OUTCOMES FOLLOWING LIVING

KIDNEY DONATION

By

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A thesis submitted for the Degree of Doctor of Medicine at

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Statement of Originality

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968.

Signed

Neil Boudville

25 May 2017

Statement of Authorship and Contribution

I hereby certify that the work embodied in this thesis contains published papers

of which I am a joint author. The extent of my personal contribution to each

publication is as follows (in order of appearance in the thesis):

1. Housawi AA, Young A, **Boudville N**, Thiessen-Philbrook H, Muirhead N, Rehman F, Parikh CR, Al-Obaidli A, El-Triki A, Garg AX. Transplant professionals vary in the long-term medical risks they communicate to potential living kidney donors: an international survey. Nephrol Dial Transplant 2007;22:3040-5 **- 50%**

2. **Boudville N**, Prasad GV, Knoll G, Muirhead N, Thiessen-Philbrook H, Yang RC, Rosas-Arellano MP, Housawi A, Garg AX. Meta-analysis: risk for hypertension in living kidney donors. Ann Intern Med 2006;145:185-96. **- 80%**

3. Garg AX, Muirhead N, Knoll G, Yang RC, Prasad GV, Thiessen-Philbrook H, Rosas-Arellano MP, Housawi A, **Boudville N**. Proteinuria and reduced kidney function in living kidney donors: A systematic review, meta-analysis, and meta-regression. Kidney Int 2006;70:1801-10 **- 80%**

4. **Boudville N**, Garg AX. Live kidney donation: who's at risk of a low glomerular filtration rate following donation? Nephrology (Carlton) 2007;12:598-9. **- 90%**

5. **Boudville N**, Garg AX. End-stage renal disease in living kidney donors. Kidney Int. 2014 Jul;86(1):20-2 **- 80%**

6. Garg AX, Meirambayeva A, Huang A, Kim J, Prasad GV, Knoll G, **Boudville N**, Lok C, McFarlane P, Karpinski M, Storsley L, Klarenbach S, Lam N, Thomas SM, Dipchand C, Reese P, Doshi M, Gibney E, Taub K, Young A; Donor Nephrectomy Outcomes Research Network. Cardiovascular disease in kidney donors: matched cohort study. BMJ. 2012 Mar 1;344:e1203 **- 30%**

7. Garg AX, Boudville N. Live kidney donation was associated with increased mortality and end-stage renal disease at 15 years: Commentary. ACP Journal Club. 2014;160(6) **- 70%**

8. Young A, Nevis IF, Geddes C, Gill J, **Boudville N**, Storsley L, Garg AX. Do biochemical measures change in living kidney donors? A systematic review. Nephron Clin Pract 2007;107:c82-9. **- 50%**

9. Young A, Hodsman AB, **Boudville N**, Geddes C, Gill J, Jassal V, Klarenbach S, Knoll G, Muirhead N, Prasad R, Treleaven D, Garg AX. Bone and Mineral Metabolism and FGF-23 after kidney donation. Am J Kidney Disease. 2012 Jun;59(6):761-9. **- 50%**

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13. Brown JB, Karley ML, **Boudville N**, Bullas R, Garg AX, Muirhead N. The experience of living kidney donors. Health Soc Work 2008;33:93-100 **– 50%**
14. Cuesta-Brian B, Wray N, **Boudville N**. Reflexivity in practice: Ethical dilemmas in research with potential living kidney donors. Research Ethics 2015;11(3):164-172   **- 80%**
15. Sickand M, Cuerden MS, Klarenbach SW, Ojo AO, Parikh CR, **Boudville N**, Garg AX. Reimbursing live organ donors for incurred non-medical expenses: a global perspective on policies and programs. Am J Transplant 2009;9:2825-36.   **- 30%**
16. Klarenbach S, Gill JS, Knoll G, Caulfield T, **Boudville N**, Prasad GV, Karpinski M, Storsley L, Treleaven D, Arnold J, Cuerden M, Jacobs P, Garg AX; Donor Nephrectomy Outcomes Research (DONOR) Network. Economic consequences incurred by living kidney donors: A Canadian multi-centre prospective study. Am J Transplant. 2014 Apr;14(4):916-22   **- 40%**
17. Cuesta Briand B, Wray N, **Boudville N**. The cost of organ donation: Potential living kidney donors' perspectives. Health Soc Work 2015 Nov;40(4):307-15.   **- 80%**
18. **Boudville N,** Isbel N. Donors at risk: Impaired glucose tolerance. Nephrology (Carlton) 2010; 15:S133-S136.   **- 80%**
19. **Boudville N**, Kanellis J, F. I. Donors at risk: hypertension. Nephrology (Carlton) 2010;15:S114-S120.   **- 80%**
20. **Boudville N**, Kanellis J. Donors at risk: proteinuria. Nephrology 2010;15:S106-S110.   **- 80%**
21. Clayton PA, Saunders JR, McDonald SP, Allen RD, Pilmore H, Saunder A, **Boudville N,** Chadban SJ. Risk-Factor Profile of Living Kidney Donors: The Australia and New Zealand Dialysis and Transplant Living Kidney Donor Registry 2004-2012. Transplantation. 2016 Jun;100(6):1278-83. **- 25%**
22. Reese PP, **Boudville N**, Garg AX. Living kidney donation: outcomes, ethics, and uncertainty. Lancet. 2015 May 16;385(9981):2003-13   **- 30%** 6

Signed,

Neil Boudville   25 May 2017

ACKNOWLEDGEMENTS

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SYNOPSIS

The research that forms the content of this thesis has been performed over the last 14 years and is an ongoing line of research that I am likely to perform for the rest of my career. While a great deal of research has been performed on transplant recipients, it became clear to me 14 years ago that there was limited good research on the outcomes of people who donate their kidneys to people with end-stage kidney disease (except for short-term outcomes in the immediate post-operative period).

I subsequently embarked on a research path that commenced with a series of systematic reviews, followed by cross-sectional studies and finally to the commencement of a large prospective observational study to explore in more detail the outcomes of living kidney donors. This dissertation reviews my research to date, with the large prospective study still years away from completion. My research efforts have not included commercial donors, who likely have quite different outcomes.

There are a number of important patient-level outcomes that I have explored and so I have divided this thesis into chapters based upon groups of these outcomes. Within the chapters I follow a primarily temporal order for my research and describe some other key publications from other research groups.

CHAPTER 1

BACKGROUND

End-stage kidney disease (ESKD) is increasingly recognised as a major public health problem in Australia and worldwide.

At the end of 2015, 12,461 (524 per million) Australians had developed end-stage kidney disease (ESKD) and commenced renal replacement therapy – dialysis (1). These patients have a 10-fold higher age- and sex-matched mortality than the general population, a prognosis worse than most forms of cancer, along with a markedly reduced quality of life, and disproportionate consumption of health resources (1-4). 2,500 Australians progress to ESKD each year requiring either dialysis or kidney transplantation (1). It is projected that by 2020, between 3,335 and 4,472 Australians per year will reach ESKD (5). In 2009, the annual cost of providing dialysis or kidney transplantation to 18,243 ESKD (dialysis and kidney transplant) patients was $900 million (2, 5). The cumulative cost of treating *all current and new* cases of ESKD from 2009 to 2020 is estimated to be $11-12 billion (5). In 2011-2012, the cost of treatment for ESKD accounted for 1.6% of the total Australian health-care budget , while ESKD patients represented <0.01% of the entire population (5).

Kidney transplantation leads to clear advantages over dialysis

Kidney transplantation, a 'miracle' of modern medicine, is the preferred treatment option for ESKD (6, 7). Compared to dialysis, patients who receive a kidney transplant have a 70% reduction in risk of death, a dramatically improved quality of life and cost the health care system considerably less (7).

Living kidney donation is better than deceased donation for the recipient

Compared with deceased donation, living kidney donation offers numerous added benefits to the recipient, including less time on dialysis and improved graft and recipient survival (8-12). The five-year graft-survival rates for recipients of kidneys from living *versus* deceased donors are 80% versus 69% (8). The healthcare costs of living donation are similar to or less than the costs of deceased donation (13, 14). By eliminating the need for dialysis, living kidney donors save the healthcare system approximately $50,000 per patient per year (15).

There is increasing demand for kidney transplantation without a commensurate rise in deceased donation.

In Australia the prevalence of kidney failure rose by 49% between 2004 and 2013, with 21,470 Australians living with kidney failure as of 2013 (16). Rising rates of kidney failure combined with the growing success of transplantation has created an increased demand for kidneys. However, the available supply of deceased donor kidneys is not keeping pace. The number of patients waiting for a transplant far exceeds transplantation rates: in 2005 wait lists were 85 per million population in Canada and in Australia with corresponding transplant rates of 51 and 38 per million population, respectively. In 2013, 1,056 Australians were waiting for a kidney, and this number will rise as the population ages. Current wait times (5-7 years) are significantly longer than the life expectancy of most middle-aged and older patients with kidney failure. In the US, the number of people who died while waiting for a kidney increased by 40%

between 1999 and 2008 (8). In Australia, living kidney donor numbers have not been increasing over the last 5 years to match the increased demand.

In many countries, genetically unrelated donors are now being considered to expand the donor pool, including emotionally involved (spousal) donors (17), paired-kidney donors (18, 19), list-paired kidney donors (18), altruistic strangers, and even commercial donors (20).

Concerns were raised in the early 2000's over the potential adverse consequences (especially long-term) of living kidney donation.

Despite its advantages for the recipient, living kidney donation remains a complex ethical, moral and medical issue. The premise for accepting living donors is that the "minimal" risk of short and long-term medical harm realized by the donor is outweighed by the definite advantages to the recipient and potential psychosocial benefits of the altruistic gift for the donor. The only potential benefit for the living donor is psychological - donors usually experience increased self-esteem, feelings of well-being and improved health related quality of life with their altruistic act of assuming medical risk to help another (21).

The short-term consequences of living donation are well established. The immediate medical risk of the operative procedure is a peri-operative mortality rate of 3 deaths per 10 000 donors (22), pulmonary embolism in less than 2% of

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patients (23), and morbidity such as minor wound infections, urinary tract infections and low-grade fever in less than 10% of patients (24). Donors are generally discharged from the hospital by the fourth day after surgery and they usually return to work within six weeks.

On the other hand the long-term implications of living kidney donation are far less certain. The main medical concerns of living kidney donation include an increased risk of hypertension, proteinuria and low glomerular filtration rate. In the early 2000's 2 publications were released in the Journal of the American Medical Association that highlighted growing concerns about the safety of living donation due to the uncertainty around some of the potential consequences of donation and the need for further investigation into this area (18, 25). These publications occurred on the background of case reports of living kidney donors developing ESKD themselves (26).

As a result of these publications I became motivated to commence research into the area of living kidney donor outcomes in 2003. This research continues to this day and it is this body of work that I am submitting for consideration for the Degree of Doctor of Medicine. As with most research, I have often investigated multiple outcomes simultaneously, so I have divided the following discourse in a roughly temporal order but assembled around specific groups of primarily patient-level outcomes.

CHAPTER 2

DEMONSTRATING THAT UNCERTAINTY IN THE LONG-TERM RISKS OF LIVING KIDNEY DONATION EXISTS AMONGST TRANSPLANT HEALTH CARE PROFESSIONALS

One of the first research projects I performed into this area was a survey conducted on transplant health professionals around the world. I developed a 10 minute survey along with a group of other transplant health care professionals involved in living kidney transplantation. The survey was pilot tested on another group of physicians (also involved in living kidney donor assessment) prior to general distribution. A contact list of members of the American Society of Transplantation, the American Society of Transplant Surgeons and the European Society of Organ Transplantation was used to electronically distribute the surveys with 203 being returned. Respondents included transplant nephrologists, surgeons and nurses from 35 different countries.

The results demonstrated uncertainty in the perceived long-term risks of living kidney donation amongst health-care professionals directly involved in living kidney donation. For example, 55% of respondents believed that the long-term risk of developing hypertension is not increased if you were to donate a kidney, while 45% believed it was increased. Similarly, 45% of respondents believed that the lifetime risk of developing a glomerular filtration rate (GFR) of less than 60ml/min (which equates to Chronic Kidney Disease (CKD) Stage 3) was not increased if you were to donate a kidney, compared to 55% who believed there was an increased risk. Even the perceived risk of cardiovascular disease and death was thought to be increased by 16% and 8% of respondents respectively following living kidney donation.

Anytime we perform a procedure or operation on a patient it is an essential requirement that we obtain informed consent from them. Living kidney donation is one of the few occasions that health care professionals inflict harm on a healthy person and it is fundamental to this process that they are fully informed of their risks. The findings of this study made it clear to me that even within the community of health care professionals who deal directly with living kidney donation there was a degree of uncertainty with respect to the long-term risks. This then begs the question as to how informed consent was being obtained from previous, current and future living kidney donors. I felt that it was the responsibility of all involved in kidney transplantation to have a better understanding of the risks to a potential donor to ensure that they are fully informed and have the appropriate long-term follow-up after the operation.

It was not clear whether the uncertainty amongst the transplant health care professionals was due to a gap in the evidence or due to a lack of understanding of what the evidence is. So my next line of investigation was to do a systematic review of the literature to examine what the current level of evidence was, with respect to the long-term outcomes of living kidney donors.

CHAPTER 3

LONG-TERM RISK OF HYPERTENSION FOLLOWING LIVING KIDNEY DONATION

Publication:

Boudville N, Prasad GV, Knoll G, Muirhead N, Thiessen-Philbrook H, Yang RC, Rosas-Arellano MP, Housawi A, Garg AX. Meta-analysis: risk for hypertension in living kidney donors. Ann Intern Med 2006;145:185-96.

Hypertension is a significant medical condition that increases the risk of heart disease, stroke, peripheral vascular disease and chronic kidney disease (27). The kidneys are key regulators of arterial blood pressure, mediated by water and sodium balance and the renin-angiotensin-aldosterone system. Kidney donation results in hypertrophy and hyperfiltration of nephrons in the remaining kidney. Physiology derived from animal models would suggest that remnant kidney single-nephron hyperfiltration is unsustainable (28) and leads to hypertension and progressive kidney disease (29). Therefore one of the initial important clinical outcomes that I wanted to examine was the development of hypertension in living kidney donors.

To this end I performed a systematic review and meta-analysis, compiling citations from 1966 through to November 2005, examining both the risk of elevation of blood pressure and the development of hypertension. Four controlled studies at least 5 years after kidney donation were identified that examined for a change in systolic blood pressure (SBP), and on meta-analysis demonstrated a 6 mmHg (95% confidence interval (95%CI): 1.6, 10.5 mmHg) higher SBP in donors compared to controls. There was a total of only 157 donors and 128 controls in these studies however, with a mean follow-up ranging from 8 to 13 years.

Five controlled studies at least 5 years post kidney donation, demonstrated a 4 mmHg (95%CI: 0.9, 6.7 mmHg) increase in diastolic blood pressure (DBP) in donors compared to controls. In total there were 196 donors and 161 controls in

these studies, with a mean follow-up ranging from 6 to 13 years. This may seem like small changes but in the general population, a 10 mmHg increase in SBP and a 5 mmHg increase in DBP is associated with a 1.5 times increased risk of death from stroke and ischaemic heart disease (27).

Of the 6 studies with controls examining for the development of hypertension, only one demonstrated a statistically significant increased risk in previous living kidney donors (relative risk = 1.9 (95%CI: 1.1, 3.5)). There was statistical heterogeneity between the studies which did not allow mathematical pooling of the results. For all 6 studies there was a total of 249 donors and 161 controls, with a mean follow-up in these studies of 2 to 13 years.

I identified significant limitations of the existing studies, including the following:

1) No study has matched living donors with the appropriate control group.

Even without donating a kidney, a proportion of patients will inevitably develop hypertension (plus other clinically important outcomes that I will discuss in later chapters, such as proteinuria and renal insufficiency). As a result, a control group of non-donors internal to the study, which is compared to a group of donors, is critical to determine if donating a kidney results in an increase in long-term medical sequelae. A portion of previous studies have matched living donors with patients from the general population as controls (28, 30-33). However people who have been accepted for kidney donation are not the same as the general population - they are extremely healthy individuals who pass

rigorous investigations to become donors. Consequently, kidney donors would be expected to have lower rates of hypertension (and other clinically important outcomes like proteinuria, renal insufficiency and mortality) over the general population (34). Furthermore no study has used a control group with confirmed absence of disease at baseline. Two studies which used siblings as the control group did not ascertain whether such patients had an absence of hypertension (proteinuria or low glomerular filtration rate) at the time of kidney donation (35, 36). Given familial clustering of renal disease and hypertension has been well documented, siblings related to the kidney recipient may form an inappropriate control group, if the absence of renal disease was not established at baseline. In all of these circumstances, the use of an inappropriate control group would lead to a higher incidence of renal sequelae at follow-up in the control group and negate the difference between living donors and controls.

2) No study has used an adequate sample size to detect a clinically important risk of hypertension.

While the one study with a more precise definition of hypertension demonstrated a trend towards increased risk (35), from the overall result one might consider that physiological theory does not bear out in human studies. A critical flaw in these studies was that none had greater than 80% statistical power to demonstrate a 20% (or less) absolute increase in the development of hypertension at their respective follow-up times (given the event rates they report in their control groups).

3) Adverse complications may be less likely to be reported.

The existence of publication biases in abstracts and full-text articles of the literature are well recognized. Studies demonstrating adverse iatrogenic events after living kidney donation may be prone to non-reporting. Specifically, such reports may be a focus for litigation, particularly if the transplant outcome was poor.

4) Retrospective design and high loss to follow-up

The studies to date have been retrospective and had considerable loss to follow-up as a result, leading to potential bias.

Therefore, my study has suggested an increase in SBP and DBP 5 to 10 years post-living kidney donation but considerable methodological issues question the validity of these findings and longer term (>10 years) outcomes remain unknown. Since this study was published there has been minimal additional evidence on blood pressure as an outcome. One recent publication did prospectively follow-up all living kidney donors in Switzerland between 1993 and 2009 (n = 1,214 donors) and demonstrated a 3.64 fold increased risk of developing hypertension at 1 year. However, follow-up was limited and the comparator was not a control group but a derived estimate of hypertension using a prediction equation on the donors from their baseline data (37).

CHAPTER 4

LONG-TERM RISK OF PROTEINURIA AND REDUCED KIDNEY FUNCTION FOLLOWING LIVING KIDNEY DONATION

Publications:

Garg AX, Muirhead N, Knoll G, Yang RC, Prasad GV, Thiessen-Philbrook H, Rosas-Arellano MP, Housawi A, **Boudville N**. Proteinuria and reduced kidney function in living kidney donors: A systematic review, meta-analysis, and meta-regression. Kidney Int 2006;70:1801-10

Boudville N, Garg AX. Live kidney donation: who's at risk of a low glomerular filtration rate following donation? Nephrology (Carlton) 2007;12:598-9.

Boudville N, Garg AX. End-stage renal disease in living kidney donors. Kidney Int. 2014 Jul;86(1):20-2

Some of the concerns in the 1990's and early 2000's were around the possibility of living kidney donors developing progressive chronic kidney disease based upon the identification of a series of donors that subsequently developed ESKD themselves (26). Many consider the reduction of renal mass that follows kidney donation may lead to nephron hyperfiltration (29). A manifestation of nephron hyperfiltration may include the development of proteinuria. Observational studies have confirmed an increased risk of progressive renal disease with a urine protein greater than 500 mg/day (38, 39). Whether this relationship between proteinuria and CKD exists in living kidney donors is unknown.

To investigate this area further I performed a systematic review of the literature to examine for the development of proteinuria and loss of kidney function that was done in parallel with my investigation into hypertension following living kidney donation. Citations were identified from 1966 until November 2005 and reviewed.

In this study I identified 42 studies that quantified urine protein in 4,793 living donors an average of 7 years (range 2-25 years) post donation. There was a wide range for the incidence of the development of proteinuria, some reporting levels less than 5% but a few reporting over 20%. Some of the differences may be related to varying definitions of proteinuria. Upon restricting the studies to those that included a definition of proteinuria as >300mg/day, there was a pooled incidence of 10% (95%CI: 7, 12%) at a mean follow-up of 7 years.

A common theme in living kidney donor research is trying to identify if the development of abnormalities (in this case proteinuria) would have developed anyway, even if the person had not donated a kidney. To try and ascertain this I restricted studies to only those that included a control group. Only 3 studies had controls that measured 24-hour urine protein – this included a total of 129 donors and 59 controls. Upon pooling their results proteinuria was higher amongst the donors, at an average of 11 years post-donation, with a weighted mean difference of 66mg/day (95%CI: 24, 108mg/day). Similar findings were seen when other measures of proteinuria (24 hour urine albumin and microalbuminuria) were examined. Once again, the numbers of donors and controls were limited.

When examining for kidney function following living kidney donation, I identified 36 studies on 3,529 donors, an average of 6 years post-donation. In these studies the average serum creatinine was 98µmol/L and the average GFR was 86ml/minute/1.73m^2. The average reduction in GFR post-donation was 26ml/min/1.73m^2 (range 8-50ml/minute/1.73m^2). When the analysis was restricted to those studies with an average follow-up of more than 10 years 0.2% of donors had a GFR < 30ml/min/1.73m^2 (range 0-2.2%), and 12% had a GFR between 30 and 59ml/min/1.73m^2 (range 0-28%).

There were 6 controlled studies identified, with a total of 239 donors and 189 controls followed between an average of 6 and 13 years post-donation. Pooling

their results demonstrated a 10ml/min/1.73m^2 reduction in GFR (95%CI: 6, 15 ml/min/1.73m^2).

These results demonstrated that proteinuria does appear to be more common in living kidney donors, however whether this is associated with progressive CKD (as is seen in the general population) is not known. A reduction in kidney function is seen following living kidney donation, as expected, however this study did not demonstrate any evidence that there is more accelerated ongoing reduction in kidney function. The existing literature at the time however had all of the issues previously described in addition to inadequate long-term follow-up, especially needed for an outcome such as kidney function, suggesting the need for more investigation in this area.

As a result of my published systematic reviews of the literature I was subsequently asked to provide an editorial on another paper published on long-term living kidney donor outcomes (40). In this editorial, I highlighted that the results in this new publication was consistent with my findings and that it still did not provide the transplant community with a definitive answer on the effects of donation on kidney function long-term, as it was cross-sectional, small and from a single-centre.

Recently, 2 publications have added more evidence into this space and I was asked to provide an editorial on them. One paper examined all 1,901 living

kidney donors in Norway between 1963 and 2007, with a median follow-up of 15.1 years (41). They also included a healthy control group, selected in such a fashion as to try and make them of comparable health to actual donors. Though complete baseline data on the controls was not available to confirm this. This paper demonstrated an 11-fold increased hazard ratio for the development of ESKD in donors compared to the matched non-donor controls.

Shortly afterwards there was another publication on over 96,000 United States (US) living kidney donors between 1994 and 2011 with a median follow-up of 7.6 years (42). They compared outcomes with a matched control group derived from a large community study performed in the US, the Third National Health and Nutrition Examination Survey (NHANES III). This control group once again tries to be as healthy as the living kidney donors but cannot be fully confirmed as healthy donors undergo extensive testing prior to donation. The results of this study were already released in abstract form and so I included it within my editorial. This group demonstrated an 8-fold increased risk of ESKD amongst living donors compared to controls. The similarity in the magnitude of these 2 independent papers strongly suggests that there may be a real association between living kidney donation and subsequent development of ESKD. These papers have made an impact on living kidney donation as adequate informed consent requires communication of these results to all prospective donors. In my editorial, I described a potential way of expressing this in a manner that is more understandable by a lay person (as a 10-fold increased risk of something happening may appear greater than the true absolute increased risk).

CHAPTER 5

LONG-TERM RISK OF CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY FOLLOWING LIVING KIDNEY DONATION

Publications:

Garg AX, Meirambayeva A, Huang A, Kim J, Prasad GV, Knoll G, **Boudville N**, Lok C, McFarlane P, Karpinski M, Storsley L, Klarenbach S, Lam N, Thomas SM, Dipchand C, Reese P, Doshi M, Gibney E, Taub K, Young A; Donor Nephrectomy Outcomes Research Network. Cardiovascular disease in kidney donors: matched cohort study. BMJ. 2012 Mar 1;344:e1203

Garg AX, **Boudville N**. Live kidney donation was associated with increased mortality and end-stage renal disease at 15 years: Commentary. ACP Journal Club. 2014;160(6)

In the general population there is a strong association between CKD and cardiovascular disease and mortality (43). This occurs from a GFR of <60 ml/min/1.73m^2 and so is not just limited to ESKD patients, though the magnitude of the relationship is more pronounced as kidney function deteriorates (44). The most common cause of death in ESKD patients is secondary to cardiovascular disease. Similarly with CKD, the most common cause of death is secondary to cardiovascular disease, with most patients dying prior to the development of ESKD.

If the relationship between reduced kidney function and cardiovascular disease and mortality holds true for living kidney donors, plus they develop an increased incidence of hypertension, then their risk may be even greater. Therefore I also explored the development of cardiovascular disease and all-cause mortality in living kidney donors.

All 2,028 living kidney donors who had a donor nephrectomy at all of the five transplant centres in Ontario, Canada between 1992 and 2009 were identified. Their baseline data was manually verified by chart review and outcomes were confirmed utilizing administrative databases with follow-up until 31 March 2010. Outcomes were compared to 20,280 matched healthy control group that was derived from the general population but selected to be as healthy as the actual donors (though this cannot be fully confirmed).

There was a median follow-up of just under 7 years for both donors and controls. The risk of death or first major cardiovascular event was significantly lower in the donors – hazard ratio 0.66 (95%CI: 0.48, 0.90). Death occurred in 0.8% of donors and 1.8% of controls (not statistically significant). Time to first major cardiovascular event, censored for death, was not statistically significantly different between donors and controls in this study.

Results of this paper, the largest controlled study to date, suggested that there was no additional increased risk of cardiovascular disease or death with donating a kidney compared to not donating one. This study does however have inherent limitations, one of which is the relatively short follow-up.

The previously discussed recent publication by the Norwegian group on a large group of 1,901 living kidney donors and matched healthy controls also examined these clinical outcomes but with a much longer follow-up (41). They found a significantly increased risk of all-cause mortality, with an adjusted hazard ratio of 1.48 (95%CI: 1.17, 1.88). They also found an increased cardiovascular mortality, hazard ratio of 1.40 (95%CI: 1.03. 1.91). Notably survival curves between these 2 groups started to separate after 10-15 years post-donation. Suggesting that much longer term follow-up than most studies to date have had is required to accurately examine for these outcomes.

CHAPTER 6

LONG-TERM RISK OF BIOCHEMICAL AND HAEMATOLOGICAL CHANGES FOLLOWING LIVING KIDNEY DONATION

Publications:

Young A, Nevis IF, Geddes C, Gill J, **Boudville N**, Storsley L, Garg AX. Do biochemical measures change in living kidney donors? A systematic review. Nephron Clin Pract 2007;107:c82-9.

Young A, Hodsman AB, **Boudville N**, Geddes C, Gill J, Jassal V, Klarenbach S, Knoll G, Muirhead N, Prasad R, Treleaven D, Garg AX. Bone and Mineral Metabolism and FGF-23 after kidney donation. Am J Kidney Disease. 2012 Jun;59(6):761-9.

Garg AX, Pouget J, Young A, Huang A, **Boudville N**, Hodsman A, Adachi JD, Leslie WD, Cadarette SM, Lok CE, Monroy-Cuadros M, Prasad GVR, Thomas SM, Naylor K, Treleavan D. Fracture risk in living kidney donors: A matched cohort study. Am J Kidney Diseases. 2012 Jun;59(6):770-6

Reductions in kidney function are associated with a multitude of biochemical and haematological changes, even at only modest reductions (45-48). These may have direct or indirect effects on the health of a CKD patient. Living kidney donation is a unique situation of a sudden reduction in kidney function that might predispose the donor to some or all of these biochemical and haematological changes. I subsequently started to explore these potential outcomes, initially with a systematic review of the literature between 1966 and June 2006.

Eight studies, that included a total of 321 living kidney donors, were identified that had biochemical or haematolgical results at least 4 months after donation. These results were compared to those performed prior to donation or to a control group. The average follow-up was 2.7 years.

Four studies examined mineral metabolism, and reported no significant change in serum phosphate, and serum calcium. Inconsistent changes (ie results between studies varied between no change, an increase or a decrease) in serum parathyroid hormone levels and 1,25-dihydroxyvitamin D were reported.

Four studies examining anaemia identified no changes in haemoglobin, haematocrit or erythropoietin levels in the long term in living kidney donors. Serum uric acid levels varied slightly between studies with one noting that 30% of donors developed hyperuricaemia post-donation. Only one study examined

homocysteine and c-reactive protein, with no change in the latter and only a mild increase in homocysteine (though it still stayed within the normal range).

Clearly, the literature at the time was inadequate with respect to this area of long-term living kidney donor outcomes. To further investigate this I performed a cross-sectional study between 2004 and 2008, recruiting 198 living kidney donors and 98 non-donor controls. Median follow-up time for this study was 5.3 years (Interquartile range: 3.3 to 8.4 years). Despite the GFR being on average 25ml/min/1.73m^2 lower in the donors than the control group, no significant difference was detected between the groups with respect to serum calcium. There was however in the donors compared to the controls:

1) Higher plasma parathyroid hormone levels – 5.7 vs 5.0 pmol/L, p=0.04

2) Lower serum phosphate levels – 0.97 vs 1.02mmol/L, p=0.02

3) High renal fractional excretion of phosphate – 17.8% vs 12.3%, p<0.001

4) Higher serum fibroblast growth factor 23 (FGF-23) – 38.1 vs 19.7pg/mL, p=0.001

5) Lower 1,25 dihydroxyvitamin D levels – 63 vs 77 pmol/L, p=0.001

This study, utilizing the unique model of a sudden decline in kidney function, was one of the first to support the challenge to previous dogma in nephrology that rising serum phosphate levels was the earliest change in CKD mineral and bone disease and the driver for elevations in serum PTH levels. The results of this study supported the more recent thoughts at the time that FGF-23 was a more important and earlier driver for the changes seen (49). Here it was noted

that changes in FGF-23 in our patient groups (with mild reduction in kidney function) occurred with an associated elevation in PTH but no change in serum calcium and indeed a lowering in serum phosphate concentrations.

Another study I performed in this area, examined the risk of developing fractures amongst living kidney donors, as a severe manifestation of CKD mineral and bone disease. This study was performed in parallel to the study previously described examining cardiovascular events and all-cause mortality. Data was collected on all 2,015 adult living kidney donors in Ontario, Canada between 1992 and 2009 with a median follow-up of 6.6 years and a median age of 50 years old (Interquartile range: 42 to 58 years old). Ten times as many matched controls were selected from the general population, with baseline information suggesting they were a healthy comparator group. Fractures were identified through administrative databases in Ontario which included discharge information, and outpatient billings. There were 25 fractures in living donors and 275 in matched controls, resulting in equivalent fracture rates – 16.4 vs 18.7 fractures/10,000 person years, p=0.05.

These studies that I have performed described changes in bone mineral metabolism that are probably most consistent with the changes in kidney function seen following kidney donation. It was one of the first studies to support the pivotal role of FGF-23 in CKD mineral and bone disease. Other biochemical and haematological changes still remain unclear due to the absence of adequate evidence.

CHAPTER 7

PSYCHOSOCIAL WELL-BEING FOLLOWING LIVING KIDNEY DONATION

Publications:

Clemens KK, Thiessen-Philbrook H, Parikh CR, Yang RC, Karley ML, **Boudville N**, Ramesh Prasad GV, Garg AX. Psychosocial health of living kidney donors: a systematic review. Am J Transplant 2006;6:2965-77.

Clemens K, **Boudville N**, Dew MA, Geddes C, Gill JS, Jassal V, Klarenbach S, Knoll G, Muirhead N, Prasad GV, Storsley L, Treleaven D, Garg A. The long-term quality of life of living kidney donors: a multicenter cohort study. Am J Transplant 2011;11:463-9.

Brown JB, Karley ML, **Boudville N**, Bullas R, Garg AX, Muirhead N. The experience of living kidney donors. Health Soc Work 2008;33:93-100

Cuesta-Brian B, Wray N, **Boudville N**. Reflexivity in practice: Ethical dilemmas in research with potential living kidney donors. Research Ethics 2015;11(3):164-172

Another key outcome to examine is the psychosocial consequences of living kidney donation. Improved psychological well-being is often quoted as being the major benefit of donating a kidney – due to the sense of doing something good for someone else. To investigate this and any potential adverse outcomes, I once again started with a systematic review of the literature from 1969 to July 2006, identifying studies in English that assessed psychosocial function in at least 10 donors using questionnaires. 51 studies were identified that met inclusion and exclusion criteria, with 10 of them following donors prospectively.

In the studies that examined donor-recipient relationships, 86-100% of donors indicated that their relationship was unchanged or improved with the donor, with many also reporting spending an increased amount of time together post-donation. Most of the studies described that donors had an increase in their self-esteem following donation, however one study did report that 6-24% felt that they had given something for nothing in return.

Ninety-five percent of donors were generally happy and most felt happier after donation. In some studies however, a small proportion of donors reported negative emotional outcomes – 4% were disappointed in their emotional experience of donation; 6-8% felt ignored; with outcomes in donors particularly worse if the recipient experienced poor outcomes. In addition, while the majority of donors did well post-donation, some studies noted some negative results with respect to depression and anxiety – 6% noting an increase in depression or anxiety symptoms.

Quality of life was reported in 29 studies and the vast majority noted high satisfaction with their quality of life, though one study reported 95% felt it was unchanged after donation. Compared to the general population, donors were consistently reported as having a higher quality of life. Once again though, studies did report a minority of donors having a deterioration in their quality of life post-donation.

This study highlighted that the vast majority of living kidney donors have a good level of psychosocial functioning. This may predate the donation however, and reflect the 'type' of person who would donate a kidney, with variable reports of changes post-donation. Of note though, was the occasional study reporting some negative experiences with small numbers of living kidney donors, emphasizing the need to be aware of this possibility in the work-up and follow-up of these patients.

To further investigate this area, I performed a retrospective study on 203 previous living kidney donors with a comparator population of 104 healthy non-donors. Donors and healthy non-donor controls were identified as described in a previous chapter, from 9 centres in Canada, Australia and Scotland.

Quality of life in this study was not significantly different between living kidney donors, healthy non-donors or general population norms. Similarly, marital

status, mental health visits, employment and income post-donation was no different between donors and non-donors.

This was followed by another study that I performed which utilised qualitative research methods, using a phenomenological approach, to evaluate the experience of donating a kidney amongst previous living kidney donors. An interesting finding from this study was the sense of loss and grief post donation noted by some donors reinforcing the need for adequate support of donors through the donation process and also afterwards. This is not necessarily being performed in all transplant units.

There has been a plateauing of living kidney donors in Australia and other countries in recent years and that stimulated my interest in examining the experience of living kidney donors during the donation process, prior to actually donating a kidney (16). The question being asked was whether a poor experience through the donation work-up was influencing future potential living kidney donors from presenting. The best way to evaluate this is through qualitative research, using a phenomenological approach. This research is ongoing but some preliminary results have been published.

I recruited 19 potential living kidney donors from one of two kidney transplant units in Western Australia. The participants were identified as having completed

their donor work-up and deemed either suitable to donate (and were awaiting an operation date) or deemed unsuitable for donation.

In the process of performing this study I faced a number of ethical dilemmas which I had not predicted beforehand and published these recently. One of the dilemmas was the optimal time for scheduling the interview – where the majority of studies in this area were performed post-donation but I felt that this may be too late in the experience and be influenced by the operation and outcome of the recipient. Likewise, I wanted to schedule the interview after all the work-up was complete (to capture the entire experience) but not too close to surgery which would be too busy and stressful a time for the potential donor. Other dilemmas highlighted the difficulty of balancing ethical considerations with the inherent limitations of the current research environment of limited funds and short time-lines and reinforced the need to ensure we maintain ethical standards despite these constraints.

This area of research indicated that the vast majority of living kidney donors have good psychosocial outcomes post-donation. However, a small proportion do have poor outcomes and there needs to be ongoing consideration and monitoring for this before and after donation.

CHAPTER 8

FINANCIAL IMPLICATIONS ON THE DONOR OF LIVING KIDNEY DONATION

Publications:

Sickand M, Cuerden MS, Klarenbach SW, Ojo AO, Parikh CR, **Boudville N**, Garg AX. Reimbursing live organ donors for incurred non-medical expenses: a global perspective on policies and programs. Am J Transplant 2009;9:2825-36.

Klarenbach S, Gill JS, Knoll G, Caulfield T, **Boudville N**, Prasad GV, Karpinski M, Storsley L, Treleaven D, Arnold J, Cuerden M, Jacobs P, Garg AX; Donor Nephrectomy Outcomes Research (DONOR) Network. Economic consequences incurred by living kidney donors: A Canadian multi-centre prospective study. Am J Transplant. 2014 Apr;14(4):916-22

Cuesta Briand B, Wray N, **Boudville N**. The cost of organ donation: Potential living kidney donors' perspectives. Health Soc Work 2015 Nov;40(4):307-15.

Living kidney donation is an amazing altruistic demonstration by a select group of people. The model of health care in most countries around the world however results in out-of-pocket non-medical expenses for most living kidney donors during their work-up period, including expenses for travel, accommodation, parking, care for dependents and meals. In addition, there may be the cost of loss of income to attend work-up appointments or for the post-donation recovery period. Some jurisdictions provide reimbursement of reasonable costs incurred through the donation process to ensure that there is not an economic obstacle to living kidney donation. This is clearly an ethically sensitive area as this will need to be weighed up against providing a financial incentive to donate.

To investigate this area I collected information on existing models of reimbursement for living kidney donors from 40 countries. Programs where reimbursement is designed to be a financial gain for the donors were excluded. 16 out of the 40 countries had legalized reimbursement of living kidney donors, 1 explicitly prohibited it and the rest were unclear.

Six of the 21 countries with reimbursement programs commenced them in the previous 5 years, with another 2 countries actively developing a program for implementation in the near future. The nature of the reimbursement varied between countries but included various components of covering costs of travel, accommodation, meals, lost income, and childcare. Fifteen of the countries have their reimbursement at least partially funded by the government.

This study illustrated the increasing recognition of the need to reimburse living kidney donors for out of pocket expenses as a means to prevent financial obstacles to donation and also for equity, recognizing the altruism of the donation. Many of the programs were new, evolving or in the planning phase to meet the needs of the donors. It also demonstrated that the wide-spread practice of reimbursement may indicate that those countries that prohibit it or do not have an existing program should consider reassessing this position.

The extensive research that I had performed made it clear that the existing literature on all of the long-term outcomes of living kidney donors had significant limitations, including – being primarily retrospective studies, with a high proportion of loss to follow-up, short follow-up period and inadequate control groups. A randomised controlled trial will never occur in this area and so my group of collaborators and myself designed a prospective observational study. We recruited healthy controls from the other people who presented as potential donors along with the actual living kidney donor (often more than one person would come forward to donate to a single recipient) or using people identified as healthy and interested by the actual donor. These control patients also underwent baseline testing to ensure that they would be healthy enough to donate a kidney. Then donors and controls were followed up prospectively.

In 2004 I commenced enrolling participants for the pilot study to test the study methodology and feasibility prior to commencing the larger prospective study. Between 2004 and 2008 100 living kidney donors were recruited from 7

transplant units in Canada as part of this pilot study. Out of pocket expenses were recorded by the donors at 3 and 12 months post-donation and results were published. This study demonstrated that 94 out of the 100 donors experienced direct out of pocket expenses, most commonly due to ground travel (94%) and accommodation (49%). The average total direct cost was estimated at $1,780 (standard deviation $2,504) Canadian, with a median cost of $821 (range $242-$2,271). In addition, over 80% of donors had work and home productivity losses and 47% experienced lost wages. In those that lost wages the average loss was $2,144.

Considerable variation of costs existed between donors but the estimated value of all costs equaled $3,268 for all 100 Canadian living kidney donors. One third experienced a loss between $5,000 and $10,000 as a result of donation. This was the first study to prospectively and comprehensively document the financial costs of donating a kidney. Its results support the existing reimbursement programs around the world, and provides guidance to the potential size of the reimbursement. It does however identify that some donors would still be receiving a financial penalty by donating a kidney.

I also explored the financial costs of donating a kidney using qualitative methods, with a phenomenological approach, in 19 potential living kidney donors in Australia. As previously described these potential donors had completed their donation work-up and were either deemed suitable to donate and were awaiting an operation date, or they were deemed unsuitable to

donate. Sixteen of the 19 potential donors were employed at the time of interview and had to take varying amounts of time off work to attend scheduled appointments, though most reported supportive and flexible employers. While most also reported travel costs, including 4 potential donors having to drive 2-4 hours to get to appointments, only 1 accessed the only existing reimbursement scheme for donors which assisted with travel expenses only.

Of the 19 participants in this study, 14 were deemed to be suitable to donate and were in the workforce. Half of these potential donors anticipated significant impact on their finances following the operation and recovery period (most were informed this would take on average up to 6 weeks). Some potential donors had no sick leave entitlements and anticipated the need to take time off without leave. In addition, those that lived a distance from the transplant unit would have additional costs for accommodation at the time of the operation and for the initial recovery period.

The results of this study suggested that there were out of pocket expenses for living kidney donors but the potentially largest financial impact would be on the loss of income during the post-operative recovery period. I had been advocating for a number of years prior to this study to introduce expanded living kidney donor reimbursement programs in Australia, and at the end of this study a scheme commenced in Australia that was aimed directly to encourage employers to support donors – The Supporting Leave for Living Organ Donors Programme. This scheme has proved to be consistent with the major findings of

my study in addressing the major financial concern for living kidney donors in

Australia.

CHAPTER 9

TRANSLATION OF LIVING KIDNEY DONOR RESEARCH IN AUSTRALIA

Publications:

Boudville N, Isbel N. Donors at risk: Impaired glucose tolerance. Nephrology (Carlton) 2010; 15:S133-S136.

Boudville N, Kanellis J, F. I. Donors at risk: hypertension. Nephrology (Carlton) 2010;15:S114-S120.

Boudville N, Kanellis J. Donors at risk: proteinuria. Nephrology 2010;15:S106-S110.

Clayton PA, Saunders JR, McDonald SP, Allen RD, Pilmore H, Saunder A, **Boudville N,** Chadban SJ. Risk-Factor Profile of Living Kidney Donors: The Australia and New Zealand Dialysis and Transplant Living Kidney Donor Registry 2004-2012. Transplantation. 2016 Jun;100(6):1278-83.

Ultimately the aim of any research is to have an impact on the patients. My research led me to be invited to write clinical practice guidelines in Australia for the management of potential living kidney donors – The Caring for Australasians with Renal Impairment (CARI) Guidelines.

Based upon the existing literature there was no level I or II evidence to propose any guidelines and all of my recommendations were suggestions for clinical care. My publications were centred on impaired glucose tolerance, hypertension and proteinuria in a potential living kidney donor. It provided clear recommendations on how to measure these, what thresholds were for relative and absolute contraindication to proceed with donation, and what follow-up donors should have after donation.

The lack of level I and II evidence reinforced the need for further properly conducted research into this area. This contributed to the development of the Australia and New Zealand Dialysis and Transplant Living Kidney Donor Registry which commenced collecting data in 2004. This came in under the auspices of the long-standing Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry.

To examine clinical practice patterns with respect to living kidney donors in Australia and New Zealand I performed a study utilizing the Living Kidney Donor Registry. Between 2004 and 2012 there were 2,932 living kidney donors and

this study compared their demographic and comorbidity information with the clinical practice guidelines that I wrote. This study noted that despite the clinical practice guidelines, donors were being accepted and operated on that had relative or absolute contraindications to donation. This included 10% of donors having hypertension (some on 2 or more antihypertensive medications), 2 donors having diabetes, 65 having impaired glucose tolerance or impaired fasting glucose, 45% of donors being overweight and 18% obese predonation. Based upon the CARI guidelines, 26% of donors had at least one relative contraindication to donation and 9% had at least one absolute contraindication to donate.

The results of this paper demonstrated that despite the lack of strong evidence to suggest long-term harm or lack thereof for living kidney donors, it was common practice in Australia and New Zealand to accept donors with one or a few isolated medical abnormalities. This is probably common practice in other countries around the world. This realization in fact adds incentive for the transplant community to more precisely define the long-term risks of living kidney donors and expand this to not only look at healthy donors but also donors with one or a few isolated medical abnormalities as this is occurring in clinical practice.

CHAPTER 10

CONCLUSION

Publication:

Reese PP, **Boudville N**, Garg AX. Living kidney donation: outcomes, ethics, and uncertainty. Lancet. 2015 May 16;385(9981):2003-13

Living kidney transplantation is the preferred option for most people who develop ESKD. There has been an expansion of the use of living kidney donors as a result, with increasing numbers of unrelated donors and increasing acceptance of donors with medical abnormalities. This is occurring despite the ongoing lack of clarity in the long-term outcomes of donation. Indeed, recent publications suggest that there may even be an increased risk of mortality and ESKD for living kidney donors.

The prevailing literature however has many limitations which have been the impetus for the research that I have performed over the last 14 years. Over this period of time I have examined and evaluated the existing literature through a series of systematic reviews. This was followed by a series of retrospective studies, with some including linkage analysis to large provincial administrative databases. I have also performed qualitative research studies both on previous living kidney donors and potential donors who have completed their work-up to explore their quality of life and their experiences. Finally I have commenced a prospective controlled observational study and have reported some of the financial findings in the first 100 pilot patients.

My research has demonstrated that there may be an increase in blood pressure of about 5mmHg, and an increased risk of proteinuria, but no evidence of accelerated progression of chronic kidney disease following living kidney donation. Despite recent publications to the contrary, I have not been able to demonstrate an increased risk of cardiovascular disease or mortality. I was able

to show some mild changes in bone and mineral metabolism markers post-donation but without any associated increase in fracture rates. In addition I have explored some of the ethical and financial issues that occur during the donor work-up period and the immediate post-donation period. Much of these findings and the existing literature was presented in a recent review paper that I published in the Lancet.

There are many more unanswered questions – in particular what are the long-term outcomes in donors with isolated medical abnormalities, or from minority ethnic groups (especially those with traditionally higher rates of ESKD). With the concerns that have been identified to date and the lack of a clear understanding of the long-term risk of living kidney donation the informed consent process for this operation remains enshrined in potential ethical issues.

To try and enable answers to some of these questions in the future my initial pilot prospective study became a vanguard study of a larger prospective study that has recruited over 1,000 living kidney donors with a cohort of healthy controls which I am currently following up long-term. Evidence from this study is likely to not become apparent for a number of years due to the long-term nature of the development of the important clinical outcomes. I expect that findings from this study however will be of high impact and form the cornerstone of the information provided for future and past living kidney donors.

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Original Article

Transplant professionals vary in the long-term medical risks they communicate to potential living kidney donors: an international survey

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Abstract

Background. Discussing long-term medical risks with potential living donors is a vital aspect of informed consent. We considered whether there are global practice variations in the information communicated to potential living kidney donors.

Methods. Transplant professionals participated in a survey to determine which long-term risks are communicated to potential living kidney donors. Self-administered questionnaires were distributed in person and by electronic mail.

Results. We surveyed 203 practitioners from 119 cities in 35 different countries. Sixty-three percent of participants were nephrologists, and 27% were surgeons. Risks of hypertension, proteinuria or kidney failure requiring dialysis were frequently discussed (usually over 80% of practitioners discussed each medical condition). However, many practitioners do not believe these risks are increased after donation, with surgeons being less convinced of long-term sequelae compared with nephrologists ($P < 0.01$). About 30% of practitioners discuss long-term risks of premature cardiovascular disease or death with potential donors.

Conclusions. Transplant professionals vary in the long-term risks they communicate to potential donors. Improving consensus will enhance decision-making, and emphasize best practices which maintain good, long-term donor health.

Keywords: consent; donor nephrectomy; living kidney donation; long-term complications; risk communication; survey

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Introduction

More assessments of potential living kidney donors are being conducted worldwide than ever before. In the United States, for example, the number of living kidney donors has now surpassed that of deceased donors [1].

Obtaining informed consent is mandatory prior to proceeding with an elective procedure such as donor nephrectomy. Transplant professionals aim to provide their patients with detailed and accurate information on the potential benefits and complications (both short- and long-term) of the procedure [2,3].

The short-term complications of donor nephrectomy are well described [4–6]. However, long-term risks of kidney donation (such as hypertension, proteinuria and renal impairment) are less certain, with different estimates in the literature [7–20]. In a recent published meta-analysis [19], blood pressure was 5 mmHg higher in donors than in control participants, with one out of six studies reporting an increase in the risk of hypertension [relative risk, 1.9 (95% CI, 1.1 to 3.5)]. Limitations of previous studies include a lack of appropriate control groups, incomplete follow-up and outcomes not defined according to modern diagnostic criteria [21–24]. Health care providers are, therefore, left with a notable uncertainty on long-term donor risks of the procedure. This uncertainty likely explains the variation in practice among health care providers and among transplant centres with regards to long-term risk estimation and, subsequently, living donor selection [25–29]. However, the degree to which this uncertainty has translated into practice variability has not been previously considered. Here we considered which long-term risks are communicated to potential donors by their practitioners, and whether this information differs across transplant centres around the world. We also assessed whether nephrologists and surgeons differ in their beliefs on these risks.

Methods

Participants

English-speaking transplant professionals (including nephrologists, surgeons, nurse practitioners and donor coordinators) who discussed long-term medical risks with at least one potential kidney donor in the prior year were eligible for survey participation. Although inviting all such practitioners worldwide to participate would have proven ideal, their contact information was not readily available. Instead, the self-administered 10-min survey was distributed to all potentially eligible practitioners we could readily identify. We used member lists of the American Society of Transplantation, the American Society of Transplant Surgeons and the European Society of Organ Transplantation. Additional contact information for practitioners in other countries was obtained through Internet searches. In total, the survey was distributed to 2727 potential participants, mainly via their unique e-mail addresses. Over 500 (521) e-mail messages were not returned as 'undelivered' mail (some accounts were no longer active, returned by mail providers' spam protection system or addresses obtained were not correct). A total of 333 potential participants responded to our survey, of which 130 respondents were known to not fulfil the eligibility criteria. A participant was eligible to participate if they were involved in the process of informing potential living kidney donors of long-term risks, and were involved in the care of at least one potential living kidney donor during the previous year.

A total of 203 complete surveys were returned. The exact response rate could not be determined, as the 'total' number of received e-mail messages and the 'total' number of eligible people (for study participation) who actually received our questionnaires were unknown.

Survey

The survey questions were developed by a group of nephrologists and epidemiologists involved in the assessment of potential living kidney donors. Once developed, the questions were pilot tested on another group of physicians also involved in living donor assessments. Interviews with these physicians confirmed the survey questions were being interpreted correctly.

