[2]	Mean (95% CI)[1]	MD (95% CI)[2]	Mean (95% CI)[1]	MD (95% CI)[2]	Median (IQR)	Median (IQR)	Median (IQR)
Direct[4]	2468 (1998 to 3312)	*ref*	1884 (1659 to 2173)	-584 (-1191 to 24)	1940 (1629 to 2382)	-528 (-1189 to 133)	1322 (529-2523)	1116 (486-2555)	1161 (465-2376)
Indirect[4]	3012 (2058 to 4779)	*ref*	2892 (2311 to 3550)	-120 (-1449 to 1210)	2041 (1535 to 2888)	-972 (-2302 to 359)	0 (0-2597)	0 (0-2422)	0 (0-2129)
Total[4]	5471 (4286 to 7279)	*ref*	4820 (4175 to 5519)	-650 (-2166 to 865)	4017 (3306 to 4939)	-1454 (-3031 to 123)	1879 (1022-6846)	2187 (787-5831)	2215 (904-5165)

[1] Bootstrapped mean and 95% confidence interval.
[2] MD = mean difference, as marginal effect from univariate generalized linear model.
[3] Among donors not participating in non-directed or kidney paired donations.
[4] Number of donors varies by response rate (Table 20); Direct (Spousal = 126, Closely = 341, Unrelated = 177); Indirect (Spousal = 121, Closely = 347, Unrelated = 172); Total (Spousal = 119, Closely = 334, Unrelated = 168).

Table 24. Complete-case adjusted[1] average marginal effects of demographic variables on direct, indirect, and total costs (2016 CAD) incurred by living kidney donors (n = 821).

Variable	Direct costs (CAD)		Indirect costs (CAD)		Total costs (CAD)	
	Marginal effect (95% CI)	*p*	Marginal effect (95% CI)	*p*	Marginal effect (95% CI)	*p*
Donation-type						
All other donors	*ref*		*ref*		*ref*	
Non-directed donors	-246 (-867 to 376)	0.44	-421 (-1328 to 486)	0.36	-980 (-1959 to 0)	0.05
Kidney paired donors	369 (-118 to 856)	0.14	39 (-800 to 877)	0.93	483 (-618 to 1584)	0.39
Relationship-type[2]						
Spousal donors	*ref*		*ref*		*ref*	
Closely related donors	-333 (-797 to 131)	0.16	-749 (-2241 to 744)	0.33	-1043 (-2311 to 224)	0.11
Unrelated donors	-77 (-921 to 767)	0.86	-1443 (-2458 to -428)	0.005	-1528 (-2818 to -238)	0.02
Distance from centre						
<100 km	*ref*		*ref*		*ref*	
≥100 km	2478 (2040 to 2915)	<0.001	-588 (-1461 to 285)	0.19	2019 (1105 to 2934)	<0.001
Sex						
Male	*ref*		*ref*		*ref*	
Female	-260 (-728 to 208)	0.28	-6 (-858 to 846)	0.99	104 (-779 to 988)	0.82
Age						
18 to 35	*ref*		*ref*		*ref*	
35 to 54	739 (453 to 1026)	<0.001	-788 (-2133 to 557)	0.25	63 (-1299 to 1426)	0.93
55+	1029 (540 to 1517)	<0.001	-1650 (-2756 to -543)	0.003	-221 (-1267 to 824)	0.68
Race						
White	*ref*		*ref*		*Ref*	
Non-White	-143 (-616 to 332)	0.56	-625 (-1656 to 406)	0.24	-311 (-1255 to 633)	0.52