The first set of questions assessed participant demographics and methods by which information about long-term risks are discussed with potential donors. The next set of questions asked whether the practitioner discussed in some capacity the following long-term risks with potential living kidney donors: hypertension, proteinuria, chronic kidney disease (i.e. a glomerular filtration rate <60 ml/min), kidney failure requiring dialysis, premature cardiovascular disease and premature death not related to surgery. A final set of questions assessed whether the practitioner believed such risks were decreased, no different, or increased, compared to if a donor had elected not to have the nephrectomy. Survey questions are summarized in Table 1. The survey was conducted between February 2005 and March 2007.

Analysis

Descriptive statistics and confidence intervals for single proportions were computed [30]. Chi-square tests were used to assess differences in opinions regarding the long-term risks by participant location and subspecialty. In cases where there were a small number of observations, Fisher's exact test was used. All analyses were conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 203 health eligible health practitioners from 119 cities in 35 different countries responded to the survey. Sixty-three percent of respondents were nephrologists, 27% were surgeons, 4% were nurse practitioners and 6% were other individuals involved in discussing risks with potential donors. Most transplant professionals were from North America (45.1%) (USA 39.6%, Canada 4.0%, Mexico 1.5%), followed by Europe (31.7%) (UK 8.4%, Germany 6.4%, Belgium 2.5%, Netherlands 2.0%, Czech Republic 2.0%, Norway 2.0%, France 1.5%, Italy 1.0%, Sweden 1.0%, Switzerland 1.0%, Denmark 0.5%, Finland 0.5%, Northern Ireland 0.5%, Poland 0.5%, Serbia 0.5%, Spain 0.5%, Cyprus 0.5%, Scotland 0.5%), Asia (14.4%) (Saudi Arabia 8.4%, India 1.0%, Korea 1.0%, Lebanon 1.0%, United Arab Emirates 1.0%, China 0.5%, Thailand 0.5%, Kuwait 0.5%, Syria 0.5%), Australia (4.5%), South America (2.5%) (Brazil 1.5%, Argentina 1.0%) and Africa (2.0%) (Egypt 1.5%, Libya 0.5%).

Table 1. Summary of questionnaire content

In your kidney transplant programme, the written consent for donor surgical nephrectomy is obtained by: (please check all that applies)
- ☐ Nephrologist　　☐ Surgeon　☐ Nurse or nurse practitioner
- ☐ Social worker　　☐ Nephrology trainee
- ☐ Surgical trainee　☐ Other (please specify):———.
- ☐ No written conset is obtained

What is your specialty?
- ☐ Nephrologist　　☐ Surgeon　☐ Nurse practitioner
- ☐ Social worker　　☐ Nephrology trainee
- ☐ Surgical trainee ☐ Other (please specify):———.

What is the number of living donor kidney transplants performed at your centre over the year 2005?———
Your programme's location: City:——— Country:———

Do you discuss the following long-term risks with the potential donor, when obtaining the consent to donate:
1. Hypertension　　　　　　　　　　　　　　　　　 Yes ☐　No ☐
2. Proteinuria　　　　　　　　　　　　　　　　　　 Yes ☐　No ☐
3. Death (not related to surgery)　　　　　　　　　 Yes ☐　No ☐
4. Premature cardiovascular disease　　　　　　　　 Yes ☐　No ☐
5. Chronic kidney disease (a GFR < 60 ml/min)　　　 Yes ☐　No ☐
6. Kidney failure　　　　　　　　　　　　　　　　 Yes ☐　No ☐

In your opinion, what is the lifetime risk of developing the following conditions as a result of kidney donation?
(compared with if the donor decided not to donate a kidney)
1. Hypertension (Systolic BP > 140 mmHg, Diastolic BP > 90 mmHg, or requiring medical treatment for hypertension):
 ☐ Increased risk　☐ No difference　☐ Decreased risk
2. Having a higher SYSTOLIC blood pressure than expected for a given age:
 ☐ Increased risk　☐ No difference　☐ Decreased risk
3. Having a higher DIASTOLIC blood pressure than expected for a given age:
 ☐ Increased risk　☐ No difference　☐ Decreased risk
4. Having a higher 24-HOUR URINE PROTEIN than expected for a given age:
 ☐ Increased risk　☐ No difference　☐ Decreased risk
5. Having a higher 24-HOUR URINE ALBUMIN than expected for a given age:
 ☐ Increased risk　☐ No difference　☐ Decreased risk
6. Microalbuminuria (30–300 mg)/24 h:
 ☐ Increased risk　☐ No difference　☐ Decreased risk
7. Proteinuria (>300 mg/24 h):
 ☐ Increased risk　☐ No difference　☐ Decreased risk
8. Having a GFR 60–80 mls/min
 ☐ Increased risk　☐ No difference　☐ Decreased risk
9. Having a GFR <60 mls/min
 ☐ Increased risk　☐ No difference　☐ Decreased risk
10. Premature cardiovascular disease:
 ☐ Increased risk　☐ No difference　☐ Decreased risk
11. Premature death (not related to surgery):
 ☐ Increased risk　☐ No difference　☐ Decreased risk

Prior to donation 95% of health care practitioners reported that written information is provided to potential donors and recipients to educate them about the living kidney donation process. Sixty-six percent of health practitioners reported that their centre has a special consent form for living kidney donation. In the majority of centres, written consent for donor surgical nephrectomy is obtained by the surgeon (70%). Consent was also obtained by the nephrologist or nephrology trainee (22%), nurse or nurse practitioner (6%) or other transplant professional (2%). An average of 45 living kidney donor transplants were performed at each centre in the year 2004 (median 30, range 1–644).

Risks of hypertension, proteinuria or kidney failure requiring dialysis were frequently discussed with potential living kidney donors; usually >80% of practitioners discussed each medical condition in some capacity (Table 2). However, many practitioners

Table 2. Long-term medical risks discussed with potential living kidney donors

	Proportion of health care providers[a] who discuss risk (with 95% confidence interval)
Hypertension	92 (87–95)%
Proteinuria	83 (77–87)%
Chronic kidney disease[b]	81 (75–86)%
Kidney failure requiring dialysis	86 (81–90)%
Premature cardiovascular disease	33 (27–40)%
Premature death not related to the surgery	34 (28–41)%

[a]Survey of 203 transplant professionals (predominantly nephrologists and surgeons) who were responsible for informing potential donors of risks prior to donation.
[b]A glomerular filtration rate <60 ml/min.

Table 3. Health care provider opinion on the lifetime risk of the following medical conditions after becoming a living kidney donor

	Proportion of health care providers[a] who believe the following medical risks are increased, compared to if a donor had elected not to have the nephrectomy	
	Not increased	Increased
Blood pressure		
Higher systolic blood pressure than expected for age	44%	56%
Higher diastolic blood pressure than expected for age	50%	50%
Hypertension[b]	55%	45%
Proteinuria		
Higher 24-h urine protein than expected for age	31%	69%
Higher 24 h urine albumin than expected for age	31%	69%
Microalbuminuria (30–300 mg/24 h)	27%	73%
Proteinuria (>300 mg/24 h)	44%	56%
Reduced kidney function		
GFR 60–80 ml/min	21%	79%
GFR < 60 ml/min	45%	55%
Other		
Cardiovascular disease	84%	16%
Death, not related to surgery	92%	8%

[a]Survey of 203 health care providers (predominantly nephrologists and surgeons) who are responsible for informing potential donors of risks prior to donation.
[b]Systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg or requiring medical treatment for hypertension.

do not believe these risks are increased after donation (Table 3). When asked, between 21% and 55% of transplant professionals believe such risks are not increased after donation, with the exact number dependent on the outcome considered. Compared with nephrologists, surgeons were less convinced of long-term sequelae. For example, 50% of nephrologists *vs* 33% of surgeons believed the risk of hypertension was increased ($P = 0.03$). Similarly, 78% *vs* 58% believed the risk of microalbuminuria was increased ($P = 0.004$), while 62% *vs* 39% believed the risk of developing a glomerular filtration rate <60 ml/min was increased ($P = 0.004$).

About 33% of practitioners also discuss the risks of premature cardiovascular disease and non-perioperative death with potential donors (Table 2). However, >80% of practitioners believe donors have no higher risk of cardiovascular disease, than if they had elected not to go through with the procedure.

We observed a few differences across continents on the risks discussed by transplant professionals (hypertension $P < 0.05$, kidney failure $P = 0.003$; all other outcomes $P > 0.18$), or what was believed about these risks (hypertension $P < 0.04$, premature cardiovascular disease $P = 0.005$; all other outcomes $P > 0.09$). For example, compared with those practising in Asia, more transplant professionals in Europe, North America and South America discuss the risk of hypertension.

Discussion

Discussing long-term medical risks with potential living donors is a vital aspect of informed consent. While a majority of potential donors do not change their mind after learning about the risks of nephrectomy, a small percentage of people elect not to pursue donation and cite potential adverse health outcomes as an important factor in their decision [31]. Discussing long-term medical risks with individuals who eventually become donors also emphasizes the need for ongoing lifestyle modification and medical surveillance to maintain good long-term health. Here our results demonstrate that most, but not all, transplant professionals discuss risks for hypertension, proteinuria and kidney failure with potential kidney donors. Many practitioners do not believe these risks are increased after donation.

There are a number of potential reasons for the observed practice variability and lack of consensus. With different estimates in the literature [7–20], it remains difficult for practitioners to reach firm conclusions, and the truth remains uncertain. In the absence of external evidence, some practitioners may be relying on local practice experience, which naturally would differ across centres. Also, the observed variability could at least be partially explained by differences between programmes in the specialties of transplant professionals communicating such risks. For example, in many centres, the surgeon was responsible for obtaining the written consent for nephrectomy. These results highlight that surgeons are less convinced of long-term medical sequelae compared with nephrologists. These findings are consistent with a survey conducted by Beasley *et al.* [25]; indeed, physician perception of the risks and benefits of a procedure can be influenced by their background specialty, as evidenced in other areas of medicine [32].

To our knowledge, this is the first survey, to evaluate global practices in the estimation and communication of long-term risks to potential living kidney donors. To maximize the accuracy of responses, the questionnaire included simple items, questions, and answer choices.

However, we encountered three major practical limitations when executing the survey, which should be appreciated.

First, it was impossible to directly observe transplant professionals speaking to potential kidney donors. There is often a discrepancy between what busy physicians say they do, and what they actually do in real practice, with self-reported results more likely to describe model behaviour. Thus, the proportion of practitioners who do not discuss long-term medical risks with potential kidney donors may be even higher than reported here, increasing variability amongst the transplant centres.

Second, all English-speaking practitioners who discuss long-term medical risks with potential kidney donors were eligible for survey participation. However, it was impossible to generate a comprehensive mailing list of all such individuals worldwide. Transplant programmes differ in their organizational structure, and contact information for many centres outside North America and Europe was limited. While we used available member lists from transplant organizations to determine who to e-mail the survey to, we were never certain whether the e-mail was seen or whether all such individuals were even eligible for study participation. Thus, the exact response rate could not be determined, although it did appear to be low. In such cases, there is always the potential concern that data provided by those who participate systematically differs from those who do not participate. Although this limitation does not impact on our major finding that some practitioners vary in the long-term medical risks they communicate to potential living kidney donors, it may impact the precise estimates reported here.

Finally, our questionnaire was not designed to assess the exact nature of information communicated about long-term risks. We believed complex aspects of the discussion including determinants of risk, communication of uncertainty and magnitude of risk would be best considered using techniques of qualitative open-ended interviewing.

In conclusion, all individuals should have an equal chance of being entirely informed of all medical, psychological and financial benefits and harms prior to consenting to be a donor. Arguably, the recipient should also be provided such information, so they can make their preferences known when accepting a kidney from a family member, friend or stranger. Standardizing such information globally may not be possible, given the remarkable cultural and practice differences in countries across the world. However, it remains desirable for there to be physician consensus on the long-term medical risks of living kidney donation. Ongoing prospective cohort studies of donors and controls will better delineate such risks, improving consensus on what information should be disclosed.

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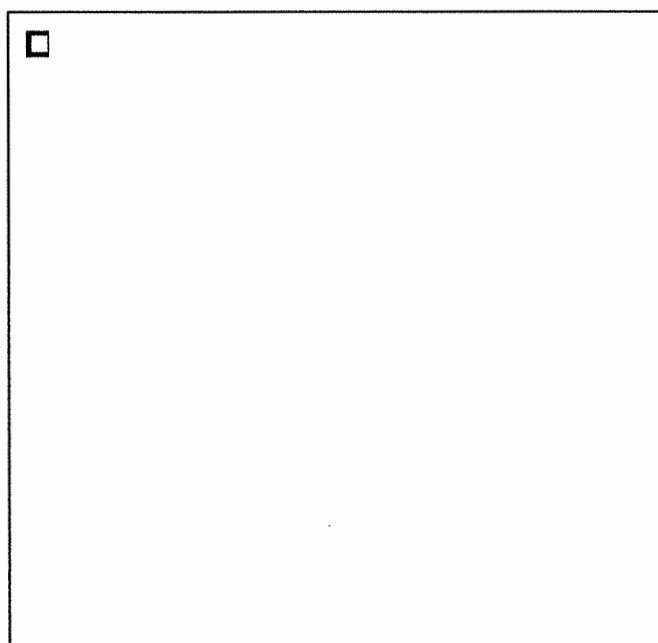
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Annals publishes a variety of article types, as listed below. The links accompanying each article type provide details about the article type and specific formatting requirements. General formatting guidelines are presented in the section following the article types, and Section II B. contains guidance on reporting statistical findings.

Authors should write for a sophisticated general medical readership; follow principles of clear scientific writing (Council of Science Editors. *Scientific Style and Format.* 8th ed. Chicago, IL: University of Chicago Press; 2014.) and statistical reporting (see Section II.B. General Statistical Guidance)); and prepare manuscripts according to recommended reporting guidelines and checklists whenever possible. Manuscripts that follow these recommendations generally fare better than those that do not.

Note that *Annals* publishes some content that is produced internally and does not represent material that is submitted for peer review by external authors. This material includes special features, such as In the Clinic, ACP Journal Club, The Consult Guys, and Virtual Patients.

Article Types

Type	Description
Original Research	Reports of original analyses of data on prevalence, causes, mechanisms, diagnosis, course, treatment, and prevention of disease. [Peer reviewed] More details
Reviews: Systematic & Meta-analyses	Reviews that systematically find, select, critique, and synthesize evidence relevant to well-defined questions about diagnosis, prognosis, or therapy. [Peer reviewed] More details
Clinical Guidelines, including synopses	Official recommendations from professional organizations on issues related to clinical practice and health care delivery. [Peer reviewed] More details
Research and Reporting Methods	Articles related to research methods or reporting standards. [Peer reviewed] More details
Reviews: Narrative	Review articles that use informal methods to collect and interpret information, which is often summarized subjectively in narrative form. Narrative reviews are especially suitable for describing cutting-edge and evolving developments and underlying theory. [Peer reviewed] More details
Academia and the Profession	Descriptions and evaluations of innovations in medical education, training, professionalism, and career development. [Peer reviewed] More details

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Meta-Analysis: Risk for Hypertension in Living Kidney Donors

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Background: The risk for hypertension after kidney donation remains uncertain.

Purpose: To see whether normotensive adults who donate a kidney develop higher blood pressure and risk for hypertension compared with nondonor adults acting as control participants.

Data Sources: MEDLINE, EMBASE, and Science Citation Index were searched from 1966 until November 2005 for articles published in any language. Reference lists of pertinent articles were also reviewed.

Study Selection: The authors selected studies involving 10 or more healthy normotensive adults who donated a kidney and in whom blood pressure was assessed at least 1 year later.

Data Extraction: Two reviewers independently abstracted data on study and donor characteristics, blood pressure measurements, outcomes, and prognostic features. Comparison data were abstracted from donor studies with control participants. Thirty primary authors provided additional data.

Data Synthesis: Forty-eight studies from 28 countries followed a total of 5145 donors. Before surgery, the average age of donors was 41 years, the average systolic blood pressure was 121 mm Hg, and the average diastolic blood pressure was 77 mm Hg for all studies. In controlled studies in which the average follow-up was at least 5 years after donation (range, 6 to 13 years), blood pressure was 5 mm Hg higher in donors than in control participants (the weighted mean for systolic blood pressure using 4 studies involving 157 donors and 128 control participants was 6 mm Hg [95% CI, 2 to 11 mm Hg], and the weighted mean for diastolic blood pressure using 5 studies involving 196 donors and 161 control participants was 4 mm Hg [CI, 1 to 7 mm Hg]). There was statistical heterogeneity among the 6 controlled studies that assessed hypertension; an increase in risk was noted in 1 study (relative risk, 1.9 [CI, 1.1 to 3.5]).

Limitations: Most studies were retrospective and did not include control groups that were assembled and followed along with donors. Approximately one third of the donors had incomplete follow-up information.

Conclusions: On the basis of the limited studies conducted to date, kidney donors may have a 5–mm Hg increase in blood pressure within 5 to 10 years after donation over that anticipated with normal aging. Future controlled, prospective studies with long periods of follow-up will better delineate safety and identify donors at lowest risk for long-term morbidity.

D espite its advantages, living kidney donation remains a complex ethical, moral, and medical issue. Living kidney donation is practiced with the expectation that the risk for minimal short-term and long-term harm for the donor is outweighed by the psychological benefits of altruism and improved recipient health. The short-term complications of living donation are well established (1). However, the long-term risk for hypertension remains uncertain. A better understanding of this risk is central to donor selection and consent. This knowledge guides health policy on reimbursing costs of antihypertensive medication and the need for ongoing surveillance of the more than 80 000 persons who have donated a kidney (2). The primary question of this review was whether normotensive adults who donate a kidney develop higher blood pressure and risk for hypertension compared with healthy nondonors acting as control participants. Reasons for considerably different estimates in the literature were also explored in meta-regression.

METHODS

Study Selection

We included studies in any language that examined 10 or more healthy normotensive adults who donated a kidney and had their blood pressure assessed at least 1 year later. We compiled citations from MEDLINE and EMBASE bibliographic databases from 1966 through November 2005. An experienced librarian developed the search strategies using sensitive terms for identifying clinical prognostic studies of living kidney donors (3, 4). We pilot-tested the search strategies and modified them to ensure that they identified known eligible articles. The final strategies included the terms *living donors, cohort studies, course, longitudinal studies, hypertension,* and *blood pressure.* We also compiled citations from information provided by primary study authors, the Science Citation Index, the "Related Articles" feature on PubMed, reference lists of previous

Context

Does kidney donation increase a person's risk for hypertension?

Contribution

This review found 10 studies that compared blood pressure between kidney donors and healthy adults with similar age, sex, and ethnicity. Studies suggested that within 5 to 10 years of donation, kidney donors may have about a 5–mm Hg increase in blood pressure over that anticipated with normal aging.

Cautions

Actual risks for hypertension were unclear because studies did not define hypertension uniformly and had incomplete follow-up information on many donors.

Implications

We need large, prospective, controlled studies with prolonged follow-up to better inform potential kidney donors of long-term risks associated with donation.

—*The Editors*

reviews (5, 6), and reference lists of all studies included in our review. All citations were downloaded into Reference Manager, version 10.0 (Thomson ISI Research-Soft, Philadelphia, Pennsylvania).

Pairs of reviewers independently evaluated the eligibility of each citation, and the full-text article was retrieved if either reviewer considered the citation potentially relevant. For all English-language publications, pairs of reviewers independently evaluated the eligibility of the full-text article; disagreements were resolved by a third reviewer. With the help of translators, a single reviewer evaluated the eligibility of all non–English-language full-text articles. When data from the same group of donors were described in multiple publications, we reviewed all of the publications and cited the most representative one.

Data Abstraction

Pairs of reviewers independently abstracted the following data from all English-language studies meeting eligibility criteria: setting, methods, donor characteristics, control group characteristics, prognostic features, and hypertension outcomes. Disagreements were resolved by a third reviewer. For Czechoslovakian, Dutch, French, German, Italian, Japanese, Norwegian, Serbo-Croatian, and Spanish articles, data were abstracted by a single reviewer with the help of a translator. We attempted to contact primary authors of all included studies to confirm data and obtain missing data.

Statistical Analysis

Reviewer agreement on study eligibility was quantified by using the κ statistic. Variance estimates for changes in blood pressure before and after donation were not reported in most studies. If not reported, variance estimates were derived from t-statistics when available. Otherwise, variance estimates were calculated with

$$SE_\Delta = \sqrt{SE_{pre}^2 + SE_{post}^2 - (2 \times \rho_\Delta \times SE_{pre} \times SE_{post})},$$

where ρ_Δ represents the correlation between the blood pressure measurements before and after donation (7). For the 2 studies that reported predonation, postdonation, and change variance estimates, we calculated average correlation coefficients of 0.92 and 0.84 for systolic blood pressure and diastolic pressure, respectively. To be conservative, we used a correlation of 0.5 to impute missing change variance estimates in the final meta-regression. We performed sensitivity analyses to this choice of correlation, and the results were qualitatively similar.

For this study-level meta-analysis, the Q statistic was used to determine whether between-study heterogeneity was present; a *P* value less than 0.1 was considered statistically significant. The I^2 statistic was used to quantify the magnitude of heterogeneity, with values of 0% to 30%, 31% to 50%, and greater than 50% representing mild, moderate, and notable heterogeneity, respectively (8). When justified, results were mathematically pooled by using techniques that accounted for within-study and between-study heterogeneity (random-effects method) (9–11).

Reasons for diversity in study results were explored by using univariate and multivariate meta-regressions of donor cohorts: mixed models for continuous outcomes (PROC MIXED procedure, SAS statistical software, SAS Institute, Inc., Cary, North Carolina) and logistic normal random-effects models for binary outcomes (PROC NLMIXED procedure, SAS statistical software, SAS Institute, Inc.). At the study level, the association between the following donor characteristics and outcomes of hypertension, postdonation blood pressure, and change in blood pressure were considered: average age, the proportion of donors who were female, and average predonation blood pressure. Although potential donors vary in race, sex, and age at the time of nephrectomy, all are healthy and are confirmed to have normal blood pressure and renal function through rigorous evaluation. Nonetheless, we hypothesized that similar to the general population, donors would be more likely to develop hypertension if they were older, were male, and had a higher predonation blood pressure. Similarly, features of study methods associated with blood pressure outcomes after donation were considered. In meta-regression, we tested whether the study was conducted prospectively, the proportion of donors lost to follow-up, the duration of follow-up after nephrectomy, and the method by which blood pressure was assessed. For each meta-regression, only studies for which the factor of interest was available were included in the analysis. The explanatory ability of each factor was quantified by the propor-

Table 1. **Characteristics of Living Kidney Donor Studies Examining Blood Pressure Changes and the Incidence of Hypertension***

Study, Year (Reference)†	Primary Location	Donors, n	Years of Donation	Prospective Study	Mean Patient Age (Range), y‡	Women, %
Mimran et al., 1993 (15)	Montpellier, France	18	NR	Yes	47 (20–62)	56
Yasumura et al., 1988 (16)	Kyoto, Japan	124	1970–1986	No	50 (21–71)	66
Sobh et al., 1989 (17)	Mansoura, Egypt	45	NR	No	26 (22–64)	53
Friedlander et al., 1988 (18)	Iowa City, Iowa	12	1980–1985	Yes	36 (19–61)	75
Kostakis et al., 1997 (19)	Athens, Greece	255	1986–1996	No	59 (24–82)	74
Beekman et al., 1994 (20)	Leiden, the Netherlands	47	1981–1988	Yes	35 (20–66)	49
Tondo et al., 1998 (21)	Parma, Italy	10	1986–1996	No	46 (NR)	30
Hida et al., 1982 (22)	Bohseidai, Japan	34	1976–1981	Yes	55 (24–66)	59
Rizvi et al., 2005 (23)	Karachi, Pakistan	736	1986–2003	No	33 (NR)	50
Thiel, 1998 (24)	Basel, Switzerland	181	1993–1997	Yes	48 (25–72)	NR
Abomelha et al., 1993 (25)	Riyadh, Saudi Arabia	70	1979–1989	Yes	31 (18–58)	29
Liu et al., 1992 (26)	St. Leonards, Australia	17	NR	No	48 (27–61)	76
Siebels et al., 2003 (27)	Munich, Germany	122	1994–2001	Yes	51 (21–77)	80
Basseri et al., 1995 (28)	Tehran, Iran	87	NR	No	32 (17–58)	43
Enger, 1973 (29)	Oslo, Norway	13	1963–1971	Yes	48 (29–65)	69
Ghahramani et al., 1999 (30)	Shiraz, Iran	136	1988–1997	Yes	34 (NR)	NR
Mendoza et al., 1987 (31)	Mexico City, Mexico	152	1968–1985	No	26 (NR)	57
Liounis et al., 1988 (32)	Sydney, Australia	39	1975–1986	No	37 (21–52)	72
Gonzalez et al., 1989 (33)	New York, New York	25	1976–1987	No	36 (20–58)	68
Fourcade et al., 2002 (34)	Lyon, France	99	1967–1994	No	37 (18–57)	54
Dunn et al., 1986 (35)	Nashville, Tennessee	250	1970–1984	Yes	34 (18–67)	44
ter Wee et al., 1994 (36)	Groningen, the Netherlands	15	1983	No	37 (NR)	40
O'Donnell et al., 1986 (37)	Johannesburg, South Africa	33	1966–1984	No	37 (NR)	45
Miller et al., 1985 (38)	New York, New York	47	1984	No	40 (18–60)	68
Rodríguez-Iturbe et al., 1985 (39)	Maracaibo, Venezuela	25	NR	No	NR (20-60)	44
Mareković et al., 1992 (40)	Zagreb, Yugoslavia	50	1973–1990	No	49 (23–69)	34
Prandini et al., 1987 (41)	Bologna, Italy	32	1970–1980	No	42 (22–54)	72
Chen et al., 1992 (42)	Taipei, Taiwan	76	1980–1991	No	44 (18–66)	59
Borchhardt et al., 1996 (43)	Vienna, Austria	22	1966–1994	No	49 (NR)	68
D'Almeida et al., 1996 (44)	Porto Alegre, Brazil	110	1977–1993	No	35 (NR)	NR
Gracida et al., 2003 (45)	Mexico City, Mexico	628	1992–2001	Yes	35 (18–64)	49
Schostak et al., 2004 (46)	Berlin, Germany	53	1974–2002	No	47 (NR)	56
Horcickova et al., 2002 (47)	Prague, Czech Republic	93	1966–1999	No	49 (26–69)	68
Lumsdaine et al., 2003 (48)	Edinburgh, United Kingdom	47	1986–2000	No	NR (NR)	NR
Wiesel et al., 1997 (49)	Heidelberg, Germany	67	1967–1995	No	NR (NR)	NR
Najarian et al., 1992 (50)	Minneapolis, Minnesota	472	1963–1980	No	34 (18–68)	69
Toronyi et al., 1998 (51)	Budapest, Hungary	30	1973–1996	No	NR (NR)	83
Haberal et al., 1998 (52)	Ankara, Turkey	102	1975–1996	No	41 (21–65)	56
Undurraga et al., 1998 (53)	Santiago, Chile	74	NR	No	39 (NR)	73
Talseth et al., 1986 (54)	Oslo, Norway	70	1969–1974	No	46 (33–55)	47
Eberhard et al., 1997 (55)	Hannover, Germany	29	1973–1990	No	NR (NR)	76
Fehrman-Ekholm et al., 2001 (56)	Stockholm, Sweden	348	1964–1995	No	49 (22–76)	74
Williams et al., 1986 (57)	Philadelphia, Pennsylvania	38	NR	No	39 (19–59)	68
Watnick et al., 1988 (58)	New Haven, Connecticut	29	1969–1978	No	NR (NR)	45
Mathillas et al., 1988 (59)	Göteborg, Sweden	46	1965–1973	No	46 (23–70)	57
Saran et al., 1997 (60)	Newcastle, United Kingdom	47	1963–1982	No	NR (NR)	51
Iglesias-Márquez et al., 2001 (61)	San Juan, Puerto Rico	20	1977–1980	No	41 (NR)	60
Goldfarb et al., 2001 (62)	Cleveland, Ohio	70	1963–1975	No	40 (19–57)	59

* NR = not reported.
† Studies are arranged by the average number of years after donation.
‡ Age is reported at the time of donation.

Table 2. Studies of Living Kidney Donors Examining Blood Pressure Changes and the Incidence of Hypertension*

Study, Year (Reference)†	Predonation		Donors Lost to Follow-up, %	Mean Years after Donation (Range)	Postdonation				Change	
	Mean Systolic Blood Pressure (SD), mm Hg‡	Mean Diastolic Blood Pressure (SD), mm Hg‡			Mean Systolic Blood Pressure (SD), mm Hg‡	Mean Diastolic Blood Pressure (SD), mm Hg‡	Incidence of Hypertension, %‡	Use of Antihypertensive Medications, %§	Mean Systolic Blood Pressure (SD), mm Hg‡	Mean Diastolic Blood Pressure (SD), mm Hg‡
Mimran et al., 1993 (15)	123 (11)	74 (8)	NR	1.2 (NR)	130 (16)	81 (11)	22	NR	7 (4)‖	6 (2)‖
Yasumura et al., 1988 (16)	NR	NR	49	1.5 (NR)	NR	NR	0	2	NR	NR
Sobh et al., 1989 (17)	NR	85 (10)	NR	1.9 (1 to 10)	NR	82 (10)	7	NR	NR	−3 (10)¶
Friedlander et al., 1988 (18)	118 (9)	76 (7)	46	2 (1 to 3)	125 (10)	80 (7)	45	NR	7 (9)¶	4 (6)¶
Kostakis et al., 1997 (19)	NR	NR	24	2 (NR)	NR	NR	0	NR	NR	NR
Beekman et al., 1994 (20)	NR	NR	0	2 (NR)	NR	NR	0	NR	NR	NR
Tondo et al., 1998 (21)	NR	NR	0	2.1 (0.2 to 5)	NR	NR	0	NR	NR	NR
Hida et al., 1982 (22)	127 (15)	76 (13)	0	2.8 (0.5 to 5)	126 (14)	77 (11)	NR	NR	−1 (14)¶	0.2 (12)¶
Rizvi et al., 2005 (23)	126 (13)	79 (9)	40	3 (0.5 to 18)	123 (15)	81 (10)	10	NR	−3 (1)‖	2 (1)‖
Thiel, 1998 (24)	125 (16)	80 (10)	0	3 (NR)	129 (16)	81 (9)	2	NR	4 (16)¶	1 (10)¶
Abomelha et al., 1993 (25)	NR	NR	64	3.1 (1 to 10)	NR	NR	3	NR	NR	NR
Liu et al., 1992 (26)	NR	NR	NR	3.1 (0.1 to 10)	124 (16)	78 (33)	NR	NR	NR	NR
Siebels et al., 2003 (27)	NR	NR	24	3.2 (0 to 5)	118 (NR)	70 (NR)	2	7	NR	NR
Basseri et al., 1995 (28)	108 (NR)	66 (NR)	0	3.2 (1 to 8)	110 (NR)	68 (NR)	0	0	2 (NR)	2 (NR)
Enger, 1973 (29)	NR	NR	0	3.5 (0.5 to 8)	NR	NR	8	8	NR	NR
Ghahramani et al., 1999 (30)	NR	NR	21	3.6 (0.3 to 9)	NR	NR	24	NR	NR	NR
Mendoza et al., 1987 (31)	120 (8)	77 (5)	15	3.7 (0.1 to 12)	122 (27)	79 (17)	9	NR	2 (24)¶	2 (15)¶
Liounis et al., 1988 (32)	122 (13)	77 (9)	5	3.9 (1 to 11)	125 (26)	81 (10)	19	8	4 (22)¶	4 (10)¶
Gonzalez et al., 1989 (33)	115 (11)	77 (6)	43	4.2 (0.5 to 12)	120 (13)	82 (10)	16	NR	5 (12)¶	5 (2)‖
Fourcade et al., 2002 (34)	116 (13)	71 (9)	0	4.3 (0.1 to 19)	116 (12)	68 (10)	2	NR	0 (7)	−3 (8)
Dunn et al., 1986 (35)	119 (NR)	76 (NR)	18	4.4 (0.5 to 15)	122 (15)	77 (9)	14	NR	3 (NR)	1 (NR)
ter Wee et al., 1994 (36)	NR	NR	38	4.9 (2 to 13)	NR	NR	0	0	NR	NR
O'Donnell et al., 1986 (37)	NR	75 (5)	62	5.8 (3 to 18)	NR	83 (10)	33	3	NR	8 (2)‖
Miller et al., 1985 (38)	NR	NR	77	6 (2 to 15)	NR	NR	33	7	NR	NR
Rodríguez-Iturbe et al., 1985 (39)	NR	NR	7	6 (1 to 11)	134 (20)	80 (10)	16	NR	NR	NR
Mareković et al., 1992 (40)	107 (8)	79 (8)	NR	6.1 (1 to 15)	135 (13)	89 (8)	10	NR	28 (12)¶	10 (8)¶
Prandini et al., 1987 (41)	NR	NR	22	6.2 (5 to 17)	119 (10)	75 (7)	0	NR	NR	NR
Chen et al., 1992 (42)	119 (16)	74 (10)	0	6.4 (NR)	118 (14)	78 (11)	10	NR	−1 (15)¶	4 (11)¶
Borchhardt et al., 1996 (43)	NR	NR	NR	6.4 (0.7 to 24)	134 (8)	86 (4)	23	5	NR	NR
D'Almeida et al., 1996 (44)	NR	NR	67	6.6 (1 to 14)	NR	NR	14	NR	NR	NR
Gracida et al., 2003 (45)	NR	NR	0	6.7 (0.5 to 10)	NR	NR	1	NR	NR	NR
Schostak et al., 2004 (46)	NR	NR	48	6.9 (NR)	NR	NR	36	30	NR	NR
Horcickova et al., 2002 (47)	NR	NR	NR	7.1 (0.2 to 31)	NR	NR	27	NR	NR	NR
Lumsdaine et al., 2003 (48)	NR	NR	69	7.1 (NR)	NR	NR	17	4	NR	NR
Wiesel et al., 1997 (49)	NR	NR	43	8 (NR)	NR	NR	27	NR	NR	NR
Najarian et al., 1992 (50)	117 (12)	73 (11)	25	8.3 (1 to 19)	122 (16)	76 (4)	7	NR	5 (14)¶	3 (8)¶
Toronyi et al., 1998 (51)	NR	NR	62	8.9 (NR)	NR	NR	17	17	NR	NR
Haberal et al., 1998 (52)	132 (21)	NR	32	10.2 (0.7 to 22)	140 (21)	NR	9	9	8 (21)¶	NR
Undurraga et al., 1998 (53)	119 (14)	76 (9)	NR	10.9 (1 to 21)	130 (20)	88 (13)	49	NR	11 (7)	12 (5)
Talseth et al., 1986 (54)	132 (10)	82 (7)	5	11 (10 to 12)	140 (17)	90 (7)	8	3	8 (3)‖	8 (2)‖
Eberhard et al., 1997 (55)	NR	NR	79	11.1 (5 to 20)	121 (12)	77 (7)	29	17	NR	NR
Fehrman-Ekholm et al., 2001 (56)	NR	NR	13	12.5 (2 to 33)	NR	NR	36	15	NR	NR
Williams et al., 1986 (57)	NR	NR	32	12.6 (10 to 18)	133 (21)	83 (12)	47	NR	NR	NR
Watnick et al., 1988 (58)	NR	NR	19	13 (9 to 18)	136 (36)	84 (18)	62	10	NR	NR
Mathillas et al., 1988 (59)	NR	NR	13	14.9 (10 to 20)	NR	NR	39	23	NR	NR

Table 2—Continued

Study, Year (Reference)†	Predonation		Donors Lost to Follow-up, %	Mean Years after Donation (Range)	Postdonation				Change	
	Mean Systolic Blood Pressure (SD), *mm Hg*‡	Mean Diastolic Blood Pressure (SD), *mm Hg*‡			Mean Systolic Blood Pressure (SD), *mm Hg*‡	Mean Diastolic Blood Pressure (SD), *mm Hg*‡	Incidence of Hypertension, %‡	Use of Antihypertensive Medications, %§	Mean Systolic Blood Pressure (SD), *mm Hg*‡	Mean Diastolic Blood Pressure (SD), *mm Hg*‡
Saran et al., 1997 (60)	NR	NR	21	19.6 (13 to 31)	NR	NR	74	28	NR	NR
Iglesias-Márquez et al., 2001 (61)	NR	NR	NR	20 (NR)	NR	NR	25	NR	NR	NR
Goldfarb et al., 2001 (62)	123 (12)	79 (7)	47	25 (20 to 32)	136 (19)	79 (9)	48	6	13 (5)‖	0 (8)¶

* NR = not reported.
† Studies are arranged by the average number of years after donation.
‡ Definitions of hypertension and a summary of various methods to assess blood pressure are presented in the Results section.
§ Percentage use of antihypertensive medications after donation is reported for the number of donors in each study.
‖ Variance estimates were derived from *t*-statistics.
¶ Variance estimates were imputed by using the formula as described in the Statistical Analysis section.

tion of between-study variability on the logit scale for binary outcomes and the proportion of between-study variability for continuous outcomes (11). A 2-tailed *P* value of 0.05 or less was considered statistically significant for binary outcomes, whereas for continuous outcomes, statistical significance was inferred by the proportion of variability explained by the factor and from the size of residual variance (11). Best-fit lines in meta-regression graphs were generated by generalized estimating equations (SAS procedure, PROC GENMOD, SAS statistical software) (12, 13). The generalized estimating equation models used estimates from the meta-regression models as the input values and were weighted by the estimated variances. An exchangeable correlation matrix was assumed for all such models. For models of binary outcomes, a binomial distribution with the logit link was used; for models of continuous outcomes, a normal distribution with the identity link was used. The 95% CI for each best-fit meta-regression line was computed as

$$g^{-1}(x_j'\hat{\beta} \pm z_{1-\alpha/2}\sigma_x),$$

where g is the link function, x_j is the vector of covariates, z is the percentile of the normal distribution, and σ_x is the estimated standard error of the linear predictor. The variance estimate of the linear predictor was calculated as

$$\sigma_x^2 = x_j'\Sigma x_j,$$

where Σ is the empirical covariance matrix. The number of studies comparing donors with control participants was small and precluded meta-regression of these results. All analyses were conducted using SAS, version 8.02 (SAS Institute Inc.), and RevMan, version 4.2 (Cochrane Collaboration, Oxford, United Kingdom). Results were graphed in R 2.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the Funding Sources

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RESULTS

We screened 2886 citations and retrieved and evaluated the eligibility of 262 full-text articles. In addition to excluding studies ineligible for our review, we excluded 1 study that only reported mean arterial pressure in the absence of systolic blood pressure, diastolic blood pressure, or hypertension results (14). Some study cohorts also contained a substantial number of extended-criteria donors with hypertension, proteinuria, or a glomerular filtration rate of less than 80 mL/min per 1.73 m^2 before surgery and did not separate reported outcomes from healthy donors. Because this review focused on risk for hypertension in healthy donors, such studies were also considered ineligible. The chance-corrected agreement was good between 2 independent reviewers who evaluated study eligibility ($\kappa = 0.83$).

Description of Studies, Methods, Donors, Control Participants, and Outcome Assessment

Forty-eight studies from 28 countries followed a total of 5145 donors an average of 7 years after donation (median, 6 years; range, 1 to 25 years) and were published from 1973 to 2005 (15–62). These studies, along with the change in blood pressure after donation and the proportion of donors who developed hypertension, are shown in **Tables 1** and **2**. Most studies were conducted in Europe (46%), followed by North America (21%), Asia (17%), Central or South America (8%), Australia (4%), and Africa (4%). The median number of donors per study was 49,

with the largest cohorts following 348, 472, 628, and 736 donors, respectively (23, 45, 50, 56). Forty-two primary authors were successfully contacted, and 30 provided additional data or confirmed the accuracy of abstracted data (17–19, 23–27, 31, 33–39, 41–43, 45, 46, 50, 52, 54, 56–58, 60–62).

Of the 48 studies, 23% initially decided to prospectively follow donors in time, 13% had donor outcomes measured at fixed years postdonation, 83% defined how blood pressure was measured, 77% provided a definition of hypertension, and 92% described the total number of donors from which the participating sample was selected. An average of 31% (range, 0% to 79%) of eligible participants were lost to follow-up in each of the 40 studies that reported this variable. Four studies described the characteristics of donors lost to follow-up (57, 58, 60, 62).

Before surgery, the mean donor age was 41 years (range, 26 to 59 years), the mean glomerular filtration rate was 111 mL/min per 1.73 m^2 (range, 91 to 151 mL/min per 1.73 m^2), the mean systolic blood pressure was 121 mm Hg (range, 107 to 132 mm Hg), the mean diastolic blood pressure was 77 mm Hg (range, 66 to 85 mm Hg), and the mean arterial blood pressure was 96 mm Hg (range, 86 to 97 mm Hg) for all studies. Fifty-eight percent of all donors were women. With the exception of 1 study (58), a minority of all donors were black. With the exception of 3 studies (21, 24, 28), almost all donors were genetically related to the recipient: When reported, 50% were parents, 40% were siblings, and 5% were children. Spouses made up only 7% of donors. No study described the use of laparoscopy for kidney removal.

Twelve of the studies also collected data on nondonor control participants to determine whether an increase in blood pressure after donation was above that attributable to normal aging (17, 26, 35, 37–39, 44, 50, 53, 54, 57, 58). Of these, 2 studies either used control participants who were younger than their donors or required control participants to have a normal blood pressure, serum creatinine level, and urine protein level at follow-up as a prerequisite to participate (26, 39). Control participants from these 2 studies were not considered further because doing so could lead to a possible exaggerated risk attributed to donation. In the remaining 10 studies, control participants were healthy volunteers or persons being evaluated as potential donors who were of similar age, sex, race, or height distributions as donors. In all studies, control groups were assembled at the time of donor follow-up evaluation. With the exception of 1 study (38), no studies seemed to follow control participants prospectively from the time of donor surgery.

When reported, blood pressure was usually measured by a transplant center nurse or physician (93%). Other methods included 24-hour ambulatory blood pressure measurement (27, 55) and averaged readings from an oscillometric device (Dinamap, GE Medical Systems Information Technologies, Inc., Milwaukee, Wisconsin) (15).

Study definitions of hypertension varied in their combined use of different thresholds of systolic blood pressure, diastolic blood pressure, and use of antihypertensive medication. Thresholds for systolic blood pressure were 130 mm Hg (45, 55), 140 mm Hg (23, 27, 28, 32, 33, 39, 43, 44, 47, 53, 57–60, 62), 150 mm Hg (35), and 160 mm Hg (38, 48), whereas thresholds for diastolic blood pressure were 80 mm Hg (45, 55), 90 mm Hg (15, 23, 24, 27, 28, 32, 33, 35, 37–39, 42, 44, 47, 48, 50, 53, 57, 58, 60, 62), 95 mm Hg (20, 31, 34, 59), 100 mm Hg (17), and 105 mm Hg (54). Fifty-six percent of studies included the use of antihypertensive medications in their reported definition of hypertension.

Risk for Blood Pressure Elevation

Controlled studies were reviewed to determine whether increases in blood pressure after donation were above those attributable to normal aging. There was no statistical heterogeneity between studies in which the average follow-up was at least 5 years (range, 6 to 13 years) after donation, suggesting that these studies could have been theoretically sampled from a common distribution. For systolic blood pressure, there were 4 studies totaling 157 donors and 128 control participants (chi-square, 0.57; $P = 0.90$; $I^2 = 0\%$), and for diastolic blood pressure, there were 5 studies totaling 196 donors and 161 control participants (chi-square, 6.33; $P = 0.176$; $I^2 = 37\%$). Thus, these results were mathematically pooled to improve statistical power for detecting any true latent effect (**Figure 1**). Most of the studies showed a statistically nonsignificant trend of increased blood pressure after donation. Because of the observed variability in blood pressure, none of the primary studies had an adequate sample size to detect a minimum 4–mm Hg increase in blood pressure with at least 80% statistical power. However, the pooled estimates were statistically significant. Approximately 1 decade after transplant surgery, donors had a 5–mm Hg increase in blood pressure (the weighted mean increase for systolic blood pressure was 6 mm Hg [95% CI, 2 to 11 mm Hg], and the weighted mean increase for diastolic blood pressure was 4 mm Hg [CI, 1 to 7 mm Hg]) compared with control participants.
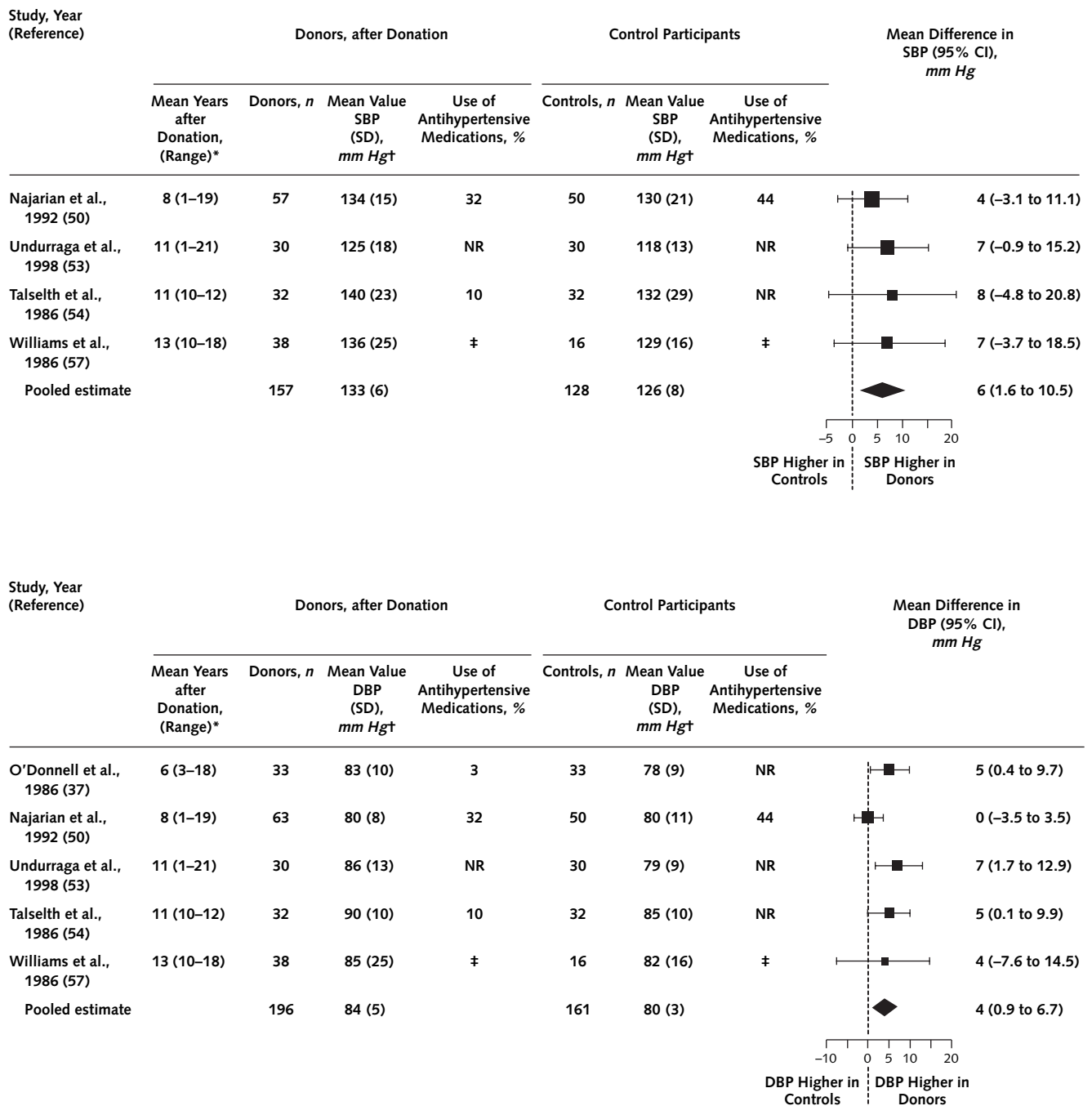
Risk for Hypertension

Six studies with average follow-up times ranging from 2 to 13 years assessed the risk for hypertension in 249 donors compared with 161 control participants (**Figure 2**). An increased risk for hypertension after donation was reported in 1 study (relative risk, 1.9 [CI, 1.1 to 3.5]) (58). Because of the observed incidence of hypertension in control participants, none of the primary studies had an adequately sized sample to detect a minimum 1.5-fold increase in risk after donation with at least 80% statistical power. Because of the statistical heterogeneity between the studies, results were not mathematically pooled (chi-square, 10.1; $P = 0.074$; $I^2 = 50\%$).

Predonation Donor Characteristics Associated with Outcomes

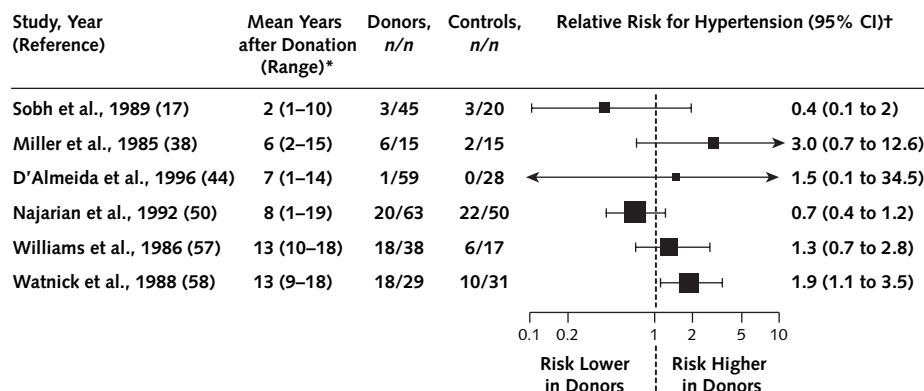Among healthy donors with normal predonation blood pressure and renal function, the primary studies described many prognostic features associated with increases in blood pressure and hypertension at follow-up. Within donors, many of these features clustered together, with multivariate regression only conducted in a minority of cases. The sample sizes of many these studies were also small, which limited statistical power to detect certain as-

Figure 1. Meta-analysis of controlled studies of systolic blood pressure (*SBP*) and diastolic blood pressure (*DBP*) at least 5 years after kidney donation.

Study, Year (Reference)	Donors, after Donation				Control Participants				Mean Difference in SBP (95% CI), mm Hg
	Mean Years after Donation, (Range)*	Donors, n	Mean Value SBP (SD), mm Hg†	Use of Antihypertensive Medications, %	Controls, n	Mean Value SBP (SD), mm Hg†	Use of Antihypertensive Medications, %		
Najarian et al., 1992 (50)	8 (1–19)	57	134 (15)	32	50	130 (21)	44		4 (–3.1 to 11.1)
Undurraga et al., 1998 (53)	11 (1–21)	30	125 (18)	NR	30	118 (13)	NR		7 (–0.9 to 15.2)
Talseth et al., 1986 (54)	11 (10–12)	32	140 (23)	10	32	132 (29)	NR		8 (–4.8 to 20.8)
Williams et al., 1986 (57)	13 (10–18)	38	136 (25)	‡	16	129 (16)	‡		7 (–3.7 to 18.5)
Pooled estimate		157	133 (6)		128	126 (8)			6 (1.6 to 10.5)

–5 0 5 10   20

SBP Higher in Controls : SBP Higher in Donors

Study, Year (Reference)	Donors, after Donation				Control Participants				Mean Difference in DBP (95% CI), mm Hg
	Mean Years after Donation, (Range)*	Donors, n	Mean Value DBP (SD), mm Hg†	Use of Antihypertensive Medications, %	Controls, n	Mean Value DBP (SD), mm Hg†	Use of Antihypertensive Medications, %		
O'Donnell et al., 1986 (37)	6 (3–18)	33	83 (10)	3	33	78 (9)	NR		5 (0.4 to 9.7)
Najarian et al., 1992 (50)	8 (1–19)	63	80 (8)	32	50	80 (11)	44		0 (–3.5 to 3.5)
Undurraga et al., 1998 (53)	11 (1–21)	30	86 (13)	NR	30	79 (9)	NR		7 (1.7 to 12.9)
Talseth et al., 1986 (54)	11 (10–12)	32	90 (10)	10	32	85 (10)	NR		5 (0.1 to 9.9)
Williams et al., 1986 (57)	13 (10–18)	38	85 (25)	‡	16	82 (16)	‡		4 (–7.6 to 14.5)
Pooled estimate		196	84 (5)		161	80 (3)			4 (0.9 to 6.7)

–10 0 5 10   20

DBP Higher in Controls : DBP Higher in Donors

The size of each square is inversely proportional to the variability of the study estimate. NR = not reported. *Studies are arranged by the average number of years after donation. †A summary of various methods to assess blood pressure are presented in the Results section. ‡Study reported that a percentage of donors were taking antihypertensive medication but did not quantify the amount.

Figure 2. **Controlled studies of hypertension risk after kidney donation.**

Study, Year (Reference)	Mean Years after Donation (Range)*	Donors, n/n	Controls, n/n	Relative Risk for Hypertension (95% CI)†
Sobh et al., 1989 (17)	2 (1–10)	3/45	3/20	0.4 (0.1 to 2)
Miller et al., 1985 (38)	6 (2–15)	6/15	2/15	3.0 (0.7 to 12.6)
D'Almeida et al., 1996 (44)	7 (1–14)	1/59	0/28	1.5 (0.1 to 34.5)
Najarian et al., 1992 (50)	8 (1–19)	20/63	22/50	0.7 (0.4 to 1.2)
Williams et al., 1986 (57)	13 (10–18)	18/38	6/17	1.3 (0.7 to 2.8)
Watnick et al., 1988 (58)	13 (9–18)	18/29	10/31	1.9 (1.1 to 3.5)

Risk Lower in Donors | Risk Higher in Donors

0.1 0.2 1 2 5 10

Results were not mathematically pooled because of statistical heterogeneity between studies (chi-square, 10.1; $P = 0.074$; $I^2 = 50\%$). The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years after donation. †Definitions of hypertension and a summary of various methods to assess blood pressure are presented in the Results section.

sociations even if they existed. Prognostic features associated with larger increases in blood pressure, higher blood pressure, or hypertension at follow-up included older age at the time of donation, age (usually >60 years) (45, 54, 56, 62, 63), male sex (56, 64), higher predonation blood pressure (15, 54, 63), higher than ideal body weight (45, 63), and a lower predonation glomerular filtration rate (63). Potential associations were described for a family history of hypertension (61) and black compared with white ethnicity (14). No association was shown for increased predonation uric acid level or cholesterol level (45).

In study-level meta-regression, higher average predonation systolic and diastolic blood pressure was associated with higher average postdonation systolic and diastolic blood pressure, respectively (explaining >19% of the between-study variability). Studies with a larger proportion of female donors showed lower average postdonation systolic blood pressures. The proportion of female donors, average donor age at the time of surgery, and average predonation systolic or diastolic blood pressure were not associated with the incidence of hypertension after donation (P values ranged from 0.28 to 0.61), nor were they associated with a change in systolic and diastolic blood pressure.

Study Methods Associated with Outcomes

Reported incidence of hypertension varied significantly among all of the donor studies ($P < 0.001$), with

Figure 3. **Studies with a higher proportion of donors lost to follow-up.**
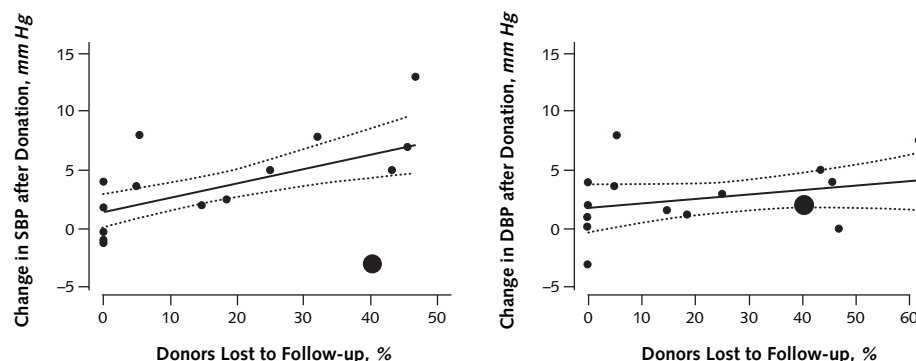
These studies on average showed a higher increase in blood pressure after donation, explaining 72% of the between-study variability for a change in systolic blood pressure (SBP) after donation and 59% for a change in diastolic blood pressure (DBP) after donation. This association remained statistically significant after adjustment for duration of follow-up. The area of each circle is proportional to the number of donors in each study. Best-fit lines with 95% CIs are from meta-regression. See the Methods section.

differences in follow-up time after nephrectomy only accounting for 42% of the between-study variability. Studies with a higher proportion of donors lost to follow-up showed higher increases in blood pressure after donation, explaining more than 59% of the between-study variability (**Figure 3**). This association remained statistically significant after adjustment for duration of follow-up after donation. Neither the manner in which blood pressure was assessed nor whether the study was conducted prospectively was associated with hypertension outcomes ($P = 0.119$ and $P = 0.67$, respectively).

DISCUSSION

Forty-eight studies of living donors varied greatly in methodologic rigor, methods of blood pressure assessment, and conclusions about whether donation increases blood pressure and the subsequent risk for hypertension. To develop consensus, we mathematically pooled results from a subset of small inconclusive studies that compared blood pressure in donors with that in nondonor control participants. In this meta-analysis, donating a kidney increased blood pressure by 5 mm Hg above that anticipated with normal aging.

Strengths and Weaknesses of This Review

The current study extends a previous quantitative review (5) in several ways. We identified 35 new articles, including 4 controlled studies (37, 44, 53, 58). The comprehensive search makes it unlikely that relevant studies were missed. Article identification, selection, and data abstraction were all performed independently in duplicate to minimize any potential biases arising from subjectivity. We also translated non–English-language articles and obtained unpublished information or clarifications from most primary study authors. Sources of bias were analyzed, and reasons for diversity in the published literature were explored. Finally, we justified our clinical and statistical reasons for mathematically combining certain results.

The results of any review are inherently limited by the quality of the primary studies. Data were often collected retrospectively, and many studies followed donors for less than 1 decade. On average, 31% of surviving donors were lost to follow-up, and in some studies larger numbers of eligible donors were missing (25, 37, 38, 44, 48, 51, 55). Estimates of long-term risk may be biased in either direction if donors who are followed systematically differ from nonparticipants in development of relevant outcomes. For example, **Figure 3** shows that higher blood pressure after surgery was evident in studies in which more patients were lost to follow-up, leading to the hypothesis that donors who became hypertensive were more likely to keep in touch with their transplant physicians than those who did not become hypertensive. For this reason, long-term risks presented in this review may be exaggerated. Conversely, transplant centers may be reluctant to report adverse outcomes after this perceived iatrogenic event. Furthermore,

we are interested in knowing what a donor's blood pressure would be if he or she had elected not to donate a kidney. The use of transplant-eligible nondonor control participants would best guide such inferences. However, in most of the existing primary studies, control participants were not assembled and followed prospectively with donors, nor was an absence of hypertension and relevant comorbid conditions confirmed when the comparable donor had surgery. Although persons accepted as kidney donors pass a rigorous set of tests and are expected to have good long-term health, those in the general population may be less fit. Thus, it remains possible that publication biases and the type of control participants used in the primary studies minimized any long-term risks attributable to donation.

Among the controlled studies, blood pressure and hypertension were assessed similarly in donors and control participants, and observed differences suggested a true increase in risk. However, inconsistent definitions of hypertension in the primary studies often relied on higher thresholds for systolic and diastolic blood pressure than those used today, which complicates the use of these results for modern-day donors.

We abstracted predonation donor characteristics associated with postdonation outcomes from the primary studies and considered such factors in additional regression analyses. Obtaining individual-patient data from 48 studies to perform patient-level regression was impractical, and deriving such data using imputation techniques from aggregate summaries remains controversial (5). Thus, our analyses were conducted at the study level, using meta-regression on subsets of studies for which information was available. These results should be considered exploratory, because associations identified across studies may not always reflect the same relationship within studies (65).

Informed Consent, Drug Cost Reimbursement, Donor Selection, and Follow-up

Providing better estimates of long-term hypertension risk will improve the informed consent process for potential donors. According to current data, it is plausible that donation increases the risk for or hastens the onset of hypertension over subsequent decades (66). However, the decision to become a donor comes out of an intense desire to help a recipient, and most donors would disregard any warnings of a future increase in blood pressure or increased risk for hypertension (67). For those select donors who do carefully consider risk and benefit (67) or in those circumstances in which the recipient has strong preferences, disclosure of these results might influence the decision to donate. For persons who consider accepting kidneys from altruistic strangers or paid donors (68, 69), risk–benefit can also be considered.

Some organizations advocate that donors be reimbursed for expenses related to donation, including transportation, accommodation, and child care costs. This concept differs from payment for financial gain. Many

countries have now implemented relevant health policies (such as federal grants, tax incentives, extended leave, and social programs) that reimburse living donors for such expenses (70). For these initiatives, a better understanding of the risk for hypertension after kidney donation might guide the need to reimburse the donor for antihypertensive prescription costs or associated higher insurance premiums.

A more complex issue relates to the selection of extended-criteria donors who have a history of hypertension before surgery. There is a paucity of current data to guide such practice. A decision to proceed in these cases should be made by an experienced transplant team who carefully considers the treatment preferences of the donor and recipient and judiciously uses the evidence summarized here for normotensive persons who become donors. It remains prudent to counsel and follow all donors, regardless of their predonation health state, to manage risk factors in an attempt to prevent hypertension and future cardiovascular disease.

Conclusions and Future Research

On the basis of the limited studies conducted to date, living kidney donors may have a 5–mm Hg increase in blood pressure within 5 to 10 years of donation over that anticipated with normal aging. Although randomly assigning eligible individuals to donation would provide the best estimate of nephrectomy effect (71), conducting such a study is impractical. Rather, results of our meta-analysis of existing literature will be best confirmed or refuted by a large, prospective, multicenter cohort study with representative numbers of donors and appropriate control participants (72). Inclusion of racially diverse, older, and genetically unrelated donors will help define whether there are any differential effects of donation among such individuals. Many previous studies were conducted in an era when higher thresholds were used to diagnose hypertension. The use of modern criteria, which also account for concurrent proteinuria and lower glomerular filtration rate, will increase the number of hypertensive events in follow-up and facilitate a better estimation of risk. In the general population, every 10–mm Hg increase in systolic blood pressure and 5–mm Hg increase in diastolic blood pressure is associated with a 1.5-fold increase in death from ischemic heart disease and stroke (73). Whether an increase in blood pressure from kidney donation is similarly prognostic requires future consideration, because closer surveillance and early intervention in otherwise healthy adults could offset any such risk.

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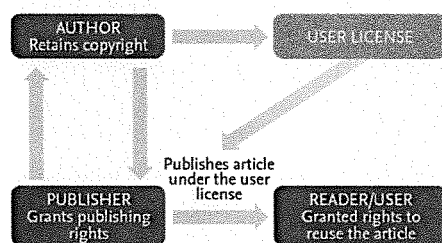
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Proteinuria and reduced kidney function in living kidney donors: A systematic review, meta-analysis, and meta-regression

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We reviewed any study where 10 or more healthy adults donated a kidney, and proteinuria, or glomerular filtration rate (GFR) was assessed at least 1 year later. Bibliographic databases were searched until November 2005. 31 primary authors provided additional information. Forty-eight studies from 27 countries followed a total of 5048 donors. An average of 7 years after donation (range 1–25 years), the average 24 h urine protein was 154 mg/day and the average GFR was 86 ml/min. In eight studies which reported GFR in categories, 12% of donors developed a GFR between 30 and 59 ml/min (range 0–28%), and 0.2% a GFR less than 30 ml/min (range 0–2.2%). In controlled studies urinary protein was higher in donors and became more pronounced with time (three studies totaling 59 controls and 129 donors; controls 83 mg/day, donors 147 mg/day, weighted mean difference 66 mg/day, 95% confidence interval (CI) 24–108). An initial decrement in GFR after donation was not accompanied by accelerated losses over that anticipated with normal aging (six studies totaling 189 controls and 239 donors; controls 96 ml/min, donors 84 ml/min, weighted mean difference 10 ml/min, 95% CI 6–15; difference not associated with time after donation ($P = 0.2$)). Kidney donation results in small increases in urinary protein. An initial decrement in GFR is not followed by accelerated losses over a subsequent 15 years. Future studies will provide better estimates, and identify those donors at least risk of long-term morbidity.

A critical reduction in renal mass may result in remnant single nephron hyperfiltration, with associated proteinuria and an accelerated loss of kidney function.[1] However, the long-term implications of donating a kidney remain uncertain. The primary questions of this review were: (1) What proportion of kidney donors develop proteinuria or a glomerular filtration rate (GFR) less than 60 ml/min? (2) Do kidney donors, compared to healthy non-donor controls, have a higher urinary protein? (3) Do kidney donors compared to controls have an accelerated loss of GFR after the initial decrement from their nephrectomy? Reasons for different estimates in the literature were also explored using meta-regression.

RESULTS
Finding studies
From screening 2886 citations, 262 full-text articles were retrieved, and 62 studies met our criteria for review. The chance-corrected agreement between two independent reviewers for article inclusion was good (kappa = 0.83). We subsequently excluded two studies which reported hypertension outcomes but not renal outcomes.[2,3] Some study cohorts contained a proportion of outcome assessment donors with hypertension, overt proteinuria, or a GFR less than 80 ml/min (per $1.73 \, m^2$) before the time of surgery, and did not separate reported outcomes from healthy donors. As this review focused on kidney function in potential donors in best health, we excluded such studies.[4–15]

Description of studies, methods, donors, controls, and outcome assessment

Forty-eight studies from 27 countries followed a total of 5048 donors an average of 7 years (median 6, range 1–25 years after donation), and were published from 1973 to 2005 (Tables 1 and 2).[16–63] Forty-three primary authors were successfully contacted, and 31 kindly provided additional data or confirmed the accuracy of abstracted data.[16,18–20,24–27,31–40,42,44,46,47,51,53,55,57–59,61–63]

Of the 48 studies, 21% prospectively followed donors in time, 15% had donor outcomes measured at fixed year(s)

post-donation, 91% defined how proteinuria was measured, 96% defined how renal clearance was measured, 67% provided a definition of clinical proteinuria, and 90% described the total number of donors from which the participating sample was drawn. When described, on average 31% of surviving donors eligible to participate in each study were lost to follow-up (range 0–79%). Four studies described the characteristics of donors lost to follow-up.[58,59,61,63]

Before surgery, over all studies, the average age of donors was 41 years (in the various studies average age ranged from 26 to 59 years), the average serum creatinine was 81 μmol/l

Table 1 | Characteristics of long-term renal prognosis studies of living kidney donors

Source[a]	Primary location	No. of donors	Years of donation	Prospective study	Patient age, mean (range), years[b]	Women (%)
Johnson et al.[16]	Boston, USA	78	2000–2003	No	44 (22–72)	60
Mimran et al.[17]	Montpellier, France	18	…	Yes	48 (20–62)	56
Sobh et al.[18]	Mansoura, Egypt	45	…	No	26 (22–64)	53
Friedlander et al.[19]	Iowa City, USA	12	1980–1985	Yes	36 (19–61)	75
Kostakis et al.[20]	Athens, Greece	255	1986–1996	No	60 (24–82)	74
Beekman et al.[21]	Leiden, Netherlands	47	1981–1988	Yes	36 (20–66)	49
Tondo et al.[22]	Parma, Italy	10	1986–1996	No	46 (…)	30
Hida et al.[23]	Bohseidai, Japan	34	1976–1981	Yes	56 (24–66)	59
Rivzi et al.[32]	Karachi, Pakistan	736	1986–2003	No	34 (…)	50
Abomelha et al.[24]	Riyadh, Saudi Arabia	70	1979–1989	Yes	32 (18–58)	29
Liu et al.[25]	St. Leonards, Australia	17	…	No	48 (27–61)	76
Edgren et al.[26]	Helsinki, Finland	46	…	No	… (20–74)	70
Siebels et al.[27]	Munich, Germany	122	1994–2001	Yes	52 (21–77)	80
Basseri et al.[28]	Teheran, Iran	87	…	No	34 (17–58)	43
Enger[29]	Oslo, Norway	13	1963–1971	Yes	48 (29–65)	69
Ghahramani et al.[30]	Shiraz, Iran	136	1988–1997	Yes	34 (…)	…
Mendoza et al.[31]	Mexico City, Mexico	152	1968–1985	No	28 (…)	57
Gonzalez et al.[33]	New York, USA	25	1976–1987	No	36 (20–58)	68
Fourcade et al.[34]	Lyon, France	99	1967–1994	No	38 (18–57)	54
Dunn et al.[35]	Nashville, USA	250	1970–1984	Yes	34 (18–67)	44
ter Wee et al.[36]	Groningen, Netherlands	15	1983	No	38 (…)	40
O'Donnell et al.[37]	Johannesburg, South Africa	33	1966–1984	No	38 (…)	45
Laskow et al.[38]	Birmingham, USA	48	…	No	40 (…)	52
Miller et al.[39]	New York, USA	47	1984	No	40 (18–60)	68
Rodriguez-Iturbe et al.[40]	Maracaibo, Venezuela	25	…	No	… (20–60)	44
Marekovic et al.[41]	Zagreb, Yugoslavia	50	1973–1990	No	50 (23–69)	34
Prandini et al.[42]	Bologna, Italy	32	1970–1980	No	42 (22–54)	72
Sato et al.[43]	Sendai, Japan	97	1968–1989	No	60 (37–77)	…
Chen et al.[44]	Taipei, Taiwan	76	1980–1991	No	44 (18–66)	59
D'Almeida et al.[45]	Porto Alegre, Brazil	110	1977–1993	No	36 (…)	…
Gracida et al.[46]	Mexico City, Mexico	628	1992–2001	Yes	36 (18–64)	49
Schostak et al.[47]	Berlin, Germany	53	1974–2002	No	48 (…)	56
Horcickova et al.[48]	Prague, Czech Republic	93	1966–1999	No	50 (26–69)	68
Lumsdaine et al.[49]	Edinburgh, UK	47	1986–2000	No	… (…)	…
Wiesel et al.[50]	Hildelberg, Germany	67	1967–1995	No	… (…)	…
Najarian et al.[51]	Minneapolis, USA	472	1963–1980	No	36 (18–68)	69
Toronyi et al.[52]	Budapest, Hungary	30	1973–1996	No	… (…)	83
Haberal et al.[53]	Ankara, Turkey	102	1975–1996	No	42 (21–65)	56
Undurraga et al.[54]	Santiago, Chile	74	…	No	40 (…)	73
Talseth et al.[55]	Oslo, Norway	70	1969–1974	No	46 (33–55)	47
Eberhard et al.[56]	Hannover, Germany	29	1973–1990	No	… (…)	76
Fehrman-Ekholm et al.[57]	Stockholm, Sweden	348	1964–1995	No	50 (22–76)	74
Williams et al.[58]	Philadelphia, USA	38	…	No	40 (19–59)	68
Watnick et al.[59]	New Haven, USA	29	1969–1978	No	… (…)	45
Mathillas et al.[60]	Göteborg, Sweden	46	1965–1973	No	46 (23–70)	57
Saran et al.[61]	Newcastle, UK	47	1963–1982	No	… (…)	51
Iglesias-Marquez et al.[62]	San Juan, Puerto Rico	20	1977–1980	No	42 (…)	60
Goldfarb et al.[63]	Cleveland, USA	70	1963–1975	No	40 (19–57)	59

Ellipses (…) indicate not reported.
[a]Studies are arranged by the average number of years after donation.
[b]Age is reported at the time of donation.

Table 2 | Long-term renal prognosis studies of living kidney donors

Source[a]	Pre-donation GFR, ml/min (per 1.73 m^2), mean (s.d.)[b]	Proportion lost to follow-up, %	Years after donation, mean (range)[a]	Post-donation Proteinuria[b] %	Proteinuria[b] mg, mean (s.d.)	GFR, ml/min (per 1.73 m^2)[b] 60–80, %	GFR, ml/min (per 1.73 m^2)[b] 30–59, %	GFR, ml/min (per 1.73 m^2)[b] mean (s.d.)	Change GFR, ml/min (per 1.73 m^2), mean (s.d.)[b]
Johnson *et al.*[16]	120 (15)	0	1 (1–1)	…	…	…	…	…	…
Mimran *et al.*[17]	126 (36)	…	1.2 (…)	…	…	…	…	73 (17)	−38 (11)[c]
Sobh *et al.*[18]	133 (28)	…	1.9 (1–10)	20	…	…	…	83 (37)	−50 (18)[c]
Friedlander *et al.*[19]	116 (19)	46	2 (1–3)	…	81 (66)	…	…	77 (21)	−36 (21)
Kostakis *et al.*[20]	…	24	2 (…)	7	…	…	…	…	…
Beekman *et al.*[21]	110 (19)	0	2 (…)	4	…	…	…	89 (25)	−21 (22)[d]
Tondo *et al.*[22]	…	0	2.1 (0.2–5)	0	…	…	…	…	…
Hida *et al.*[23]	92 (18)	0	2.8 (0.5–5)	0	…	…	…	75 (20)	−17 (19)[d]
Rivzi *et al.*[32]	101 (28)	40	3 (0.5–18)	5	139 (248)	…	7	87 (20)	−14 (25)[d]
Abomelha *et al.*[24]	118 (21)	64	3.1 (1–10)	1	…	…	…	82 (15)	−36 (10)[c]
Liu *et al.*[25]	…	…	3.1 (0.1–10)	0	…	…	…	81 (16)	…
Edgren *et al.*[26]	105 (26)	28	3.2 (0.2–6)	…	…	…	…	80 (17)	−24 (7)[c]
Siebels *et al.*[27]	…	24	3.2 (0.1–5)	5	…	…	…	…	…
Basseri *et al.*[28]	151 (…)	0	3.2 (1–8)	1	…	…	…	105 (…)	−46 (…)
Enger[29]	110 (8)	0	3.5 (0.5–8)	0	…	23	15	84 (8)	−26 (7)[c]
Ghahramani *et al.*[30]	…	21	3.6 (0.3–9)	33	…	…	…	…	…
Mendoza *et al.*[31]	130 (37)	15	3.7 (0.1–12)	1	…	0	0	117 (32)	−13 (35)[d]
Gonzalez *et al.*[33]	…	43	4.2 (0.5–12)	4	…	…	…	…	…
Fourcade *et al.*[34]	115 (15)	0	4.3 (0.1–19)	29	…	41	6	80 (12)	−35 (12)
Dunn *et al.*[35]	129 (31)	18	4.4 (0.5–15)	3	…	…	…	85 (33)	−43 (32)[d]
ter Wee *et al.*[36]	111 (21)	38	4.9 (1.5–13)	33	150 (232)	…	…	76 (14)	−35 (18)[d]
O'Donnell *et al.*[37]	108 (16)	62	5.8 (3–18)	6	…	…	…	100 (22)	−8 (20)[d]
Laskow *et al.*[38]	…	…	5.9 (…)	2	…	…	…	…	…
Miller *et al.*[39]	…	77	6 (2–15)	41	144 (121)	…	…	…	…
Rodriguez-Iturbe *et al.*[40]	…	7	6 (1–11)	…	…	…	…	115 (43)	…
Marekovic *et al.*[41]	103 (30)	…	6.1 (1–15)	0	72 (13)	…	…	86 (34)	−17 (32)[d]
Prandini *et al.*[42]	…	22	6.2 (5.2–17)	0	…	…	…	99 (25)	…
Sato *et al.*[43]	…	3	6.3 (2–17)	12	…	…	…	…	…
Chen *et al.*[44]	…	0	6.4 (…)	…	194 (89)	…	…	…	…
D'Almeida *et al.*[45]	…	67	6.6 (1–14)	18	142 (121)	…	…	87 (45)	…
Gracida *et al.*[46]	115 (…)	0	6.7 (0.5–10)	0	…	…	…	79 (…)	−36 (11)[c]
Schostak *et al.*[47]	…	48	6.9 (…)	23	…	…	…	…	…
Horcickova *et al.*[48]	…	…	7.1 (0.2–31)	30	…	…	…	…	…
Lumsdaine *et al.*[49]	…	69	7.1 (…)	0	…	…	…	…	…
Wiesel *et al.*[50]	…	43	8 (…)	19	…	…	…	…	…
Najarian *et al.*[51]	…	25	8.3 (1–19)	6	…	…	…	…	…
Toronyi *et al.*[52]	…	62	8.9 (…)	0	…	…	…	98 (…)	…
Haberal *et al.*[53]	109 (9)	32	10.2 (0.7–22)	4	…	…	…	97 (19)	−12 (16)[d]
Undurraga *et al.*[54]	92 (22)	…	10.9 (1–21)	18	…	…	…	81 (22)	−10 (3)[c]
Talseth *et al.*[55]	108 (26)	5	11 (10–12)	24	…	…	…	87 (29)	−21 (28)[d]
Eberhard *et al.*[56]	…	79	11.1 (5–20)	3	…	38	28	75 (22)	…
Fehrman-Ekholm *et al.*[57]	…	13	12.5 (2–33)	12	…	…	…	64 (13)	…
Williams *et al.*[58]	106 (30)	32	12.6 (10–18)	32	135 (174)	…	8	85 (23)	−20 (27)[d]
Watnick *et al.*[59]	…	19	13 (9–18)	14	…	…	0	85 (16)	…
Mathillas *et al.*[60]	…	13	14.9 (10–20)	26	306 (232)	52	20	…	…
Saran *et al.*[61]	…	21	19.6 (13–31)	34	…	36	19	77 (…)	…
Iglesias-Marquez *et al.*[62]	126 (…)	…	20 (…)	5	…	…	…	98 (…)	−27 (16)[c]
Goldfarb *et al.*[63]	102 (41)	47	25 (20–32)	20	230 (60)	…	…	73 (23)	−29 (36)[d]

GFR, glomerular filtration rate.

Ellipses (…) indicate not reported.

[a]Studies are arranged by the average number of years after donation.

[b]A summary of various methods to assess GFR and proteinuria are presented in the 'Results' section.

[c]Variance estimates were derived from *t*-statistics.

[d]Variance estimates were imputed using the formula described in the 'Materials and methods' section.

(0.92 mg/dl, range 51–100 μmol/l), the average GFR was 111 ml/min (range 91–132), the average systolic blood pressure was 121 mmHg (range 107–132), and the average diastolic blood pressure was 77 mmHg (range 75–79). No donors had overt proteinuria before surgery. The average pre-donation urinary protein was quantified in six studies at 95 mg per day (range 55–124).[19,32,41,44,58,63]

Eleven of the studies also collected data on suitable non-donor controls to determine if increases in urinary protein and reductions in GFR after donation were above that

attributable to normal aging.[18,35,37,39,45,51,54,55,58-60] Controls were healthy volunteers, or individuals under evaluation as potential donors, with similar age, sex, race, and / or, height distributions as donors. In all studies control groups were assembled at the time of donor follow-up evaluation. With the exception of a single study,[39] none appeared to follow controls prospectively from the time of donor surgery.

Forty-one studies described the method of urine protein quantification, which usually was a timed (i.e. 24 h) urine. Other methods included a random urine protein,[16,23,25,28,29,49,54,57,62] dipstick,[27,47] a timed urine albumin,[18,46,51,59,61] a random urine albumin to creatinine ratio[34] and a first am urine albumin concentration.[56] Thresholds for clinical proteinuria varied, and included >100,[37,53] >150,[35,39,48,55,58,59,63] >200,[45] >300,[24,30,32,33,42,43,46,56,60] >500,[21] or >600 mg[20] of protein per day, or various levels on urinary dipstick.[18,23,25,27,28,47,49,54,57]

Forty-four studies described the method of GFR estimation, which usually was a timed urine creatinine clearance.[17-19,23-25,29-32,37,40,41,45,48,49,51,55,58,62,63] Other methods included the use of inulin or radioisotopes,[20,34,36,46,52,53,59-61] or a predictive equation for GFR.[28,54,56,57] Ten studies only described a serum creatinine result.[16,22,27,33,35,38,39,44,47,50] In 61% of studies the reported GFR was standardized to 1.73 m^2 of body surface area.

Death, kidney failure, and cardiovascular disease

Thirty-three studies described the number of donors who died during follow-up, which ranged from 0 to 16% of the study cohort. In one of these studies, a total of two donors died with kidney failure.[63] A total of 10 donors from eight different studies were living with kidney failure at the time of last assessment.[32,39,43,48,51,57,61,63] Seven studies described a proportion of donors who developed cardiovascular disease during follow-up,[46,48,55-57,60,63] although these events were not systematically assessed.

Incidence of proteinuria

The incidence of clinical proteinuria after donation was quantified in 42 studies, which followed 4793 living donors an average of 7 years (range 2–25 years). There was significant heterogeneity between the studies ($P<0.0001$). Some studies reported an incidence of proteinuria over 20%,[30,34,36,39,47,48,55,58,60,61] whereas in others the incidence was less than 5%.[21-25,28,29,31-33,35,38,41,42,46,49,52,53,56] (Table 2). The pooled incidence of proteinuria was 12% (95% confidence interval (CI) 8–16%). These results were similar in a supplementary analysis which only considered those nine studies which consistently defined proteinuria as >300 mg/ day based on 24 h urine.[24,30,32,33,42,43,46,56,60] The pooled incidence of proteinuria among these nine studies which followed a total of 1799 donors for 7 years was 10% (95% CI 7–12%).

Risk of proteinuria

Three studies compared a total of 129 donors to 59 controls on 24-h urine protein, to determine if increases in proteinuria after donation were above that possibly attributable to normal aging (Figure 1).[45,58,60] Proteinuria appeared to be increased after donation in each of these three studies, although the CIs were wide. There was no evidence of statistical heterogeneity between these three studies, suggesting they could have been theoretically sampled from a common distribution (χ^2 0.51, $P=0.78$, $I^2=0\%$). Thus the results were mathematically pooled, to establish a more precise estimate. The 24-h urine protein was higher in donors compared to controls an average of 11 years after donation (controls 83 mg/day, donors 147 mg/day, weighted mean difference 66 mg/day, and 95% CI 24–108). This difference increased with the time from donation ($P<0.001$).

Four studies compared a total of 146 donors to 105 controls on 24-h urine albumin (Figure 2).[45,55,59,60] There was evidence of extreme statistical heterogeneity between these studies; thus results were not mathematically pooled (χ^2 57.4, $P<0.00001$, $I^2=95\%$). In two of the four studies, 24-h urine albumin was approximately 56 mg higher in donors compared to controls 14 years after donation.[59,60]

Two studies assessed the risk of microalbuminuria after kidney donation in a total of 67 donors and 51 controls at 2 and 13 years after donation (Figure 2).[18,59] The mathematically pooled result should be interpreted with the understanding that notable heterogeneity was present between these studies (χ^2 2.3, $P=0.13$, $I^2=56\%$). The pooled risk of microalbuminuria after kidney donation was 3.9 (95% CI 1.2–12.6).

Kidney function after donation

Among the 36 studies of 3529 donors which reported a post-donation serum creatinine or GFR with an estimate of variance, the average time after donation was 6 years, the average serum creatinine was 98 μmol/l (1.11 mg/dl, range 58–119 μmol/l), the average GFR was 86 ml/min (per 1.73 m^2) (range 64–117). In 22 studies where it was described, the average decrement in GFR after donation was 26 ml/min (per 1.73 m^2) (range 8–50). Nine studies reported a post-donation GFR which could be assessed in categories (Table 2).[29,31,32,34,56,58-61] The average post-donation GFR in these studies did not differ from the remaining studies (88 vs 85 ml/min (per 1.73 m^2), $P=0.4$). In these eight studies a mean of 10 years after donation, 40% of donors developed a GFR between 60 and 80 ml/min (per 1.73 m^2) (range 23–52%), 12% of donors developed a GFR between 30 and 59 ml/min (per 1.73 m^2) (range 0–28%), and 0.2% a GFR less than 30 ml/min (per 1.73 m^2) (range 0–2.2%). These results were no different in a supplementary analysis which only considered those studies where the GFR was measured, rather than estimated from a predictive equation.

Risk of reduced kidney function

Controlled studies were reviewed to determine if the initial decrement in GFR after nephrectomy was accompanied by subsequent accelerated loss in GFR over that anticipated with

24 h urine protein

Source*	Donors, post-donation		Controls		24 h urine protein	
	Years after donation, Mean (range)	24 h urine Protein (mg/day) N mean (s.d.)	24 h urine Protein (mg/day) N mean (s.d.)		Mean difference (mg/day) 95% CI	
D'Almeida *et al.*[45]	7 (1–14)	59 151 (125)	28 96 (116)			54 (1, 108)
Williams *et al.*[58]	13 (10–18)	37 115 (135)	17 31 (125)			84 (10, 157)
Mathillas *et al.*[60]	15 (10–20)	33 306 (320)	14 212 (255)			94 (−79, 267)
Pooled estimate		129 147 (22)	59 83 (30)			66 (24, 108)

−50 0 50 150 250
Higher in controls | Higher in donors

24 h urine albumin†

Source*	Donors, post-donation		Controls		24 h urine albumin	
	Years after donation, Mean (range)	24 h urine Albumin (mg/day) N mean (s.d.)	24 h urine Albumin (mg/day) N mean (s.d.)		Mean difference (mg/day) 95% CI	
D'Almeida *et al.*[45]	7 (1–14)	59 19 (21)	28 11 (5)			8 (2, 14)
Talseth *et al.*[55]	11 (10–12)	32 8 (7)	32 5 (6)			3 (0, 6)
Watnick *et al.*[59]	13 (9–18)	22 61 (40)	31 4 (1)			57 (40, 73)
Mathillas *et al.*[60]	15 (10–20)	33 66 (66)	14 11 (9)			55 (32, 78)

0 50 100
Higher in controls | Higher in donors

Microalbuminuria ‡

Source*	Years after donation, Mean (range)	Donors n/N	Controls n/N	Relative risk of microalbuminuria 95% CI
Sobh *et al.*[18]	2 (1–10)	8/45	2/20	1.8 (0.4, 7.6)
Watnick *et al.*[59]	13 (9–18)	6/22	0/31	18.1 (1.1, 305.3)
Pooled estimate		14/67	2/51	3.9 (1.2, 12.6)

0.1 1 10 100
Lower risk in donors | Higher risk in donors

Figure 1 | Controlled studies of proteinuria after kidney donation. The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years after donation. ‡Microalbuminuria was assessed by 24 h urine. †Mathematically pooled results are not presented graphically because of statistical heterogeneity between studies. See 'Results' section.

		Donors, post-donation		Controls		
Source*	GFR Assessment	Years after Donation Mean (range)	GFR (ml/min) (per 1.73 m²) N mean (s.d.)	GFR (ml/min) (per 1.73 m²) N mean (s.d.)	GFR mean difference, 95% CI ml/min (per 1.73 m²)	
O'Donnell *et al.*[37]	24 h urine	6 (3–18)	33 100 (22)	33 111 (17)		−12 (−21, −2)
D'Almeida *et al.*[45]	24 h urine	7 (1–14)	59 86 (37)	28 98 (37)		−12 (−28, −5)
Najarian *et al.*[51]	24 h urine	8 (1–19)	57 82 (15)	50 89 (23)		−7 (−15, 1)
Undurraga *et al.*[54]	Cockroft-Gault	11 (1–21)	30 86 (22)	30 97 (27)		−11 (−24, 1)
Williams *et al.*[58]	24 h urine	13 (10–18)	38 86 (39)	17 103 (31)		−17 (−37, 2)
Watnick *et al.*[59]	Inulin	13 (9–18)	22 66 (14)	31 78 (22)		−12 (−22, −2)
Pooled estimate			239 84 (11)	189 96 (14)		−10 (−15, −6)

−40 −30 −20 −10 0 10

Lower in donors | Lower in controls

Figure 2 | Meta-analysis of controlled studies of kidney function at least 5 years after donation. GFR – glomerular filtration rate. The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years since donation.

normal aging. There was no statistical heterogeneity between those where the average follow-up was at least 5 years after donation (χ^2 1.49, $P = 0.91$, $I^2 = 0\%$) and these results were mathematically pooled (Figure 2).[37,45,51,54,58,59] The pooled post-donation GFR was 10 ml/min (per 1.73 m²) lower in donors compared to controls (six studies totaling 189 controls and 239 donors; controls 96 ml/min, donors 84 ml/min, weighted mean difference 10 ml/min, and 95% CI 6–15). The difference was similar across studies, irrespective of the time from donation ($P = 0.2$).

Pre-donation prognostic features
Among healthy donors, the primary studies reported a number of prognostic pre-donation features associated with a higher proteinuria or lower GFR after donation. Within donors many of these features clustered together, and multivariate regression was only reported in a minority of studies. Potential true associations may also have gone undetected, as the sample size of many studies was small.

In the primary studies, compared to women, men were reported to have larger increases in proteinuria after donation.[58,59,63] Although there was a nonsignificant trend in one study,[30] there was no reported association between the time after donation and the amount of proteinuria at

last follow-up.[39,56,58,59] Neither donor age at the time of surgery,[16,39,55,58,63] nor pre-donation blood pressure[55] was associated with proteinuria after donation.

When we conducted study level meta-regression, average age at donation, the proportion of female donors, and the average pre-donation blood pressure were not associated with proteinuria after donation (P-values ranged from 0.22 to 0.69).

In the primary studies, compared to men, women were reported to have a lower GFR both before and after donation.[61,63] There was no gender differences in the decrement in GFR after donation.[63] Similarly, compared to those who were younger, older donors demonstrated a lower GFR both before and after donation.[34,46,63] In older donors, the decrement in GFR after donation tended to be smaller,[46,61] larger[16,26,34,39,55,57] or no different than younger individuals.[63] Pre-donation obesity,[46] plasma uric acid,[46] and serum cholesterol[46] were not associated with the post-donation GFR. Black and white donors were similar in their renal response to donation.[38] The time after donation was not associated with post-donation GFR or change in GFR.[25,27,56,58,59] In one study, a higher pre-donation blood pressure was associated with a larger decrement in GFR after donation.[55]

When we conducted study level meta-regression, older age at the time of donation was associated with both lower pre- and post-donation GFR (explaining 26 and 38% of the between study variability respectively). For example, donors aged 25 years old at the time of donation developed an approximate post-donation GFR of 94 ml/min (per $1.73\,m^2$), whereas in donors aged 55 it was 74 ml/min (per $1.73\,m^2$). However, the change in GFR after donation was not statistically associated with donor age at the time of donation. The proportion of female donors, and average pre-donation systolic or diastolic blood pressure were not associated with change in GFR or post-donation GFR (explaining 2–7% of the between study variability).

Prognostic methods features
Studies with more donors lost to follow-up demonstrated a somewhat larger decrement in GFR after donation (explaining 22% of the between study variability). The average follow-up time after donation was associated with the proportion of donors who developed clinical proteinuria. Otherwise, none of the other methodological features tested in meta-regression were associated with outcomes in multivariate analyses (*P*-values ranged from 0.09 to 0.68).

DISCUSSION
In this quantitative review, kidney donation resulted in small increases in urinary albumin, which increased with the time after donation. Many would consider this indicative of single nephron hyperfiltration from a reduced renal mass. Whether such hyperfiltration leads to a progressive deterioration in kidney function has been the subject of many debates. Ten years after nephrectomy, donors had a GFR that was 10 ml/min lower compared to controls. In addition approximately 12% of donors developed a GFR less than 60 ml/min during follow-up. However, after the initial decrement in GFR from the nephrectomy, there was no evidence of an accelerated loss in GFR over that anticipated with normal aging.

Strengths and weaknesses of this review
This review summarized 48 single center studies, and shares similar strengths and weaknesses to a parallel review conducted on hypertension risk in living donors.[64] In brief, since the last quantitative review on this topic, we identified 35 new articles.[65] Relevant data was rigorously identified and abstracted, articles were translated, information was clarified with a majority of primary study authors, and reasons for diversity in the published literature were explored. We justified reasons for mathematically combining certain results. However, results from any meta-analysis are inherently limited by the quality of the primary studies. As described, on average about one-third donors were lost to follow-up. Most of the studies also did not have an internal control group, making it difficult to interpret the donor results. A proportion of donors would have developed certain medical conditions even if they had not donated a kidney. Those studies, which did have a control group often,

recruited participants from the general population. Such individuals are not as fit as donors, which may have biased towards demonstrating no increased risk of certain medical conditions after donation. Similarly, long-term sequelae after donation may be underreported, if transplant centers were reluctant to describe significant morbidity after this perceived iatrogenic event.[66] Among the controlled studies proteinuria and GFR were assessed in a similar manner in both donors and controls, with observed differences suggesting a true difference between the groups. However, inconsistent methods of measuring and reporting proteinuria and renal function in the primary studies complicate the interpretation of these results. For example, only a few studies reported post-donation GFR in categories consistent with modern cutoff points used to assess renal function.[67] In most studies it was unclear whether donors who developed a low GFR also had concurrent hypertension and proteinuria.

Renal sequelae, donor selection, and long-term surveillance
The proportion of donors who develop clinical proteinuria appears to be higher than expected in the general population – whereas kidney donation increases urinary protein often within the range considered normal, approximately 10% of donors exceed a threshold of 300 mg/day over a subsequent decade. Similarly, about 12% of donors develop a GFR less than 60 ml/min over this same period. Although some donors may have been predestined to develop such a GFR even if they had not donated a kidney, a decrement of 10 ml/min after their nephrectomy likely hastens this event. Thus the central question remains – what is the prognostic significance of proteinuria or reduced kidney function in this patient population? In the general population, low GFR and proteinuria may be signs of systemic atherosclerosis, and both are associated with concurrent metabolic disturbances, future premature mortality, cardiovascular disease, and kidney failure.[68–70] For this reason some, but not all, consider a GFR of 30–59 ml/min as the pathologic state of stage 3 chronic kidney disease.[67,71] However, kidney donors develop reduced kidney function or low-grade proteinuria through a different mechanism, and their prognostic significance in this segment of the population remains uncertain. Indeed, donors undergo rigorous evaluation and selection, and their incidence of death is lower than the general population.[72] Thus, without evidence of adverse health outcomes, small changes in measurements of proteinuria or GFR should not be the sole reason for deterring a practice which benefits recipients, donors, and society.

Living donors whose data were summarized in this review demonstrated no evidence of hypertension, proteinuria or reduced kidney function before donation. However, in the current era, the eligibility criteria for donation are being extended, and some centers now accept potential donors with a GFR less than 80 ml/min.[73] It is important to consider that many donors may have a genetic predisposition to developing kidney disease, and a total of 10 donors (0.2%, one in 500 donors) in this review were reported to have developed

kidney failure requiring dialysis. Thus the acceptance of living donors at potentially higher incremental risk for future adverse events remains contentious. A decision to proceed in such cases should be made by an experienced transplant team that carefully considers donor and recipient preferences, in conjunction with judicious use of the evidence summarized here for healthy donors. It also remains prudent to counsel all donors, irrespective of their pre-donation health state, on modifiable risk factors which prevent future renal and cardiovascular disease.[74,75]

Unlike in the case of blood pressure measurements, routinely screening the general population to detect an elevated serum creatinine or the presence of urine protein is not recommended. However, living donors are a group who may be at higher risk of renal sequelae, and to prevent future morbidity it remains unclear which renal screening tests should be performed, how long donors should be followed, and which health care providers should be responsible for such follow-up. Some transplant centers assume responsibility for follow-up, whereas others examine donors once or twice before returning care back to the primary physician. Some advocate limiting renal follow-up to 5 years, to prevent the perception that being a donor is pathological.[73] The results summarized here support the safety of live kidney donation. However, until the prognostic significance of low-grade proteinuria or reduced kidney function in some kidney donors is better understood, we would advocate for a lifetime of annual serum creatinine and urine protein screening.

Future research

Results from this quantitative review will be best confirmed by the completion of a large, prospective, multi-center cohort study with representative numbers of donors and appropriate controls followed for extended periods of time.[76,77] Inclusion of racially-diverse, older and genetically unrelated donors, and controls will help define if there are any differential effects of donation among such individuals. Finally, by assessing definitive outcomes such as death and cardiovascular disease, the prognostic significance of small increases in urinary protein or reduced kidney function after donation will be better understood.

MATERIALS AND METHODS
Studies eligible for review

We included a study in any language where 10 or more healthy adults donated a kidney, and either proteinuria or GFR was assessed at least 1 year later.

Finding relevant studies, data abstraction, and statistical analysis

We recently published a parallel review on the risk of hypertension after living kidney donation, where methods used in this review are fully described.[64] In brief, until November 2005 we screened relevant citations from multiple sources including MEDLINE, EMBASE, and Science Citation Index bibliographic databases. Pairs of reviewers independently evaluated the eligibility of each full-text article, and data was abstracted in duplicate. Studies in languages other than

English were translated. When data from the same group of donors were described in multiple publications,[64] we cited the most representative publication of the greatest number of donors with longest follow-up. We attempted to contact primary authors of all included studies to confirm data and provide missing information.

Reviewer agreement on study eligibility was quantified using the kappa statistic. Variance estimates for pre- and post-donation changes GFR were not reported in a majority of studies. If not reported, variance estimates were derived from *t*-statistics when available. Otherwise variance estimates were calculated with $SE_\Delta = \sqrt{SE_{pre}^2 + SE_{post}^2 (2 \times \rho_\Delta \times SE_{pre} \times SE_{post})}$, where ρ_Δ represents the correlation between the pre- and post-donation GFR measurements.[78] For the two studies that did report pre donation, post-donation and change variance estimates, we calculated an average correlation coefficient of 0.59 for GFR. Thus we utilized a correlation of 0.5 to impute missing change variance estimates in the final meta-regression. We performed sensitivity analyses to this choice of correlation and results were qualitatively similar. For those few studies, which only reported a range of donor follow-up, we considered the average follow-up time as the midpoint of the provided range.

For this study level meta-analysis, the *Q*-statistic was used to determine if between study heterogeneity was present, with a *P*-value of <0.1 considered statistically significant. The I^2-statistic was used to quantify the magnitude of heterogeneity, with value of 0–30%, 31–50% and greater than 50% representing mild, moderate, and notable heterogeneity respectively.[79] When justified, results were mathematically pooled using techniques which accounted for within and between study heterogeneity (random effects method).[80–82] Although creatinine clearance is conceptually different from GFR, it is commonly used as an estimate of GFR and therefore was used interchangeably for this outcome. Although some studies reported GFR standardized to body surface area, others did not. In pooled estimates we combined all studies irrespective of whether GFR was standardized to body surface area, and reported the unit as ml/min (per 1.73 m^2).

Reasons for diversity in primary study estimates were explored using univariate and multivariate meta-regression of donor cohorts: mixed models for continuous outcomes (SAS PROC MIXED) and logistic normal random effects models for binary outcomes (SAS PROC NLMIXED). At the study level, the association between the following donor characteristics and outcomes of proteinuria or lower GFR after donation were considered: older age, a higher pre-donation blood pressure, and a lower pre-donation GFR. We hypothesized that these factors would be associated with increased proteinuria or a lower GFR after donation.[83,84] Features of study methodology associated with renal outcomes after donation were also considered. The methodological features tested in meta-regression were whether the study was conducted prospectively, the duration of follow-up, the proportion of donors lost to follow-up, and the method by which renal function was assessed. The explanatory ability of each factor was quantified by the proportion of between study variability on the logit scale for binary outcomes, and the proportion of between study variability for continuous outcomes.[82] A two-tailed $P \leqslant 0.05$ was considered statistically significant for binary outcomes, whereas for continuous outcomes statistical significance was inferred by the proportion of variability explained by the factor and from the size of residual variance.[82] Best fit lines in meta-regression graphs were created using generalized estimating equations (SAS PROC GENMOD).[85,86] Generalized estimating equations models used estimates from the

meta-regression models as the input values, and were weighted by the variance of each estimate. An exchangeable correlation matrix was assumed for all generalized estimating equations models. For models of binary outcomes, a binomial distribution with the logit link was used and for models of continuous outcomes, a normal distribution with the identity link was used. The 95% CI for each best fit meta-regression line was computed as $g^{-1}(x_j'\hat{\beta} \pm z_{1-\alpha/2}\sigma_x)$, where g is the link function, x_j is the vector of covariates, z is the percentile of the normal distribution, and σ_x is the estimate s.e. of the linear predictor. The variance estimate of the linear predictor was calculated as $\sigma_x^2 = x_j'\Sigma x_j$, where Σ is the empirical covariance matrix. All analyses were conducted using SAS 8.02 (SAS Institute Inc., Cary, NC, USA) and Revman 4.2 (Cochrane Collaboration, Oxford, England). Results were graphed in R 2.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

AUTHOR CONTRIBUTIONS

Dr Garg, Ms Thiessen-Philbrook, Dr Rosas-Arellano, and Dr Boudville had full access to all of the data in the study and take responsibility for the accuracy of the data analysis. *Study concept and design:* Garg, Muirhead, Rosas-Arellano, Boudville; *Acquisition of data:* Garg, Muirhead, Knoll, Yang, Prasad, Thiessen-Philbrook, Rosas-Arellano, Housawi, Boudville; *Analysis and interpretation of data:* Garg, Muirhead, Knoll, Yang, Prasad, Thiessen-Philbrook, Rosas-Arellano, Housawi, Boudville; *Drafting of the manuscript:* Garg, Boudville; *Critical revision of the manuscript for important intellectual content:* Garg, Muirhead, Knoll, Yang, Prasad, Thiessen-Philbrook, Rosas-Arellano, Housawi, Boudville; *Statistical analysis:* Garg, Thiessen-Philbrook; *Obtained funding:* Garg, Muirhead, Boudville; *Administrative, technical, or material support:* Garg, Muirhead, Rosas-Arellano, Boudville; *Study supervision:* Garg.

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Editorial

Live kidney donation: Who's at risk of a low glomerular filtration rate following donation?

With the limited supply of cadaveric kidney donors, there is an increasing demand for living kidney donation worldwide. In Australia, living donation accounted for 39% of all kidney transplants in 2005.[1] However, a donor nephrectomy is one of the few occasions that modern medicine inflicts harm and medical risk upon a healthy individual. It is performed in the knowledge of improved recipient and graft survival, and benefits of altruism for the living kidney donor but with the hope of minimal long-term adverse effects.