Variable	Direct costs (CAD)		Indirect costs (CAD)		Total costs (CAD)	
	Marginal effect (95% CI)	*p*	Marginal effect (95% CI)	*p*	Marginal effect (95% CI)	*p*
Income						
<$20,000	*ref*		*ref*		*ref*	
$20,000 to $40,000	1314 (617 to 2011)	<0.001	890 (-2193 to 3973)	0.57	2674 (-310 to 5657)	0.08
$40,000 to $60,000	1208 (594 to 1822)	<0.001	-855 (-3944 to 2234)	0.59	603 (-2406 to 3613)	0.69
$60,000 to $80,000	1254 (594 to 1915)	<0.001	-308 (-3557 to 2941)	0.85	1309 (-1532 to 4151)	0.37
$80,000 to $100,000	623 (166 to 1081)	0.008	-1730 (-4614 to 1154)	0.24	-572 (-3248 to 2285)	0.70
>$100,000	597 (233 to 961)	0.001	-1708 (-4260 to 844)	0.19	-771 (-2963 to 1421)	0.49
Employment status						
Employed	*ref*		*ref*		*ref*	
Unemployed	-820 (-1424 to -215)	0.008	-1822 (-3103 to -541)	0.005	-2357 (-3969 to -746)	0.004
Retired	-246 (-649 to 157)	0.23	-2347 (-3004 to -1689)	<0.001	-2157 (-3030 to -1284)	<0.001
Other	267 (-544 to 1007)	0.56	-101 (-2217 to 2016)	0.93	-26 (-2325 to 2273)	0.98
Province of transplant centre						
Ontario	*ref*		*ref*		*ref*	
Alberta	-565 (-1022 to -109)	0.02	161 (-1304 to 1626)	0.83	-125 (-1575 to 1326)	0.87
British Columbia	142 (-258 to 542)	0.49	-371 (-1355 to 614)	0.46	-54 (-1076 to 968)	0.92
Manitoba	-966 (-1494 to -439)	<0.001	385 (-2071 to 2842)	0.76	-368 (-2611 to 1876)	0.75
Nova Scotia	-185 (-811 to 442)	0.56	74 (-2279 to 2427)	0.95	50 (-2363 to 2463)	0.97
Quebec	902 (-406 to 2211)	0.18	917 (-1721 to 3555)	0.50	1940 (-1040 to 4920)	0.20

[1] Adjusted for age, sex, income, Clavien score, and transplant centre.
[2] Among donors not participating in non-directed or kidney paired donations.

Appendix I: STROBE checklist for reporting of cohort studies

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Curriculum Vitae

Name:	Sebastian Przech	
Post-secondary Education and Degrees:	University of Western Ontario London, Ontario, Canada BMSc. - Medical Sciences	2010-2014
	University of Western Ontario London, Ontario, Canada MSc. - Epidemiology and Biostatistics	2014-2017
	McGill University Montreal, Quebec, Canada MDCM - Doctor of Medicine	2016 - ongoing
Honours and Awards:	Western Graduate Research Scholarship	2014 - 2016
	Ontario Graduate Scholarship	2015 - 2016
	LHSC - IRF Studentship	2015 - 2016
Related Work Experience:	Clinical Research Assistant VISION Study Kidney Clinical Research Unit London, Ontario, Canada	2013 - 2013
	Clinical Research Assistant Living Kidney Donor Study Kidney Clinical Research Unit London, Ontario, Canada	2013 - 2015
	Graduate Teaching Assistant Inflammation in Disease University of Western Ontario London, Ontario, Canada	2015 - 2015

Publications:

Nash DM, **Przech S**, Wald R, O'Reilly D. (2017)	*Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit*	DOI: http://dx.doi.org/10.1016/j.jcrc.2017.05.002
Habbous S, **Przech S**, Acedillo R, Sarma S, Garg AX, Martin J. (2017)	*The safety and effectiveness of sevelamer in treating hyperphosphatemia in patients with chronic kidney disease: a systematic review and meta-analysis*	DOI: https://doi.org/10.1093/ndt/gfw312
Habbous S, **Przech S**, Martin J, Garg AX, Sarma S. (2017)	*Cost-Effectiveness of First-Line Sevelamer and Lanthanum versus Calcium-Based Binders for Hyperphosphatemia of Chronic Kidney Disease*	DOI: http://dx.doi.org/10.1016/j.jval.2017.08.3020