There is some uncertainty about the long-term affects of living kidney donation, in particular the risk of the development of chronic kidney disease (CKD) and hypertension.[2,3] A more precise understanding of predonation risk factors that predict an individual's future risk may improve the process of potential donor evaluation. There is now global consensus that we need more precise estimates of any potential long-term risks to the living donor.

In this issue of *Nephrology*, Han *et al.* reported on a cross-sectional study of 104 out of a total of 756 living kidney donors from a single centre.[4] In this cohort, 25% (26/104) had CKD, a median of 7 years after donation. CKD was defined as a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2. For the definition of CKD, the GFR was primarily estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation, though it was also estimated using the Cockcroft–Gault equation and a 24 h urine creatinine clearance as well.

On multivariate analysis, they found that age and hypertension at the time of donation were significantly associated with the future development of CKD in living kidney donors. For donor age, each subsequent year was associated with an odds ratio (OR) of 1.06 for CKD (95% confidence interval (CI) 1.01–1.10). Similarly, a history of hypertension at the time of donation was associated with an OR of 7.91 (95% CI 1.13–55.2).[4]

These results should be viewed cautiously however, in view of a few methodological issues with this study. The retrospective design, the lack of controls and large proportion of the total donor population lost to follow up introduce potential bias. Those lost to follow up may feel, and be, too well to continue seeking medical review. There is empirical evidence of such 'informative censoring' in a recent follow-up report of living donors, which demonstrated a greater increase in blood pressure after donation in studies with a higher proportion of donors lost to follow up.[2]

It should be noted that the method utilized to estimate the GFR (abbreviated MDRD equation) has not been validated in a Korean population. In addition, a recent study of living kidney donors found that the MDRD equation underestimated iohexol GFR by 6.45 ± 9.5 mL/min per 1.73 m^2 and was within 10% of the actual GFR in only half of the cases.[5] As this formula includes age as one of the variables, it may also be no great surprise that GFR is subsequently found to be lower with older age.

Most living kidney donors have to attain a high level of 'good' health before being able to donate. The reason most transplant centres do this is to minimize the perceived long-term risk on the potential donor. For example, diabetic patients are not utilized as living kidney donors due to their high risk of developing CKD themselves. The difficulty that most transplant units have is deciding upon what threshold of risk they are willing to accept on behalf of a potential donor as the long-term outcomes of donation are unclear and identification of baseline risk factors remains ill-defined.[6]

Some transplant centres do allow so-called 'marginal' donors, based on the presence of a reduced nuclear GFR (<80 mL/min per 1.73 m^2), hypertension or proteinuria before donation. In fact, the cohort of donors that Han *et al.* followed included some 'marginal' donors, with six being hypertensive at baseline and acceptance of donors with a GFR as low as 75 mL/min per 1.73 m^2 based on 24 h urine collection.

They are deemed 'marginal' because of a possible future increased risk of developing adverse outcomes like CKD (as assessed by Han *et al.*[4]), end-stage renal disease, hypertension, death or cardiovascular disease. Therefore, it would be useful to be able to answer the question – what are the risk factors that predict adverse sequelae after donation? From the answer to this question an assessment of who is a 'marginal' donor can be made, although determining the true effect of donation in such cases would also require the recruitment of non-donor controls who share the same predonation characteristic.

In a recent systematic review of the literature, nine papers were identified as reporting the postdonation GFR according to stages of CKD.[3] These studies demonstrated that at a mean time of 10 years post donation, 12% (range 0–28%) of donors developed a GFR between 30 and 59 mL/min per 1.73 m^2 and 0.2% (range 0–2.2%) a GFR less than 30 mL/min per 1.73 m^2. Han *et al.* found a higher prevalence rate than this (25%), but this was consistent with rates discovered by other investigators and also may reflect the underestimation of true GFR with the MDRD equation.[4,7,8]

The available literature, however, is scant, conflicting and performed retrospectively. One study that followed 68 out of their 74 donors, all over 9 years post nephrectomy, did also identify that older age and higher blood pressure at the time of donation were significantly associated with a greater reduction in kidney function.[9] However, in other studies there has been no consistent observed effect of age on the decrement in GFR after donation; in older donors the decrement in GFR tended to be smaller, larger, or no different than younger individuals.[3]

Other studies have identified that gender is important in predicting renal function with women having a lower GFR both pre and post donation,[10,11] but gender was not associated with decrement in GFR after donation.[11] All studies have been troubled by methodological issues and small sample sizes; therefore, potential true associations may have gone undetected.

In a meta-regression of previous studies, changes in GFR in healthy donors (i.e. no hypertension, no proteinuria and GFR > 80 mL/min per 1.73 m^2 at donation) at the study level were examined.[3] Older age was associated with a lower pre- and postdonation GFR (mostly measured by 24 h urine creatinine clearance), and accounted for about a quarter of the variability in results observed across the studies. However, the change in GFR after donation was not statistically associated with donor age at the time of donation. Similarly, there was no association with gender, predonation blood pressure, or time since donation. Results, however, of this meta-regression should be viewed as exploratory in nature as the analysis was performed at the study level rather than at the patient level.[12]

Some people in the transplant community are concerned that a better estimate of the true long-term outcomes following donation, and the risk factors associated with a poor outcome may create negative press and impact poorly on the living kidney donation programme. However, it can also be considered irresponsible for the international community to continue promoting living transplantation as the preferred treatment option for kidney failure, without concurrent efforts to also obtain better information on the long-term health implications. Early in the history of living donation, it was necessary and appropriate to obtain quick data to provide preliminary reassurance that donation posed no great harm. However, the methods used in the existing literature do not meet modern evidence-based standards for risk assessment.[13]

An increased understanding of the risks involved for an individual to donate their kidney will allow improved informed consent. It would lead to improved selection and follow-up processes, minimizing any risks due to donation. This will lead to an increase in the level of confidence for all members involved in the transplant, including the donor.

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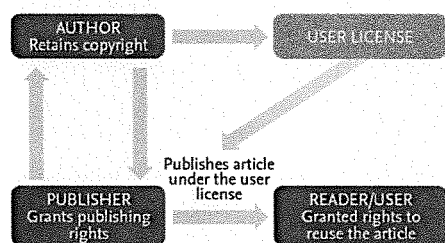
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issues in the neonate, which makes very clearly the argument that a decision to treat a neonate differently from an older child is unjustified.[8]

Finally, and most importantly, van Stralen *et al.* provide outcome data over the first 5 years of life.[4] However, the data have to be viewed in the context that we do not know their completeness. It is likely not only that the sickest children have been excluded, but also that others with equally poor renal function may not have been included because of purposeful delay in initiating dialysis. The importance of this is that the missing data will influence the survival and causes of death in the cohorts that have been treated. However, that said, the large numbers are likely to override these difficulties. The survival figures are impressive. Figure 1 illustrates the percentage survival up to 5 years of age of both the data of van Stralen *et al.*[4] and data on 193 neonates and 505 children aged 1–24 months starting chronic dialysis in the United States during a slightly earlier era (1992–2005).[2] Survival until 2 years of age seems very similar, but thereafter there is a suggestion that survival in the current study by van Stralen *et al.* may be superior to that of both the neonates and the under-2-year-olds in the United States. That 22% of the children have renal transplants is also encouraging. However, despite the suggestion that survival is improving, the incidences of growth retardation (63%), anemia (55%), and hypertension (76%) at 2 years are disappointing.[4] All three of these factors are well known to affect long-term outcome. All can be successfully managed with careful attention to detail. We owe this to these youngest children, who have the greatest potential life expectancy of all our patients.

DISCLOSURE
The author declared no competing interests.

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End-stage renal disease in living kidney donors

Neil Boudville[1] and Amit X. Garg[2,3]

The paper by Mjøen *et al.* raises important concerns about the long-term consequences of living donation, including a long-term increased risk of end-stage renal disease after an individual undergoes donor nephrectomy. These potential risks need to be communicated to future living kidney donors and should be an impetus for ongoing investigation.

More than 27,000 living kidney donations are performed worldwide each year.[1] In certain countries it is the only financially viable treatment option for most patients with kidney failure. The practice, however, is predicated on the assumption that the advantages to the recipient, society, and the donor (for instance, psychological benefit) outweigh any harms (or risk of harm) to the donor. The perioperative (<90 days) outcomes of donor nephrectomy are well documented, including a perioperative mortality rate of 0.03% and a complication rate of 5–15%.

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Adverse psychological outcomes in donors, including those related to poor recipient outcomes, are uncommon.[2]

The long-term medical risks following living kidney donation remain an area of study. Ibrahim *et al.*'s findings from Minnesota were reassuring: approximately 3700 donors had a similar survival and a lower estimated incidence of end-stage renal disease (ESRD) compared with non-donors selected from population surveys.[3] A Canadian study also demonstrated no increased mortality or major cardiovascular events in approximately 2000 living kidney donors compared with 20,000 matched non-donors, with no separation of the survival curves (follow-up was a median of 6.5 years, with a maximum of 17.7 years).[4]

Mjøen *et al.*[5] (this issue) now describe the long-term outcomes of 1901 living kidney donors in Norway. Such data are welcome, and Mjøen and colleagues should be congratulated for undertaking this study. A major

advantage of this study is the comprehensive nature of the data, with all kidney transplantations in Norway being performed within one center. In addition, few Norwegian nationals emigrate, ensuring a high rate of follow-up through national registries, though we presume the emigration rate is unlikely to have been zero (as the authors report). These characteristics enabled the authors to obtain a longer follow-up than most prior studies on living donors. The authors also accessed another Norwegian population-based sample to generate a matched non-donor comparison group.

This paper demonstrates that living donors have poorer survival compared with matched non-donor controls, with the difference apparent only after 10 years of follow-up (there were 224 deaths in the living donor group). The hazard ratio for all-cause mortality in living donors compared with controls was 1.3, in the fully adjusted model (95% confidence interval 1.1–1.5), and the hazard ratio for cardiovascular death was similar. More details about event rates to better understand absolute risks would have been useful to enhance our understanding of these results.

The paper also demonstrates an approximately 11-fold increase in the hazard ratio for ESRD in donors compared with matched non-donor controls (95% confidence interval 4.4–29.6), with 9 donors developing ESRD. All such donors were genetically related to the recipient, and the etiology of kidney failure appeared predominantly immunological.

The commencement of observation of the living donor cohort was different from that of the non-donor controls: 1963–2007 for the living donors and 1984–1987 for the non-donor controls. In the baseline table it would have been useful to see the year of cohort entry (in categories) to better appreciate this difference between donors and non-donor controls. The difference in year of cohort entry between the two groups has two implications: (1) Secular changes in individuals' health and their health care mean that the two groups are not fully comparable at baseline and

follow-up, and these between-group differences that impact outcome may not be fully accounted for in 'adjusted' analyses that consider inclusion year. (2) The longer duration of follow-up in donors (maximum follow-up 43.9 years) compared with non-donors (maximum follow-up 24.9 years) may also result in a higher incidence of ESRD in donors if the incidence is not constant over time and increases with the duration of follow-up. (For example, there is some relationship between the duration of follow-up and the risk of ESRD that requires clarification. The authors note a significant inverse association between inclusion year and ESRD risk; however, they also indicate that the proportional hazards assumption was not violated.)

There are other limitations to this study, including the lack of measurement of kidney function or proteinuria in the control group at baseline, and the lack of such measurements in both groups during follow-up. Adjustment may not fully account for differences between the two groups in baseline age, which was higher in donors than in non-donor controls. Acceptance of living kidney donors with an estimated glomerular filtration rate as low as 70 ml/min/1.73 m^2—compared with 80 ml/min/1.73 m^2, which is an accepted lower threshold for most units—may also lead to worse outcomes in the donor group than would be seen in other centers. Finally, with only 31 ESRD events, there may be some concerns about model overfitting, particularly with multiple adjusters.

This all being said, an increased incidence rate of ESRD in donors

compared with non-donor controls is now also corroborated in a recently presented abstract on almost 100,000 living kidney donors from the United States.[6] In that study, the incidence rate of ESRD was eightfold higher in donors (comparable to the 11-fold increase in the incidence rate in this Norwegian study). Thus, there are now at least two studies describing an approximately tenfold increase in the incidence of ESRD after donation, which is a serious concern.

The findings from these two studies are very important and should influence the information we provide to potential donors. In terms that patients may easily understand, we can state that if we follow 10,000 donors for 20 years (with the assumption all survive 20 years), 60 will develop ESRD (which approximates 302 in 1,000,000 person-years as in the Mjøen et al. study[5]). In many nations the average life expectancy is now 90 for women, and 85 for men. Thus, many donors may live 40, 60, or more years with one kidney. Rough lifetime estimates of ESRD (assuming a constant incidence over time, which may not be the case) would then be as noted in Figure 1.

These findings may impact our criteria for donor selection. We will likely want a higher level of pre-donation kidney function (estimated glomerular filtration rate >90 ml/min/1.73 m^2) for younger individuals who are expected to live 50 or more years with one kidney (recognizing we do not have ideal evidence to inform what is the optimal acceptance threshold). The importance of excellent health behaviors, both before and after donation,
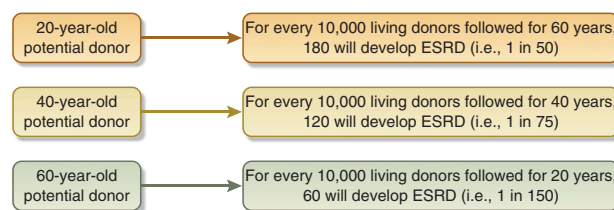
Figure 1 | Estimating the risk of developing end-stage renal disease (ESRD) for potential living kidney donors during their expected lifespan as part of the informed consent process. Uses an incidence rate of 300 per 1,000,000 person-years (which approximates the incidence rate noted by Mjøen et al.[5]). Assumptions: (1) Incidence is constant as someone ages and with duration after donation (which it may not be). (2) All donors live to the age of 80 (that is, with no censoring for death or other reasons prior to this time).

should continue to be emphasized. This should include an annual serum creatinine, urine protein, and blood pressure measurement in follow-up.

Despite this lack of consistent evidence on the long-term outcomes of living kidney donation, fueled by the increasing demands for organs, there has been a growing trend worldwide to accept donors with features that historically would have precluded donation.[7] If indeed living kidney donation does lead to some adverse outcomes, accepting donors with additional comorbidities (such as obesity, hypertension, and impaired glucose tolerance) may accentuate these poor outcomes. However, the practice of accepting donors with extended criteria may continue to be reasonable—but defensible only if there are ongoing detailed efforts to better understand the long-term outcomes, so practice can be corrected if donor harm over many decades is greater than initially anticipated.

Finally, we need better information on the incidence of a very low estimated glomerular filtration rate prior to ESRD in kidney donors. This is expected to be an order of magnitude higher than the incidence of a need for dialysis or a kidney transplant and may be an important source of patient morbidity. Rather than registries, such data would be best obtained through a long-term prospective cohort study with a comparable group of non-donor controls.

DISCLOSURE

The authors declared no competing interests.

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RESEARCH

Cardiovascular disease in kidney donors: matched cohort study

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Abstract

Objective To determine whether people who donate a kidney have an increased risk of cardiovascular disease.

Design Retrospective population based matched cohort study.

Participants All people who were carefully selected to become a living kidney donor in the province of Ontario, Canada, between 1992 and 2009. The information in donor charts was manually reviewed and linked to provincial healthcare databases. Matched non-donors were selected from the healthiest segment of the general population. A total of 2028 donors and 20 280 matched non-donors were followed for a median of 6.5 years (maximum 17.7 years). Median age was 43 at the time of donation (interquartile range 34-50) and 50 at the time of follow-up (42-58).

Main outcome measures The primary outcome was a composite of time to death or first major cardiovascular event. The secondary outcome was time to first major cardiovascular event censored for death.

Results The risk of the primary outcome of death and major cardiovascular events was lower in donors than in non-donors (2.8 *v* 4.1 events per 1000 person years; hazard ratio 0.66, 95% confidence interval 0.48 to 0.90). The risk of major cardiovascular events censored for death was no different in donors than in non-donors (1.7 *v* 2.0 events per 1000 person years; 0.85, 0.57 to 1.27). Results were similar in all sensitivity analyses. Older age and lower income were associated with a higher risk of death and major cardiovascular events in both donors and non-donors when each group was analysed separately.

Conclusions The risk of major cardiovascular events in donors is no higher in the first decade after kidney donation compared with a similarly healthy segment of the general population. While we will continue to follow people in this study, these interim results add to the evidence base supporting the safety of the practice among carefully selected donors.

Introduction

In the general population there is a robust association between reduced kidney function and an increased risk of cardiovascular disease.[1] It is possible that this risk could apply to the over 27 000 registered people who donate a kidney worldwide each

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year.[2] Donors lose half their renal mass, and, similar to reduced kidney function for other reasons, donor nephrectomy can increase blood pressure and metabolites such as uric acid.[3] [4] These physiological markers, however, might not be valid surrogates in donors for the clinically relevant outcomes that patients and their providers are most interested in. Cardiovascular disease is a key event of interest and is a leading cause of death. Five studies have considered the risk of all cause mortality after kidney donation (studies from the United States, Sweden, Norway, and Japan.[5-9]) Reassuringly, all five showed no evidence of increased long term mortality among kidney donors. One of these studies also found no higher risk of cardiovascular mortality.[8] In a preliminary study we also found no evidence of a higher risk of major cardiovascular events in 1278 people who donated a kidney.[10] Limitations of the analysis with respect to study size and characteristics of the matched non-donors, however, meant that uncertainties persisted with these findings.[11-13]

We conducted a study that dealt with many of the previous limitations. We manually reviewed the medical charts of over 2000 living kidney donors in the largest province in Canada, linked this information to universal healthcare databases to reliably identify major cardiovascular events long term with little loss to follow-up, and used methods of restriction and matching to select the healthiest segment of the general population with which donor outcomes could be compared. We also performed subgroup analyses according to the year of nephrectomy (duration of follow-up) to identify any trends in risk with a longer period of follow-up. We did this study because better knowledge of major cardiovascular events in people who become living kidney donors maintains public trust in the transplantation system, informs the choices of potential donors and recipients, and guides follow-up care to maintain good long term health.

Methods

Design and setting

We conducted a population based matched cohort study in Ontario, Canada. Ontario currently has about 13 million residents.[14] Residents have universal access to hospital care and physician services. The reporting of this study follows guidelines set out for observational studies.[15]

Data sources

We ascertained personal characteristics, covariate information, and outcome data from records in four databases. Trillium Gift of Life is Ontario's central organ and tissue donation agency. This database is unique in that it captured information on living kidney donors in the province at the time of donation. We manually reviewed the medical charts of all people who underwent donor nephrectomy at all five major transplant centres in Ontario between 1992 and 2009 to ensure the accuracy of donor information in the Trillium database. The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) records detailed diagnostic and procedural information for all admissions to hospital in Ontario. The Ontario Health Insurance Plan database (OHIP) contains all health claims for inpatient and outpatient physician services. The Ontario Registered Persons Database (RPDB) contains demographic and vital status information on all Ontario residents. These databases have been used extensively to research health outcomes and health services.[16-20] The databases were essentially complete for all variables used in this study.

Population

We included all living kidney donors who were permanent residents of Ontario. The date of the nephrectomy served as the start date for donor follow-up and was designated the index date. Choosing the best type of non-donors with which donors can be compared is central to any study of relative risks associated with donor nephrectomy.[21] Donors go through a detailed selection process and are inherently healthier than the general population. We used techniques of restriction and matching to select the healthiest segment of the general population. We randomly assigned an index date to the entire adult general population according to the distribution of index dates in donors. We then identified comorbidities and measures of access to healthcare from the beginning of available database records (1 July 1991) to the index date. This provided an average of 11 years of medical records for baseline assessment, with 99% of people having at least two years of baseline data for review. Among the general population we excluded any adult with any medical condition before the index date that could preclude donation. This included evidence of diagnostic, procedural, or visit codes for any of genitourinary disease, diabetes, hypertension, cancer, cardiovascular disease, pulmonary disease, liver disease, rheumatological conditions, chronic infections, a history of nephrology consultation, and evidence of frequent physician visits (more than four visits in the previous two years). We also excluded any person who failed to see a physician at least once in the two years before the index date (given that Ontario has a shortage of physicians we wanted to ensure that non-donors had evidence of access for routine healthcare needs including preventative health measures; we conducted a sensitivity analysis in which we removed this exclusion and the study results were not materially different). From a total of 9 643 344 adult Ontarians during the period of interest, our selection procedures resulted in the exclusion of 85% of adults (n=8 216 038). From the adults remaining we then matched 10 non-donors to each donor. We matched on age (within two years), sex, index date (within six months), rural (population less than 10 000) or urban residence, and income (categorised into fifths of average neighbourhood income on the index date).

Outcomes

All people were followed until 31 March 2010 or emigration from the province. The primary outcome was a composite of time to death or first major cardiovascular event (myocardial infarction, stroke, coronary angioplasty, coronary bypass surgery, carotid endarterectomy, repair of abdominal aortic aneurysm, or peripheral vascular bypass surgery). The secondary outcomes were time to first major cardiovascular event censored for death and components of the primary outcome analysed separately. These outcomes were defined by using codes proved to have good validity when compared with chart review (see appendix on bmj.com). We examined the characteristics associated with death and first major cardiovascular event separately in donors and non-donors. These characteristics were age (per five years), sex, rural or urban residence, income fifth, and year of index date (per year).

Statistical analysis

We assessed differences in baseline characteristics between donors and non-donors using standardised differences.[22] [23] This metric describes differences between group means relative to the pooled standard deviation; differences greater than 10% reflect the potential for meaningful imbalance. We used a two

sided log rank test stratified on matched sets to compare differences in death and cardiovascular outcomes between donors and non-donors. We used Cox regression stratified on matched sets to calculate the hazard ratios with 95% confidence intervals. The proportional hazards assumption was met (non-significant donor×follow-up time interaction term, P=0.27). We repeated the primary analysis in four prespecified subgroups defined by the median age at the index date (≤55 *v* >55), sex, first degree relative with kidney failure, and index date (1992-2001 (median follow-up 11.4 years, interquartile range 9.5-13.8) *v* 2002-9 (4.0 years, 2.4-4.8)). We defined subgroups by the characteristic in donors, with non-donors following their matched donor. We examined whether hazard ratios differed among subgroups using a series of pairwise standard z tests.[24] We examined the characteristics associated with a first major cardiovascular event separately in donors and non-donors using Cox regression. We conducted all analysis with SAS software version 9.2.

Results

Baseline characteristics

Table 1 shows the baseline characteristics for 2028 living kidney donors and 20 280 matched non-donors⇓. The median age was 43 (interquartile range 34-50), and 60% were women. As expected, donors had more physician visits in the year before the index date than non-donors because such visits are a necessary part of the evaluation process.

Most living kidney donors were siblings of the recipients (35%), followed by spouses (19%), parents (14%), and children (13%). Nearly half (43%) of the nephrectomies were performed laparoscopically, and the rest were done with an open procedure. Before donation, the median serum creatinine was 77 µmol/L (interquartile range 66-86 µmol/L) (equivalent to 0.87 mg/dL, 0.75-0.97 mg/dL) and the estimated glomerular filtration rate (eGFR) was 97 mL/min/1.73 m^2 (86-109) (with the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI).[25] The median length of follow-up was 6.5 years (6.8 years in donors, 6.4 years in non-donors, maximum 17.7 years). A total of 609 donors and 5744 non-donors were followed for a period of 10 years or more. The median age at the time of last follow-up for the entire cohort was 50 (42-58). Of the 22 308 individuals (2028 donors, 20 280 non-donors), 20 450 (91.7%) were alive at the end of study follow-up (31 March 2010) and had not experienced a major cardiovascular event, and 1206 (5.4%) were censored at a time of emigration from the province (48 (2.4%) donors, 1158 (5.7%) non-donors). The total person years of follow-up was 162 508 (15 176 donors, 147 332 non-donors).

Outcomes

Figure 1 and table 2 present the main outcomes⇓⇓. There were 381 deaths (16 donors, 365 non-donors) and 313 major cardiovascular events (26 donors, 287 non-donors). The risk of death or first major cardiovascular event was lower in donors than in non-donors (2.1% *v* 3.0%; 2.8 *v* 4.1 events per 1000 person years; hazard ratio 0.66, 95% confidence interval 0.48 to 0.90; log rank P=0.01). Table 2 shows the types of cardiovascular events⇓. There was no significant difference in the risk of major cardiovascular events censored for death between donors and non-donors (1.3% *v* 1.4%, 1.7 *v* 2.0 events per 1000 person years; hazard ratio 0.85, 0.57 to 1.27). Figure 2 shows the subgroup analyses⇓. An earlier index date (longer period of follow-up) did not influence the association between kidney donation and the primary outcome, nor did older age at

index date, sex, or history of a first degree biological relative with kidney failure (P value for interaction ranged from 0.10 to 0.48). Subgroup results were similar for the outcome of time to first major cardiovascular event censored for death. Older age and lower income were associated with a higher risk of death or first major cardiovascular event in both donors and non-donors when each group was examined separately (table 3)⇓.

Discussion

The risk of major cardiovascular events in people who donate a kidney is no higher in the first decade after transplantation than in matched non-donors. There is no trend of increased cardiovascular risk in subgroups of donors with a longer (compared with shorter) period of follow-up, nor do Kaplan Meier curves after 10 years of follow-up suggest any higher risk of death or major cardiovascular events in donors compared with non-donors.

We conducted this study to determine whether people who donate a kidney have a higher risk of cardiovascular disease than a similarly healthy segment of the general population. While we will continue to follow up people in this study, these interim results provide important safety reassurances to donors, their recipients, and transplant professionals. Reassuringly, with longer follow-up the observed risk for the primary outcome continued to be lower in donors than in non-donors. As stated by others, we attribute this lower risk to the rigorous selection process of establishing excellent health before donation, which includes psychological assessment and counselling, abdominal imaging, cancer screening, and an assessment for chronic infectious diseases.[7] Healthy lifestyle behaviours are also emphasised at this time. Restriction of non-donors to the healthiest segment of the general population, as done in this study, still did not replicate this process.

Strengths and limitations of study

Our analyses meaningfully assessed major cardiovascular events in previous kidney donors.[10] We were able to do this because of the universal healthcare benefits in the province of Ontario, with the collection of all healthcare encounters for all citizens. This reduces concerns about selection and information biases. As mentioned, for the present study we manually reviewed over 2000 consecutive medical charts to ensure the accuracy of donor information presented in this study. The large number of donors and non-donors provided good precision for the estimates we provide. Outcomes of death and major cardiovascular events were ascertained in a reliable and valid manner in our data sources. Loss to follow-up, a concern in many long term follow-up studies of donors, was minimal in our setting (less than 6% of people emigrated from the province during follow-up). Our data, however, are not without limitations. Cause of death could not be reliably assessed in our data sources. Our results describing major cardiovascular events, however, are consistent with a study from Norway that showed no higher risk of cardiovascular mortality in people who donated a kidney compared with the general population (median follow-up 14.3 years from nephrectomy).[8] Accurate racial information was not available. Given that 75% of Ontario residents are white, these results might generalise less well to non-white donors.[26] The acceptance criteria of living donors in our region during the period of review were quite stringent.[27] Thus, these data should not be generalised to the recent practice of accepting donors with health conditions such as obesity or hypertension.[28] Information on kidney function and family history of kidney

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disease were unavailable in non-donors, and measurements such as blood pressure and body mass index (BMI) before transplantation were unavailable in both donors and non-donors. This information might have allowed for better selection of non-donors. Collection of such information in the number of individuals needed to adequately examine cardiovascular events in our setting, however, would have been prohibitively expensive, with results unavailable for another decade. Finally, we did not have data on glomerular filtration rate in donors during follow-up, which precluded an assessment of cardiovascular risk according to this feature.

Comparison with other studies

A collaborative meta-analysis of multiple general population non-donor cohorts has recently summarised the association between reduced kidney function and cardiovascular disease.[1] Over a median follow-up of eight years, the risk of cardiovascular mortality increases with a lower estimated glomerular filtration rate. Compared with an estimated glomerular filtration rate of 90-104 mL/min/1.73 m², hazard ratios for cardiovascular mortality are 1.03 (95% confidence interval 0.85 to 1.24) for an estimated rate of 75-89 mL/min/1.73 m², 1.09 (0.92 to 1.29) for an estimated rate of 60-74 mL/min/1.73 m², 1.52 (1.18 to 1.97) for an estimated rate of 45-59 mL/min/1.73 m², and 2.04 (1.80 to 3.21) for an estimated rate of 30-44 mL/min/1.73 m². Similar associations with narrower confidence intervals are seen for all cause mortality. Concurrent evidence of albuminuria increases these risks. In the donor setting, about 10% of individuals show 300 mg or more of proteinuria a day in the decade after donation. Donors are more likely to develop microalbuminuria than the general population. In addition, in the decade after donation 40% of people who donate a kidney have a glomerular filtration rate of 60-80 mL/min/1.73 m² and 10% have a of 30-59 mL/min/1.73 m².[29 30]

So how does one reconcile the lack of observed risk of cardiovascular disease among living donors in the current study with the observed risk among individuals with reduced glomerular filtration rate in general population cohorts? Firstly, the association seen in the general population might not be causal. It might, for example, reflect systemic atherosclerosis related to diabetes, hypertension, and older age, which coexist with reduced glomerular filtration rate but which are not fully accounted for in multivariable models. On the other hand, donors develop reduced glomerular filtration rate and low grade proteinuria through a non-pathological process, which might not carry the same prognostic relevance. Secondly, the process of donor evaluation is used to select individuals who are in excellent health with good long term prognosis. In our setting, follow-up healthcare is a universal benefit to all Canadians, and we have previously confirmed that donors tend to have more have routine primary healthcare visits in follow-up than non-donors.[10] These elements of healthcare, which can include early detection and management of cardiovascular risk factors, could offset any increase in risk of cardiovascular disease attributable to reduced glomerular filtration rate. If unmeasured baseline cardiovascular risk factors were more prevalent in non-donors than donors in our study, however, this could have masked evidence of an increased risk of cardiovascular disease in donors. For these reasons it remains prudent to counsel all donors on modifiable risk factors that prevent future cardiovascular disease both before and after the donation process. In our study the non-modifiable factor of older age and the difficult to modify factor of low income were similarly associated with death and cardiovascular events in donors and

non-donors. Finally, it is possible that an association between living donation and risk of cardiovascular disease does exist but takes much longer to manifest. It might depend on more donors entering an older age range and manifesting a glomerular filtration rate less than 60 mL/min/1.73 m² in the decades after donation. For this reason, ongoing follow-up of this and other donor cohorts is warranted.

Conclusion

Taken together with other studies that have shown no increase in mortality in the decades after kidney donation, the present study adds to the available evidence base supporting the safety of the practice among carefully selected donors.[27] The results do not provide evidence to justify relaxing the rigorous criteria used to select people who become kidney donors.

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What is already known on this topic

Each year over 27 000 people around the world become a kidney donor, and the number is increasing in response to a shortage of kidneys for transplantation from deceased donors

In the general population there is a robust association between reduced kidney function and an increased risk of cardiovascular disease

Similar to reduced kidney function for other reasons, donor nephrectomy could increase blood pressure, which is a potent risk factor for cardiovascular disease

What this study adds

The risk of major cardiovascular events was no higher in the first decade after people had donated a kidney than in a similarly healthy segment of the general population

The results add to the evidence base supporting the safety of the practice among carefully selected donors

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Tables

Table 1| Characteristics of kidney donors and non-donors at time of transplantation*. Figures are numbers (percentage) unless stated otherwise

	Donors (n=2028)	Non-donors (n=20 280)
Median (IQR) age (years)	43 (34-50)	43 (34-50)
Women	1216 (60)	12 160 (60)
Income fifth:		
Lowest	301 (15)	3010 (15)
Middle	430 (21)	4300 (21)
Highest	470 (23)	4700 (23)
Rural town	278 (14)	2780 (14)
Median (IQR) No of visits to physician in previous year†	11 (8-15)	1 (0-2)
Year:		
1992-5	217 (11)	2170 (11)
1996-2000	531 (26)	5315 (26)
2001-5	683 (34)	6833 (34)
2006-9	597 (29)	5962 (29)

IQR=interquartile range.

*Also referred to as index date, randomly assigned to non-donors to establish start of time follow-up.

†Indicates standardised difference between donors and non-donors >10%. Standardised differences are less sensitive to sample size than traditional hypothesis tests. They provide measure of difference between groups divided by pooled SD; value >10% is interpreted as meaningful difference between groups. As expected, donors had more physician visits in year before index date than non-donors, as such visits are necessary for donor evaluation process.

Table 2| **Death or major cardiovascular events among kidney donors and non-donors**

	Donors (n=2028)	Non-donors (n=20 280)
Median (IQR) follow-up (years)	6.8 (3.7 to 10.9)	6.4 (3.5 to 10.6)
Range follow-up (years)	0.5-17.7	0.1-17.7
Total follow-up (person years)	15 176	147 332
No (%) of events	42 (2.1)	610 (3.0)
No of events per 1000 person years*	2.8	4.1
Model based risk ratios (95% CI)	0.66 (0.48 to 0.90)	1.0 (reference)
No (%) of types of events†:		
Death	16 (0.8)	365 (1.8)
Acute myocardial infarction	14 (0.7)	141 (0.7)
Coronary artery angioplasty or surgery	15 (0.7)	179 (0.9)
Stroke	5 (0.2)	51 (0.2)

IQR=interquartile range.

*P=0.01, stratified log rank test.

†Events of carotid endarterectomy, abdominal aortic aneurysm repair, and peripheral vascular bypass surgery were rare (≤25 events for all three outcomes combined for donors and non-donors combined) and are not reported here for reasons of privacy. Events reported here are not mutually exclusive; individual might have had more than one event in follow-up. In survival models we considered time to first event.

Table 3| Risk factors for death or major cardiovascular events in kidney donors and non-donors* when each group was analysed separately. Figures are rate ratios (95% CI)

	Donors	Non-donors
Death or major cardiovascular event		
Older age (per 5 years)†	1.44 (1.25 to 1.66)	1.61 (1.55 to 1.68)
Women (*v* men)	0.73 (0.40 to 1.33)	0.43 (0.37 to 0.51)
Rural residence (*v* urban residence)	0.58 (0.21 to 1.62)	1.06 (0.86 to 1.32)
Higher income fifth (per fifth)	0.77 (0.61 to 0.96)	0.85 (0.80 to 0.90)
More recent year of index (per year)	0.97 (0.88 to 1.08)	0.99 (0.96 to 1.01)
Major cardiovascular event (death censored)		
Older age (per 5 years)†	1.47 (1.23 to 1.75)	1.60 (1.51 to 1.69)
Women (*v* men)	0.57 (0.26 to 1.23)	0.27 (0.21 to 0.35)
Rural (*v* urban) residence	0.70 (0.21 to 2.34)	1.23 (0.91 to 1.65)
Higher income fifth (per fifth)	0.83 (0.63 to 1.10)	0.86 (0.79 to 0.93)
More recent year of index (per year)	0.92 (0.81 to 1.04)	0.98 (0.94 to 1.01)

*Separate multivariable Cox regression models created for kidney donors and non-donors.

†Refers to individual's age at beginning of follow-up (also referred to as index date or cohort entry date).

Figures
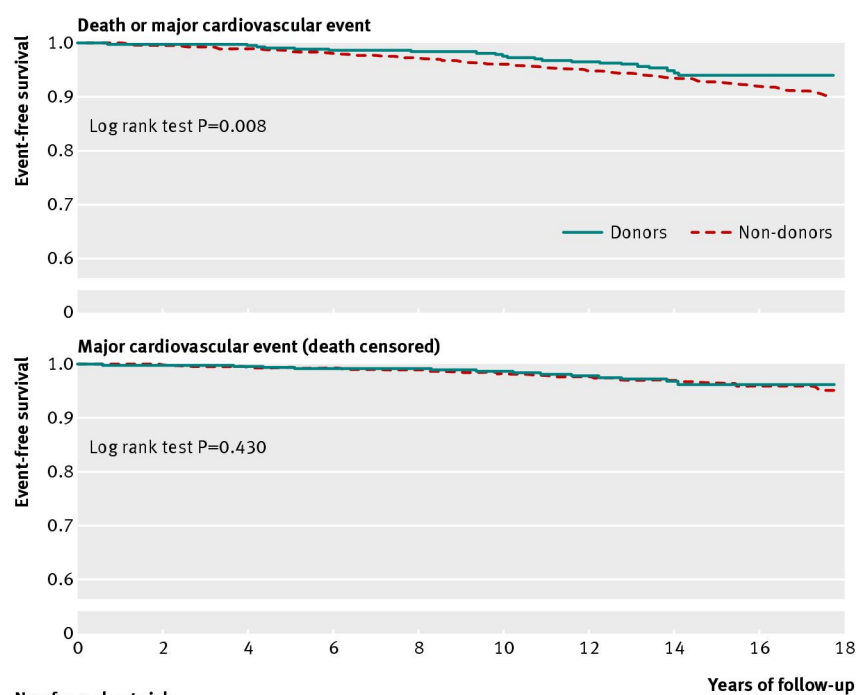
Fig 1 Kaplan-Meier estimates of survival probability without death or major cardiovascular event (top) and without major cardiovascular event (censored for death, bottom)

Study	No of events/ No at risk		Event rate/ 10 000 person years		Hazard ratio (95% CI)	Hazard ratio (95% CI)	Interaction test P value
	Donor	Control	Donor	Control			
Death or major cardiovascular event							
Overall	42/2028	610/20 280	2.8	4.1		0.7 (0.5 to 0.9)	
Age (years)							
<55	29/1741	372/17 410	2.2	2.9		0.8 (0.5 to 1.1)	0.3
≥55	13/287	238/2870	7.2	13.7		0.5 (0.3 to 0.9)	
Sex							
Men	20/812	367/8120	3.3	6.2		0.5 (0.3 to 0.8)	0.1
Women	22/1216	243/12 160	2.4	2.8		0.9 (0.6 to 1.4)	
Index date							
1992-2001	34/874	448/8740	3.3	4.5		0.7 (0.5 to 1.0)	0.3
2002-9	8/1154	162/11 540	1.6	3.4		0.5 (0.2 to 1.0)	
Relative with kidney disease							
Yes	29/1261	391/12 610	2.8	3.9		0.7 (0.5 to 1.0)	0.48
No	13/767	219/7670	2.7	4.7		0.6 (0.3 to 1.0)	
Major cardiovascular event (death censored)							
Overall	26/2028	287/20 280	1.2	1.4		0.9 (0.6 to 1.4)	
Age (years)							
<55	18/1741	181/17 410	1.4	1.4		0.9 (0.6 to 1.5)	0.48
≥55	8/287	106/2870	4.4	6.1		0.7 (0.3 to 1.4)	
Sex							
Men	14/812	203/8120	2.3	3.4		0.6 (0.4 to 1.1)	0.08
Women	12/1216	84/12 160	1.3	1.0		1.3 (0.7 to 2.4)	
Index date							
1992-2001	22/874	216/8740	2.1	2.2		1.0 (0.6 to 1.5)	0.31
2002-9	4/1154	71/11 540	0.8	1.5		0.5 (0.2 to 1.5)	
Relative with kidney disease							
Yes	17/1261	191/12 610	1.6	1.9		0.8 (0.5 to 1.4)	0.87
No	9/767	96/7670	1.9	2.0		0.9 (0.4 to 1.8)	

Hazard ratio axis: 0   0.5   1   1.5

Risk lower in donors — Risk higher in donors

Fig 2 Influence of age, sex, index date (duration of follow-up), and relative with kidney failure on risk of death or first major cardiovascular event (top) and first major cardiovascular event (censored for death, bottom). Individuals with index date of 1992-2001 had median follow-up 11.4 years (interquartile range 9.5-13.8); individuals with index date of 2002-9 had median follow-up 4.0 years (2.4 to 5.8)

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Etiology

Live kidney donation was associated with increased mortality and end-stage renal disease at 15 years

Mjoen G, Hallan S, Hartmann A, et al. **Long-term risks for kidney donors.** *Kidney Int. 2013 Nov 27. [Epub ahead of print]*

Clinical impact ratings: GM ★★★★☆☆ Np ★★★★★★★

Question

Do live kidney donors have an increased long-term risk for mortality or end-stage renal disease (ESRD) compared with nondonors who would have met eligibility for donation?

Methods

Design: Comparison of a retrospective cohort of living kidney donors (Oslo University Hospital, Oslo, Norway, 1963 to 2007), with a median follow-up of 15 years (95% CI 1.5 to 44), and a matched control cohort of healthy nondonors identified from a population-based survey (1984 to 1987), with a median follow-up of 25 years (CI 0.1 to 26).

Setting: Norway.

Patients: 1901 living kidney donors, 20 to 70 years of age (mean age 46 y, 59% women, 100% white, 1519 first-degree relatives of transplant recipients, 89 other relatives, 293 unrelated). Exclusion criteria were antihypertensive medication, blood pressure (BP) > 140/90 mm Hg, body mass index (BMI) > 30 kg/m², macroalbuminuria, or estimated glomerular filtration rate < 70 mL/min/1.73 m². The control cohort comprised 32 621 matched, healthy nondonors ≥ 20 years of age (mean age 38 y, 53% women) with self-reported "good" or "excellent" health, BP ≤ 140/90 mm Hg, and BMI ≤ 30 kg/m². Exclusion criteria were diabetes, cardiovascular (CV) disease, use of antihypertensive medication, or reduced general health.

Risk factors: Live kidney donation.

Outcomes: All-cause mortality, CV mortality (excluding sudden death), and ESRD receiving long-term dialysis or kidney transplantation.

Main results

Live kidney donation was associated with increased risk for all-cause mortality, CV mortality, and ESRD (Table).

Conclusion

Live kidney donation was associated with increased risk for mortality and end-stage renal disease at a median 15 years after donation.

Commentary

Kidney failure is a terrible disease. Compared with dialysis, kidney transplantation improves the length and quality of the recipient's life. An inadequate supply of kidneys from deceased donors means that 27 000 living kidney donor transplantations are performed worldwide each year (1). The donor, the recipient, and the transplantation team must all believe that the overall benefits of transplantation outweigh any long-term risks to the donor. 4 previous studies of ≥ 1000 donors compared with nondonor controls were reassuring and reported no increased risk for long-term mortality, ESRD, or major adverse CV events after donation (2, 3).

The Norwegian study by Mjoen and colleagues adds to the 2 recent American studies, which report a relative 10-fold increase in risk for ESRD in living kidney donors compared with nondonor controls (4, 5). The Norwegian study also found increased risks for all-cause and CV mortality. All 3 studies have limitations; for the Norwegian study, these include differences in the years of accrual between donors and nondonors and differences in baseline age, possibly not offset by statistical adjustment. Nonetheless, consistent results across the 3 studies now leave it indefensible not to disclose the risk for ESRD as part of the informed consent process and emphasize the importance of surveillance and lifestyle choices to keep kidney donors in good health.

For risk communication, more work is needed to accurately describe the "lifetime" absolute incidence of ESRD in an easily understood way. Given the recent estimates by Mjoen and others, this may approach 1 in 150 (vs the expected 1 in 1500) in a 60-year-old donor and may be as high as 1 in 50 (vs the expected 1 in 500) in a 20-year-old donor (assuming a rate of 330/1 000 000 person-y; that the risk is linear as someone ages [which it may not be]; and that all donors live to the age of 80 y). This new information (and its remaining uncertainty) does not reduce our support for living kidney donation, but it does highlight the real risks faced by donors, including the uncommon tragic outcome of a living kidney donor who later develops kidney failure.

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Association between live kidney donation and mortality or end-stage renal disease*			
Outcomes	**Event rates (*n*)**		**Adjusted HR (95% CI)†**
	Live kidney donors (*n* = 1901)	**Healthy nondonors (*n* = 32 621)**	
All-cause mortality	12% (224)	7.4% (2425)	1.30 (1.11 to 1.52)
Cardiovascular mortality	3.6% (68)	2.1% (688)	1.40 (1.03 to 1.91)
End-stage renal disease	0.47% (9)	0.06% (22)	11.38 (4.37 to 29.63)

*HR = hazard ratio; other abbreviations defined in Glossary. Median follow-up was 15 y for kidney donors and 25 y for healthy nondonors.

†Adjusted for age, sex, year of inclusion, and after multiple imputation and further adjustments for missing data for systolic blood pressure, smoking, and body mass index.

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Do Biochemical Measures Change in Living Kidney Donors?

A Systematic Review

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Abstract

Background: Living kidney donation provides a unique opportunity to assess possible biochemical changes attributable to small decrements in glomerular filtration rate. We reviewed studies which followed 5 or more healthy donors, where changes in biochemical measures or anemia were assessed at least 4 months after nephrectomy. **Methods:** We searched MEDLINE, EMBASE, and Science Citation databases, and reviewed reference lists from 1966 through June 2006. We abstracted data on study and donor characteristics and biochemical outcomes of interest. **Results:** Eight studies examined at least one outcome of interest. The average time after donation ranged from 0.4 to 11 years, the postdonation creatinine clearance ranged from 73 to 99 ml/min, and the decrement after donation ranged from 11 to 38 ml/min. Nephrectomy did not change hemoglobin, erythropoietin, serum phosphate, calcium or C-reactive protein levels. The studies were inconsistent as to whether parathyroid hormone levels increased and 1,25-dihydroxyvitamin D levels decreased after nephrectomy. Uric acid levels increased variably post-donation. Plasma homocysteine increased in the single study included in this review. **Conclusions:** The mechanistic changes described above and their prognostic significance need clarification. Based on existing evidence, it is not necessary to routinely monitor living kidney donors for changes in these biochemical measures.

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Introduction

The kidneys play an important role in mineral metabolism, erythropoiesis and other types of biochemical regulation. In several studies, patients with relatively modest reductions in kidney function (glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2) demonstrated increases in serum phosphate and decreases in serum calcium [1] and vitamin D levels [2], contributing to the pathogenesis of hyperparathyroidism [3, 4]. At this same decrement in renal function, patients also produced inadequate amounts of erythropoietin, resulting in reduced hemoglobin and anemia [5]. Left untreated, anemia may negatively affect cardiac health, cognitive function, exercise capacity, and quality of life among patients [6]. There is also a strong association between reductions in GFR and elevated plasma homocysteine [7], uric acid [8] and C-reactive protein (CRP) [9] concentrations. Homocysteine, uric acid and CRP have all been studied as novel risk factors for cardiovascular morbidity and mortality.

It is a key consideration that metabolic changes associated with reduced GFR are generally described in patients with chronic kidney disease. Such patients tend to be older, with co-morbid conditions such as diabetes and pre-existing cardiovascular disease, compared to individuals with a normal GFR. Thus, when patients with low GFR demonstrate biochemical changes compared to healthier individuals, the true biochemical changes attributable to reductions in GFR are unclear. Even when associations are identified in multivariable analysis, there is still the concern that the observed association may by 'residually confounded' by the other conditions which coexist with low GFR. One way to mitigate this potential source of bias would be to study a healthy group of individuals who have isolated reductions in GFR. Living kidney donation provides such a unique model. The GFR of donors is reduced an average of 26 ml/min/1.73 m^2 (range 8–50) after donation [10]. Observing biochemical changes after living kidney donation could also have implications for the informed consent process and care of donors.

The purpose of this review was to systematically assemble all current literature reporting key biochemical and hematological outcomes in living kidney donors, including: (1) mineral metabolism; (2) anemia parameters; (3) uric acid metabolism; (4) homocysteine regulation, and (5) C-reactive protein levels.

Methods

The MOOSE consensus statement guided the conduct and reporting of this systematic review [11]. In brief, case series or cohort studies published in English were relevant if they: (1) described a study population of 5 or more healthy living kidney donors; (2) followed donors for at least 4 months after nephrectomy, and (3) reported on at least one metabolic outcome of interest. Many studies assessed a metabolic outcome of interest exclusively in the early postoperative period [12–15]. We excluded such studies from review, as their interpretation was complicated by acute blood losses and stress attributable to the surgical process. Rather we considered studies which followed donors for a longer period of time, to provide adequate time to equilibrate to new values [16, 17].

We compiled citations from MEDLINE (1966 – June 2006) and EMBASE (1980 – June 2006) bibliographic databases. The search strategy consisted of the terms living donor or nephrectomy in conjunction with metabolic, mineral metabolism, homocysteine, C reactive protein, inflammation, uric acid, erythropoiesis or anemia. The search strategy was pilot tested to ensure that articles of known relevance were identified. In the context of conducting other reviews, any reference to a metabolic condition of interest was also abstracted [10, 18]. We also compiled citations from the Science Citation Index, PubMed's 'see related articles' feature and reference lists for all studies included in this review. All citations were downloaded into Reference Manager, version 11.0 (Thomson ISI Research-Soft, Philadelphia, Pa., USA).

Two authors from our reviewing team (A.Y. and I.N.) independently evaluated each citation. Full text articles were retrieved for further consideration if either reviewer considered the citation to be of potential relevance. Disagreements on the eligibility of an article were resolved by consensus. When data from the same group of donors were described in multiple publications, we reviewed all of them and cited the most representative publication [19].

One reviewer from our team (A.Y.) abstracted the following data from all relevant articles: study design, baseline donor characteristics (age, gender) and pre- and postuninephrectomy outcomes including: (1) serum phosphate, tubular reabsorption of phosphate, serum calcium, urine calcium, parathyroid hormone (PTH) and 1,25(OH)$_2$ vitamin D$_3$ to assess mineral metabolism; (2) hemoglobin, hematocrit and erythropoietin to assess for possible anemia; (3) uric acid; (4) homocysteine, and (5) C-reactive protein. A second reviewer (I.N.) independently confirmed the accuracy of all abstracted data. All numeric data were converted to similar SI units for ease of comparison.

Reviewer agreement on study eligibility was quantified using the kappa statistic. Variance estimates for pre-/postdonation changes in creatinine clearance were not reported in many of the studies. If not reported, variance estimates were calculated with:

$$SE_\Delta = \sqrt{SE_{pre}^2 + SE_{post}^2 - \left(2 \times \rho_\Delta \times SE_{pre} \times SE_{post}\right)},$$

where ρ_Δ represents the correlation between the pre- and postdonation creatinine clearance [20]. Based on two other studies that reported predonation, postdonation and change variance estimates [19, 21], we calculated an average correlation coefficient of 0.59. To be conservative, we used a correlation of 0.5 to impute missing change variance estimates.

Table 1. Characteristics of long-term metabolic studies of living kidney donors

Source	Donors n	Proportion lost to follow-up, %	Women %	Patient age, mean (range), years[a]	Years of donation	Prospective study	Pre-/post study	Controls or external references
Friedlander et al., 1988	17	19	53	36 (19–61)	n.r.	yes	yes	no
Gonzalez et al., 1989	25	n.r.	68	36 (20–58)	1976–1987	no	yes	no
Gossmann et al., 2005	135	7	71	45 (n.r.)	1973–2001	no	no	yes
Hida et al., 1982	34	n.r.	59	55 (24–66)	1976–1981	yes	yes	no
Mimran et al., 1993	18	n.r.	56	47 (20–62)	n.r.	yes	yes	no
Romero et al., 2000	8	20	25	n.r. (19–52)	n.r.	yes	yes	no
Tsai et al., 2004	10	n.r.	60	44 (23–58)	n.r.	yes	yes	no
Undurraga et al., 1998	74	n.r.	73	39 (n.r.)	n.r.	no	yes	yes

n.r. = Not reported.
[a] Age is reported at the time of donation.

Results

A total of 568 citations were screened from which 54 fulltext articles were retrieved for more detailed evaluation. Studies that did not meet the eligibility criteria were excluded (fig. 1). The chance-corrected agreement between two independent reviewers who evaluated study eligibility was excellent (kappa = 0.89).

Eight studies, published from 1982 to 2005, described a biochemical outcome of interest in donors at least 4 months after uninephrectomy [19, 22–29] (table 1). All identified studies either compared donors before and after donation, or compared donors with select controls. The follow-up time ranged from 5 months to 28 years after donation (the average for all studies was 2.7 years). The number of donors in the studies ranged from 8 to 135 (median = 18). A total of 321 patients were included across the eight studies. Changes in creatinine clearance after uninephrectomy are outlined in table 2.

Mineral Metabolism

Four studies described the effects of uninephrectomy on mineral metabolism [19, 22–24] (table 3). Of these studies, three compared donors before and after uninephrectomy [19, 22, 24].

There was no increase in serum phosphate after donation [19, 22–24]. Friedlander [19] noted a significant decrease in serum phosphate one year after donation (–0.10 ± 0.05 mmol/l, p < 0.05), but the decrease was no longer evident at 3 years. Two studies described reduced renal tubular reabsorption of phosphate after uninephrectomy compared to pre-donation values. Friedlander et al. [19]
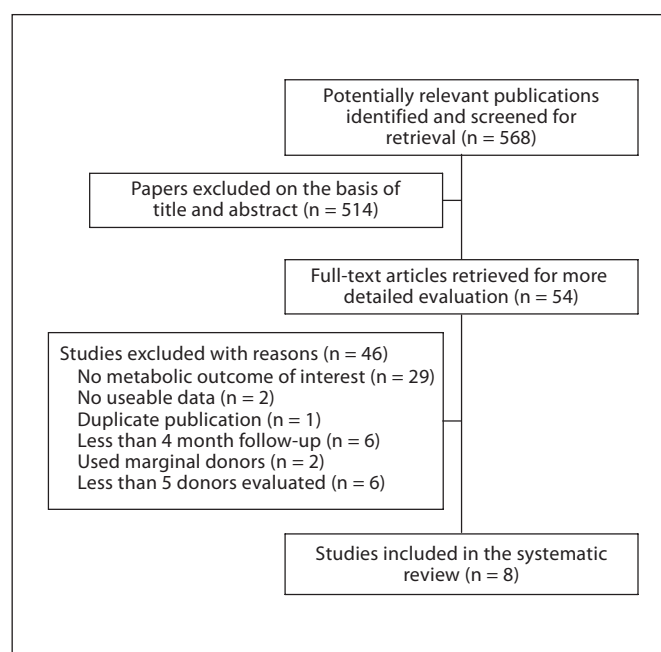
Fig. 1. Flow diagram of inclusion and exclusion of studies.

noted a significant difference at one and three years after donation, while Gossmann et al. [23] reported that 30% of donors had a reduced renal tubular reabsorption of phosphate.

There were no significant changes in serum calcium levels after donation [19, 22, 23]. A significant decrease in total urinary excretion of calcium was noted 1 year

Table 2. Creatinine clearance in uninephrectomized donors*

Source	Mean follow-up, years (range)	Predonation mean ± SD[a]	Postdonation mean ± SD[a]	Change[a]	p	Method of assessment
Romero et al., 2000	0.4	n.r.	n.r.	n.r.	n.r.	n.r.
Tsai et al., 2004	0.5	n.r.	n.r.	n.r.	n.r.	n.r.
Friedlander et al., 1988	1.0	122 ± 24	n.r.	−36 ± 21	<0.01	n.r.
Mimran et al., 1993	1.2 (n.r.)	126 ± 36	73 ± 17	−38 ± 11[c]	0.001	24-hour urine
Gonzalez et al., 1989	4.2 (0.5–11.8)	n.r.	n.r.	n.r.	n.r.	n.r.
Hida et al., 1982	n.r. (0.5–5.0)	91 ± 17[b]	75 ± 20[b]	−17 ± 19[b, c]	n.r.	n.r.
Undurraga et al., 1998	10.9 (1–21)	97 ± 27[b]	86 ± 22[b]	−11 ± 25[b, c]	0.08	estimated by Cockcroft-Gault
Gossmann et al., 2005	11 (1–28)	119 ± 30	99 ± 30	−20 ± 30[a]	<0.001	24-hour urine

* Studies arranged by mean follow-up time. n.r. = Not reported.
[a] Reported in ml/min/1.73 m^2 unless otherwise indicated; [b] reported in ml/min; [c] variance estimates were imputed using the formula as described in the 'Statistical Analysis' section.

Table 3. Impact of donor uninephrectomy on mineral metabolism

Source	Mean follow-up, years (range)	Predonation, mean ± SD	Postdonation, mean ± SD	Change	p	Method of assay
Serum phosphate, mmol/l						
Friedlander et al., 1988	1.0	1.10 ± 0.22	1.09 ± n.r.	−0.1 ± 0.2	<0.05	multichannel autoanalyzer (N.Y., USA)
Gonzalez et al., 1989	4.2 (0.5–11.8)	1.2 ± 0.15	1.15 ± 0.15	−0.05 ± n.r.	n.s.	n.r.
Gossmann et al., 2005	11 (1–28)	n.r.	0.9 ± 0.19	n.r.	n.r.	n.r.
Hida et al., 1982	n.r. (0.5–5.0)	1.04 ± 0.19	0.97 ± 0.19	0.07 ± n.r.	n.s.	n.r.
Tubular reabsorption of phosphate, %						
Friedlander et al., 1988	1.0	83.8 ± 1.5	75.5 ± n.r.	−8.3 ± 2.0	<0.01	n.r.
Gossmann et al., 2005	11 (1–28)	n.r.	77 ± 8	n.r.	n.r.	calculated
Serum calcium, mmol/l						
Friedlander et al., 1988	1.0	2.36 ± 0.485	2.36 ± n.r.	−0.003 ± 0.145	n.s.	atomic absorption (Conn., USA)
Gonzalez et al., 1989	4.2 (0.5–11.8)	2.39 ± 0.10	2.47 ± 0.11	0.08 ± n.r.	n.s.	n.r.
Gossmann et al., 2005	11 (1–28)	n.r.	2.4 ± 0.09	n.r.	n.r.	n.r.
Hida et al., 1982	n.r. (0.5–5.0)	2.34 ± 0.28	2.39 ± 0.13	0.05 ± n.r.	n.s.	n.r.
Total urine calcium, mmol/day						
Friedlander et al., 1988	1.0	4.775 ± 2.875	3.375 ± n.r.	−1.4 ± 1.75	<0.01	n.r.
Gossmann et al., 2005	11 (1–28)	n.r.	4.2 ± 2.4	n.r.	n.r.	n.r.
PTH						
Friedlander et al., 1988	1.0	56.4 ± 8.7 pmol/l	72.9 ± n.r. pmol/l	16.5 ± 17.7 pmol/l	<0.01	c-terminal radioimmunoassay (Minn., USA) n-terminal
Gonzalez et al., 1989	4.2 (0.5–11.8)	n.r.	17.54 ± 5.5 ng/ml	n.r.	n.s.	
Gossmann et al., 2005	11 (1–28)	n.r.	77 ± 52% of the upper limit of the normal range	n.r.	n.r.	iPTH
1,25-Dihydroxyvitamin D, pmol/l						
Friedlander et al., 1988	1.0	63.6 ± 19.6	78.72 ± n.r.	15.12 ± 24.72	n.s.	Chromatography (Ill., USA)
Gossmann et al., 2005	11 (1–28)	n.r.	77.5 ± 30	n.r.	n.r.	n.r.

n.r. = Not reported; n.s. = not significant. Conversion factors: serum phosphate × 0.323 (mg/dl → mmol/l); serum calcium × 0.25 (mg/dl → mmol/l); total urine calcium × 0.025 (mg/24 h → mmol/day); 1,25-dihydroxyvitamin D × 2.6 (pg/ml → pmol/l).

after donation, which was no longer evident at 3 years [19].

Three studies were inconsistent as to whether parathyroid hormone (PTH) increases after nephrectomy [19, 22, 23]. Friedlander et al. [19] found significant increases in PTH (+37%) and Gossmann et al. [23] observed that 19% of the donors studied had PTH levels exceeding the upper limit of normal. Gonzalez et al. [22] reported no significant change in PTH levels after donation.

Two of the four studies reported on 1,25-dihydroxyvitamin D $(1,25(OH)_2D)$ levels in donors [19, 23]. Friedlander et al. [19] described no significant changes in $1,25(OH)_2D$, while Gossmann et al. [23] reported that 12% of donors had decreased levels of $1,25(OH)_2D$ after donation.

Overall, Friedlander et al. [19] noted that, while changes in mineral metabolism seen in their donor cohort 1 week after surgery were consistent with mild renal insufficiency, by several months after uninephrectomy the changes were actually suggestive of mild 'normocalcemic' hyperparathyroidism. Other studies in this review did not have adequate data to fully support or refute this claim [22–24].

Anemia

Four studies compared donors before and after uninephrectomy on changes in anemia [22, 24–26] (table 4). Follow-up time for these studies ranged from 5 months to almost 12 years after donation. There was no significant change in hemoglobin or hematocrit after donation [22, 24–26]. Erythropoietin (EPO) levels were measured in one study. There was no decrease in EPO. Rather, a significant increase over predonation values was observed in the first 3 months after donation. Beyond the fourth month these differences were no longer evident [26].

Uric Acid Metabolism

Three studies compared donors before and after uninephrectomy on changes in uric acid metabolism [24, 26, 29]. One study provided control group data [29]. Hida et al. [24] observed a 24% increase in uric acid levels after donation, however, these levels still remained within the normal range. Romero et al. [26] did not report pre- and postnephrectomy values, but did note that uric acid levels were within the normal range both before, and up to 5 months after surgery. Similarly, Undurraga et al. [29] did not provide pre- and postdonation values, but did note that 30% of the donors developed hyperuricemia (defined in the study as uric acid >446 μmol/l).

Other Metabolic Effects

A single study examined changes in homocysteine and C-reactive protein (CRP) 6 months after donation. A significant increase in total homocysteine (tHcy) levels was observed immediately after surgery (+47%) and 6 months after surgery (+2.1 ± 0.9, p < 0.05). The absolute level was below what is classified as moderate hyperhomocysteinemia (tHcy >12 μmol/l). A significant increase in high-sensitivity C-reactive protein 2 days postuninephrectomy was no longer evident beyond 6 weeks [28].

Discussion

To our knowledge, this is the first systematic review to summarize existing knowledge on changes in biochemical measures and anemia after living kidney donation. Small decrements in GFR after nephrectomy do not appear to change hemoglobin or erythropoietin levels, nor do they change serum phosphate, calcium or C-reactive protein levels. 1,25-dihydroxyvitamin D levels may decrease after nephrectomy which may explain the documented increase in parathyroid hormone levels, although these changes were not consistent across studies. Homocysteine increased in the single study in which it was examined. Uric acid levels increased after donation. However, the absolute increase varied across studies, providing little support for the pathogenic role of uric acid in the development of hypertension, vascular disease and renal disease [30] in kidney donors. Rather, these biochemical changes are interesting from a mechanistic perspective, and based on current evidence should not be interpreted as needing attention in clinical care.

Strengths and Limitations of This Review

To compile relevant information, we performed a comprehensive search making it unlikely that we missed relevant studies. Article identification, selection and data abstraction were all performed independently in duplicate, to minimize potential biases inherent in the subjective nature of these tasks. However, as with many reviews, the number and heterogeneous quality of primary studies limited the strength of the conclusions. Using some of the guidelines outlined by Hayden et al. [31], we systematically assessed the quality of the studies on which these findings were based. Just over half of the studies collected data prospectively. Follow-up times ranged from 5 months to 28 years; many of the signifi-

Table 4. Impact of donor uninephrectomy on anemia

Source	Mean follow-up, years (range)	Predonation, mean ± SD	Postdonation, mean ± SD	Change	p	Method of Assay
Hemoglobin, g/l						
Hida et al., 1982	n.r. (0.5–5.0)	133.9 ± 13.1	130.6 ± 17.7	–3.3 ± n.r.	n.s.	n.r.
Romero et al., 2000	0.4	155 ± 18	159 ± 16	4 ± n.r.	n.s.	TKS cytometer (Coulter)
Hematocrit, %						
Gonzalez et al., 1989	4.2 (0.5–11.8)	40 ± 4.21	40.54 ± 4.08	0.54 ± n.r.	n.s.	n.r.
Hida et al., 1982	n.r. (0.5–5.0)	40.17 ± 3.63	39.62 ± 4.50	–0.55 ± n.r.	n.s.	n.r.
Mimran et al., 1993	1.2 (n.r.)	42.0 ± 3.8	43.0 ± 4.2	1.0 ± n.r.	n.s.	n.r.
Erythropoietin, IU/l						
Romero et al., 2000	0.4	14.8 ± 1.3	15.3 ± 0.8	0.5 ± n.r.	n.s.	ELISA kit (Bio-meriux, France)

n.r. = Not reported; n.s. = not significant. Conversion factors: hemoglobin × 10 (g/dl → g/l); erythropoietin × 1 (mIU/ml → IU/l).

Table 5. Power calculations for future controlled studies, which aim to detect a difference between donors and controls in the change in a biochemical measure after donation, if in truth it did exist

Outcome	Estimation of SD[a]	Clinical effect being considered[b]	Minimum sample size per group[c]
Serum phosphate, mmol/l	0.2	0.05	251
		0.10	63
		0.15	28
		0.20	16
Serum calcium, mmol/l	0.15	0.05	141
		0.10	35
		0.15	16
		0.20	9
PTH, intact, pmol/l	2	0.5	251
		0.8	98
		1	63
		2	16
1,25-Dihydroxyvitamin D, pmol/l	25	15	44
		20	25
		25	16
Hemoglobin, g/l	17	3	504
		5	181
		8	171
		10	45
		12	32
Uric acid, μmol/l	75	20	221
		30	98
		50	35
		60	25
Plasma tHyc, μmol/l	2	1	63
		2	16
		3	7

[a] Variance estimates for difference between the pre-/post- change in donors and controls were based on studies included in this systematic review [19, 22–26, 28].
[b] The clinical effect being considered is the difference between the pre-post change in donors and controls.
[c] Based on two-group comparisons between donors and controls; type I error rate of 0.05, power of 0.8 (assuming no loss to follow-up and an equal number of donors and controls per group).

cant findings were observed in studies with short, and possibly inadequate, follow-up. Only three studies reported on the number of subjects lost to follow-up and the reasons for losses were not described in detail. Many of the studies used a pre-/post- design and infrequently used any internal control groups. The use of transplant-eligible nondonor controls would allow for a more accurate interpretation of the observed results. The sample sizes for the existing studies examining biochemical changes after donation were limited. The majority of studies did not describe their method of assay. When described, no two studies used the same technique to assess a similar outcome. The studies did not present enough data for subgroup analysis by age. Without patient-level data, it is possible that significant metabolic changes may have occurred in patients postdonation, but such abnormalities may have gone undetected since only mean group-level data are presented. Additionally, although many transplant programs have been accepting donors with isolated medical abnormalities such as hypertension and obesity, biochemical changes in these donors were not described in the available studies.

Future Research

Based on the studies conducted to date, absolute changes in some biochemical measures remain unclear, and the natural history of these changes is uncertain. This is a valuable exploratory review as it concisely summarizes what is currently known, the limitations of this information and an agenda for future research. There is now global consensus that we need rigorously conducted prospective controlled studies to obtain better estimates on the long-term implications of living kidney donation [32]. While such studies will focus on outcomes such as death, premature cardiovascular disease, kidney failure and hypertension, they also provide a unique opportunity to better understand mechanistic biochemical effects attributable to small decrements in kidney function.

For the purposes of future studies, we have included power calculations for biochemical and hematological parameters of interest (table 5). These calculations are based on the difference between the pre-/post- change in donors and controls at single specified time in follow-up, assuming an equal number of donors and controls with a type I error rate of 0.05 and power of 0.8. It appears quite feasible to recruit for the required sample, making it likely that new information from ongoing studies will be forthcoming. Parameters that should be particularly considered include parathyroid hormone, 1,25-dihydroxyvitamin D, uric acid and homocysteine.

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Original Investigation

Bone and Mineral Metabolism and Fibroblast Growth Factor 23 Levels After Kidney Donation

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Amit X. Garg, MD, PhD,[1,2] on behalf of the Donor Nephrectomy Outcomes Research
(DONOR) Network*

Background: Living kidney donation offers a unique setting to study changes in phosphate and vitamin D homeostasis attributable to mild isolated decreases in estimated glomerular filtration rate (eGFR).

Study Design: Cross-sectional study.

Setting & Participants: 198 living kidney donors and 98 nondonor controls from 9 transplant centers across 3 countries. For donors, median time after donation was 5.3 years. At assessment, donors had a lower eGFR than controls (73 vs 98 mL/min/1.73 m^2).

Predictor: Living kidney donation (mildly decreased eGFR).

Outcomes: Biochemical markers of chronic kidney disease–mineral and bone disorder.

Measurements: Serum creatinine, total serum calcium, serum and urine inorganic phosphate, plasma intact parathyroid hormone, serum calcidiol and calcitriol, renal fractional excretion of inorganic phosphate, and intact serum fibroblast growth factor 23 (FGF-23).

Results: Serum FGF-23 levels were significantly higher in donors (38.1 vs 29.7 pg/mL; $P < 0.001$). For every 10-mL/min/1.73 m^2 decrease in eGFR, FGF-23 level was higher by 3.2 (95% CI, 2.0-4.4) pg/mL. Compared with controls, donors showed higher renal tubular fractional excretion of inorganic phosphate (17.8% vs 12.3%; $P < 0.001$), lower serum phosphate (0.97 vs 1.02 mmol/L; $P = 0.03$), and lower serum calcitriol values (63 vs 77 pmol/L; $P < 0.001$). Serum calcium levels were not significantly different between the 2 groups. Plasma intact parathyroid hormone levels were significantly higher in donors (5.7 vs 5.0 pmol/L; $P = 0.03$), but were not correlated with FGF-23 or calcitriol levels.

Limitations: Enrollment of a small proportion of past donors at participating centers; assessment of only postdonation values; unable to assess seasonal variation or other temporal patterns in biochemical markers; assessment of kidney function was based on eGFR, not measured GFR.

Conclusions: The FGF-23 pathway may be activated in living kidney donors who show early biochemical changes compatible with chronic kidney disease–mineral and bone disorder. Whether these changes influence bone mineral density and fracture rates warrants consideration.

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INDEX WORDS: Nephrectomy; glomerular filtration rate (GFR); bone; fibroblast growth factor 23 (FGF-23); metabolic complications.

Many patients with moderate chronic kidney disease (CKD) and virtually all patients receiving dialysis experience increases in serum phosphate, fibroblast growth factor 23 (FGF-23), and plasma intact parathyroid hormone (iPTH) levels, along with altered vitamin D metabolism.[1] These changes have been associated with a complex termed CKD-mineral and bone disorder (CKD-MBD), fragility (osteoporotic) fractures, osteoporosis, progressive loss of kidney function, cardiovascular disease, and mortality.[1-4]

When these changes are observed in patients with CKD, it is difficult to know whether they are attribut-

able entirely to glomerular filtration rate (GFR) decrease because patients with CKD are older and frequently have comorbid conditions that may influence their biochemical measurements. Living kidney donation offers a unique setting to study the effect of mild isolated decreases in GFR on these biochemical parameters with less confounding. Living donors are healthy individuals who experience an average decrease in GFR of 26 (range, 8-50) mL/min/1.73 m² after nephrectomy.[5] Although the impact of donor nephrectomy on biochemical measures at various times has been described, results generally have been inconsistent (see a review summarizing 8 studies[6] and an additional recent study[7]). For this reason, we conducted this study to better understand the impact of donor nephrectomy on phosphate and vitamin D homeostasis. We also explored the evolving paradigm that circulating FGF-23 levels may be one of the proximal mechanisms in regulating renal tubular phosphate handling to allow kidney(s) with less function to adapt to external phosphate balance.

METHODS

Study Design

In 2004-2008, we performed a cross-sectional study comparing 198 living kidney donors with 98 nondonor controls. Participants were recruited from 7 transplant centers across Canada and 2 centers from Scotland and Australia. Psychosocial outcomes for the cohort are described elsewhere.[8] The study was approved by the research ethics boards at each participating center. The conduct and reporting of this study was guided by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement.[9]

Participants

Previous living kidney donors were identified through patient databases of participating transplant centers. Donors were eligible to participate if they donated in 1970-2007 and were at least 18 years of age at the time of donation. Eligible candidates were contacted by telephone. Predonation information (birth and transplant dates, age at time of donation, sex, and race) was collected from medical charts for consenting participants.

A comparison group of nondonor controls was also assembled. As a recruitment strategy, consenting donors were asked to suggest potential controls who, to their knowledge, would have met the following criteria at the time of their donation: at least 18 years of age and healthy (ie, no kidney disease, hypertension, diabetes, cardiovascular disease, pulmonary disease, or active cancer[10]). We suggested to the participating donors that the most suitable nondonor control(s) would be individuals who also had undergone donor evaluation and had been deemed medically eligible to donate by the transplant team, but ultimately had not donated. However, the health status of recruited nondonor controls ultimately was assessed by historical recall. Donors could identify more than one potential nondonor to act as their control(s). In some cases, donors were not able to identify any. Potential controls were contacted by telephone. Informed consent was obtained for all participants. Nondonor controls were assigned the donation date of the referring donor.

Laboratory Outcomes

Participants were each sent a study kit containing a standardized set of collection tubes, vials for storage, and laboratory requisitions for blood sample collection. This kit was taken to a local laboratory, where ~45 mL of blood was drawn by venipuncture at each visit. Samples then were shipped and stored at −80°C at a central site within 24 hours of collection (London Health Sciences Centre, London, Ontario, Canada). Serum and urine inorganic phosphate, total serum calcium, and serum creatinine were measured by standard automated methods. The serum creatinine measurement was traceable to isotope-dilution mass spectrometry. Plasma iPTH was measured by the Immulite 2000 assay (Diagnostics Product Corp, reference range, 3.5-6.5 pmol/L). Serum calcidiol (25-hydroxyvitamin D_3, in nanomoles per liter) and calcitriol (1,25-dihydroxyvitamin D_3, in picomoles per liter) were determined by enzyme immunoassay (IDS Ltd, www.idsplc.com/). Intact serum FGF-23 (in picograms per milliliter) was measured by enzyme-linked immunosorbent assay (Kainos Laboratories, www.kainos.co.jp). Renal fractional excretion of inorganic phosphate (FE_{Pi}, in percent) was calculated as 100 multiplied by the product of urine phosphate and serum creatinine divided by the product of serum phosphate and urine creatinine, with all analytes expressed in millimoles per liter.

Estimating Kidney Function

GFR was estimated using the CKD Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine: $141 \times \min(SCr/k,1) \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times (1.018$ if female$) \times (1.159$ if African American$)$, where SCr is serum creatinine level, k is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of SCr/k or 1, and max is the maximum of SCr/k or 1.[11] In the general population, this equation performs better than the MDRD (Modification of Diet in Renal Disease) Study equation,[12] especially at higher GFRs, with less bias, improved precision, and greater accuracy.[11]

Statistical Analyses

Sample size calculations were based on 2-sided independent-sample comparisons of mean postdonation biochemical measurements between donors and controls ($\alpha = 0.05$). We focused on achieving adequate statistical power for parameters that have been suggested to be influenced by mild decreases in GFR.[6] With our sample, we had 80% statistical power to detect a difference of 0.7 pmol/L in plasma iPTH levels or 11 pmol/L in calcitriol levels if they existed.

Kidney function and biochemical parameters were reported as mean ± standard deviation. Mean values were compared using independent-samples *t* tests. The proportion of donors and controls above and below threshold values reported to be prognostic of cardiovascular events or mortality in the general population were compared using Fisher exact test.[13-15] Multivariable linear and logistic regression were used to determine the association of kidney donation with the biochemical outcomes considered (linear biochemical outcomes presented as adjusted mean difference [AMD] and binary biochemical outcomes based on clinical cutoff values presented as odds ratios [ORs]). Models were adjusted for prespecified factors: age at the time the donation took place, sex, and time from kidney donation to biochemical evaluation. Models for serum calcitriol also were adjusted for serum calcidiol level. To assess for linear correlations between estimated GFR (eGFR) and FGF-23 level and between FGF-23 level and measures of CKD-MBD, Pearson correlations were calculated (Fisher Z transformation was used to compute 95% confidence intervals [CIs] on Pearson correlations). Multivariable linear regression was also performed to assess the effect of: (1) a 10-mL/min/1.73 m²

decrease in eGFR on serum FGF-23 level, and (2) a 10-pg/mL increase in FGF-23 level on serum phosphate, renal FE_{Pi}, plasma iPTH, and serum calcitriol values. All analyses and figures were produced using SAS, version 9.13 (SAS Institute Inc, www.sas. com).

RESULTS

Participants

Participating transplant centers identified 1,140 potentially eligible living kidney donors; however, many could not be contacted. Of 421 donors contacted, 235 (56%) consented to participate and 198 (47%) completed the study elements and were included in the analysis. These donors identified 241 potential nondonor controls. Of potential controls suggested, 172 were contacted, 114 (66%) consented to participate, and 98 (57%) completed the study elements.

Characteristics of donors and nondonor controls are listed in Table 1. Donors were slightly older when the donation took place. Most donors and controls were women and white. Median time from kidney donation to biochemical evaluation was 5.3 (25th-75th percentile, 3.3-8.4) years. At the time of biochemical evaluation, donors had higher serum creatinine levels compared with controls (91 ± 19 vs 69 ± 13 μmol/L) and lower eGFRs (73 ± 15 vs 98 ± 14 mL/min/1.73 m²; $P < 0.001$; Fig 1). A scatterplot comparing age at the time of biochemical evaluation and eGFR for donors and nondonor controls is shown in Fig 2.

Biochemical measures in donors and nondonor controls are listed in Table 2. Serum calcium levels were not appreciably different between the 2 groups when assessed continuously or dichotomously (using a threshold value of 2.48 mmol/L).[15] Mean plasma iPTH level was significantly higher in donors compared with controls (5.7 vs 5.0 pmol/L; AMD, 0.6; 95% CI, 0.0-1.2; $P = 0.04$). Using a threshold of 5.3 pmol/L,[13] the proportion with an elevated plasma iPTH level was higher for donors than controls (54%
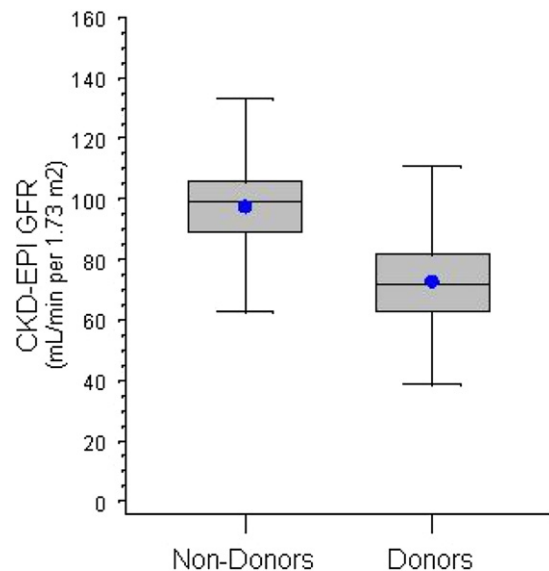
Figure 1. Box plot of donor and nondonor estimated glomerular filtration rate (eGFR) at the time of biochemical evaluation. The line within the box indicates the median, and the symbol represents the mean. The whiskers are drawn from the 25th percentile to the minimum and 75th percentile to the maximum. The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation for eGFR is 141 × min(SCr/k,1)^α× max(SCr/k,1)$^{-1.209}$× 0.993^{Age}× (1.018 if female)× (1.159 if African American), where SCr is serum creatinine level, k is 0.7 for females and 0.9 for males, *a* is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1.[11]

vs 38%; adjusted OR, 1.9; 95% CI, 1.1-3.3; $P = 0.01$).

The comparison of serum phosphate, renal tubular FE_{Pi}, FGF-23, and calcitriol values for donors and controls is shown in Table 2 and Fig 3. Serum phosphate levels were significantly lower in donors than controls (0.97 vs 1.02 mmol/L; AMD, −0.05; 95% CI, −0.10 to −0.01; $P = 0.02$), although there was no difference between groups when using a threshold of 1.13 mmol/L (adjusted OR, 0.64; 95% CI, 0.33-1.21; $P = 0.2$). Renal FE_{Pi} was significantly higher for donors compared with controls (17.8% vs 12.3%; AMD, 4.8; 95% CI, 2.6-6.9; $P < 0.001$). Serum FGF-23 level also was significantly higher in donors compared with controls (38.1 vs 29.7 pg/mL; AMD, 7.8; 95% CI, 3.4-12.1; $P = 0.001$). There was no significant difference between groups in mean calcidiol levels (75 vs 79 nmol/L; $P = 0.3$). However, serum calcitriol level was significantly lower in donors than controls (63 vs 77 pmol/L; AMD, −11; 95% CI, −18 to −5; $P = 0.001$). Using a cutoff of 54 pmol/L,[14] 36% of donors were below this threshold compared with 19% of nondonors ($P = 0.008$), although this was no longer statistically significant after adjustment (OR, 1.8; 95% CI, 0.8-4.0; $P = 0.1$).

Biochemical measures by CKD stage (as defined by the NKF-KDOQI [National Kidney Foundation

Table 1. Characteristics of Donors and Nondonor Controls

	Donors (n = 198)	Nondonors (n = 98)	P
Age at time of donation (y)	44 (21-67)	41 (17-66)[a]	0.03
Age at time of biochemical evaluation			
Mean and range (y)	51 (26-76)	49 (20-68)	0.08
No. and percentage ≥60 y	40 (20)	21 (21)	0.9
Women	122 (61)	63 (64)	0.7
White	189 (95)	97 (99)	0.7

Note: Continuous variables are given as mean (range); categorical variables, as number (percentage).

[a]Nondonor controls were assigned the donation date of their referring donor.
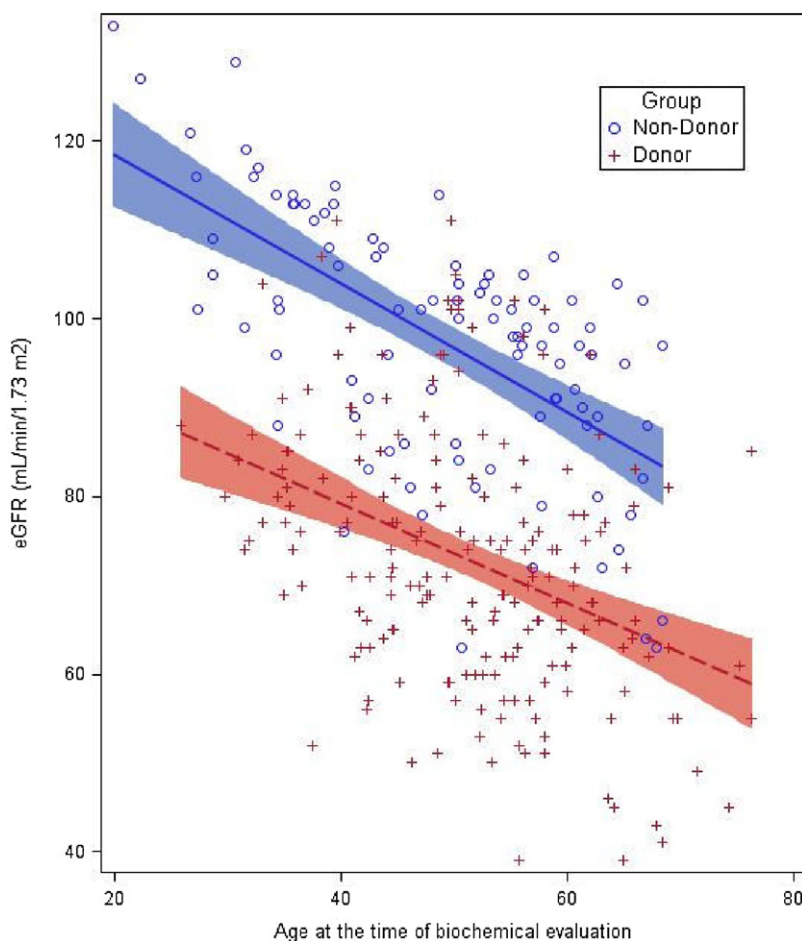
Figure 2. Scatterplot comparing age at the time of biochemical evaluation and estimated glomerular filtration rate (eGFR) for donors and nondonor controls.

Kidney Disease Outcomes Quality Initiative] CKD guidelines) are listed in Table 3. Fourteen percent of donors had eGFR ≥90 mL/min/1.73 m², whereas 18% had eGFR of 30-59 mL/min/1.73 m². In contrast, 72% of controls had eGFR ≥90 mL/min/1.73 m² and no control had an eGFR of 30-59 mL/min/1.73 m². For donors, serum FGF-23 levels increased progressively across the stages of kidney function (negative linear correlation, $r = -0.36$; 95% CI, -0.47 to -0.23; $P < 0.001$). For every 10-mL/min/1.73 m² decrease in eGFR, FGF-23 level was higher by 3.2 pg/mL (95% CI, 2.0-4.4; $P < 0.001$). Renal FE_{Pi} also was incrementally higher across CKD stages ($P = 0.002$). Serum calcitriol levels were incrementally lower across the kidney function stages ($P = 0.02$), without significant alterations in serum calcidiol levels ($P = 0.7$).

Unadjusted and multivariable-adjusted models for the relationship between FGF-23 and renal FE_{Pi}, serum phosphate, and serum calcitriol values are listed in Table 4. Serum FGF-23 level was correlated significantly with renal FE_{Pi} ($r = 0.15$; 95% CI, 0.02-0.28; $P = 0.03$) and serum phosphate level ($r = 0.19$; 95% CI, 0.06-0.32; $P = 0.004$). Serum FGF-23 level was correlated negatively with serum calcitriol

level ($r = -0.39$; 95% CI, -0.50 to -0.26; in adjusted analysis, -5.6 pmol/L of calcitriol for every 10-pg/mL elevation in FGF-23 level; $P < 0.001$). There was no significant linear correlation between serum FGF-23 and plasma iPTH levels ($r = 0.04$; $P = 0.6$), between serum phosphate and plasma iPTH levels ($r = -0.11$; $P = 0.06$), or between serum calcitriol and plasma iPTH levels ($r = -0.04$; $P = 0.6$).

DISCUSSION

Most studies describing the relationship of decreased GFR with disordered mineral metabolism focus on patients with CKD stage 4 or 5 and particularly those receiving long-term dialysis therapy (typically hemodialysis).[2] Less information is available about the altered pathways of mineral and bone metabolism in nondialysis patients with milder decreases in GFR, although such changes begin to be observed in patients with GFR <80 mL/min/1.73 m² (CKD stages 2 and 3).[1,2,16-18] Through rigorous screening, living kidney donors represent a subset of the healthiest individuals in the population.[19] Nephrectomy imparts a mild isolated decrease in kidney function while maintaining their otherwise healthy status. A proportion of donors (~10%) achieve a measured GFR <60

Table 2. Biochemical Measures in Donors and Nondonor Controls

	Donors	Nondonors	*P*
Serum calcium			
No. with measurement	198	98	
Mean ± SD (mmol/L)	2.21 ± 0.09	2.21 ± 0.12	0.8
Multivariable AMD[a]	0.00 (−0.03 to 0.02)[b]		0.9
No. with measurement <2.48 mmol/L threshold[c]	196 (99)	97 (99)	0.9
Multivariable aOR[a]	1.1 (0.1 to 12.6)[d]		0.9
Plasma iPTH			
No. with measurement	184	90	
Mean ± SD (pmol/L)	5.7 ± 2.4	5.0 ± 2.1	0.03
Multivariable AMD[a]	0.6 (0.0 to 1.2)[b]		0.04
No. with measurement ≥5.3 pmol/L threshold[a]	99 (54)	34 (38)	0.01
Multivariable aOR[a]	1.9 (1.1 to 3.3)[d]		0.01
Serum phosphate			
No. with measurement	198	98	
Mean ± SD (mmol/L)	0.97 ± 0.16	1.02 ± 0.21	0.03
Multivariable AMD[a]	−0.05 (−0.10 to −0.01)[b]		0.02
No. with measurement ≥1.13 mmol/L threshold[c]	29 (15)	20 (20)	0.3
Multivariable aOR[a]	0.64 (0.33 to 1.21)[d]		0.2
Renal FE$_{Pi}$			
No. with measurement	149	65	
Mean ± SD (%)	17.8 ± 7.9	12.3 ± 5.2	<0.001
Multivariable AMD[a]	4.8 (2.6 to 6.9)[b]		<0.001
Serum FGF-23			
No. with measurement	151	64	
Mean ± SD (pg/mL)	38.1 ± 15.7	29.7 ± 10.6	<0.001
Multivariable AMD[a]	7.8 (3.4 to 12.1)[b]		0.001
Serum calcidiol			
No. with measurement	151	64	
Mean ± SD (nmol/L)	75 ± 26	79 ± 29	0.4
Multivariable AMD[a]	−4 (−12 to 4)[b]		0.3
Serum calcitriol			
No. with measurement	155	70	
Mean ± SD (pmol/L)	63 ± 21	77 ± 24	<0.001
Multivariable AMD[e]	−11 (−18 to −5)[b]		0.001
No. with measurement <54 pmol/L threshold[c]	56 (36)	13 (19)	0.008
Multivariable aOR[e]	1.8 (0.8 to 4.0)[d]		0.1

Note: Conversion factors for units: phosphate in mmol/L to mg/dL, ×1/0.323; calcium in mmol/L to mg/dL, ×4; PTH in pmol/L to pg/mL, ×1/0.105; calcitriol in pmol/L to pg/mL, ×1/2.6; FGF-23 in pg/mL to pmol/L, ×0.0395.

Abbreviations: AMD, adjusted mean difference; aOR, adjusted odds ratio; FE$_{Pi}$, fractional excretion of phosphate; FGF-23, fibroblast growth factor 23; iPTH, intact parathyroid hormone; SD, standard deviation.

[a]Multivariable adjustment for prespecified variables: age at the time the donation took place, sex, and time from kidney donation to biochemical evaluation. Values shown in parentheses are 95% confidence intervals.

[b]AMD refers to the difference comparing donors with nondonor controls.

[c]Percentage given in parentheses.

[d]OR compared with nondonors (referent group).

[e]Adjusted for all of the above, as well as serum calcidiol. Values shown in parentheses are 95% confidence intervals.

mL/min/1.73 m^2 in the decade after nephrectomy, with few, if any, comorbid conditions.[5,20] Observational studies comparing living donors with healthy nondonors thus serve as a good model to examine the effect of mild decreases in GFR on biochemical changes in otherwise healthy individuals.

Consistent with this premise, approximately 5 years after nephrectomy, we observed a lower eGFR in past kidney donors compared with nondonor controls (by an average of 25 mL/min). Almost one-fifth had an eGFR of 30-59 mL/min/1.73 m^2 (ie, CKD stage 3), whereas no control had an eGFR in this range. In this context, we observed higher serum FGF-23 levels in past kidney donors compared with controls, as well as higher fractional urinary excretion of phosphate. There was a slight (but statistically significant) lower serum
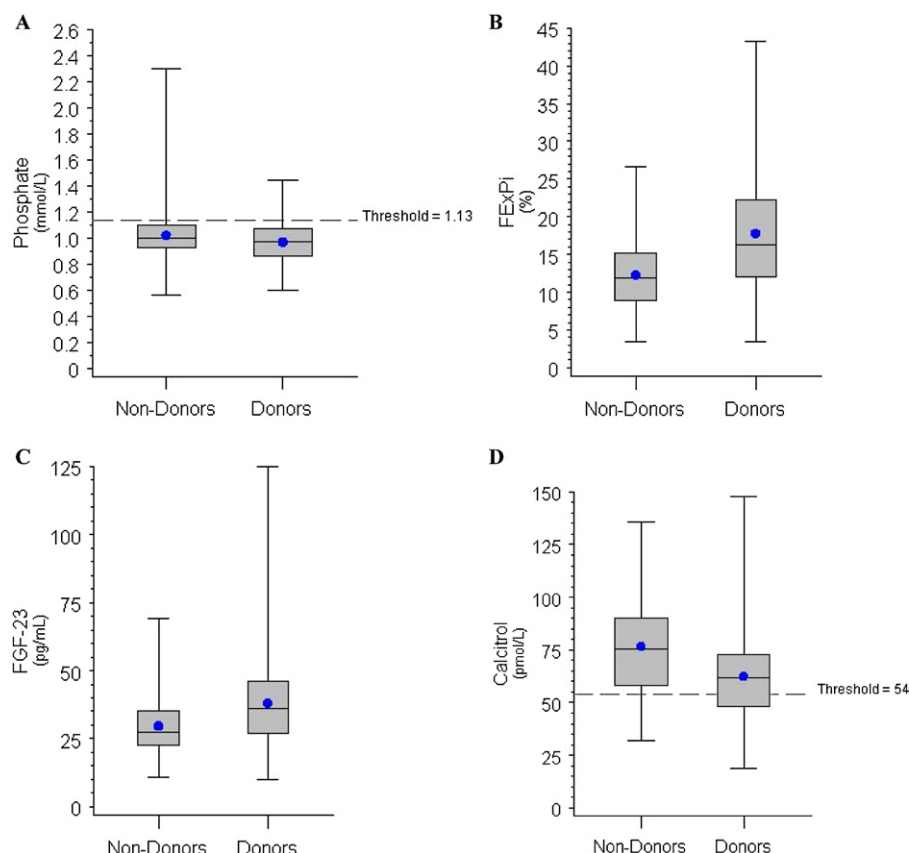
Figure 3. Box plots of (A) serum phosphate, (B) fractional excretion of phosphate (FE$_{Pi}$), (C) serum fibroblast growth factor 23 (FGF-23), and (D) serum calcitriol values in donors and nondonors. The line within the box indicates the median, and the symbol represents the mean. The whiskers are drawn from the 25th percentile to the minimum and 75th percentile to the maximum. Conversion factors for units: phosphate in mmol/L to mg/dL, ×1/0.323; calcitriol in pmol/L to pg/mL, ×1/2.6; FGF-23 in pg/mL to pmol/L, ×0.0395.

phosphate level and significantly lower serum calcitriol levels. Calcium levels were not appreciably different between donors and nondonor controls. Serum FGF-23 levels were correlated negatively with serum calcitriol levels, but not plasma iPTH levels. Nonetheless, plasma iPTH levels were found to be higher in donors compared with controls.

Previous models of the development of CKD-MBD assumed that hyperphosphatemia initiated the cascade of events leading to progressive secondary hyperparathyroidism.[2] However, abnormal serum calcium and phosphate levels generally are not seen until eGFR decreases to <40 mL/min.[16] However, progressive increases in PTH levels and decreasing serum calcitriol levels are seen at milder decreases in kidney function, typically when eGFR is <60 mL/min (CKD stage 3).[16] This suggests that other pathways are active earlier in the course of kidney function decrease. Our study results support this assertion.

The role of an osteocyte-derived factor, FGF-23, which is crucial to the regulation of phosphate homeostasis, may be central to this evolving paradigm.[21] There now are several observational reports showing that serum FGF-23 level is higher early in the course

of decreasing kidney function, in CKD stages 1 and 2, in which GFR is still preserved at >60 mL/min.[22-26] These studies recruited patients from specialty clinics and many patients were older, had underlying kidney disease, and were prescribed drugs to modify their underlying disease (eg, glucocorticoids) or kidney failure (eg, active vitamin D metabolites). Shigematsu et al[25] found no increase in serum FGF-23 levels in patients with CKD stage 1 compared with healthy controls, but a slight increase in those with eGFR of 30-80 mL/min. Pavik et al[22] found striking increases in serum FGF-23 levels in patients with autosomal dominant polycystic kidney disease who had eGFR >60 mL/min (CKD stages 1 and 2), but no differences in either diabetic or nondiabetic patients with similar GFR stages compared with healthy controls. This suggests that autosomal dominant polycystic kidney disease is associated with a distinct disturbance of phosphate homeostasis.[22] It also is apparent that serum phosphate levels might be decreased in early stages of kidney function decline.[23,25,26] Evenepoel et al[23] studied 125 patients with CKD stages 1-3, with findings that were similar to those reported here in living donors. Serum phos-

Table 3. Biochemical Measures in Donors and Nondonor Controls by GFR category

| | GFR (mL/min/1.73 m²)[a] | | | |
	≥90	60-89	30-59	*P*
Donors				
No.	27	133	36	—
Serum creatinine (μmol/L)	69 ± 12	90 ± 14	112 ± 18	<0.001
Plasma iPTH (pmol/L)	5.8 ± 3.0	5.6 ± 2.4	5.7 ± 2.1	0.9
Serum phosphate (mmol/L)	0.97 ± 0.18	0.96 ± 0.16	0.98 ± 0.17	0.9
Renal FE$_{Pi}$ (%)	13.1 ± 5.8	17.6 ± 7.6	21.4 ± 8.6	0.002
Serum FGF-23 (pg/mL)	30.1 ± 12.6	37.0 ± 13.7	46.4 ± 20.6	0.001
Serum calcidiol (nmol/L)	70 ± 29	76 ± 25	73 ± 29	0.7
Serum calcitriol (pmol/L)	73 ± 31	62 ± 20	56 ± 15	0.02
Nondonors				
No.	70	27	0	—
Serum creatinine (μmol/L)	64 ± 11	81 ± 11	—	<0.001
Plasma iPTH (pmol/L)	5.1 ± 2.0	4.7 ± 2.3	—	0.4
Serum phosphate (mmol/L)	1.03 ± 0.21	1.00 ± 0.19	—	0.6
Renal FE$_{Pi}$ (%)	11.9 ± 4.9	13.3 ± 5.7	—	0.3
Serum FGF-23 (pg/mL)	28.2 ± 8.6	33.1 ± 13.7	—	0.09
Serum calcidiol (nmol/L)	78 ± 30	79 ± 28	—	0.9
Serum calcitriol (pmol/L)	77 ± 24	75 ± 22	—	0.8

Note: All measurements reported as mean ± standard deviation. Conversion factors for units: serum creatinine in μmol/L to mg/dL, ×1/88.4; phosphate in mmol/L to mg/dL, ×1/0.323; PTH in pmol/L to pg/mL, ×1/0.105; calcitriol in pmol/L to pg/mL, ×1/2.6; FGF-23 in pg/mL to pmol/L, ×0.0395.

Abbreviations: FE$_{Pi}$, fractional excretion of phosphate; FGF-23, fibroblast growth factor 23; GFR, glomerular filtration rate; iPTH, intact parathyroid hormone.

[a]Estimated by Chronic Kidney Disease Epidemiology Collaboration equation. No participant had estimated GFR <30 mL/min/1.73 m² (chronic kidney disease stage 4).

phate and FGF-23 levels were related inversely to eGFR; higher serum FGF-23 levels were associated with both higher tubular FE$_{Pi}$ and lower serum calcitriol levels.[23] In this context, preserving external

Table 4. Relationship of FGF-23 With FE$_{Pi}$, Serum Phosphate, and Serum Calcitriol

Outcome	Per 10-pg/mL ↑ FGF-23[a]	*P*
Renal FE$_{Pi}$ (%)		
Unadjusted	0.8 (0.1 to 1.5)	0.03
Multivariable adjusted[b]	0.6 (−0.1 to 1.3)	0.09
Serum phosphate (mmol/L)		
Unadjusted	0.02 (0.01 to 0.03)	0.004
Multivariable adjusted[b]	0.02 (0.01 to 0.03)	0.002
Serum calcitriol (pmol/L)		
Unadjusted	−6.0 (−8.1 to −3.9)	<0.001
Multivariable adjusted[c]	−5.6 (−7.5 to −3.6)	<0.001

Note: Based on data from all included donors and nondonor controls.

Abbreviations: CI, confidence interval; FE$_{Pi}$, fractional excretion of phosphate; FGF-23, fibroblast growth factor 23.

[a]95% confidence interval is given in parentheses.

[b]Multivariable adjustment for prespecified variables: age at the time the donation took place, sex, and time from kidney donation to biochemical evaluation.

[c]Adjusted for all of the above, as well as serum calcidiol level.

phosphate balance through the FGF-23 pathway may initiate a cascade of events leading to CKD-MBD, with subsequent downstream disturbances of vitamin D and parathyroid homeostasis.[21,27,28]

As kidney function decreases, there is a need for the renal tubule to adapt to accommodate the excretion of dietary phosphate. FGF-23 acts to decrease renal tubular phosphate reabsorption (increasing FE$_{Pi}$), which prevents an increase in serum phosphate level.[28] It is unclear how the signal for increased FGF-23 production is mediated; there is conflicting experimental evidence in humans that altering dietary phosphate load results in corresponding changes in serum FGF-23 levels.[29-32] FGF-23 also inhibits renal hydroxylation of calcidiol (the circulating form of vitamin D) to calcitriol. Similar to our observation in living donors, several reports in early kidney failure have documented a decrease in serum calcitriol levels in proportion to increasing serum FGF-23 levels.[23-26,31] These changes would decrease intestinal phosphate absorption and facilitate dietary phosphate adaptation. However, decreased intestinal calcium absorption and the decreased action of calcitriol on the parathyroid cells in turn lead to a counter-regulatory increase in PTH secretion and elevated PTH levels.[27] The additional secretion of PTH promotes phosphaturia and calcium reabsorption. It also increases renal 1α hydroxylase

activity to restore the conversion of calcidiol to calcitriol. In the setting of normal kidney function, this feedback loop would restore PTH to its former level.

Unilateral nephrectomy for the purpose of kidney donation serves as a unique model to study the relationship between phosphate homeostasis and FGF-23 levels because the individuals concerned must be in otherwise near-perfect health. In this study, we have been able to contrast the observed measurements with nondonor controls. Our findings are consistent with the developing hypothesis that changes in the FGF-23 axis in response to a decrease in kidney function are one of the earliest signals to the development of disturbed mineral metabolism in kidney failure. Our results also are consistent with the acute increases in serum FGF-23 levels seen in the first days after unilateral donor nephrectomy, as recently reported by Westerberg et al.[7] Although these authors found a return of serum FGF-23 to baseline values within several months of nephrectomy and no associated changes in serum phosphate or calcitriol levels, they studied fewer than 10 patients over a very short period. The mean age of their donors also was markedly different (57 vs 44 years in our study). In this study, we have extended these findings to long-term changes in a much larger cohort in whom kidney function has remained in a steady state.

The current standard of care for living kidney donors does not include routine monitoring or treatment of mineral metabolism and bone density other than for indications that are similar to the nondonor population. Our findings do not warrant modification of current recommendations. However, research should be conducted to determine whether these observed biochemical changes influence bone mineral density, fracture rates, or other outcomes, such as left ventricular hypertrophy.[33]

Our study has several strengths. It was a multicenter study with representation from several centers across Canada and 2 centers in Scotland and Australia. A control group was recruited for comparison. Biosamples were stored centrally, and all tests were batch-analyzed in a central laboratory. The study had adequate statistical power to detect clinically important effects on various biochemical markers.[6] Time after donation was longer than most previous studies in this theme.[6,7] The potential confounding effects of age at the time the donation took place, sex, time from kidney donation to biochemical evaluation, and nutritional vitamin D status were considered in multivariable models. To our knowledge, it is the first study to describe long-term steady-state changes in FGF-23 levels in living kidney donors. However, the limitations of cross-sectional studies and our methods need to be recognized. Despite repeated attempts, we were able to enroll only a small proportion of past donors at our participating centers. This raises the possibility that nonparticipants may have experienced different measurable or unmeasurable outcomes than those who took part in our study. We were able to assess only postdonation values for our biochemical parameters. Ideally, having a predonation measurement would be more informative, allowing for assessment of change over time. Most participants were from Canada, and their vitamin D levels can differ from individuals who reside closer to the equator; confirming that these observations generalize to other populations would be useful. Previous studies have shown that GFR estimating equations are inferior to measured GFR in the donor setting.[20,34,35] For reasons of feasibility, we were able to only estimate GFR in the present study. However, despite the added measurement error this would introduce, we were still able to see striking differences in our biochemical measurements across eGFR strata in both donors and controls (Table 3). Finally, we studied individuals a mean of 5 years after donation and cannot comment on the seasonal variation or other temporal patterns in the development of these biochemical changes after donation.

In conclusion, the FGF-23 pathway may be activated in living kidney donors who show early biochemical changes compatible with CKD-MBD. Ongoing prospective cohort studies of donors and nondonor controls followed up regularly for years after donation (US National Institutes of Health ALTOLD [Assessing Long Term Outcomes of Living Donation] study, Canadian Institutes of Health Research Donor Nephrectomy Outcomes Research [DONOR] study) may help provide additional information about this issue in the near future. Whether these changes influence bone mineral density and fracture rates warrants additional consideration.

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Original Investigation

Fracture Risk in Living Kidney Donors: A Matched Cohort Study

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(DONOR) Network*

Background: Chronic kidney disease increases the risk of bone fragility fractures (osteoporotic fractures). Living kidney donors lose 50% of their renal mass and show changes in calcium homeostasis. We studied whether living kidney donation increases the risk of fragility fracture.

Design: Retrospective matched-cohort study.

Setting & Participants: We reviewed the medical charts of all 2,015 adults in Ontario, Canada, who donated a kidney between 1992 and 2009 (surgeries performed across 5 transplant programs). We linked this information to health care databases and randomly selected 20,150 matched nondonors from the healthiest portion of the general population. Median age was 43 (95% CI, 24-50) years at study enrollment. Donors and nondonors were then followed up for a median of 6.6 years and a maximum of 17.7 years.

Predictor: Living donor nephrectomy.

Outcomes: The primary outcome was lower- and upper-extremity fragility fractures. Individuals who reached 66 years or older in follow-up had bisphosphonate prescriptions recorded.

Results: The rate of fragility fracture was no higher in donors compared with nondonors (16.4 vs 18.7 events/10,000 person-years; rate ratio, 0.88; 95% CI, 0.58-1.32). Results were similar in multiple additional analyses. There was little difference in the proportion of older adults in follow-up who received a bisphosphonate prescription (17.1% vs 15.2%; $P = 0.4$).

Limitations: These are interim results. Ongoing surveillance of this and other donor cohorts is warranted to be sure an association does not manifest with longer follow-up.

Conclusions: To date, there is no evidence of increased fragility fracture risk in living kidney donors. Our results meet an information need and are reassuring for the safety of the practice.

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INDEX WORDS: Living kidney donation; fracture; cohort study; prognosis; bone.

Bone fragility fractures, a consequence of osteoporosis, arise spontaneously or follow minor trauma.[1] The health consequences of such fractures are considerable, with excess mortality, morbidity (including acute and chronic pain), and economic costs.[2] Fragility fractures are common in older adults and represent ~80% of fractures in men and women older than 50 years.[3] Patients with altered bone metabolism may experience such fractures at an earlier age.

The kidneys regulate serum calcium and phosphate levels both directly by controlling their level of excretion and indirectly by regulating vitamin D metabolism. In individuals with decreased kidney function, a number of complex biochemical changes have been implicated in a weakened skeleton. Patients with stages 3 and 4 chronic kidney disease (estimated glomerular filtration rate [eGFR], 15-60 mL/min/1.73 m^2) have 1.5- to 3-fold higher risk of fragility fracture compared with patients with preserved kidney function.[4-8] This raises the question of whether this risk extends to the more than 27,000 individuals who donate a kidney worldwide each year.[9] Kidney donors have a 50% decrease in renal mass. Similar to decreased kidney function for other reasons, donor ne-

phrectomy decreases serum calcitriol levels and increases parathyroid hormone and fibroblast growth factor 23 levels.[10-13] However, these are surrogate outcomes, and patients and their providers are most interested in clinically relevant events. This prompted us to study the risk of fragility fracture in living kidney donors. We did so because public trust in the transplantation system is maintained if such long-term living kidney donor outcomes are considered and studied.

METHODS

Design and Setting

We conducted a retrospective population-based matched cohort that used manual chart review and linked health care databases in Ontario, Canada. Ontario currently has about 13 million residents[14]; its residents have universal access to hospital care and physician services and all older adults have prescription drug coverage. We conducted this study according to a prespecified protocol that was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada). Reporting of this study follows guidelines set for observational studies.[15]

Data Sources

We ascertained individual characteristics, covariate information, outcome data, and drug use from records in 5 databases. Trillium Gift of Life is Ontario's central organ and tissue donation agency. We manually reviewed medical charts of all living kidney donors across 5 transplant centers in Ontario to ensure the accuracy of donor information in the Trillium database. We abstracted information for donations in 1992-2009. The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) records detailed diagnostic and procedural information for all hospitalizations in Ontario. The Ontario Health Insurance Plan (OHIP) database contains all health claims for inpatient and outpatient physician services. The Ontario Registered Persons Database (RPDB) contains demographic and vital status information on all Ontario residents. The Ontario Drug Benefit Plan (ODB) database contains highly accurate records for all outpatient prescriptions dispensed to patients 65 years or older.[16] These databases have been used extensively to research health outcomes and health services.[17-22] The databases were virtually complete for all variables used in this study.

Participants

We reviewed medical charts of all living kidney donors who were permanent residents of Ontario. The date of nephrectomy served as the start date for donor follow-up and was designated the index date, also referred to as the study enrollment date. In Ontario, the evaluation of individuals to become living kidney donors is stringent, but does not involve a specific assessment of bone health, such as bone mineral density measurement. Similarly, donors were followed up long term by their primary care physician (rather than the transplant center) and were not provided donor-specific routine advice regarding long-term bone health.

Choosing the best type of nondonors with which donors can be compared is central to any study of relative risks associated with donor nephrectomy.[23] Donors, having undergone a detailed selection process, are inherently healthier than the general population. To address this concern, we used techniques of restriction and matching to select the healthiest portion of the general population.

We randomly assigned an index date to the entire adult general population according to the distribution of index dates in donors. We then looked for comorbid conditions and measures of health care access from the beginning of available database records (July 1, 1991) to the index date. This provided an average of 11 years of medical records for baseline assessment, with 99% of people having at least 2 years of baseline data for review. In the general population, we excluded any adult with any medical condition before the index date that could preclude donation. This included evidence of any of the following: genitourinary disease, diabetes, hypertension, cancer, cardiovascular disease, pulmonary disease, liver disease, rheumatologic conditions, chronic infections, history of nephrology consultation, and evidence of frequent physician visits. We also excluded any individual who failed to see a physician at least once in the 2 years before the index date (given that Ontario has a physician shortage, we wanted to ensure access for health care needs, including routine preventive health measures). From 9,643,334 adult Ontarians during the period of interest, this resulted in the exclusion of 85% of adults (n = 8,216,038). From the remaining adults, we matched 10 nondonors to each donor. We matched on age (within 2 years), sex, index date (within 6 months), rural (population <10,000) or urban residence, and income (categorized into quintiles, using average neighborhood income on the index date). Before matching, we excluded any donor or nondonor with a fragility fracture before the index date because we wanted to focus on de novo fractures in follow-up (<0.8% of donors and nondonors were excluded for this reason).

Outcomes

All patients were followed up until March 31, 2010; death; or emigration from the province. Valid health care database codes to identify fractures are well described (very high sensitivity and positive predictive value compared with reference standards, which include radiographic reports[24-28]). However, agreement on fragility fracture definitions is less uniform. For this reason, we convened 4 group meetings with a panel of osteoporosis experts (authors J.D.A., S.M.C., A.H., and W.D.L.). We developed consensus for the fragility fracture definition before any analyses. The final consensus definition is presented as Item S1 (available as online supplementary material). The primary outcome was a composite of lower-extremity fractures (pelvis, hip, or femoral shaft) and upper-extremity fractures (forearm [radius and ulna] and humerus) not accompanied by major trauma. Expert panels have described fracture locations caused by or attributable to osteoporosis.[29-32] For fractures located in the pelvis, hip, femoral shaft, forearm, humerus, and spine, the percentage attributable to osteoporosis ranges from 40%-80% at the age of 45 years and increases with an individual's age. However, more than two-thirds of vertebral (spinal) fractures do not come to clinical attention.[33] Thus, we excluded vertebral fractures from the primary outcome and analyzed it with primary fracture elements as a secondary outcome. In addition, we considered a secondary outcome restricted to hip and forearm fractures. These sites are amenable to case definitions that include orthopedic procedural codes and show high positive predictive values for radiographic verified acute fractures.[34] Individuals who reached 66 years or older in follow-up had their dispensed medications recorded in the provincial drug plan database for at least 1 year (a universal benefit). Among such individuals, we compared the proportion of donors and nondonors that filled at least one prescription for an oral bisphosphonate (alendronate, etidronate, or risedronate). In the entire cohort, we compared rates of bone mineral density testing in follow-up in donors and nondonors (fee-for-service claims for this test were available in our data sources, but not results or the indication).

Table 1. Characteristics of Donors and Matched Nondonors at the Time of Study Enrollment

	Donors (n = 2,015)	Nondonors (n = 20,150)
Age (y)[a]	43 (34-50)	43 (34-50)
Women	1,216 (60)	12,160 (60)
Income, lowest quintile	299 (15)	2,990 (15)
Rural residence	277 (14)	2,770 (14)
Physician visits in prior year[b]	11 (8-15)	1 (0-2)
Era		
1992-1995	217 (11)	2,170 (11)
1996-2000	529 (26)	5,295 (26)
2001-2005	682 (34)	6,822 (34)
2006-2009	587 (29)	5,863 (29)

Note: Continuous data presented as median (25th-75th percentile); categorical data, as number (percentage). The time of study enrollment also is referred to as the index date. It was the date of nephrectomy in donors and was randomly assigned to nondonors.

[a]Refers to an individual's age at the beginning of follow-up.

[b]Indicates a standardized difference between donors and matched nondonors greater than 10%. Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% is interpreted as a meaningful difference between groups. As expected, donors had more physician visits in the year before the index date compared with matched nondonors because such visits are a necessary part of the donor evaluation process.

Statistical Analysis

We assessed differences in baseline characteristics between donors and matched nondonors using standardized differences.[35,36] This metric describes differences between group means relative to the pooled standard deviation, and differences greater than 10% reflect the potential for meaningful imbalance. We used a Poisson regression model stratified on matched sets to estimate the rate ratio (RR) and 95% confidence interval (CI) for the association between living donation and fragility fractures. We repeated the primary analysis in 3 prespecified subgroups defined by age (median; ≤55 vs >55 years at index date), sex, and index date (1992-2001 [median follow-up, 11.4; 25th-75th percentile, 9.5-13.8 years] vs 2002-2009 [median follow-up, 4.0; 25th-75th percentile, 2.4-4.8 years]). We examined whether RRs differed among subgroups using a series of pair-wise standard z tests.[37] We repeated the primary analysis using Cox proportional hazards regression stratified on matched sets to examine the first fragility fracture in follow-up. We examined characteristics associated with first fragility fracture separately in donors and nondonors using Cox regression. We used conditional logistic regression to compare the proportion of older donors and nondonors who filled at least one prescription for a bisphosphonate in follow-up. We used a Poisson regression model stratified on matched sets to compare the rate of bone mineral density testing in donors and nondonors. We conducted all analysis with SAS software, version 9.2 (www.sas.com).

RESULTS

Baseline Characteristics

We observed 2,015 living kidney donors and 20,150 matched nondonors. Donors and nondonors had simi-

lar baseline characteristics; median age was 43 (25th-75th percentile, 34-50) years and 60% were women (Table 1). As expected, donors had more physician visits in the year before study enrollment compared with nondonors because such visits are a necessary part of the donor evaluation process. Of 2,015 donors, 1,250 (62%) were a first-degree relative to the recipient (711 siblings, 276 parents, and 263 children), and 391 (19%) were a spouse. Forty-three percent of nephrectomies were performed laparoscopically, and the rest were done with an open procedure. Before donation, median serum creatinine level was 0.87 mg/dL (77 μmol/L; 25th-75th percentile, 0.75-0.97 mg/dL [66-86 μmol/L]), and eGFR calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation[38] was 98 (25th-75th percentile, 86-109) mL/min/1.73 m^2. Donors and nondonors were followed up for a median of 6.6 years and a maximum of 17.7 years. Median age at last follow-up was 50 (25th-75th percentile, 42-58) years. Of 22,165 individuals, 20,589 (92.9%) reached the end-of-study

Table 2. Fragility Fractures in Donors and Matched Nondonors

	Donors (n = 2,015)	Nondonors (n = 20,150)
Years of follow-up		
Median[a]	6.9 (3.8-11.0)	6.6 (3.5-10.7)
Range[b]	0.5-17.7	0.4-17.7
Total follow-up (person-years)	15,260	147,960
No. of fragility fractures		
0	1,990 (98.8)	19,877 (98.6)
1	25 (1.2)	270 (1.3)
≥2	0 (0.0)	≤5 (≤0.1)
Fracture rate/10,000 person-years[c]	16.4 (11.1-24.2)	18.7 (16.5-21.1)
Model-based rate ratio[c,d]	0.88 (0.58-1.32)	1.00 (reference)
No. of fractures by location[e]		
Pelvis	0	11
Femoral shaft/head/neck	0	0
Forearm (radius, ulna)	18	215
Humerus	6	39

[a]Values in parentheses represent 25th-75th percentile.

[b]Values represent minimum and maximum.

[c]Values in parentheses are 95% confidence intervals.

[d]$P = 0.5$.

[e]There were 15 hip fracture events (donors and nondonors combined), with the exact number not presented by group for reasons of privacy (cell size, 1-5). In the primary composite fragility fracture definition, unique fracture events were counted if they were separated by at least 180 days. When describing fractures by location, unique fracture events were counted if they were separated by at least 180 days for fractures of that location.
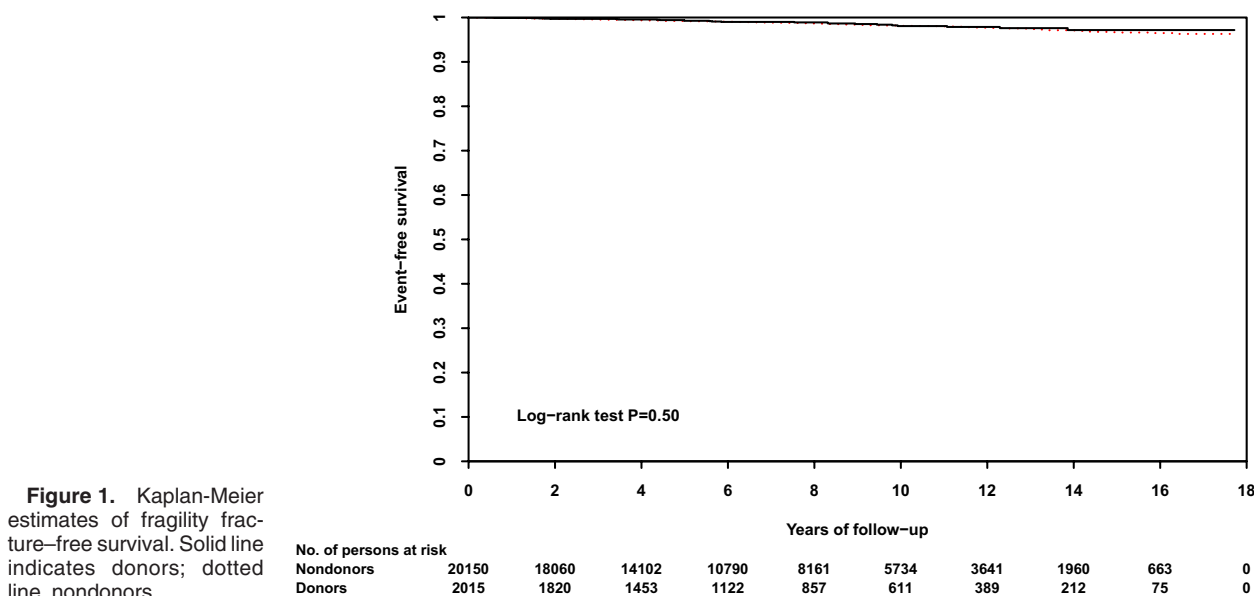
Figure 1. Kaplan-Meier estimates of fragility fracture–free survival. Solid line indicates donors; dotted line, nondonors.

No. of persons at risk									
Nondonors	20150	18060	14102	10790	8161	5734	3641	1960	663	0
Donors	2015	1820	1453	1122	857	611	389	212	75	0

follow-up (March 31, 2010), 1,223 (5.5%) were censored at the time of emigration from the province, and 353 (1.6%) were censored at the time of death. Total person-years of follow-up were 163,220 (15,260 donors and 147,960 nondonors).

Outcomes

Outcomes are listed in Table 2. There were 301 primary fragility fracture events. The rate of fragility fractures was no higher in donors compared with nondonors (16.4 vs 18.7 fractures/10,000 person-years; RR, 0.88; 95% CI, 0.58-1.32; $P = 0.5$). Results were no different when we considered an outcome of time to first primary fracture event (hazard ratio, 0.87; 95% CI, 0.58-1.31; Kaplan Meier curves presented in Fig 1, and with a truncated y axis, as Item S2). Similarly, results were no different when we included vertebral fractures in the outcome definition (17.7 vs 19.5 fractures/10,000 person-years; RR, 0.91; 95% CI, 0.61-1.34; $P = 0.6$) or when we assessed a composite outcome of hip and forearm fractures alone (12.4 vs 15.4 fractures/10,000 person-years; RR, 0.81; 95% CI, 0.51-1.29; $P = 0.4$). Subgroup analyses are shown in Fig 2. Older age at study enrollment, sex, and earlier date of enrollment (longer follow-up) did not influence the association between kidney donation and fragility fracture (P range $= 0.5$-0.9). Older age was associated with fragility fractures in both donors and nondonors when each group was analyzed separately (Table 3). Medication records were available for the 146 donors and 1,177 nondonors who reached 66 years or older in follow-up. Median follow-up was 10.8 (95% CI, 7.4-13.9) years, and median period of drug benefit coverage was 4.5 (95% CI, 2.7-7.3) years. For these older adults, there was no difference

in the proportion of donors and nondonors who had evidence of at least one prescription for a bisphosphonate (25 [17.1%] vs 179 [15.2%]; $P = 0.4$). In the entire cohort, the rate of bone mineral density testing was higher in donors compared with nondonors (648 vs 405 tests/10,000 person-years; $P < 0.001$).

DISCUSSION

We conducted this study to determine whether living donor nephrectomy increases the risk of fragility fracture. The results provide important safety reassurances to potential donors, their recipients, and transplant professionals. We found no evidence of increased fragility fracture risk in the follow-up of our donors. There was no trend of increased fragility fracture risk in subgroups of donors with a longer (compared with shorter) period of follow-up, nor did Kaplan Meier curves after 10 years of follow-up suggest any higher risk of fragility fracture events in donors compared with nondonors.

To our knowledge, this is the first report to assess fragility fractures in kidney donors. This was made possible by universal health care benefits available to all Ontario citizens, which reduced concerns about selection and information biases. For the present study, we manually reviewed more than 2,000 consecutive medical charts across 5 transplant centers to ensure the accuracy of donor information. For the period of interest, this essentially represents all living donation activity for Ontario, the largest province in Canada. Loss to follow-up, a concern in many long-term donor follow-up studies, was minimal in our setting (<6% of individuals emigrated from the province). However, our data have some limitations. We defined our primary outcome using a consensus definition of

Subgroup	No. Events/ No. at Risk		Event Rate/ 10,000 person−years		Rate Ratio (95% Confidence Interval)	interaction test (P value)
	Donor	Nondonor	Donor	Nondonor		
Overall	25 / 2015	276 / 20150	16.4	18.7	0.9 (0.6,1.3)	
Age,years						
<55	17 / 1730	206 / 17300	12.7	15.8	0.8 (0.5,1.3)	0.5
>=55	8 / 285	70 / 2850	43.2	39.5	1.1 (0.5,2.2)	
Sex						
Male	8 / 805	79 / 8050	12.9	13.1	1.0 (0.5,2.0)	0.7
Female	17 / 1210	197 / 12100	18.8	22.4	0.8 (0.5,1.4)	
Index Date*						
1992−2001	17 / 872	184 / 8720	16.4	18.4	0.9 (0.5,1.5)	0.9
2002−2009	8 / 1143	92 / 11430	16.4	19.2	0.9 (0.4,1.8)	

```
        0    1    2    3
      ←────      ────→
   risk lower   risk higher
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Figure 2. Influence of age, sex, and index date (duration of follow-up*) on risk of fragility fracture in kidney donors compared to nondonors. *The index date refers to the date of study enrollment. Individuals with an index date of 1992-2001 had a median follow-up of 11.4 (25th-75th percentile, 9.5-13.8) years. Individuals with an index date of 2002-2009 had a median follow-up of 4.0 (25th-75th percentile, 2.4-5.8) years.

fragility fracture (Item S1). Although fractures captured in this way are suggestive of osteoporosis, we cannot say this with complete certainty given an absence of bone mineral density results in follow-up. We also did not have eGFRs in follow-up, which precluded assessment of fracture risk according to this feature.

There is a growing literature describing the association between decreased kidney function (chronic kidney disease) and fragility fracture.[4-8] Compared with those with normal kidney function (which in prior studies was defined as eGFR >60 mL/min/1.73 m^2), the association with fragility fracture is about 1.5- to 3-fold higher in individuals with eGFR of 15-59

Table 3. Risk Factors for Fragility Fracture for Donors and Matched Nondonors

	Donors	Nondonors
Age (/5 y)[a]	1.28 (1.05-1.54)	1.27 (1.20-1.36)
Women (vs men)	1.40 (0.61-3.22)	1.62 (1.26-2.10)
Rural (vs urban) residence	0.78 (0.24-2.53)	1.05 (0.75-1.46)
Income quintile (/quintile)	1.23 (0.90-1.67)	0.99 (0.91-1.08)
Year of index date (/y)	1.00 (0.92-1.08)	0.99 (0.96-1.01)

Note: Values shown are rate ratio (95% confidence interval). Separate multivariable Poisson regression models were created for donors and matched nondonors.

[a]Refers to an individual's age at the beginning of follow-up (which is also referred to as the index date or cohort entry date).

mL/min/1.73 m^2. In longitudinal studies, this was observed during a mean follow-up of about 3-4 years. In the decade after donation, ~40% of donors have a GFR of 60-80 mL/min/1.73 m^2, and 10% have a GFR of 30-59 mL/min/1.73 m^2.[39,40] So how does one reconcile the risk of fragility fracture observed with decreased eGFR in the chronic kidney disease setting to the results we obtained in our cohort of living kidney donors? First, it is possible that the association seen with chronic kidney disease is not causal. It may reflect other comorbid conditions that co-occur with decreased eGFR that are not fully accounted for in multivariable models. However, donors develop decreased eGFR through a nonpathologic process that may not carry the same prognostic significance. Second, the donor evaluation process is used to select individuals who are in excellent health with good long-term prognosis. We also previously showed that donors have more health care surveillance in follow-up compared with similar nondonors.[22] In the present study, donors were more likely to receive a bone mineral density test in follow-up compared with nondonors. All these factors may offset any increase in fragility fracture risk attributable to decreased GFR. Although we selected nondonors to be similar to donors in a number of key attributes, we were unable to account for baseline levels of physical fitness, falling tendency, smoking, and bone mineral density because this information was not available in our data

sources. If unmeasured risk factors for fragility fracture were more prevalent in selected nondonors than donors, this may have masked a true risk of fragility fracture attributable to donation. Finally, it is possible that an association between living donation and fragility fracture risk exists, but takes longer to manifest and more events to precisely quantify. It may depend on more donors entering an older age range and manifesting eGFR <60 mL/min/1.73 m^2 in the years after donation. For this reason, ongoing follow-up of this and other cohorts is warranted. At this time, no evidence of fragility fracture risk in the decade after living donation is reassuring for the safety of the practice among carefully selected donors.

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SUPPLEMENTARY MATERIAL

Item S1: Database codes used to identify fracture diagnoses.
Item S2: Kaplan-Meier estimates of fragility fracture–free survival.

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2012.01.013) is available at www.ajkd.org.

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Psychosocial Health of Living Kidney Donors: A Systematic Review

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Knowledge of the psychosocial benefits and harms faced by living kidney donors is necessary for informed consent and follow-up. We reviewed any English language study where psychosocial function was assessed using questionnaires in 10 or more donors after nephrectomy. We searched MEDLINE, EMBASE, Web of Science, Psych INFO, Sociological Abstracts and CINAHL databases and reviewed reference lists from 1969 through July 2006. Independently, two reviewers abstracted data on study, donor and control group characteristics, psychosocial measurements and their outcomes. Fifty-one studies examined 5139 donors who were assessed an average of 4 years after nephrectomy. The majority experienced no depression (77–95%) or anxiety (86–94%), with questionnaire scores similar to controls. The majority reported no change or an improved relationship with their recipient (86–100%), spouse (82–98%), family members (83–100%) and nonrecipient children (95–100%). Some experienced an increase in self-esteem. A majority (83–93%) expressed no change in their attractiveness. Although many scored high on quality of life measures, some prospective studies described a decrease after donation. A small proportion of donors had adverse psychosocial outcomes. Most kidney donors experience no change or an improvement in their psychosocial health after donation. Harms may be minimized through careful selection and follow-up.

Key words: Living kidney donors, quality of life, depression, anxiety, systematic review

Introduction

Living kidney donation is a complex ethical, moral and medical issue. It is practiced with the expectation that the risk of short and long-term harm to the donor is outweighed by the psychosocial benefits of altruism and improved recipient health. As reported in the literature, the psychosocial benefits of donation include improved relationships and increased self-esteem. However, depression, anxiety and marital stress have also been described. A detailed understanding of the potential psychosocial benefits and harms of living donation is critical in guiding informed consent and promoting practices which optimally maintain the long-term health of donors. The purpose of this review was to consider systematically, all studies that used a questionnaire-based approach to quantify donor psychosocial health after nephrectomy.

Methods

Research question and definitions

The primary question of this review was: As assessed by questionnaires, what impact does living kidney donation have on a donor's social function, self-concept, body-image, psychological well-being and quality of life? *Questionnaires* were defined as predetermined sets of questions used to collect relevant psychosocial data (1). *Social function* included the donor's perception of the quality of their personal relationships. *Self-concept* included a donor's feelings of self-esteem and sense of accomplishment. *Body-image* described a donor's perception of their appearance and surgical scar. *Psychological well-being* included stress, depression, anxiety, emotions and other psychiatric symptoms. *Quality of life* is a concept 'affected in a complex way by the person's physical health, psychological state, personal beliefs, social beliefs and their relationship to salient features of their environment (2).

Study selection

We included English language studies, which described the use of any questionnaire to examine the psychological and or social functioning of 10 or more kidney donors after nephrectomy. Studies of for-profit kidney vendors were not eligible for this review as their outcomes are known to differ from nonvendors (3).

We screened citations from MEDLINE, EMBASE, Web of Science, Psych INFO, Sociological Abstracts and CINAHL databases from 1969 through July 2006. Terms such as *living donors, kidney transplantation, psychosocial,*

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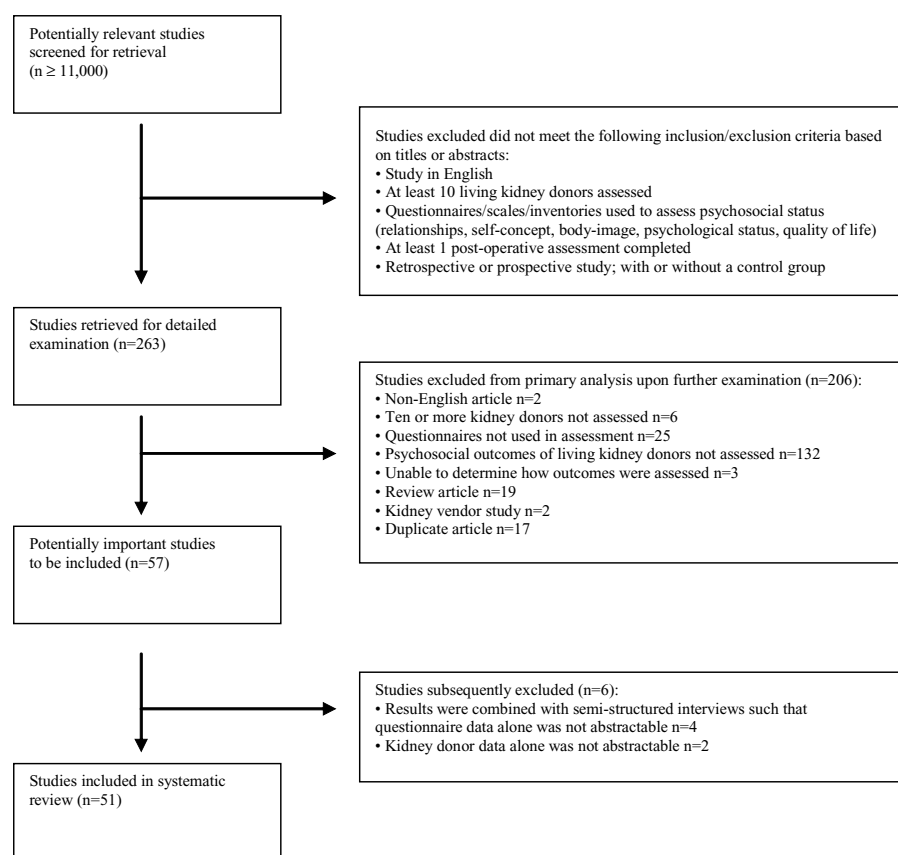
Figure 1: Selection of psychosocial outcome studies of living kidney donors.

psychological, social, quality of life and *questionnaires* were used in the search strategies. We pilot-tested the search strategies and modified them to ensure that they identified known eligible articles. The "Related Articles" feature on PubMed, reference lists of previous review articles (4,5) and reference lists of all included studies were also reviewed. The eligibility of each citation was evaluated and the full-text article was retrieved for any citation considered potentially relevant. When psychosocial outcomes from the same group of donors were described in multiple publications, we reviewed them all and cited the most representative one (6–22).

Data abstraction and analysis

Two reviewers (KKC, HTP) abstracted the following data from all studies meeting eligibility criteria: setting, methods, donor characteristics, control group characteristics, psychosocial measurements and their outcomes. Questionnaire-based outcomes were reported in a descriptive fashion, as substantial differences amongst the primary studies precluded the use of a meta-analysis to combine results.

Results

Study selection

We screened over 11,000 citations, retrieved 263 full-text articles and evaluated the eligibility of each article (Figure 1). Fifty-seven studies met our review criteria and six were subsequently excluded (23–28).

Description of studies

The 51 studies were published between 1969 and 2006 (Table 1) (29–79). Studies were from 19 countries; most were conducted in the United States (43% of studies) followed by Germany (10%), Canada (6%), India (4%), Sweden (4%), Australia (4%), the Netherlands (4%) and Switzerland (4%). During follow-up, 46 studies assessed the physical health of donors (29–36,38,40–46,48–51,53–61,63–79) and 26 reported that some donors had faced graft failure or recipient death (29,31–36,38,40,41,43–46,48–50,53,60,63,67,70–73,77). Some reported outcomes for a select subgroup of donors, such as those where the recipient was still alive (51) or where donors were parents to recipient children who were of minor age (42,73,75). Ten compared the outcomes of laparoscopic donors to those who received an open nephrectomy (50,53,57,60,62,66,75–77,79) and one compared the outcomes of donors who underwent two different open procedures (69).

Methods appraisal

Fourteen studies provided minimal to no demographic information or relevant descriptors for their donor participants (29–32,39,41,55,58,59,69,73,75–77). A decision to follow donors prospectively in time was described in 10 studies (32,37,39,52,53,63,65,71,72,77).

Table 1: Characteristics of psychosocial outcome studies of living kidney donors

Source	Journal	Primary location	Prospective study	No. of donors	Year(s) of donation	Donor age in years, mean (range)[1]	Years after donation, mean (range)	Control group[2]	Response rate, %[3]
Eisendrath et al., 1969 (29)	Surg Gynecol Obstet	Boston, USA	No	57	1954–1967	...	...	No	88
Bennett et al., 1974 (30)	Surg Gynecol Obstet	Boston, USA	No	80	1954–1973	...	...	No	53
Brown et al., 1982 (31)	Dial Transplant	Burlington, USA	No	26	1972–1980	...	...	No	72
Simmons et al., 1982 (32)	Transplant Proc	Minneapolis, USA	Yes	135	1970–1973	...	...(5-9)	Yes	90
Smith et al., 1986 (33)	Am J Kidney Dis	USA[4]	No	536	1974–1986	37 (17-75)	...	No	58
Morris et al., 1987 (34)	Transplant Proc	Newcastle, Australia	No	12	1980–1985	32 (19-57)	1.4 (0.75-1.92)	No	80
Prandini et al., 1987 (35)	Transplant Proc	Bologna, Italy	No	32	1970–1980	42 (22-54)	6.2 (5.2-16.5)	No	82
Gouge et al., 1990 (36)	Transplant Proc	Washington, USA	No	36	1970–1984	...	...	Yes	80
Varma et al., 1992 (37)	Indian J Med Res	Chandigarh, India	Yes	31	...	46 (20-70)	0.02 (...)	No	...
Westlie et al., 1993 (38)	Nephrol Dial Transplant	Oslo, Norway	No	494	1969–1987	48 (18-81)	6.7 (1-19)	Yes	87
Yoo et al., 1996 (39)	Transplant Proc	Seoul, Korea	Yes	50	...	...	...	Yes	...
Schover et al., 1997 (40)	J Urol	Cleveland, USA	No	167	1983–1995	39 (...)	6 (1-12)	Yes	61
Terasaki et al., 1997 (41)	Clin Transpl[5]	USA[4]	No	176	1987–1997	...	...	No	...
Karrfelt et al., 1998 (42)	Transplantation	Huddinge, Sweden	No	35	1981–1994	...	5.2 (0.1-10)	Yes	73
Toronyi et al., 1998 (43)	Transpl Int	Budapest, Hungary	No	30	1973–1996	...	8.9 (...)	No	39
Duque et al., 1999 (44)	Urology	Boston, USA	No	52	...	43 (...)	2.5 (0.6-4.8)	No	52
Johnson et al., 1999 (45)	Transplantation	Minneapolis, USA	No	524	1984–1996	41(17-74)	5 (...)	Yes	60
Vlaovic et al., 1999 (46)	Can J Urol	Toronto, Canada	No	104	1991–1996	42 (24-66)	3.2 (0.7-6.5)	No	68
Corley et al., 2000 (47)	Nephrol Nurse J	Virginia, USA	No	55	...	...	...	Yes	76
Ferhman-Ekholm et al., 2000 (48)	Transplantation	Stokholm, Sweden[4]	No	370	1964–1995	49 (25-76)	12.5 (2-34)	Yes	92
Peters et al., 2000 (49)	Clin Transplant	Jacksonville, USA	No	42	1989,94,95–98	45 (25-64)	...	No	70
Wolf et al., 2000 (50)	J urol	Ann Arbor, USA	No	33	1997–1999	37 (...)	0.1 (...)	No	66
De Graaf Olson et al., 2001 (51)	Prog Transplant	San Francisco, USA	No	62	1995–1998	42 (24-66)	1.9 (0.2-4)	Yes	56
Taghavi et al., 2001 (52)	Transplant Proc	Mashhad, Iran	Yes	40	1998–1999	22 (18-40)	0.2 (...)	No	...
Wolf et al., 2001 (53)	Transplantation	Ann Arbor, USA	Yes	47	1998–1999	40 (19-67)	0.1 (...)	No	94
Isotani et al., 2002 (54)	Urology	Japan[4]	No	69	1981–2001	45 (17-63)	7 (0.3-14)	Yes	66
Ramcharan et al., 2002 (55)	Am J Transplant	Minnesota, USA	No	256	1963–1979	...	... (20-37)	Yes	33
Cabrer et al., 2003 (56)	Transplant Proc	Barcelona, Spain	No	22	2000–2002	53 (28-66)	0.5 (...)	No	...
Perry et al., 2003 (57)	J Urol	Los Angeles, USA	No	120	...	40 (...)	0.7 (0.5-1)	Yes	76
Schostak et al., 2003 (58)	Transplant Proc	Berlin, Germany	No	52	1992–2002	...	6.9 (...)	No	51
Chen et al., 2004 (59)	Transplant Proc	Taoyuan, Taiwan	No	17	1992–2002	...	...	Yes	...
Giessing et al., 2004 (60)	Transplantation	Berlin, Germany	No	106	1983–2001	46 (19-67)	6.3 (1-18.8)	Yes	90
Jordan et al., 2004 (61)	J Nephrol	Frankfurt, Germany	No	112	1973–2001	45 (...)	11.1 (...)	Yes	77
Lind et al., 2004 (62)	Surg Endosc	The Netherlands	No	125	1994–2001	49 (22-76)	4.9 (1.8-8.9)	No	72
Smith et al., 2004(63)	Transplantation	Melbourne, Australia	Yes	48	1998–2002	49 (26-72)	0.7 (...)	Yes	94
Tanriverdi et al., 2004 (64)	Transplant Proc	Ankara, Turkey	No	18	2002–2003	40 (21-59)	3 (0.1-10)	Yes	90
Bergman et al., 2005 (65)	Am J Transplant	Montreal, Canada	Yes	35	2001–2004	40 (...)	0.1 (...)	Yes	45
Buell et al., 2005 (66)	Clin Transplant	Cincinatti, USA[4]	No	67	1991–2001	43 (...)	...	Yes	53
Fisher et al., 2005 (67)	Nephrol Nurse J	Akron, USA	No	87	1967–2005	...	7.4 (0.5-31)	Yes	...
Goecke et al., 2005(68)	Transplant Proc	Santiago, Chile	No	29	...	...(21-50)	..(10-26)	No	...

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Table 1: continued

Source	Journal	Primary location	Prospective study	No. of donors	Year(s) of donation	Donor age in years, mean (range)[1]	Years after donation, mean (range)	Control group[2]	Response rate, %[3]
Jackobs et al., 2005 (69)	World J Urol	Hannover, Germany	No	139	1996–2002	...	...	Yes	80
Rudow et al., 2005 (70)	Prog Transplant	New York, USA	No	32	2000–2002	...	...	No	46
Lumsdaine et al., 2005 (71)	Transpl Int	UK[4]	Yes	40	2000–2004	49 (24-71)	1 (0.1-1)	Yes	73
Minz et al., 2005 (72)	Transplant Proc	Chandigarh, India	Yes	75	2003	43 (...)	0.3 (...)	Yes	...
Neuhaus et al., 2005 (73)	Pediatr Nephrol	Zurich, Switzerland	No	19	1992–1999	...	...	Yes	95
Stothers et al., 2005 (74)	Kidney Int	Vancouver, Canada	No	98	1997–2001	44 (...)	...	Yes	77
Troppmann et al., 2005(75)	Peditr Nephrol	Sacramento, USA	No	19	...	...	...	Yes	66
Dahm et al., 2006 (76)	Nephrol Dial Transplant	Zurich, Switzerland	No	108	1977–2003	...	... (1-21.3)	No	88
Kok et al., 2006 (77)	BMJ	The Netherlands[4]	Yes	89	...	...	0.5 (...)	No	88
Reimer et al., 2006 (78)	Transplantation	Essen, Germany	No	47	1999–2003	51 (28-71)	2.6 (...)	Yes	72
Rodrigue et al., 2006 (79)	Prog Transplant	Florida, USA	No	84	1988–2002	43 (...)	5.9 (...)	Yes	42

Studies organized by the year of publication.
Ellipses (...) indicate not available.
[1] Age is reported at the time of donation.
[2] Control groups included samples of the general population, potential donors, partners of living kidney donors, relatives of potential recipients newly listed on the deceased transplant wait-list, or parents of children who received kidney transplants but did not donate because either they were not medically suitable or had other reasons.
[3] Response rate for those donors who were considered for study.
[4] Multicenter study.
[5] Nonpeer reviewed source.

The remaining studies contacted previous donors' months to years after nephrectomy, with 20 studies not reporting the average time since donation (29–33,36,39,41,47,49,55,59,66,68–70,73–76). The number of donors considered for follow-up was often unreported and thus for some studies, the response rate could not be calculated (37,39,41,52,56,59,64,68,72). When reported, an average of 71% (range of 33–95%) of eligible participants responded. Reasons for incomplete responses were offered by 20 studies (29,30,32,34,38,40,45,46,48,51,55,58,61,63,65; 67,71,73,78,79). Furthermore, 11 collected information on nonresponders (40,44,46,48,50,60,62,63,65,73,78) and five compared their characteristics to responders (40,44,46,50,65).

Description of donors

Across all studies, a total of 5139 donors were assessed. When reported, the average time since donation was 4 years (range 1 week to 37 years), the mean age at donation was 42 years, an average of 61% were female and the majority were Caucasian. Furthermore, an average of 43% were parents, 31% were siblings, 16% were spouses and 8% were children of the recipient. The majority were married and employed at the time of follow-up. Twenty-three studies described the use of routine preoperative screening (30–32,34,40,45,46,49–51,53,54,56,60,61,63,67,70,71,73,74,77,78) and 3 reported that some donors had a psychiatric history prior to donation (30,34,63).

Description of controls

Twenty-nine studies compared the psychosocial functioning of donors to nondonor controls from diverse sources, including the general population, medical outpatients, potential donors, healthy individuals, or family members of the recipient (32,36,38–40,42,45,47,48,51,54,55,57,59–61,63–67,69,71–75,78,79). Demographics or other relevant descriptors were provided for the control group in four studies (36,38,40,64). In some studies, donors and controls were matched for age (40,48,55,57,60,64,65,71), sex (48,60,64) and level of education (64).

Description of questionnaires

A number of questionnaires were used across studies (Table 2). Many used standardized instruments such as the Short-Form 36 health survey (45,48,51,54,55,57,59,60,63–66,68,69,75,77–79) and the Beck Depression Inventory (39,64,72). Investigator-developed questionnaires were also used in a majority of studies (29–33,35,36,38,40–49,54,56–58,60,64,67,69–76,78,79). Some studies reported that questionnaires were valid (33,36,38,70,74), reliable (32,38,47,67,74) and pilot tested (33,74). When reported, questionnaires were most often self-administered through the mail, internet, or in clinic (29–31,33,36,38, 40–42,44–46,48–51,53–57,59,60,62,63,66,67; 69–71,73–76,78).

Social Function

Twenty-five studies examined the quality of a donor's relationship with their recipient, spouse, nonrecipient children and family members after donation (Table 2).

Many donor-recipient relationships were similar or improved in the 21 studies which examined this outcome (30–33,35,36,40,42,44–46,58,60,67,69–73,75,76). Across 15 studies, which reported results in a similar manner, 86 to 100% of donors indicated that their relationship was unchanged or improved (Table 3). Donors also reported a significant increase in the amount of time they spent with the recipient (33). Additionally, 68% of parental donors reported that it was "true" or "very true" that their relationship with their recipient child had since improved, with many of their partners noting a similar improvement (73). Twenty percent of laparoscopic and 78% of open donors noted an improved relationship with their recipient (75) and in another study, 36% from each group felt closer to their recipient emotionally (76).

Many donor-partner relationships including the marital relationships of spousal and nonspousal donors, were similar or improved in the majority of 10 studies which examined this outcome (33,36,40–42,45,46,49,73,75). Across five studies, which reported results in a similar manner, 82 to 98% of donors indicated that their relationship was unchanged or improved (Table 3). Likewise, 58% of parental donors indicated it was "true" or "very true" that their marital relationship had since improved with many partners noting a similar improvement (73). In another study, 90% noted no change or an improvement in their marital, recipient, personal, or sexual relationships (49). Eighty and 89% of donors who had laparoscopic and open procedures respectively, perceived no change in their relationship with their partner (75). However, in one study, a third of divorce(e)s cited donation as a reason for separation, although the divorce rate amongst donors in the study was lower than the general population (33). In another study, one donor believed the transplantation experience led to their divorce (40).

Across two studies, 95 to 100% of spousal and parental donors had a similar or better relationship with their nonrecipient children (Table 3). In another, 37% of parental donors indicated that it was "true" or "very true" that their relationship(s) had improved, with similar improvements described by their partners (73).

Across four studies, 83 to 100% of donors reported that their general family relationships were similar or improved (Table 3), a finding which was analogous to another study (71). Twenty-five percent felt that their family was closer to them (32). However, five donors in another study reported that the experience led to family conflicts (78). Social relationships and community involvement were found to be unchanged or improved (36,38,41,45,46,72).

Table 2: Psychosocial outcomes assessed by questionnaires in studies of living kidney donors

Source	General standardized or validated instruments	Used structured questionnaires developed by kidney donor investigators	Psychosocial outcomes				
			Social function	Self-concept	Body image	Psychological function	Quality of life
Eisendrath et al. (29)	None	Yes		✓		✓	
Bennett et al. (30)	None	Yes	✓	✓		✓	
Brown et al. (31)	None	Yes	✓			✓	
Simmons et al. (32)	Rosenberg self-esteem scale, Affect balance scale	Yes	✓	✓	✓	✓	
Smith et al. (33)	None	Yes	✓		✓	✓	
Morris et al. (34)	General health questionnaire	No				✓	
Prandini et al. (35)	None	Yes	✓			✓	
Gouge et al. (36)	Affect balance scale, Index of general affect, Index of well-being, other satisfaction items	Yes	✓	✓	✓	✓	✓
Varma et al. (37)	PEN inventory, middlesex hospital questionnaire, PGI locus of control	No		✓		✓	✓
Westlie et al. (38)	None	Yes	✓	✓		✓	✓
Yoo et al. (39)	BDI, hostility scale from SCL90, death anxiety scale, rotter's internal-external control, index of well-being	No		✓		✓	
Schover et al. (40)	SF 20	Yes	✓		✓	✓	✓
Terasaki et al. (41)	None	Yes	✓				
Karrfelt et al. (42)	None	Yes	✓	✓		✓	
Toronyi et al. (43)	None	Yes		✓			
Duque et al. (44)	None	Yes	✓	✓	✓	✓	✓
Johnson et al. (45)	SF 36	Yes	✓	✓		✓	✓
Vlaovic et al. (46)	Illness intrusiveness subscale	Yes	✓	✓		✓	
Corley et al. (47)	Rosenberg self-esteem scale, affect balance scale, ferrans and powers, ladder of life	Yes		✓		✓	✓
Fehrman-Ekholm et al. (48)	SF 36	Yes				✓	✓
Peters et al. (49)	None	Yes	✓				
Wolf et al. (50)	SF 12	No					✓
De Graaf Olson et al. (51)	SF 36	No					✓
Taghavi et al. (52)	SCL90	No				✓	
Wolf et al. (53)	SF 12	No					✓
Isotani et al. (54)	SF 36	Yes				✓	✓
Ramcharan et al. (55)	SF 36	No					✓
Cabrer et al. (56)	None	Yes				✓	✓
Perry et al. (57)	SF 36	Yes			✓	✓	✓
Schostak et al. (58)	None	Yes	✓		✓		
Chen et al. (59)	SF 36	No					✓
Giessing et al. (60)	SF 36, giessen subjective complaints list	Yes	✓			✓	✓
Jordan et al. (61)	BSI, questionnaire of self-efficacy and locus of control, antonovsky's sense of coherance	No		✓		✓	
Lind et al. (62)	Body image questionnaire	No			✓		
Smith et al. (63)	SF 36, patient health questionnaire	No				✓	✓
Tanriverdi et al. (64)	BDI, BAI, SF 36	Yes				✓	✓
Bergman et al. (65)	SF 36	No					✓
Buell et al. (66)	SF 36, HrQOL item	No					✓

Table 2: continued

Source	General standardized or validated instruments	Used structured questionnaires developed by kidney donor investigators	Psychosocial outcomes				
			Social function	Self-concept	Body image	Psychological function	Quality of life
Fisher et al. (67)	SF 12	Yes	√			√	√
Goecke et al. (68)	SF 36	No					√
Jackobs et al. (69)	SF 36	Yes	√		√	√	√
Rudow et al. (70)	None	Yes	√			√	
Lumsdaine et al. (71)	WHO QOL bref	Yes	√			√	√
Minz et al. (72)	BDI, State and trait anxiety, social support questionnaire	Yes	√			√	
Neuhaus et al. (73)	None	Yes	√			√	
Stothers et al. (74)	None	Yes		√		√	
Troppmann et al. (75)	SF 36	Yes	√	√			√
Dahm et al. (76)	None	Yes	√	√		√	
Kok et al. (77)	SF 36, body image questionnaire	No			√		√
Reimer et al. (78)	SF 36, BSI	Yes	√	√		√	√
Rodrigue et al. (79)	SF 36	Yes				√	√

BDI/BAI = Beck depression/anxiety inventory; SF 36/20/12 = short form 36/20/12 health survey; SCL90 = symptom checklist 90; BSI = brief symptom inventory; WHO QOL = World Health Organization quality of life; HrQOL = health-related quality of life.

Self-Concept

Self-concept was examined in 18 studies (Table 2). In 6 studies, many donors reported an increase in self-esteem or self-worth after donating (29,32,45,47,74,78) and in another, 2% felt more confident (30). In three studies, donors scored the same or better on measures of self-esteem compared to the general population or nondonor controls (32,36,38). Also, increases in self-satisfaction were noted in a third of parental donors (42) and compared to the general population, donors felt more satisfied with themselves (38). Fifteen to 58% felt proud, brave, or heroic (32,47) and 35% and 42% felt that they were a better person (32,47). Some developed a better understanding of others (29,30), gained deeper religious faith (29), experienced a sense of accomplishment (29) and noted personal improvements (46). Comparing donors who had different operative procedures, 60% and 89% of laparoscopic and open donors respectively, felt better about themselves after donating (75) and one quarter of donors from both groups felt rewarded by their experience (76). Scores on a questionnaire of self-efficacy and locus of control and on a measure of personal coherence were higher than the general population (61). On other locus of control measures, scores were not different after surgery (37,39) and were not different from controls (39).

However in one study, donors reported that they did not feel any better about themselves after donation (43) and 6% and 24% felt that they had given up something for nothing in return (32,47).

Body Image

Ten studies considered the donors perception of their physical appearance and their nephrectomy scar after donation (Table 2). The majority of donors in two studies perceived no meaningful change in their appearance (33,36) (Table 3) and most were either not bothered or did not consider their nephrectomy scar unattractive (33,40,44). In fact, 15% in another study indicated that their scar made them feel more attractive (40). In a study of flank donors, 83% felt that their scar had no impact on their self-esteem or quality of life (44). Comparing donors who had different operations, the mean body image and cosmetic scores of both laparoscopic and open donors were high and similar in one study (62) and nonsignificantly favored donors who underwent laparoscopic surgery over mini-incision surgery in others (57,77).

Adverse outcomes were noted in a minority of donors. Two percent perceived themselves as less attractive to their partner (33). Thirteen percent reported major cosmetic impairment in relation to their nephrectomy scar with fewer mini-incision donors reporting impairment over classical flank incision donors (69). In another study of donors who had a flank incision, 8% reported that their scar was too long or that its position was unfavorable and had decreased their self-esteem (58). Shortly after surgery, 26% were bothered at least a little by the size of their scar (32).

Psychological Well-Being

Thirty-six studies considered the emotional well-being of donors after nephrectomy, along the development

Table 3: Psychosocial outcomes in studies of living kidney donors

| Source | Years after donation | No. of donors | Proportion who reported no change or an improvement | | | | Proportion who reported no change | Proportion who reported no symptoms | |
			Relationship with recipient	Relationship with spouse/ partner	Relationship with non-recipient children	Relationship with family	Attractiveness	Depression	Anxiety
Bennett et al. (30)	. . .	80	86%	. . .	. . .	. . .	. . .	. . .	94%
Brown et al. (31)	. . .	26	96%	. . .	. . .	. . .	. . .	. . .	. . .
Simmons et al.[1] (32)	1	111	94%	. . .	. . .	. . .	. . .	. . .	. . .
Smith et al. (33)	6.7	174	96%	. . .	. . .	. . .	93%	. . .	86%
Prandini et al. (35)	6.2	32	100%	. . .	. . .	100%	. . .	91%	. . .
Gouge et al. (36)	. . .	36	. . .	. . .	. . .	. . .	83%	. . .	. . .
Schover et al. (40)	6	167[2]	96%	87%	. . .	. . .	. . .	93%	. . .
Terasaki et al.[3] (41)	. . .	176	. . .	98%	100%	. . .	. . .	. . .	. . .
Karrfelt et al. (42)	. . .	35[2]	100%	89%	95%	. . .	. . .	. . .	. . .
Duque et al. (44)	2.5	52	94%	. . .	. . .	. . .	. . .	. . .	. . .
Johnson et al. (45)	5	524[2]	98%	92%	. . .	97%	. . .	. . .	. . .
Vlaovic et al. (46)	3.2	104	98%	82%	. . .	83%	. . .	. . .	. . .
Schostak et al. (58)	. . .	52	96%	. . .	. . .	. . .	. . .	. . .	. . .
Giessing et al. (60)	6.3	106	100%	. . .	. . .	. . .	. . .	. . .	. . .
Fisher et al. (67)	7.4	87	97%	. . .	. . .	. . .	. . .	89%	. . .
Minz et al. (72)	0.3	75	100%	. . .	. . .	96%	. . .	95%	. . .
Troppmann et al. (75)	. . .	19	100%	. . .	. . .	. . .	. . .	. . .	. . .

Studies organized by the year of publication.
Ellipses (. . .) indicate not reported or not reported in a similar way.
[1] Recipients had successful transplant.
[2] A small proportion of donors did not answer the questions for all outcomes. The proportions presented are for those donors who provided a valid response. For example, for the study by Karrfelt, 89% of donors reported no change or an improvement in their martial relationship, while 11% reported a deterioration in their martial relationship.
[3] Study of spousal donors.

of stress, depression, anxiety and other psychiatric symptoms (Table 2).

Emotions and general affect

Ninety-five percent of donors were generally happy (47) and a majority (greater than 80% in one study) felt happier after donation (44,67). Twenty-four percent had improved emotions (69) and none experienced problems requiring medical attention (33). After surgery, 35% and 55% felt that they were treated as special people (40,67). Compared to the general population, donors were more calm, content, cheerful, less likely to feel life was meaningless and felt more strongly that life was worth living (38). Most donors felt that at least some of their psychological expectations had been met (69). In other studies, there was no change in various emotions or feelings after the surgery, with some studies demonstrating similarities between donors, potential donors and the general population (35–39).

Some donors experienced less positive outcomes. In one study, 4% were disappointed with the emotional experience of donation (40). Two studies reported that 6% and 8% felt ignored (40,67) and one donor felt unappreciated (31). Feelings of abandonment were noted (33). Two

percent of donors reported disappointment related to the surgery (67). Nine percent of laparoscopic donors felt sadness and loss (76). Of donors faced with adverse recipient outcomes, 13% felt the procedure had been a waste and 5% felt guilty (40) and of those whose recipient died, only 50% felt that their experience had been worth it (31). When assessed for hostility, donor scores at one and six months after donation were higher than predonation and control group scores (39).

Depression and anxiety

Across five studies, 77 to 95% of donors experienced no symptoms of depression after donation (35,40,45,67,72) (Table 3). On the Beck Depression Inventory, one study noted that donors demonstrated less depressive symptoms than controls though scores were not statistically different (64) and in another study, there was no difference between preoperative, postoperative and control group scores (39). On another measure, compared to their preoperative scores, donors scored as less depressed at 1 year and 5 to 9 years after their donation and also scored significantly better than nondonor controls (32). Across 2 studies, 86 to 94% of donors experienced no undue anxiety after donation (30,33) (Table 3). On the Beck Anxiety Inventory,

donors did not score statistically different from matched controls (64). In another study, donors scored lower in state and trait anxiety 3 months after nephrectomy and none had a major anxiety disorder (72). Analogous results were noted when donors were questioned about symptoms of depression or anxiety as a combined outcome (29,45).

Some donors had less positive outcomes. In another study that used the Beck Depression Inventory, scores were significantly worse three months after nephrectomy (72). Six percent of donors experienced an increase in pre-existing depression or anxiety (35). One donor reported feeling downhearted all of the time (67). Shortly after their surgery, 31% felt depressed and 19% felt more like crying (32). In another study, donors were more anxious about death 1 and 6 months after donation (39).

Stress
Donation-related stress was noted by donors. For 39%, the overall experience was at least somewhat stressful (45). When donors who underwent laparoscopic nephrectomy were compared to those who underwent open nephrectomy, stress scores were not significantly different (57).

Across studies, donors were questioned about specific causes of distress. Six to 22% found the surgery and recovery stressful (33,45,48,72) and several in another found it unsettling (29). Their physical postoperative state was stressful for 34% and 49% of donors (40,67) and 53% experienced at least some physical distress at work (78). Having one kidney caused worry for 3 to 36% (40,67,72–74,76) and 31% of donors in two studies worried about their kidney failing (36,64). However, a prospective study noted no significant change in donors' level of worry about their remaining kidney after donation (71). Across other studies, a proportion were worried about the complications of nephrectomy (50% of donors) (64), an insult to their own health (14% and 36%) (32,47), future kidney problems (6%) (70) and their future health in general (14%) (45). Eight percent of laparoscopic donors worried about needing a kidney transplant in the future (76). Furthermore, 8% were concerned about medical costs and 14% were worried about loss of income (45). The acquisition of insurance was worrisome for 11% to 14% (33,45,46,54). Donors experienced financial stress and hardship (31,33,40,45,46,54,56,57,60,67,69,73,74,78,79) and difficulty obtaining insurance (33,40,67,69). Four to 50% worried about recipient outcomes (31,64) and some worried about the side effects of immunosuppression (31). In other studies, more than a third of donors reported feeling anxious about their own health, work, health insurance and recipient health after donation (60).

Other psychiatric symptoms
In one study, 72% of donors experienced no psychiatric and psychosomatic symptoms and reported fewer symptoms than nondonors both before and after donation (42).

Ninety-four percent of donors in another study, reported no concerning mental problems (78). Compared to the general population, donors had lower psychiatric symptom scores (61) and on a measure that assessed physical complaints attributable to psychosomatic reasons, donors scored better, with no significant difference noted in the scores of laparoscopic and open donors (60).

Less positive outcomes were noted. A donor scored high in psychiatric symptomatology, but incidentally also had a history of drug abuse (34). On a measure of psychiatric symptoms, 6 donors exhibited relevant mental distress, although their average scores were in the normal range (78). Of those who faced adverse recipient outcomes, 11% experienced suicidal ideation (40). In one study, two of four donors whose recipients died considered counseling and one followed through with it (31). The psychological status and distress scores of 33% of donors worsened 1 and 3 months after surgery, with cases of depression, anxiety, sensitivity, paranoia, aggression, intractability and obsession noted (52). The one-week postoperative scores of donors were significantly higher in the area of somatization, although other scores did not meaningfully change (37).

Quality of life

Quality of life was assessed in 29 studies (Table 2). Donors reported a high satisfaction with their quality of life (47,64) and 95% in one study indicated that it was unchanged after donation (56). Twenty-two studies used versions of the Short Form Health Survey (i.e. SF 36, 12 and 20) (Table 2). In 17 of these studies, many donor scores were similar or better than the general population (45,48,51,54,55,57,59,60,63–67,69,75,78,79). Similarly, donors scored higher than the general population on a measure of quality of life for the past, present and future (47). Additionally, quality of life scores were no different or better for donors who received a laparoscopic nephrectomy compared to those who received an open procedure (50,53,57,60,66,75,77,79) and there was a trend to better quality of life scores in those donors who received an anterior vertical miniincision compared to a classical flank incision (69).

Less positive outcomes were also noted. In one study, the donor mental component summary score of the SF 36 was significantly worse at 4 and 12 months after surgery, although it was not below the level of the general population (63). In another study that used the SF 36, donors scored worse on some dimensions postdonation (including social functioning), although their mental component summary score did not change (65). Another noted that donors had an adequate quality of life perception but had a slight tendency toward depression (68). On a World Health Organization quality of life survey, donors had a lower mean psychological domain score 6 weeks after donation,

although their score was significantly higher than the general population (71). On a questionnaire assessing social, vocational, personal, family and cognitive functioning, insignificant dysfunction was noted after donation (37). In a study of open nephrectomy donors, their average mental health scores on the SF 20 were between medical outpatients and healthy adults (40).

Discussion

When all available literature is considered, the psychosocial health of most donors appears unchanged (36,71) or positively improved (33,46,54) by donation. While negative outcomes such as lower-quality relationships, feelings of unattractiveness, depression, anxiety, stress, a decrease in quality of life and psychiatric symptoms were noted, the proportion of donors who experienced these events was small (32,40,44,59,64,72,73). Importantly, a majority reported that they would undergo the experience again (29,31,33,38,40,42,44,45,48,49,54,56,58,60,61,67–72,75,76,78).

Several factors may have contributed to negative outcomes described in several donors. Existing marital or familial discord may have been aggravated by the stress of donation (33). Adverse recipient outcomes may have lead to depression, feelings of waste or guilt and conflict in the donor-recipient relationship (67). Lack of support (37,72) may have contributed to distress. The physical stress of donation may have lead to feelings of hostility and anxiety about death. Comparing nephrectomy techniques, there was a trend of lower quality of life and poorer body image in donors who received a classical flank or mini-incision compared to a laparoscopic procedure. Finally, it is possible that some individuals would have developed negative outcomes even if they had not become a donor.

Strengths and Weaknesses of this Review

This comprehensive review summarized all available questionnaire-based literature on the psychosocial implications of living kidney donation. The 51 studies were published over 37-years and included donors from around the world, who had different operative experiences and who faced variable recipient outcomes.

We systematically assessed the quality of existing studies (80). Pertinent information often went unreported, including methods of recruitment, characteristics of eligible and participating donors and reasons for loss to follow-up or missing data. Spurious conclusions may have resulted from small study samples and low response rates (33,34). Nonresponders may have differed from responders, as highlighted in a study where some with adverse outcomes did not participate (78). The majority of studies were conducted retrospectively and donors contacted

many years after donation may have a biased recall. Having already gone through the experience, donors may find it difficult to express negative feelings (33,34,40). Few studies collected data anonymously and donors may have been less likely to report adversity if studies were conducted by members of the transplant team.

It is noteworthy that the few studies that did assess donors prospectively were more likely to report postdonation depression, poorer quality of life scores and psychological functioning. However, such assessments were often made shortly after surgery and whether such findings are persistent remains unclear (78). Also, a study reporting several adverse postdonation outcomes used different donor sub samples before and after donation, which may have not been a valid approach if the groups were inherently different (39).

The suitability of control groups warrants consideration. Most donors are agreeable, motivated (38,39), altruistic (38,39) and healthy (38). Thus, ideal controls are those who are medically and psychologically fit to donate, but do not do so for other reasons. In most studies, national data from population surveys were used and the use of such controls may underestimate any psychosocial morbidity attributable to donation.

The suitability of questionnaire-based assessments also requires examination. Generic, standardized measurements allow comparisons to be made with other patient populations. However, answers on such surveys may be superficial for such a complex experience. Indeed, donors show high social desirability (39,40) and often, regardless of their experiences, respond to questionnaires in a positive manner. Most studies used investigator-developed questionnaires, only a few of which had been externally validated. None provided definitions for their outcomes of interest. Furthermore, surveys were administered in different settings and in different fashions. While qualitative and open interview based approaches can be used to solicit a rich narrative experience, such techniques did not lend themselves easily to quantitative summary, thus, only questionnaire-based findings were reported in the current review.

Informed Consent, Support and Follow-up

The psychosocial function of most donors appears to be unaffected or improved by kidney donation. However, some donors may experience psychosocial morbidity and the seriousness of such events cannot be underestimated (45). Potential donors need to be informed of all the outcomes they may potentially face (33,45,51,60,63)· Harms may be minimized through careful donor selection (32,71,78). Also, health policies which fairly reimburse live organ donors for their nonmedical expenses may help reduce undue stress (81,82).

Donor support and follow-up is essential. Support from family and friends (31), the health care team (67) and other donors (30,31,56,67) should be routine and long-term (31,34,39,48,51,54,60,67,72,74). Suggested strategies for implementing follow-up include having nurses act as liaisons for donors (47), phone calls after donation (51) and using validated surveys to standardize the assessment of outcomes (63,78). Many donors desire such follow-up (31,40,42,49,51,52,54,60,63,67,70). For those facing adverse outcomes, early counseling may help alleviate psychosocial morbidity (40,67,78).

Future Research

A better understanding of the psychosocial implications of living kidney donation will come from large, multicentre, prospective, cohort studies, which use appropriate controls and follow participants regularly, for a prolonged period. Studies should aim to limit participation and recall biases and minimize loss to follow-up especially amongst those donors who face poor transplant outcomes. Key characteristics of eligible and participating donors should be reported, along with study recruitment methods and response rates (80). Reporting any pertinent information on nonresponders would be of interest (80). To reduce response bias, studies should be carried out by individuals not directly associated with the transplant team or those blinded to whether the participant is a donor or a control. Donor relationships, depression, anxiety, stress, psychiatric symptomatology and quality of life may be assessed. Such studies may highlight greater adversity after donation and help elucidate those at risk. This knowledge is essential for better donor selection and guides methods to best identify those donors in most need of support and education (52).

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The Long-Term Quality of Life of Living Kidney Donors: A Multicenter Cohort Study

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Previous studies that described the long-term quality of life of living kidney donors were conducted in single centers, and lacked data on a healthy nondonor comparison group. We conducted a retrospective cohort study to compare the quality of life of 203 kidney donors with 104 healthy nondonor controls using validated scales (including the SF36, 15D and feeling thermometer) and author-developed questions. Participants were recruited from nine transplant centers in Canada, Scotland and Australia. Outcomes were assessed a median of 5.5 years after the time of transplantation (lower and upper quartiles of 3.8 and 8.4 years, respectively). 15D scores (scale of 0 to 1) were high and similar between donors and non-donors (mean 0.93 (standard deviation (SD) 0.09) and 0.94 (SD 0.06), p = 0.55), and were not different when results were adjusted for several prognostic characteristics (p = 0.55). On other scales and author-developed questions, groups performed similarly. Donors to recipients who had an adverse outcome (death, graft failure) had similar quality of life scores as those donors where the recipient did well. Our findings are reassuring for the practice of living transplantation. Those who donate a kidney in centers that use routine pretransplant donor evaluation have good long-term quality of life.

Key words: Nephrectomy, psychosocial, quality of life

Introduction

As they donate a part of themselves to another person, there is an ethical imperative to provide living kidney donors with full and accurate knowledge of the potential risks and benefits that they may face (1,2). In a systematic review of their psychosocial health after living kidney donation, studies generally reported that the majority of donors experience no change or an improvement, with a minority experiencing adverse outcomes including depression and anxiety (3). On standardized quality of life scales including the Short Form 36 Health Survey (SF36), donors and nondonors have scored similarly (1, 4–8). Past studies, however, were often limited as they lacked a suitable healthy, nondonor comparison group to whom donor outcomes could be contrasted.

To extend current knowledge, we conducted a multicenter, retrospective cohort study examining the medical and quality of life outcomes of the live kidney donor. The medical outcomes of this study will be described in a separate report (9). Quality of life is a 'multidimensional concept which encompasses the physical, emotional and social components associated with illness or its treatment'

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(10). To examine quality of life years after donation we (1) investigated if donors and healthy nondonors scored differently on standardized quantitative quality of life scales and (2) used author-developed questions, to assess their marital status, visits to mental health professionals, use of psychotropic medications, employment status and income, and donation-related attitudes.

Materials and Methods

Recruitment of participants

In brief, living kidney donor databases from nine centers in Canada, Scotland and Australia were reviewed, and donors were contacted by telephone for study participation. Across the centers, all donors were medically and psychosocially fit to donate according to accepted standard criteria for donation (11). Kidney donors were eligible for study participation if they were (1) at least 18 years of age at the time of donation, (2) donated a kidney between the years 1970 and 2007, and (3) spoke English. During the period of accrual no paired exchanges or nondirected donations were performed at any of the participating centers.

A comparison group of healthy nondonors was also assembled. Such individuals had to (1) be healthy at the time of the transplant (i.e. no renal disease, hypertension, diabetes, cardiovascular disease, pulmonary disease or active cancer by historical recall), (2) be at least 18 years of age at the time of the transplant and (3) they had to speak English. As a recruitment strategy, individuals for this healthy nondonor group were suggested by our donor participants. A database of potential nondonors was then generated. Donors could identify more than one potential nondonor. In some cases, donors were not able to identify any such an individual.

Participant assessment

All participants provided written, informed consent before taking part in our study. Participant assessments took place between April 2004 and June 2008. Donors and nondonors were assessed in person or at a distance (by mail or telephone), by research personnel not directly associated with the transplant team. As it has been utilized in prior living donor studies, we used the SF36 as one of our standardized quality of life scales. This validated tool measures quality of life based upon eight dimensions. Raw scores range from 0 to 100 with higher scores indicating a better quality of life. Physical and mental component summary (MCS) scores are also generated. The physical component summary (PCS) is an aggregate score of the physical functioning, role physical, bodily pain and general health domains of the SF36. The MCS is an aggregate of the energy/vitality, social functioning, role emotional and mental health domains (12). The average MCS and PCS scores of the general U.S. population are 50.

To add to our standardized quality of life assessment, we also used the 15D^{TM} version 2.0, a 15-dimensional standardized, validated, questionnaire of health-related quality of life, based upon multiattribute utility theory (10). This measure is thought to be more comprehensive than other quality of life scales in that it assesses dimensions including vision and eating along with mobility, hearing, breathing, sleeping, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity (10). Composite scores range from 0 (representing 'dead') to 1 (representing 'ideal health').

We also utilized the Feeling Thermometer, a visual analogue scale. Participants are able to choose from a continuum of values with scores ranging from 0 (the worst score, representing 'worst imaginable health state') to 100 (the best score, representing 'best imaginable health state'). Furthermore, using 11 author-developed questions, demographic information was collected including participant marital status and their employment and income levels after the transplant. Participants were also asked to indicate if they had seen a psychologist, counselor or psychiatrist since the time of the transplant. We assessed their use of psychotropic medications by analyzing their reported medication list. Donation-related attitudes were investigated by asking donors about the benefit of donation to the recipient, if they felt adequately informed about the risks and benefits of donation around the time of informed consent, and if they would make the same decision to donate again. Questions were pilot tested by a group of experts in living donor issues. We report outcomes according to published STROBE guidelines (strengthening the reporting of observational studies in epidemiology guidelines) (13). Our study was approved by research ethics boards across participating centers.

Statistical methods

We compared donors and healthy nondonors using independent t-tests and Wilcoxon rank sum tests. Our method of identifying nondonors was a recruitment strategy only, and in many cases donors were unable to identify a nondonor participant. Thus, in our primary analysis, donors and controls were considered independent of one another. Based on our power calculations, we were able to detect (with 80% power) differences of 2.72 on the SF36 PCS, 2.80 on the SF36 MCS, 0.26 on the 15D and 4.35 on the Feeling Thermometer, if in truth such differences existed.

Appreciating the possibility of group interdependence, in an additional analysis we calculated the Pearson correlation coefficient of 98 donors and controls who were pairs (i.e. donors who were able to identify a nondonor to participate in the study). There was evidence of some correlation in the SF36 MCS score and some subscales (energy/vitality, social functioning, mental health) (correlation 0.3). Thus a paired dyad analysis was also employed in these instances to examine the consistency of the results with the unpaired primary analysis.

We used linear regression models to determine if SF36 scores and 15D scores differed between donors and nondonors after prespecified adjustment for race, gender, age, relationship to recipient, time since donation and marital status.

Finally, we carried out subgroup analyses using interaction terms to determine whether the effect of donor status (donor vs. control) on the MCS of the SF36 was modified by age at the time of donation (younger or older than the mean age of 43), year of donation (before or after the median year 2000) or relationship to recipient (genetically vs. not genetically related, spousal vs. nonspousal donors). We restricted these analyses to the MCS of the SF36, as it measures the psychological, social and emotional function of an individual, whereas the PCS score is thought to correlate more with one's physical health (12). Within donors, we used linear regression models to determine if SF36 MCS scores differed by surgery type (laparoscopic or open surgery) or recipient outcome (defined by the presence or absence of recipient death or graft failure at any time after donation).

We performed all statistical analyses using SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA). A p value of less than 0.05 for a test was considered statistically significant.

Results

Description of participants

Across participating centers, there were 1140 donors identified from donor databases. A total of 421 donors were eligible for participation and contactable. A total of 235 donors provided informed consent for study participation.

These donors identified the names of 241 potential non-donor controls. In many cases, these were individuals who had come forward for donor evaluation and were deemed medically and psychosocially fit to donate by the transplant team, but for another reason, had not gone on to donate. In some instances another person with a more optimal HLA match to the recipient was chosen instead. Other reasons for nondonation included logistical issues such as work responsibilities and long travel distances. To our knowledge, none of our nondonors were excluded from donation because of psychosocial unfitness. Of those nondonor controls suggested, 172 were subsequently found to be eligible for the study and contactable. Of these, 114 consented to participate.

Questionnaires were completed by 203 donors and 104 nondonors (86% and 91% of individuals who provided informed consent, respectively) (Table 1). Participants who did not complete the study dropped out for personal reasons or we lost contact with them soon after they signed the initial consent form.

Table 1: Study centers involved in living kidney donation psychosocial study

Hospital	Location	Number of donor participants	Number of nondonor participants (controls)
London Health Sciences Centre	London, Ontario, Canada	36	27
University Health Network	Toronto, Ontario, Canada	87	19
St. Michael's Hospital	Toronto, Ontario, Canada	11	7
St. Joseph's Healthcare	Hamilton, Ontario, Canada	39	23
The Ottawa Hospital	Ottawa, Ontario, Canada	15	15
University of Alberta Hospital	Edmonton, Alberta, Canada	2	2
St. Paul's Hospital	Vancouver, British Columbia, Canada	6	3
Western Infirmary	Glasgow, Scotland	2	2
Sir Charles Gairdner Hospital	Perth, Australia	5	6
Total completed		203	104

Table 2: Characteristics of donors and nondonor controls at the time of transplant surgery

	Donors (n = 203)	Nondonors (n = 104)
Age, years, mean (SD)*	44 (10)	40 (12)
Female	126 (62%)	65 (63%)
Caucasian	192 (95%)	103 (99%)
Relationship to recipient*	–	–
Genetic	–	–
Parent	35 (17%)	15 (15%)
Sibling	85 (42%)	31 (29%)
Child	18 (8%)	11 (11%)
Other	6(2%)	8 (8%)
Nongenetic	–	–
Spouse/partner	30 (15%)	7 (7%)
Friend	13 (6%)	7 (7%)
Other	16 (8%)	24 (23%)
Married	166 (82%)	81 (78%)

*$p < 0.05$.

The baseline characteristics of donor and nondonor control groups are presented in Table 2. The characteristics of donors and nondonors were similar, although donors were slightly older than nondonors at the time of transplant and had different relationships to the recipient. Donors and nondonors were assessed an average of 7 (SD 6) and 8 years (SD 6) after the recipient's surgery, respectively. Eighteen percent (n = 36) of donors underwent a laparoscopic nephrectomy.

Recipient outcomes

Most recipient charts were available for review (n = 194). At the time of donor follow-up, 12 (6%) recipients had died and 20 (10%) had grafts which failed. Graft failure occurred 1 day to 14 years after transplant, and recipient death occurred 2 weeks to 13 years after transplant.

Quality of life outcomes

SF36, 15D and Feeling Thermometer scores: In the primary analysis there were no significant differences between donors and nondonors on any of the eight subscales or the physical and MCS scores of the SF36 (p values ranged from 0.33 to 0.98). Their scores were similar to the Canadian population norms (14) (Figure 1). When adjusted for age, gender, race, marital status at time of surgery, relationship to the recipient and year since donation, the groups remained similar (adjusted p values of 0.42–0.56). As we did note some correlations between donor and nondonor pairs in our dyad analysis, an additional analysis was completed, accounting for this correlation. Similar to the primary analysis we found no significant differences between donors and nondonors controls (p values ranged from 0.14 to 0.97).

The mean 15D quality of life score of donors was 0.93 (SD 0.09). Nondonors had a mean score of 0.94 (SD 0.06). There was no significant difference between groups (p = 0.55). When results were adjusted for race, gender, age, relationship to recipient, time since donation and marital

Donors ■ Non donors □ Age/Sex matched Canadian Norms
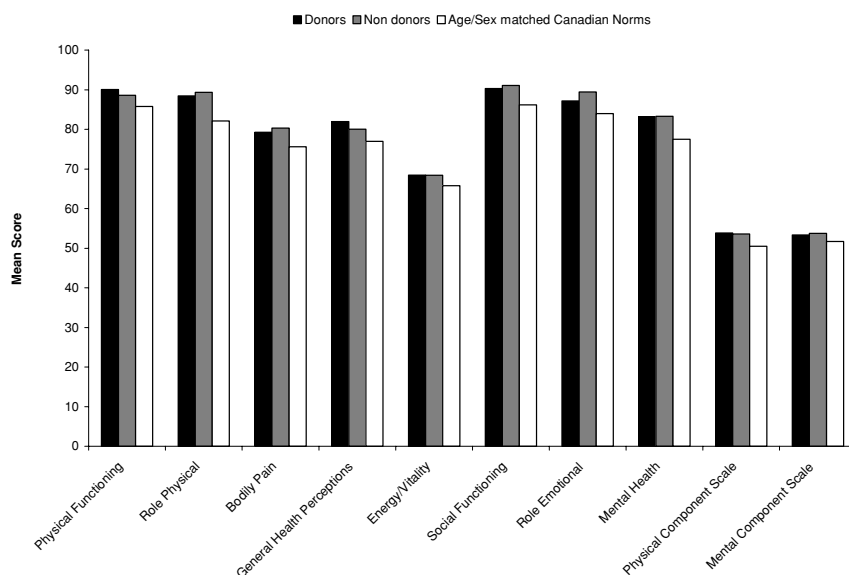
Figure 1: SF36 scores of donors, nondonors and age/sex-matched Canadians.

status, the difference between groups (0.03, p = 0.55) was not statistically or clinically meaningful (15).

The mean MCS scores of various donor and nondonor subgroups are illustrated in Table 3. The association between donation and the SF36 MCS score was not modified by age, year of donation, or relationship to the recipient (interaction term p values ranged from 0.50 to 0.98). Donors who underwent laparoscopic nephrectomy did not experience a better MCS score on the SF36 than those who underwent open surgery (p = 0.32). Donors whose recipients experienced an adverse outcome did not score differently from those whose recipients faced no adverse outcome (p = 0.74).

On the Feeling Thermometer, donors had an average score of 84 (SD 16), and nondonors, an average score of 85 (SD 10). There was no significant difference between groups (p = 0.46).

Marital status: In order to examine potential donation effects on marital status, we restricted our analysis to those participants who were married at the time of donation. At the time of follow-up, 74% of donors (n = 150) and 69% (n = 72) of nondonors reported that they were still married to the same person (p = 0.67). For those who were not,

6% in both groups cited divorce as the reason for no longer being married (p = 0.69), with the death of their partner cited by the remainder.

Mental health visits and psychotropic medication use: Beyond 3 months after transplantation, 10% (n = 20) of donors and 11% (n = 11) of nondonors had visited a psychologist or counselor (p = 0.84) and 3% (n = 6) of donors and 1% (n = 1) of nondonors had visited a psychiatrist (p = 0.27). Additionally, 12% of donors (n = 25) and 7% of nondonors (n = 7) reported the current use of psychotropic medications (p = 0.17) including tricyclic antidepressants (n = 4), selective serotonin reuptake inhibitors (n = 16), selective norepinephrine reuptake inhibitors (n = 8) or benzodiazepines (n = 8) (some participants used medications from multiple classes). Thus, rates of mental health visits and psychotropic medication use were comparable between donors and nondonors.

Employment and income: In the year prior to their follow-up assessment, 80% (n = 163) of donors and 81% (n = 84) of nondonors were employed (p = 0.13). The family income of donors and nondonors was not significantly different, with a combined postdonation family income often greater than 80 000 Canadian dollars in both groups (42% and 50%, respectively).

Table 3: Mean mental component summary scores (± SD) of donor and nondonor subgroups

	Age ≥ 43	Age <43	Spousal relationship to recipient	Nonspousal relationship to recipient	Donation prior to year 2000	Donation in the year 200 or later	Laparoscopic nephrectomy	Open nephrectomy	Recipient with adverse outcome	Recipient without adverse outcome
Donors	54 ± 8	52 ± 9	54 ± 7	53 ± 9	53 ± 8	54 ± 8	52 ± 9	54 ± 8	53 ± 9	54 ± 8
Nondonors	56 ± 6	52 ± 9	54 ± 14	54 ± 7	N/A	N/A	N/A	N/A	N/A	N/A

N/A = not applicable to nondonor population.
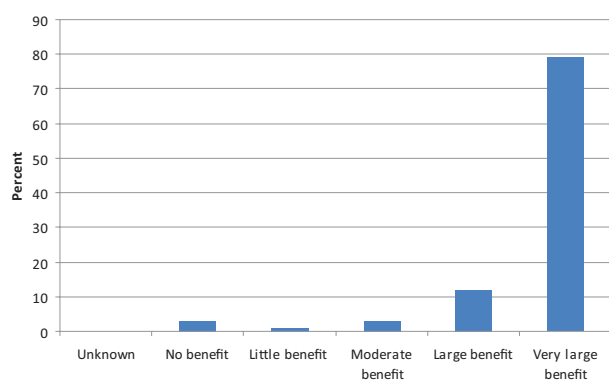
Figure 2: Donor response to 'because of kidney donation, what has been the overall benefit to the person who received your kidney?'

Donation-related attitudes: Donor thoughts on the overall benefit of donation to the recipient are illustrated in Figure 2. Ninety percent (n = 182) of donors felt that they were adequately informed about the risks and benefits of donation at the time of informed consent. Ninety-seven percent confirmed that they would make the same decision to donate again.

Discussion

Main study findings
We conducted a multicentered study to compare the quality of life of living kidney donors to a healthy nondonor group using standardized scales and author-developed questions. Overall, our findings are reassuring. On quality of life scales donor scores were similar to nondonors. The marital status and income levels of donors were similar to nondonors in spite of their donation experience. About 1 in 10 donors visited a psychologist or counselor after donation with similar rates in nondonor controls. Our donors generally expressed positive attitudes about their experience.

Comparison with the previous literature
The results of our study are generally consistent with the previous literature. On standardized measures of quality of life including the SF36, past studies demonstrate that donor and nondonor scores tend to be comparable (1,4–8). In our study, we also noted similar SF36 and 15D scores in our donor and nondonor groups. Additionally, in past reports, donor relationships are often unchanged or positively impacted by the donation experience (16–19). We found that a similar number of donors and nondonors remained married after surgery. In the previous literature, on standardized psychological questionnaires including the Beck Depression Index, donors and nondonor scores tended to be comparable (20,21). A similar number of donors and controls in our study were using psychotropic medications and had visited mental health professionals. Also, donors

have been noted to demonstrate positive donation related attitudes after their experience. Most would donate again if given the opportunity (5,6,8,17,22,23). This feeling was also expressed by donors in our study.

In previous subgroup analyses, more distant relatives had lower SF36 scores (4), laparoscopic donors demonstrated higher quality of life scores (24, 25) and donors whose recipient died or experienced graft failure had worse SF36 scores (26). In our study no subgroup analyses demonstrated differences that reached statistical significance. However, one must also appreciate that these analyses had adequate statistical power only for large effects.

Strengths and limitations
To our knowledge, our study is one of the first to compare donor outcomes with a healthy internal comparison group. Previous studies have compared donors with the general population, with three studies utilizing only 'healthy' controls that were identified from the general population (7,20,27). However, as donors tend to be inherently different from the public, it is possible that beneficial psychosocial outcomes were overestimated.

Our nondonor comparison group was more suitable as it consisted of individuals who were identified by donor participants and possibly had similar values, ideals and interpersonal qualities. Furthermore, they had personal ties with the kidney recipient and in many instances they had been assessed by a transplant professional to be medically and psychosocially fit to donate, but had not done so for another reason. Their demographic characteristics were also generally similar to those in our donor group.

The other strengths of our study include our sampling of a diverse group of participants from multiple countries and centers, as well as our comprehensive quality of life assessment.

There are limitations to our study. Despite our best efforts, recruitment was difficult. It was especially challenging to contact donors from our databases. Since donating, their contact information frequently changed, and in many cases we were not successful in speaking with anyone in their household. We cannot then exclude the possibility that nonparticipants experienced different measurable or unmeasurable outcomes from those who took part in our study, and that our study was biased toward participants who were functioning well.

We also used a questionnaire-based assessment which some individuals and cultures may find limiting. Some participants may have felt restricted in their responses and may have preferred an open-ended assessment where details could be fully described.

Further, the study was retrospective in nature, and some participants may have had a biased recall of past events.

Having already gone through the experience, they may have found it difficult to express negative feelings. We also relied upon self-reporting and thus outcomes may have been either over- or underestimated. Additionally, as donors were not assessed prior to their surgery, we could not accurately measure changes in outcomes after donation.

Lastly, our participants were mainly Caucasian, were from a higher socio-economic class and had access to universal health care. They also came from an era when good access to life insurance has been documented (28,29) and when donor reimbursement strategies were not commonplace (30). The effect of these characteristics on our study findings is uncertain, but they may impact our study's applicability to other populations (31).

Practical implications

Our study has several practical implications for transplant centers and for future donors. First, most of our donors underwent a detailed psychosocial assessment with psychologists, psychiatrists or social workers prior to their donation. Their high function after donation supports the utility of these assessments (32,33).

In our study, only 90% of donors felt adequately informed about the donation process. It is difficult to know whether they felt inadequately informed about medical or quality of life outcomes. However, a survey of U.S. and non-U.S. transplant professionals noted that donors, especially with regard to psychosocial outcomes, are often presented variable information, with risks often omitted or inaccurate (2). Based on the results of our study, we can communicate clearer quality of life information to potential donors. We suggest that during the time of informed consent, potential donors be informed that based on structured questionnaires, donors have a similar quality of life as other healthy and motivated individuals. However, potential donors should also be made aware of the possible negative psychosocial outcomes reported in the previous literature, including strain in family relationships, impaired body image secondary to their surgical scar, depression and anxiety (3).

Finally, in our study, donors commented that they appreciated being reassessed by the transplant community. The literature suggests that this is a common desire of donors (17,22,34,35). Although we found no significant impact of recipient outcomes on quality of life, this seems to be especially important for those who have faced adverse recipient outcomes as early intervention and counseling may be facilitated (36).

Future research

In the past literature, some donors scored lower on measures of depression (37), and expressed more feelings of hostility in the early postoperative period (21). Additionally, the postdonation SF36 scores of some donors have been noted to decrease (25,35,38) with some (31%) developing incident episodes of diagnosable psychiatric disorders (35). Thus, future research should include long-term, multi-centered, prospective studies, to clarify whether such observations are reproducible. Having participants complete assessments prior to the transplant, and at a variety of time points after the time of their surgery, will help identify any periods of vulnerability for donors.

Future research should also provide the opportunity to study the impact of paired exchange, nondirected donation and donor reimbursement programs on quality of life outcomes. Additionally, as the use of structured psychological scales is limited in the literature, their use in future studies may help to further elucidate any risks to the donor to aid in optimally maintaining their long-term health and well-being.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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The Experience of Living Kidney Donors

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Ruth Bullas, Amit X. Garg, and Norman Muirhead

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This article describes the experiences, feelings, and ideas of living kidney donors. Using a phenomenological, qualitative research approach, the authors interviewed 12 purposefully selected living kidney donors (eight men and four women), who were between four and 29 years since donation. Interviews were audiotaped, and transcribed verbatim, and the analysis of the data was both iterative and interpretive. Three key themes emerged. The first was how witnessing their loved ones' experience of illness and the threat of losing the recipient influenced the participants' decision to donate. The second focused on intrapersonal (philosophy of life) and interpersonal factors (comprehensive social support networks) that influenced the decision to be tested as a potential donor and the actual process of donation. The third was the impact of giving the gift of life, which was emotional and life changing. This article provides a rich description of the experiences of living kidney donors, revealing the multiple factors influencing the decision to donate, and provides insight on how social workers and other health care professionals need to identify and address the psychosocial needs of living kidney donors and their families from the process of decision making through after donation.

KEY WORDS: *decision making; living kidney donor; organ donation; qualitative methodology; social work assessment*

In 2004, living-donor kidney transplants performed in Canada represented 41 percent of all transplanted kidneys (Canadian Institute for Health Information, 2005). More recently, there has been more focus on the long-term psychosocial implications of nonpaid living donation. Donation might improve quality of life to levels higher than those of the general population (Corley, Elswick, Campbell Sargeant, & Scott, 2000; Gouge, Moore, Bremer, McCauly, & Johnson, 1990; Isotani et al., 2002; Jacobs, Johnson, Anderson, Gillingham, & Matas, 1998; Johnson et al., 1999; Johnson, Najarian, & Matas, 1997) and might also improve living kidney donor self-esteem (Corley et al., 2000; Jacobs et al., 1998; Zargooshi, 2001). However, anxiety, depression, and suicide also have been occasionally witnessed after donation (Jacobs et al., 1998; Johnson et al., 1999; Schover, Streem, Navdeep, Duriak, & Novick, 1997; Schweitzer, Seidel-Weisel, Verres, & Weisel, 2003; Sharma & Enoch, 1987). Donation may have both positive and negative effects on marital, family, and sibling dynamics (Fehrman-Ekholm et al., 2000; Jacobs et al., 1998; Schover et al., 1997; Schweitzer et al., 2003; Zargooshi, 2001).

Living kidney donors do not appear to receive a routine psychosocial assessment (Johnson et al., 1997; Johnson et al., 1999), despite evidence suggesting how routine assessments before donation are important (Fukunishi et al., 2001; Schweitzer et al., 2003; Sharma & Enoch, 1987; Westlje, Fauchald, Talseth, Jakobsen, & Flatmark, 1993), particularly when the living donor is unrelated to the recipient or is considered to be at high risk emotionally (Johnson et al., 1997; Johnson et al., 1999). The importance of psychological consultation has been related to presurgical preparation, postsurgical care, and ensuring voluntary consent (Binet et al., 1997; Conrad & Murray, 1999; Eggeling, 1999; Westlje et al., 1993). Psychological follow-up is recommended in the case of transplant failure (Hirvas, Enckell, Kuhlback, & Pasternack, 1980) or with evidence of serious emotional problems after donation (Schweitzer et al., 2003).

Another relevant area of inquiry is the decision-making process of living kidney donors and the factors that contribute to the decision to donate. The most influential factor in the decision to donate is the desire to help (Lennerling, Forsberg, Meyer,

& Nyberg, 2004; Lennerling, Forsberg, & Nyberg, 2003). Other factors influencing the decision to donate are a sense of guilt, pressure from others, religious motives, and increased self-esteem (Lennerling et al., 2003; Lennerling et al., 2004). Siblings and parents often donated "out of love" (Franklin & Crombie, 2003, p. 1249), with love being identified as the most powerful motivator (Binet et al., 1997). Love has been implicitly linked to the concepts of moral duty and altruism (Lennerling et al., 2003; Lennerling et al., 2004).

This qualitative study was conducted to gain a deeper understanding of the decision-making processes and psychosocial issues for living kidney donors. Our intent was to gather data that would inform transplant programs about the particular needs of living donors and to guide quality improvement.

METHOD

We used a qualitative, phenomenological approach to explore the experiences, feelings, and ideas of living kidney donors.

Sample Selection

The purposeful sample included 12 living kidney donors who donated their kidney in Ontario, Canada. These participants were part of a larger randomly selected sample in which quantitative techniques were used to assess medical and psychosocial outcomes of living kidney donors. From the larger sample, a maximum variation sample was chosen on the basis of gender, age range, geographical location, donor–recipient relationship, and time since donation. The latter characteristic was used to capture the changes in the donor assessment process from inpatient to outpatient. Participants were invited to participate through a telephone call made by the research assistant. Once they consented to participate in the larger study, which required two clinic visits, a separate consent was obtained from them to participate in the qualitative interview at their second clinic visit. The study was approved by the University of Western Ontario Review Board for Health Sciences Research Involving Human Subjects.

The final sample reflected a wide range of experiences and characteristics. There were eight men and four women. Donor–recipient relationships consisted of six sibling pairs, three spousal pairs, two parent–child pairs, and one father-in-law to daughter-in-law pair. Time since donation ranged from four to 29 years. All participants had a psychosocial assessment before donation. The age range of the living kidney donors at the time of donation was 26 to 65 years, and the recipients' ages ranged from 18 to 51 years. Eleven of the 12 recipients had been on dialysis prior to receiving a kidney transplant. Six of the donations were successful at the time of the study, two failed at the time of donation, and four kidneys failed following donation, ranging in time from nine months to 16 years. All of the recipients in the latter group returned to dialysis, with one recipient dying two years after donation. Geographically, seven donors were located in southwestern Ontario within a 60-mile radius of the transplant center. Two donors were from northern Ontario, two donors were from eastern Ontario, and one donor was from another province. All but one donor were from a single transplant center.

Data Collection

Interviews were semistructured and were based on questions determined by the researchers after a literature review. The interview guide was reviewed by the research team and underwent some minor revisions following the second participant interview. Questions included the following: What factors influenced your decision to donate? In what way has your relationship changed with the recipient? What advice would you give to a person considering donation?

Interviews were conducted by one of the researchers (Karley), who is not employed by the transplant center, who used the interview guide and additional probes to explore areas in greater depth. Eleven interviews were conducted face-to-face in conjunction with a hospital clinic visit in a separate confidential room. One participant was interviewed by telephone. Interviews lasted 50 to 75 minutes and were augmented by field notes.

Analysis

The analysis was iterative in nature. After each interview, two of the researchers independently read the transcripts, looking for key words and emerging themes. They then met to compare and combine their independent analyses. A template was developed that allowed for the coding and organization of data. All the transcripts were coded according to the same template; however, as new themes

emerged in subsequent interviews, they were added to the template. Hence, initial categories were very broad, but as the analysis progressed the various categories and final themes were synthesized by using the analysis techniques of immersion and crystallization (Crabtree & Miller, 1999). Data saturation was reached following the 11th interview. During the 12th interview, key themes were explored for clarification and confirmation (Crabtree & Miller, 1999).

Credibility and Trustworthiness of Data

Throughout the analysis process, phrases or quotes that most accurately supported the key themes were identified. This supported the credibility and trustworthiness of the findings (Crabtree & Miller, 1999). The trustworthiness of the data was further enhanced by field notes and debriefing sessions after each interview. Team analysis assisted in identifying potential personal or professional bias of the researchers. The final analysis was reviewed by the entire research team.

RESULTS

The following three key themes emerged in the exploration of the living kidney donors' experience of donation: (1) how witnessing their loved ones' experience of illness and the threat of losing the recipient influenced the participants' decision to donate, (2) interpersonal and intrapersonal factors influencing the living kidney donor's decision to be tested as a potential donor and the actual process of donation, and (3) the impact of giving the gift of life.

The Role of the Illness Experience and Threat of Loss in the Decision to Donate

For most participants, witnessing the recipient's illness experience was a powerful motivator in the decision to consider donation. "I went and saw her on dialysis. . . and I said, 'Oh my God.' If anybody had a question [about donation] then go and see them put on a machine." The recipient's quality of life was also a major consideration. As one participant noted, ". . . he was on dialysis three days a week, and I think his quality of life obviously was suffering." Perhaps even more influential was the impending threat of loss or severe disability of the recipient as a result of kidney failure: ". . .at that point she had high blood pressure, and it was high enough that she could have had a stroke."

Threat of loss was also relevant to the donors' own well-being as they questioned whether their life was at risk. This threat was perceived as immediate in terms of surgical risk—"[I was] nervous, obviously, because I thought you never know if you're going to die on the table"—or long-term should they experience kidney failure in the future—". . . at the time I was probably afraid myself, holy Lord, what happens if my kidneys fail now?" Furthermore, participants expressed concern about no longer having a kidney to donate to a child should he or she experience kidney disease in the future: "The only thing that really worried me is that if one of my kids had to have a kidney. . . ." Spousal donors were in a unique position with regard to the threat of loss. As one living kidney donor stated, "My wife and I sat down and said, 'This is very risky, both of us could die.'" Family members of the donor and recipient shared a similar level of anxiety. A participant recalled, "My husband said, 'I could lose my daughter and my wife at the same time.'"

A sense of determination and commitment was expressed by all participants in their decision to donate. As one donor, a mother, explained, "Once I made up my mind, that was it. I told my daughter, 'Somehow we're going to make you feel better . . . we're going to do whatever it takes.'" Another living kidney donor, a spouse, described her experience of the decision-making process: "I felt like it was time. I think we waited long enough . . . and now it was okay, we have a goal, let's move on." The decision to donate was not an isolated process. Many living kidney donor families went through a process of examining who was the most eligible donor. One donor explained as follows:

> I talked to my Dad. He couldn't do [it] because he has skin cancer, and then they found out my mom had something when she was younger, and that eliminated her right away too. When I found out that they were both eliminated, I said, 'Could I do it?'

Intrapersonal and Interpersonal Factors Influencing the Decision to Donate

Participants described intra- and interpersonal factors that influenced their decision to donate. From an intrapersonal perspective, they shared how their philosophy of life had influenced their decision to donate. A strong sense of faith and spirituality, including an appreciation of the cycle of life,

was evident among the majority of participants: "I prayed about it, and I told him I have a peace about it, everything's going to work out." For several participants, their faith preempted a position of negativity or a belief that the donation would not be successful. "My faith kept me believing that nothing would go wrong." For some, the decision to donate involved a deep soul searching process: "I had these long soul searches and everything seemed to point to this [decision] . . . this was meant to be." For others, their philosophy of life is best described as an appreciation of the circle of life: "I was brought up on a farm, nature takes its course, and that's the way we lived. Things will happen, and if it's supposed to happen it will."

In addition, a positive attitude reflected the philosophy of life adopted by some of the participants. A participant explained, ". . . if you start thinking negative before you even do anything, you're already half defeated . . . and with something that important there's no room for negatives." For many, altruism was a hallmark of their philosophy of life as reflected in the following statement: "I mean what I did, I did for my brother, and it was a personal decision. I'm not looking to be sort of glorified or praised." Even when the transplant failed, the sense of altruism remained: "I can go to bed every night knowing that, even though it didn't work, I still tried. . . . Yes, I did what I could do."

For many participants, their philosophy of life enabled them to proceed with donation without any conscious concerns regarding surgical complications, problems with recovery, or the long-term impact on their quality of life. One parent expressed this as follows:

> I didn't even think about it. It was not even a decision I had to make. I knew she was sick and I wanted to get her better. . . . I didn't even think about the complications or ramifications I could have.

Another participant stated, "I felt so assured and so confident about it, so I don't recall any apprehension at all."

From an interpersonal perspective, participants explained how support received by family, friends, employers, and their broader community endorsed their decision to donate. Extended family provided both instrumental and emotional support. From an instrumental perspective, a participant explained,

". . . we were fortunate enough that we had so many friends and family that offered to take care of them [the children]." On an emotional level a participant stated, ". . . my [wife] was up there, pretty well most of the time. My sister and my brother-in-law were up there steady and then all kinds of friends dropped in [and provided] really good support, psychological-wise."

In addition to familial support, there was open encouragement from the broader community: "All the people at the church, they were all praying of course before, during, and after." Employers as well as work colleagues were also important supports to the living kidney donor, both emotionally and financially: "The people at my work all took up a [collection and got a] thousand bucks and they had a BBQ for me too."

Impact of Giving the Gift of Life

Despite the altruistic nature of donating a kidney and the lack of conscious concern about any ramifications of giving, participants described an emotional impact of giving. Participants described how they experienced a sense of loss or grief after donation: "When you have a child, you're going to come out of the operating room with something. And now you're going into surgery and you're coming out of there without something." Another participant expressed his powerful emotional response after donation: "I guess the full impact really hit home. I just started bawling like a baby for some reason, and at that point I just completely lost it."

Some participants described how they had received a tangible recognition of the gift they had provided to the recipient: "The day I went home after the transplant, they bought me a fountain . . . that was their way of thanking me for what I did for them." Recognition also included some small ritual on the anniversary of the transplant date: ". . . she always remembers . . . she would send me flowers, and I would tell her to buy something for herself on the anniversary day."

Several participants expressed a greater sense of vigilance about the well-being of the donor kidney after donation. One sibling donor stated, "I was always telling him, 'Don't do that,' or always at him, which I shouldn't have been, but, you know, I gave it to him." Another participant spoke of her worry that the recipient would not care adequately for the donor kidney: "I think the worst feeling I've

had would be him not focusing on his health, like physically, maybe overdoing it with things." For other participants, this sense of vigilance was coupled with the respect they had for the recipient's autonomy. A spousal donor described the challenge of finding the balance: "The struggle has been knowing how much to push and how much to stay back."

Giving the gift of life prompted many participants to reflect on their enhanced appreciation of life. One participant stated, "Going through any kind of major illness, you look at life so differently, and you don't take a lot of things for granted." Other participants indicated specific changes in lifestyle behaviors as a result of living kidney donation: "I think it was a good thing because it stopped me doing what I was doing [drugs]." The giving of a kidney was, for some, an act that increased their self-esteem: "I really felt good about myself. [I] did something pretty incredible that most people never do."

For participants in this study, the act of giving a living kidney also had a positive impact on their relationship with the recipient: "I still feel a very great closeness to her, and it's quite an interesting thing." Some participants also described a positive impact on relationships within the family, particularly when acknowledging the possibility of transplant failure in the future: "I think we're all feeling like we need to appreciate each other and enjoy what we have now."

Just as witnessing the effect of the illness and treatment on the recipient was a powerful motivator to donate, witnessing the effect of a functioning kidney on the recipient reinforced the act of donating a kidney. One donor, a father-in-law, expressed his delight in the marked improvement in the recipient's quality of life:

> . . . [now] she's busy as a cat on a hot tin roof . . . prior to the donation, she was looking very pale [and feeling] very tired and [was] not able to do the things she wanted to do . . . to see the change in her has just been wonderful.

One spousal donor revelled in her husband's improved health after donation:

> I just remember him smiling, being strong and being happy to have an unlimited amount of drinks and food. He just felt free. It's almost like your husband ages 15 years and all of a sudden he's got his youth back.

Since donating a kidney, all participants had become proponents of living kidney donation. Some participants actively promoted donor awareness in the community: "Where I work, we have this health and safety day and hold a thing there for organ awareness, and we make sure everyone's got a donor card in their wallet." However, they described the need to make the decision to donate free from any pressure or coercion and with the support of family:

> As long as the people that are most important to you are supportive, that's all that really counts. . . . I don't think you should make a decision on what the other people tell you to do; you have to know in your heart what you want to do. And once you've made that decision, you shouldn't let people change your mind either.

Participants advised that one has to be comfortable with the decision to donate and that it is a highly personal decision:

> It's a decision you have to make and you have to be comfortable with. If you can't do that then don't do it. You can listen to other people, you can get advice from other people, but at the end of the day this is a personal decision and you're the one that has to make it and live with it.

Finally, when asked if they would make the same decision to donate, participants responded with phrases such as "Without hesitation," "It was an honor to be able to do that," and "I'd do it again in a minute." Even with a recipient death two years after transplant, a participant stated, "Yes, but I would still do it again . . . even if I gave him a week, at least I gave him something."

DISCUSSION

This study has highlighted the experiences of living kidney donors from the process of decision making to after donation. Witnessing a recipient's illness experience and the threat of loss of the recipient were powerful motivators in considering donation. This included the effect of the progressive disease on the recipient and the effect of witnessing hemodialysis. Study findings are consistent with previous research that has described concern for recipient health as a key factor in the decision to donate (Franklin & Crombie, 2003; Lennerling et al., 2003; Westlje et al., 1993). The participants' decision-making process is

> *Social work follow-up is particularly indicated in the case of transplant failure, in the event of emotional difficulties after donation, and at the time of discharge.*

similar to that of donating "out of love" (Franklin & Crombie, 2003). Contrary to some literature, none of our participants described being motivated to donate for any personal gain (Lennerling et al., 2003; Lennerling et al., 2004). Neither did the nature of the relationship between donor and recipient (that is, parent, spouse, child, sibling) seem to influence the strength or the source of the motivation to donate (Franklin & Crombie, 2003).

Intrapersonal factors that influenced the participants' decision to donate included their philosophy of life reflected through faith and altruism. Religion has been cited in the literature as a weak motivator, whereas altruism is often reported (Franklin & Crombie, 2003; Lennerling et al., 2003; Lennerling et al., 2004; Westlje et al., 1993). From an interpersonal perspective, none of the participants in this study reported any negative effects on their marital, sibling, and family relationships or on their mental health, which is in contrast to existing literature (Fehrman-Ekholm et al., 2000; Jacobs et al., 1998; Johnson et al., 1999; Lennerling et al., 2003; Schweitzer et al., 2003). The participants in this study confirmed the importance of voluntary consent and the support of family, friends, and community throughout the donation process. The opportunity to donate had, for many, created an increased awareness of organ donation and prompted many participants to promote organ donor awareness. This finding has not been reported in other studies.

A unique finding in this study was the experience of loss and grief after donation described by some of the participants. This was not specific to graft loss, but rather appeared to reflect the personal loss of a body part (Haljamae, Nyberg, & Sjostrom, 2003). This finding suggests the need for increased assessment of living kidney donors' loss and grief both before and after donation. Many studies describe increased self-esteem or quality of life for living kidney donors after donation (Corley et al., 2000; Gouge et al., 1990; Isotani et al., 2002; Jacobs et al., 1998; Johnson et al., 1999; Zargooshi, 2001). In

this study, the participants were more focused after donation on the recipient's well-being. They also described being quite vigilant about the function of the donated kidney and subsequent care of the donated kidney by the recipient. Furthermore, the participants had a renewed appreciation for life that occurred whether or not the transplant had been successful. Although other studies reported on regrets by living donors (Jacobs et al., 1998; Johnson et al., 1997; Johnson et al., 1999; Schover et al., 1997; Westlje et al., 1993), none of the participants in this study expressed hesitation or regrets about donating a kidney.

Many studies describe how psychological/psychiatric consultation is used routinely in assessment of a living kidney donor (Binet et al., 1997; Fukunishi et al., 2001; Schweitzer et al., 2003; Sharma & Enoch, 1987; Westlje et al., 1993) or in situations in which the donor is considered to be at high risk (Johnson et al., 1999). However, rarely is the routine use of psychosocial assessments reported as part of the living kidney donor workup (Johnson et al., 1999). All the participants in this study were assessed from a psychosocial perspective before donation. As noted earlier, participants exhibited a high degree of altruism and faith and expressed no regrets about donating a kidney. It is noteworthy that all were assessed from a psychosocial perspective that explored specific areas such as psychological and emotional stability, family history and family dynamics, absence of coercion, relationship to the recipient, understanding of and attitude to donation, and support networks (see Table 1).

Thus, this study reinforces the need for routine social work involvement with living kidney donors during the decision-making process, presurgical preparation, and postsurgical care. Study findings suggest how the emotional support and intervention provided by a social work assessment might enable living kidney donors' expression of loss and grief as a result of donation and might assist in the exploration of the potential threat of loss of the kidney or family member. Social work interventions based on a psychosocial assessment may also assist in ameliorating the emotional impact of issues related to hospitalization and overall quality of care. Social work follow-up is particularly indicated in the case of transplant failure, in the event of emotional difficulties after donation, and at the time of discharge.

The findings of this study cannot be generalized to all living kidney donors; however, the

Table 1: Psychosocial Assessment for Living Kidney Donors	
Assessment Item	**Description**
Referral statement	Source and reason for referral
	Date and nature of first contact
Donor/family history	Family constellation and demographics
	Living arrangements
	Relationship to recipient
	Level of education, occupation, employment history, financial situation
	Family functioning, factors that might affect donor's recovery or care after discharge
	Extended family involvement and other support networks
	Family reaction/response to donation
	Other significant events (recent loss or death)
	Other significant information (substance abuse, child welfare concerns, violence)
	Previous hospitalizations (health and mental health)
Clinical dynamics	General attitude to illness, hospitalization, medication, pain
	Range of affect and appropriateness of expression
	Donor/family usual response to crisis, coping mechanisms, communication patterns before donation
	Spirituality, use of faith as a support
	Donor/family strengths, limitations, family dynamics, life cycle issues
	General level of insight and awareness, understanding of and attitude to donation, decision making regarding living donation, absence of coercion
Summary of issues	Analysis of data, summary of problems
	Key issues that may influence living donation
Intervention	Summary of recommendations: short- and long-term goals
	Specific needs for education: before surgery and postsurgical care
	Discharge needs

rigorous methodology used in this study reflects the lived experience of the participants. Although the interviews were conducted retrospectively, the participants' recall of the emotional nature of this experience was extensive. One limitation was that the participants reflected a highly motivated study population as they had already agreed to participate in another study.

The study findings suggest that inquiry into the living kidney donors' philosophy of life, as reflected by their faith and altruism, is important. Future research could quantitatively examine the relationship between the participants' degree of altruism and lack of regret regarding donation. Additional research could compare donors who received a psychosocial assessment with those who did not, to explore differences between a readiness to donate and emotional sequelae after donation. Future studies could also explore the experience of individuals who elect not to donate and the role of the psychosocial assessment in this decision.

CONCLUSION

Witnessing their loved ones' experience of illness and the threat of losing the recipient influenced participants' decision to donate. Despite their own concerns regarding their future health, participants described interpersonal and intrapersonal factors that influenced their decision to donate, including their philosophy of life and comprehensive social support network. The impact of giving the gift of life was emotional and life changing, leading all participants to become proponents of living kidney donation. Finally, the findings of this study provide insight on how social workers and other health care professionals can better address the psychosocial needs of living kidney donors. HSW

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Reflexivity in practice: Ethical dilemmas in research with potential living kidney donors

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Abstract
"Ethics in practice" are the ethical dilemmas that arise during the conduct of research. In this article, we describe the ethical issues we faced when conducting an exploration of the experiences of 19 potential living kidney donors, and demonstrate how reflexivity can guide the ethical decision-making throughout the research process. We discuss how we addressed issues of risk of potential psychological discomfort and distress to participants; autonomy and consent; and power imbalance, disclosure and reciprocity. We also address the practical implications of our decisions. Through this discussion of the "ethically important" moments we faced, we aim to spark debate about the ethical and practical challenges facing qualitative health researchers today, and demonstrate how reflexivity can contribute to navigating the "ethical labyrinth" of qualitative health research.

Keywords
data collection and management, ethics/moral perspectives, interviews, organ donation, reflexivity, transplantation

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Ethical conduct is a central tenet of clinical research, and pervades every aspect of the research process (Goodwin et al., 2003). The guiding document setting the standards of research involving humans in Australia is the *National Statement on Ethical Conduct in Human Research* (National Statement). This document informs the design, ethical review and conduct of research and is underpinned by the values of research merit and integrity, justice, beneficence, and respect (NHMRC, 2007a). The National Statement provides comprehensive guidelines on two themes: risk and benefit, and consent. The document defines "risk" as "a potential for harm, discomfort or inconvenience" (p. 15), and states that "research is ethically acceptable only when its potential benefits justify any risks involved in the research" (NHMRC, 2007a: 17). With regard to consent, the guiding principle is that of voluntary participation in research; according to this principle, consent must be based on sufficient and adequate information, and understanding about the research and the implications of participating in it (NHMRC, 2007a).

As part of the "procedural ethics" (Guillemin and Gillam, 2004), researchers must seek formal approval from ethics committees to ensure that the principles of autonomy, privacy, dignity, beneficence and justice underpinning research are upheld in their protocols. Similarly to other countries, in Australia, ethics committees review research proposals involving humans to ensure that they are ethically acceptable and comply with relevant standards and guidelines. All universities and major hospitals in Australia have a formally established ethics committee, and these committees are registered with the National Health and Medical Research Council (NHMRC) (NHMRC, 2007a).

Ethics committees are able to consider 'predictable' issues that may arise in the conduct of research and ensure that researchers have addressed them adequately in their research protocols. However, these formal or procedural ethics are different from what is termed "microethics" (Guillemin and Gillam, 2004), "ethics in practice" or "ethics in action" (Morse, 2007), which are the day-to-day ethical issues that arise throughout the research process (Guillemin and Gillam, 2004). It is these day-to-day ethical dilemmas which are particularly relevant to qualitative research, and they are especially challenging, as they are difficult to anticipate, they arise unexpectedly and spontaneously (Goodwin et al., 2003) and they must be resolved as they occur.

In this article, we reflect on the ethical dilemmas we encountered in our study of the experiences of potential living kidney donors. We also discuss how we used reflexivity – the process through which researchers demonstrate self-awareness and awareness of the research setting (Grbich, 1999) – as a tool to evaluate the research process (Finlay, 2002b). The study is described first, and is followed by a reflection on the ethical issues encountered throughout the pre-recruitment, recruitment and data collection phases as they unfolded. Some of

these issues were difficult to predict and others, in hindsight, could have been at least partly anticipated. A final section discusses the lessons we learned and the implications for qualitative health researchers today. With our candid account, we hope to contribute to the body of knowledge on ethical issues in qualitative research and the challenges researchers face.

The study

Our study was a qualitative exploration of the experiences of potential living kidney donors (PLKDs) as they undergo the assessment process to determine their suitability to donate. As part of their assessment or "work-up", PLKDs undergo a series of medical tests as well as a psychosocial assessment consisting of a session with a social worker, psychologist or psychiatrist (NHMRC, 2007b). We wanted to explore how PLKDs experience this work-up process and the time leading up to the potential transplant operation, and we were interested in the experiences of both those who were deemed suitable to donate and those who were deemed unsuitable.

Our study was informed by the principles of phenomenology, insofar as we were interested in participants' lived experiences (Starks and Trinidad, 2007). We collected the data through semi-structured in-depth interviews consisting of a series of exploratory, open-ended questions; the questions provided a blueprint to guide the interview and the semi-structured format was flexible enough to allow participants to tell their story in their own words and introduce new topics. The interview schedule was iteratively developed, so that topics which were introduced by participants were further explored in subsequent interviews.

We recruited a total of 19 participants through one of the two kidney transplant units in Western Australia. All participants were genetically or emotionally related to the intended recipient; 13 were going to donate directly to the recipient, while six were part of a paired kidney exchange program whereby potential donor-recipient pairs who are incompatible with each other can be matched with other incompatible pairs (NHMRC, 2007b). With the exception of two, all participants had been deemed suitable to donate.

The interviews were conducted between February and August 2013, they had an average duration of approximately 45 minutes, and they were conducted at the participants' convenience either at home or at the hospital, or on the telephone for those living in regional areas. The research team consisted of a Principal Investigator (PI), an Associate Investigator, and the Study Coordinator (SC), who was the person responsible for recruiting participants and conducting the interviews. The study was funded by the hospital's Research Advisory Committee, and we sought and were granted ethics approval from the hospital's ethics committee (reference number 2012-172).

Our ethical dilemmas

As the study unfolded, we noted that our participants were in a position of 'situational vulnerability', a type of vulnerability which is context specific and may be short-term (Meek Lange et al., 2013), and that, in our study, involved participants' personal circumstances and the circumstances surrounding the recipients. As a result, we encountered a number of ethical dilemmas we had not anticipated. These largely occurred during the recruitment and data collection phases. In this section, we describe these ethical issues following a chronological sequence as they arose from the pre-recruitment phase through to the end of data collection.

Pre-recruitment phase

Because we were interested in exploring how PLKDs experienced the work-up process to assess their suitability to donate, we needed to approach potential participants after completion of the work-up so that they would be able to share with us their insights and experiences of the whole process from beginning to end. We soon realized that, for some participants, this recruitment time would be very close to the transplant operation. This triggered our first dilemma: should we have a recruitment and interview cut-off point before the operation? If so, what should it be? How long before the operation? We consulted the literature, but it did not provide us with a satisfactory answer. Most qualitative studies reporting on the experiences of living kidney donors are retrospective and the interviews have been conducted post-donation, from one week (Andersen et al., 2005) to many years after transplant (Crombie and Franklin, 2006; Williams et al., 2007). Studies reporting on experiences pre-donation tend to explore the experiences of donors at different points in time and they do not always report on the time of the interviews (Gill and Lowes, 2008; Sanner, 2005). In their exploration of the experiences of 11 families who had undergone kidney transplantation conducted in the United Kingdom, Gill and Lowes reported that interviews were conducted "pre-transplant" (2008: 1610), but the authors did not specify the time frame. Meanwhile, in her study of the experiences of 39 donors, Sanner (2005) conducted the pre-donation interviews the day before surgery. We found this to be problematic, because evidence shows that the time before transplantation is a stressful period for PLKDs. For example, when Pradel and colleagues (2003) conducted focus group interviews with potential donors, donors, potential recipients and recipients, the authors reported fewer participants in the potential donor and potential recipient groups. This lower participation was due to the short time window between the mailing of the letter of invitation and the date for the transplantation, which led to several potential donors and potential recipients declining to participate "because it was a busy and/or stressful period for them" (Pradel et al., 2003: 205).

After consideration of the literature, and guided by concerns regarding participants' situational vulnerability (Meek Lange et al., 2013), we agreed upon a cut-off point of two weeks prior to transplant surgery; thus potential participants who had completed their work-up and whose transplant operation was scheduled a minimum of two weeks later or not yet scheduled were invited to participate, while those whose transplant was scheduled to take place within the two-week window were not approached. We acknowledge that this was an arbitrary time frame, but it was a compromise between maximizing the richness of the data we were hoping to collect and minimizing the risk of emotional distress to participants.

This ethical decision had two practical consequences: firstly, although we had originally planned to recruit participants after the surgeon's appointment (the last appointment potential donors are required to attend before the transplant operation), we decided to modify our protocol and bring recruitment forward. Thus, we set the new recruitment point after the final meeting at which the suitability of the donor is reviewed by the transplant team (this is the final stage of the work-up process, and occurs before the surgeon's appointment is scheduled). Secondly, as a result of this decision, we had to forego the recruitment of several potential participants whose operations were scheduled within the two-week window.

It is worth noting that, in our study, this critical two-week window only applied to PLKDs who had a scheduled date for the transplant surgery; it did not apply to either participants deemed unsuitable or to those deemed suitable whose operation was on hold because the intended recipient's kidney function was stable.

Recruitment phase

As we began recruiting participants to our study, we realized that recruitment was ongoing for two other studies which also targeted PLKDs at the same hospital. We became concerned that this might cause confusion among potential participants, and that PLKDs might feel overburdened or experience 'research fatigue' (Clark, 2008). This was especially relevant in our study given the characteristics of the sample and the small sample pool – in 2012, only 17 living kidney transplants were performed at the hospital where we recruited our participants (Boudville, 2014). Thus, a meeting between the research team, the renal team's research coordinator and the transplant nurse coordinator was convened and it was agreed that recruitment efforts for the studies would be coordinated. As a result, the PI and SC worked closely with the renal team's research coordinator throughout the recruitment process, ensuring that potential participants were aware of the other studies being conducted and what participation involved in each of them, thus minimizing the risk of confusion.

During this phase we faced another dilemma relating to negotiating consent to participate in the study. Recruitment strategies described in the literature reporting on qualitative studies of PLKDs include recruitment through an invitation letter (Gill and Lowes, 2008), a social worker (Adams-Leander, 2011), via recipients (Crombie and Franklin, 2006) and through an invitation letter with an opt-out slip to be returned if potential participants did not want to have any further contact (Pradel et al., 2003). Because of privacy concerns relating to the disclosure of personal information to a third party and given the study's funding constraints and tight deadlines, in our study we adopted a recruitment strategy similar to that described by McGrath and Holewa (2012) in a study involving PLKDs conducted in Queensland: the PI – a consultant nephrologist at the hospital – made the first contact with potential participants; the PI provided a brief overview of the study and gained verbal consent for potential participants' contact details to be forwarded to the SC. The SC followed up with a telephone call, provided an overview of the study, invited potential participants to take part in the study, and finalized recruitment by mailing an information sheet and consent form to potential participants, and gaining written consent prior to the interview.

The National Statement states that "even where there is no overt coercion or pressure, consent might reflect deference to the researcher's perceived position of power, or to someone else's wishes" (NHMRC, 2007a: 20), further stating that a person should only be included as a participant when their consent is voluntary (NHMRC, 2007a). Despite the fact that the PI did not recruit participants to the study and did not have any involvement in data collection, we were concerned that participants might feel compelled to participate out of deference towards him, especially given that the PI was involved in the medical care of several potential participants.

Guided by our concern for participants' autonomy, the SC carefully negotiated consent with each participant and apprised potential issues, ensuring that participation was voluntary and participants provided free, informed consent. This ethical concern led us to the last-minute cancellation of one interview, after the SC became concerned that the participant showed signs of feeling uncomfortable about the interview, and gave indications of consenting to participate out of respect and deference towards the PI.

Data collection phase

Issues of power imbalance and disclosure were also addressed during the interview process. There is ample literature addressing the power imbalance between researcher and participant during the interview encounter (Ribbens, 1989; Oakley, 1981), and while some argue that a power differential is inevitable (Hammersley and Atkinson, 1993), in this study we implemented some strategies to address this

issue. The SC disclosed her status as a non-health professional; furthermore, she disclosed that she had no information on participants' medical records. This approach proved to be especially relevant in our study, as the SC observed that participants assumed she had a clinical background and was familiar with their medical history. While this approach does not negate power imbalance during the interview encounter, it helped bridge the gap between the SC and participants and build rapport.

Throughout the conduct of the study, we were also mindful of the potential economic cost of participation derived from the petrol expenses and parking fees incurred in driving to the venue of the interview. Thus, when participants chose the hospital as their preferred venue, a date was chosen that would coincide with a scheduled hospital appointment and the interviews were conducted in an office away from the renal unit. Participants who chose to be interviewed at home were appreciative of having that option, and seemed surprised, as they had the expectation that they would need to come to the hospital for the interview; one participant stated that this had been the first time that someone had "offered to go to them".

We incorporated reciprocity to the research process by giving participants the option to receive a copy of the transcript of the interview, providing them with an opportunity to comment on it. It is noteworthy that the majority of our participants (10) requested a copy of the transcript and the feedback received indicates that this was valued by participants. At the time of writing, a lay summary of results is under preparation; all participants will receive a copy of this summary, which will provide them with a further opportunity to comment on the study results and become more actively engaged in the research process.

Lessons learned and implications for practice

In this article, we reviewed the ethical issues we faced as our study of the experiences of PLKDs unfolded. We learned that, despite our best efforts, we faced issues that were difficult to anticipate and had to be addressed as they arose, and, in hindsight, we acknowledge that some of the recruitment issues might have been at least partly anticipated. We also learned that the ethical decisions we made had practical implications, slowing down our recruitment efforts.

Perhaps the biggest lesson we learned is that often there is a tension between ethical considerations and research constraints and requirements. As qualitative health researchers, we are required to comply with formal ethical requirements; thus, we develop ethically-sound research protocols which are underpinned by ethical principles and values, and must seek and obtain ethics clearance from the relevant ethics committee. However, our ethical responsibility does not end there. As researchers, we must be able to recognize those 'ethically important moments' (Guillemin and Gillam, 2004) that arise during the conduct of research. These are

moments when we need to pause and think about the implications of what we are doing, and make decisions which, as we have demonstrated, have practical implications that can have an impact on recruitment and data collection plans. At the same time, we are increasingly operating in an environment where funding constraints often result in tight time frames and limited resources, and we must balance this tension very carefully.

Reflexivity is a cornerstone of qualitative research and has different interpretations: as introspection, intersubjective reflection, mutual collaboration, social critique or discursive deconstruction (Finlay, 2002a). We conceptualized reflexivity in its broadest sense, as the ethical practice of research (Guillemin and Gillam, 2004), and found that this notion helped us identify and address potential issues in the conduct of our research.

We suggest that at a time when researchers increasingly face funding and time constraints, we may be at higher risk of cutting "ethical corners" as we try to balance ethics and pragmatic challenges. As qualitative researchers, we must remember that the practical decisions we make have ethical implications, and, conversely, our ethical decisions will inevitably have practical implications. In conclusion, we suggest that reflexivity is an effective tool to help us navigate the labyrinth of ethically-sound qualitative research, and that more emphasis should be placed on nurturing the ethical awareness of novice qualitative researchers working in today's challenging environment.

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Reimbursing Live Organ Donors for Incurred Non-Medical Expenses: A Global Perspective on Policies and Programs

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Methods to reimburse living organ donors for the non-medical expenses they incur have been implemented in some jurisdictions and are being considered in others. A global understanding of existing legislation and programs would help decision makers implement and optimize policies and programs.

We searched for and collected data from countries that practice living organ donation. We examined legislation and programs that facilitate reimbursement, focusing on policy mechanisms, eligibility criteria, program duration and types of expenses reimbursed.

Of 40 countries, reimbursement is expressly legal in 16, unclear in 18, unspecified in 6 and expressly prohibited in 1. Donor reimbursement programs exist in 21 countries; 6 have been enacted in the last 5 years. Lost income is reimbursed in 17 countries, while travel, accommodation, meal and childcare costs are reimbursed in 12 to 19 countries. Ten countries have comprehensive programs, where all major cost categories are reimbursed to some extent. Out-of-country donors are reimbursed in 10 jurisdictions. Reimbursement is conditional on donor income in 7 countries, and recipient income in 2 countries.

Many nations have programs that help living donors with their financial costs. These programs differ in operation and scope. Donors in other regions of the world are without support.

Key words: Financing, health policy, living donors, personal, program development, program evaluation

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Introduction

About 27 000 living kidney transplants occur around the world each year, and the number is increasing (1). In addition, about 2000 living donor liver transplants are performed annually (2) and 250 living donor lung transplants have been performed worldwide (3). Living donor kidney transplantation is preferred to deceased donor transplantation or dialysis, as it improves recipient outcomes at a reduced cost to the healthcare system (4). It is estimated that one living kidney donation results in a net increase of 2 to 3.5 quality-adjusted life-years, and a net health care savings of $100 000 Canadian (5).

Non-medical expenses are frequently incurred by the living organ donor as part of the transplant process (6). These expenses include travel, parking, accommodation, meal and dependent care costs, as well as lost income. One Canadian study estimated that 53% of organ donors incur transportation and parking costs (7). In another American multi-center study, transportation and accommodation costs were reported by 99% and 88% of donors, respectively (8). Lost income has been reported in 14–30% of organ donors, averaging as much as $4410 Canadian in 2004 (7,9,10). In a single center study involving 133 potential donors to a family member, 24% chose not to donate because of anticipated financial hardship (11).

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To ease the financial burden of organ donation, experts advocate reimbursement of legitimate expenses, stating that it is just and ethically responsible, and should be considered a cost associated with treating living organ recipients (12–18). In 2008, the Declaration of Istanbul on Organ Trafficking and Transplant Tourism, the European Parliament, and the Asian Taskforce on Organ Trafficking each issued formal statements urging member states to define conditions in which reimbursement can be granted (12,13,16). All groups make a clear distinction between the acceptable practice of reimbursement of legitimate expenses incurred as a result of the transplant process, and payment resulting in financial gain which is illegal in most jurisdictions.

A comprehensive understanding of existing reimbursement programs would provide a global context for decision makers as they look to implement or refine reimbursement programs within their jurisdictions. The lack of a published comprehensive account of global legislation and practices prompted this review.

Materials and Methods

Data of interest

We considered countries where 10 or more living donations are performed each year, based on an average between 2004 and 2007 as described in the Global Observatory on Organ Transplantation and Horvat et al. (1,2). While reimbursement is implicit in payment programs, we excluded programs where payment is intended for financial gain, as this practice contravenes international recommendations and standards (12,16,19,20).

The data collection plan is presented in Figure 1. We first determined if reimbursement of legitimate expenses was legal in member countries. Based on legislation, the legality of reimbursement was classified into one of four categories: legal, illegal, unclear and unspecified. An example of a reimbursement clause that was interpreted as legal was '[1] A person commits an offence if he [a] gives or receives a reward for the supply of, or for an offer to supply, any controlled material;...[6]... payment in

money or money's worth to the holder of a license shall be treated as not being a reward where [a] it is in consideration for transporting, removing, preparing, preserving or storing controlled material (21)'. We were not able to find a clause that was interpreted as illegal; reimbursement would have been categorized illegal if the legislation clearly stated that reimbursement of expenses incurred during the organ donation process, as opposed to reimbursement for an organ, was prohibited. Unclear legislation did not explicitly address the issue of reimbursement for non-medical expenses, but addressed the issue of organ and/or tissue donation. An example of an unclear clause was 'no person shall buy, sell or otherwise deal in, directly or indirectly, for a valuable consideration, any tissue for a transplant (22)'. Unspecified refers to legislation that did not address the broader subject of organ and/or tissue donation or when the country representative indicated otherwise. Countries with provincial legislation, where provinces differed in their legislation, were counted in all applicable categories. Therefore, the sum of the number of countries across all types of legislation may be greater than the total number of countries.

We then ascertained characteristics of programs that facilitate donor reimbursement, including program history, mechanisms, types of non-medical expenses reimbursed (travel, accommodation, meals, lost income and childcare) and eligibility criteria (Figure 1). We also gathered information on "umbrella" programs, which compensate donors as part of other broader initiatives. Information on national programs was collected for countries with both national and provincial/territorial/state reimbursement initiatives. Countries with provincial programs, where provinces differed in program details, were counted in all applicable categories. Therefore, the sum of the number of countries in each program category may be greater than the total number of countries.

Data sources and collection

Data collection was updated until July 2009. [Correction made after online publication 4 Nov 2009: 2008 changed to 2009] Data were extracted by a single author (MS) from government and ministry websites, legal databases (International Digest of Health Legislation and World Legal Information Institute), and kidney, nephrology and transplantation foundations' websites. Data were independently reviewed for accuracy by a second author (MC). In most cases, information was also collected directly from country representatives by the same single author (MS) in order to obtain English language legislation or to obtain information that was not available from other sources (Appendix A). Country representatives included members of
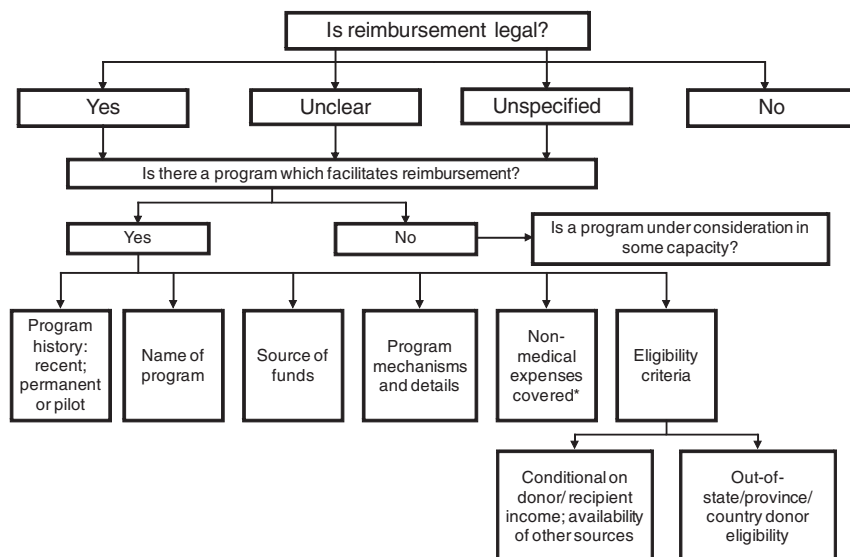
Figure 1. Flow chart of data collected for each eligible country. *Non-medical expenses included travel, accommodation, meals, lost income and childcare.

national kidney, nephrology and transplant foundations, Ministries of Health, and health care providers involved in living organ transplantation. All data that were not collected directly from country representatives were sent to representatives for verification. Legislation that was not available in English was obtained in the native language and translated with the help of a country representative, a translator, Google Translator (translate.google.com) or Yahoo Babel (babelfish.yahoo.com).

Results

One hundred ninety-three countries were considered for this review. One hundred twenty-one countries were excluded: the Global Observatory on Organ Transplantation (2) did not recognize 88 nations as performing living organ donation (LOD); data on the number of LODs per year were missing for 14 countries; all LODs were performed outside of 1 country; a country representative confirmed that LOD was illegal in 1 country; less than 10 LODs were performed per year on average between 2004 and 2007 in 16 countries and a legal payment program had been established in 1 country. In total, 72 countries were eligible. We were able to collect data from 40 (56%) countries. For the remaining 32 nations, data collection was either incomplete due to unavailability of information and/or because the country representative was non-responsive. Data sources for each country are provided in Appendix B.

Of the 40 countries examined, 16 expressly legalize reimbursement, 1 explicitly prohibits any form of compensation, 18 have unclear legislation and 6 are unspecified. Legislation or information on legislation was not available for 2 countries.

Reimbursement programs exist in 21 of the 40 countries; 14 programs in the 16 countries where reimbursement is expressly permitted by law, another 8 programs in the 18 countries where legislation is unclear and 1 in the 6 countries where reimbursement is unspecified (Table 1).

Six of the 21 countries implemented reimbursement programs in the past 5 years (Australia, Canada, New Zealand, Saudi Arabia, the United Kingdom and the United States). Two countries (Israel and Singapore) are in the process of implementing a program that will take effect within the year 2009. Permanent reimbursement programs exist in 20 countries; 2 countries have programs in a pilot phase (USA and Canada). Representatives from 7 countries indicated their reimbursement programs were currently being re-evaluated or improved (Belgium, France, the Netherlands, New Zealand, Saudi Arabia, Switzerland and the United States). Of the 18 countries in which reimbursement is not illegal and no program exists, representatives from 2 countries indicated active pursuit of a donor reimbursement program (Austria and India).

As shown in Table 2, 10 countries have comprehensive programs where 5 major types of costs (travel, accommodation, meals, lost income and childcare) are reimbursed

in some capacity. Most of the 21 countries with programs reimburse some lost income (17 countries), travel expenses (19 countries) and accommodation (17 countries). A smaller number of countries reimburse meals (14 countries) and childcare costs (12 countries). Out-of-province/state/country donors are eligible for reimbursement in 10 jurisdictions. Reimbursement is conditional on donor income in 7 countries, and on recipient income in 2 of these countries (Bolivia and the United States). In one country (Bolivia) the recipient and donor have the option to meet with a lawyer to negotiate the type and amount of reimbursement to be granted the donor by the recipient; this can include travel, accommodation, meal and other postsurgical expenses (Table 2).

Health care travel assistance programs exist in some countries, providing financial assistance to all types of patients including living organ donors. For example, a program in Australia reimburses donors for travel, accommodation and meals (Travel Reimbursement Policy offered by Western Australia Country for Health Services). Programs in Canada reimburse similar costs (Canadian Medical Transportation Assistance Program in Newfoundland and Labrador; Northern Health Travel Grant in Ontario) (Tables 2 and 3).

Countries have differing sources of funding for reimbursement; some countries have multiple sources. In 15 of the 20 countries with programs, reimbursement is at least partially government funded. In 5 countries, lost income can be covered in some capacity by the donor's employer through sick leave, paid leave and/or employment insurance (Belgium, Canada, Czech Republic, the United Kingdom and the United States). In 3 countries donors receive reimbursement from charity organizations (Canada, the Philippines and Saudi Arabia). Funds are available through the recipient's health/sickness insurance in 4 countries (Germany, Netherlands, Switzerland and Turkey). In Bolivia, where the recipient and donor can meet with a lawyer to agree upon donor reimbursement, the recipient may be responsible for reimbursing the donor (Table 3). Similarly, in Singapore, the recipient may choose to reimburse the donor and those who are unable to afford reimbursement may be referred to volunteer welfare organizations for assistance (Table 3).

Programs and policies in specific jurisdictions
The United States' National Living Organ Donor Assistance Program (NLODAP) is a 4-year pilot program (commenced in October 2007), that is unique in the way it determines which donors are eligible for compensation. This program considers both donor and recipient income and classifies each donor into one of four categories based on financial need. Preference is given to low-income donors with low-income recipients; donors are ineligible for reimbursement when donor and recipient have incomes greater than 300% above the poverty line. An additional distinguishing feature of the NLODAP is that it provides donors with a prepaid

Table 1: Global non-medical expense reimbursement: legislation

Country	Province/territory/state/region	Reimbursement coverage in legislation (legal, unspecified, illegal)	Does a reimbursement program exist?
Australia	Australian Capital Territory	Legal	No
	New South Wales	Legal	No
	Northern Territory	Legal	No
	Queensland	Unclear	No
	South Australia	Legal	No
	Tasmania	Legal	No
	Victoria	Legal	No
	Western Australia	Legal	Yes
Austria		Unspecified	No
Bangladesh		N/A	No
Belgium		Legal	Yes
Bolivia		Unclear	Yes
Bosnia and Herzegovina		Unspecified	No
Brazil		Unclear	No
Canada	Alberta	Unclear	Yes
	British Columbia	Unclear	Yes
	Manitoba	Legal	Yes
	New Brunswick	Unclear	Yes
	Newfoundland and Labrador	Unclear	Yes
	Northwest Territories	Unspecified	Yes
	Nova Scotia	Unclear	Yes
	Ontario	Unclear	Yes
	Prince Edward Island	Unclear	Yes
	Quebec	Unspecified	N/A
	Saskatchewan	Unclear	Yes
Chile		Legal	Yes
Czech Republic		Unclear	Yes
Denmark		Legal	Yes
Ecuador		Unclear	No
France		Legal	Yes
Germany		Unclear	Yes
India		Legal	No
Israel		Legal	Yes
Italy		Unclear	No
Japan		Unspecified	No
Jordan		N/A	No
Kuwait		Illegal	No
Libya		Unclear	No
Malaysia		Unclear	No
Netherlands		Legal	Yes
New Zealand		Unclear	Yes
Norway		Legal	Yes
Philippines		Unclear	Yes
Poland		Unclear	No
Romania		Unspecified	No
Saudi Arabia		Legal	Yes
Singapore		Legal	Yes
South Africa		Legal	No
Spain		Unclear	No
Sweden		Unclear	Yes
Switzerland		Legal	Yes
Syria		Unspecified	No
Taiwan		Unclear	No
Turkey		Unclear	Yes
United Kingdom		Legal	Yes
United States		Legal	Yes
Venezuela		Unclear	No

N/A = data not available.

Table 2: Global non-medical expense reimbursement programs: coverage and program details

Country	Province/territory/state/region/(program)	Non-medical expenses covered					Reimbursement is dependant on			Program in pilot phase	Out-of-province/state/country donors eligible
		Travel	Accommodation	Meals	Lost income	Childcare	Donor income	Recipient income	Availability from other programs[1]		
Australia	Western Australia	Yes	Yes	Yes	No	No	No	No	Yes	No	No
Belgium		No	No	No	Yes	No	No	No	Yes	No	No
Bolivia[2]		Yes	Yes	Yes	No	No	Yes	Yes	N/A	No	N/A
Canada	British Columbia	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
	Manitoba	Yes	Yes	Yes	Yes	Yes	TBD	No	TBD	No	No
	New Brunswick	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	No	Yes
	Newfoundland and Labrador	Yes	Yes	Yes	No	No	No	No	Yes	No	No
	Northwest Territories	Yes	Yes	Yes	No	No	No	No	Yes	No	No
	Nova Scotia	Yes	N/A	N/A	N/A	N/A	Yes	N/A	Yes	N/A	N/A
	Ontario	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
	Prince Edward Island	Yes	No	No	No	No	N/A	No	N/A	No	Yes
	Quebec	Yes	No	No	No	No	Yes	No	N/A	N/A	N/A
	Saskatchewan	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
Chile		No	No	No	Yes	No	No	No	No	No	No
Czech Republic		Yes	No	No	Yes	No	No	No	Yes	No	No
Denmark		Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
France		Yes	Yes	Yes	Yes	Yes	No	No	N/A	No	Yes
Germany		Yes	Yes	No	Yes	No	N/A	N/A	Yes	No	N/A
Israel		Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Netherlands		Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
New Zealand	(Live Organ Donors Welfare Program)	No	No	No	Yes	Yes	No	No	No	No	Yes
	(National Travel Assistance Program)	Yes	Yes	No	No	No	No	No	Yes	No	No
Norway		Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Philippines		Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
Saudi Arabia		Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Singapore		Yes	Yes	Yes	Yes	Yes	No	No	TBD	No	Yes
Sweden		Yes	Yes	Yes	Yes	No	Yes	No	N/A	No	Yes
Switzerland		Yes	No	No	No	No	No	No	No	No	No
Turkey		Yes	Yes	No	Yes	Yes	No	No	Yes	No	No
United Kingdom		Yes	Yes	No	Yes	Yes	No	No	Yes	No	Yes
United States		Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No

N/A = data not available; TBD = to be determined.
[1] Other sources refers to other sources of reimbursement, such as sickness insurance or travel expense programs.
[2] Recipient and donor may consult with a lawyer to determine whether the donor will cover all medical and pharmacological expenses. See Table 3.

Table 3: Summary of non-medical expense reimbursement opportunities

Country	Province/territory/ state/region	Name and type of program	Source of funds	Program mechanisms and additional details
Australia	Western Australia	Western Australia Country Health Service (WACHS)	Government	Donors must provide travel and accommodation receipts, along with supporting taxation receipts and documentation. Escort expenses are not reimbursable. Only Western Australia residents traveling to Perth are covered.
Belgium		Umbrella program	Government and employer	Only lost income is covered. During the first month of incapacity, 100% of the donor's salary is paid by the employer. After the first month, 60% of the lost income is covered by insurance/mutuelle. All citizens have a 'mutuelle' which provides reimbursement for medications, hospitalizations and operations.
Bolivia		No formal program	Recipient	The recipient and donor have the option to meet with a lawyer to negotiate the type and amount of reimbursement to be granted the donor by the recipient; this can include travel, accommodation, meals and other postsurgical expenses This is possible only when transplant is done at private center. There is no government involvement during this process.
Canada	Alberta	No formal program	Charity (Hope Air)	Social workers work with Hope Air to assist with air transportation expenses; they also attempt to facilitate financial support through various charitable organizations.
	British Columbia	Living organ donor expense reimbursement program	Government, pharmaceutical companies and health charity (Kidney Foundation of Canada)	Two-step process: (1) predicted expenses are submitted for preapproval, (2) expense claim forms and receipts are submitted following surgery and assessment stages.
	Manitoba	TBD	Government and health charity (Kidney Foundation of Canada)	TBD
	New Brunswick	No formal program	Government and charities	All transportation, meal and accommodation expenses are reimbursed, provided receipts. Donor out-of-pocket expenses are submitted to the Provincial Donor Coordinator who recommends reimbursement to the Department of Health and Wellness Hospital Services Branch. Social workers assess the donor's need for other types of expenses.
	Newfoundland and Labrador	Umbrella program	Government	The Medical Transportation Assistance Program states that donors are required to pay medical and travel expenses out-of-pocket and subsequently apply for reimbursement of allowable expenses. Expenses are assessed based on travel dates in relation to medical appointment/service date(s). Applicants must provide receipts and boarding passes for air travel for eligible expenses.
Canada	Northwest Territories	Umbrella program	Government	The Medical Travel Assistance Policy states that travel must originate in the NWT and health care must not be available within the resident's home community. A co-payment fee is required for every round-trip.

Continued.

Table 3: Continued

Country	Province/territory/ state/region	Name and type of program	Source of funds	Program mechanisms and additional details
	Nova Scotia	No formal program	Charity (Hope Air)	Charitable help is available.
	Ontario	Program for reimbursing expenses of living organ donors	Government and employer	The program is a last resort for donors. Donors apply for reimbursement through the Trillium Gift of Life Network, administering the program on behalf of Ministry of Health and long-term care. For lost income, the donor is expected to apply for reimbursement from his/her employer and employment insurance before applying to PRELOD.
		Northern Health Travel Grant		The Northern Health Travel Grant defrays transportation costs for residents of Northern Ontario who must travel long distances within Ontario or Manitoba to receive health care services not available locally; applicants must apply for reimbursement, and must live at least 100 km from the nearest facility.
	Prince Edward Island	No formal program	Government and charity	Any reimbursement, above travel expenses, is generally provided for donors with financial issues and is provided by non-governmental sources, through the help of social workers.
	Saskatchewan	Umbrella program	Employer	An agreement is made between the donor and his/her employer for paid leave during transplant process.
		No formal program	Charity (Kinsmen Foundation)	Social workers contact charitable organizations to check availability of funds, and the donor's suitability for assistance.
Chile		No formal program	Government and private system	All donors receive reimbursement for time away from work. Donors must apply before the transplant surgery or up to 48 h after transplant surgery, and physician signature is required.
Czech Republic		No formal program	Government, recipient health insurance and employer	Donors receive a social security payment to substitute lost income during hospitalization. Travel expenses are covered by recipient health insurance. Recipients must apply for reimbursement. Out-of-country donors may be eligible with prior approval. Minimal salary loss is covered by employer.
Denmark		Reimbursement included in health care system	Government	Expenses are estimated and paid by the hospital; the hospital is then reimbursed by government. The system for reimbursement was expanded in 2003 to cover a reasonable amount of medical examinations postdonation.
France		Reimbursement included in health care system	Government	The health care establishment reimburses the donor and is then reimbursed by social security public insurance. There is no maximum amount reimbursable; most reasonable expenses are covered. A new decree is in preparation and will be published by 2009; substantial changes will be implemented, including the shift of the payer role to national or regional social security instead of the healthcare establishment.

Continued.

Table 3: Continued

Country	Province/territory/ state/region	Name and type of program	Source of funds	Program mechanisms and additional details
Germany		No formal program	Recipient Health Insurance	Travel, accommodation and some lost wages are automatically covered by the recipient's health insurance. Travel abroad is covered along with medical costs through health insurance and sickness benefits under the national social security program. Lost income is partially reimbursed by the recipient's employer as sick leave; a new proposal has been submitted to standardize reimbursement for loss of income.
Israel		Umbrella program Organ Transplant Bill: Financial Compensation Package and a series of benefits	Government	Expenses are reimbursed via a compensation package that depends on donor income. This is in addition to a series of other benefits (recovery of expenses for psychological treatment, recovery leave, merit certificate from State and free entrance to nature reserves and national parks).
Netherlands		No formal program	Government and recipient sickness insurance	The Dutch Kidney Foundation is awarded a grant from the Dutch Ministry of Health, Welfare and Sport. Any donor can apply for reimbursement through the Kidney Foundation before or after expenses are incurred. Lost income is also repaid through this program for a maximum of 6 weeks, in case of sever e complications it can cover up to 12 weeks. Reimbursement of all non-medical costs not covered by sickness insurance is provided by the government.
New Zealand		Live Organ Donors Welfare Programme and Ministerial Direction	Government	Reimbursement is tax free and subject to limits. Donors must apply to District Health Board. Payments are made directly to the donor's bank account with proof of lost income and dependents' birth certificates. Donors are eligible for reimbursement for expenses incurred during the 12 weeks posttransplant surgery.
		Umbrella Program; National Travel Assistance Scheme (NTAS)	Government	A completed claim form is required for reimbursement, along with itemized receipts. Some accommodation expenses may be covered by District Health Board. Support person costs may be covered.
Norway		Reimbursement included within healthcare system	Government	Recipients apply for reimbursement with proof of expenses. There is no maximum amount reimbursable, provided that expenses are documented and within reason.
Philippines		Private foundation offers compensation package	Transplantation Foundation of the Philippines	The Transplantation Foundation of the Philippines reports rejecting offers from potential organ donors seeking to 'sell' an organ. The total reimbursement package is fixed. The donor must apply to the Foundation.

Continued.

Table 3: Continued

Country	Province/territory/ state/region	Name and type of program	Source of funds	Program mechanisms and additional details
Saudi Arabia		New Organ Donation law offers compensation package	Government and Prince Fahd Bin Salman Charity	Saudi riyals may be reimbursed and awarded the King Abdul Aziz medal of the third degree and a discount card with Saudi airlines. SCOT (a governmental agency) coordinates the dispensing of incentives with the ministry of health. Donors can decline the incentive. The reimbursement committee meets with the unrelated living donor and interviews him at least 3 times to make sure that he is donating out of his conscience and with complete willingness, not out of poverty, need or pressure. The Prince Fahed Ibn Salman Charitable Society has the right to supervise reimbursement.
Singapore		No formal program	Recipient, and voluntary welfare organizations	Donor may be reimbursed for donation related expenses such as travel, accommodation, medical and surgical, loss of income and miscellaneous expenses such as eldercare and childcare. Recipients who cannot afford to reimburse their donor can be referred to voluntary welfare organizations for assistance.
Sweden		No formal program; Reimbursement is provided by the healthcare system	Government	Donors must apply for reimbursement, providing receipts of expenses, and proving loss of income. Reimbursement is facilitated by social workers. Expenses are paid for out-of-pocket by the donor and the donor is then reimbursed. All costs are reimbursed if proper documentation is provided.
Switzerland		No formal program	Recipient Health Insurance; Health care system	Reimbursement is administered by the association of medical insurance. All expenses within reason are reimbursable.
Turkey		No formal program	Recipient's Social Insurance	The donor's physician must provide a sickness report for the donor in order for the donor to receive reimbursement for transportation as well as accompanying person expenses through the recipient's social insurance. Accommodation and meals outside of hospital are not covered.
United Kingdom		Formal department of health policy on reimbursement for living organ donor expenses	Government and employer	Expenses are covered by the donor out-of-pocket; the donor is then reimbursed. Donors must claim expenses before expenses are incurred, within 12 weeks of surgery. Personal expenses are repaid in full once receipts are provided. Mileage can be reimbursed at the standard National Health Service rate. Payments are not subject to tax liability. Tax liability for loss of earnings depends on the employment status of the donor. Payments for loss of earnings are legal under the HOT Act but the method of payment and position with respect to any tax liability depends on the employment status of the individual.

Continued.

Table 3: Continued

Country	Province/territory/ state/region	Name and type of program	Source of funds	Program mechanisms and additional details
United States		National Donor Assistance Program	Government and employer	Donors must apply online before expenses are incurred. A review committee then votes on the eligibility of the donor. Escort expenses are reimbursable. The maximum number of donors per recipient for reimbursement is 3 for kidney, 5 for liver and 6 for lung donations. Amount of reimbursement depends on the amount of reimbursement received from other sources, such as employment insurance policies.

TBD = to be determined.

credit card for use during the donation process, instead of reimbursing costs that have already been incurred.

Reimbursement programs exist in many European countries. In France and Denmark, reimbursement of expenses is required for all donors undergoing a live organ transplant; hospitals automatically reimburse donors and are subsequently reimbursed by the government.

Donor reimbursement programs are less common in South America (23).

Saudi Arabia and Israel both offer a series of benefits to ensure that donors do not suffer as a result of their donations. Saudi Arabia provides long-term medical insurance to aid donors with future medical care. Israel will supply donors with insurance against the loss of ability to work or loss of earning power as well as life insurance so that these benefits remain affordable after surgery. Rewards of non-monetary value are offered as well, such as a discount on Saudi Airlines or free entrance to national parks in Israel. If needed, Israel will also cover psychologist expenses to ensure that donors make a full recovery after surgery. Finally, in both Israel and Saudi Arabia, a modest financial package that depends on donor income will be provided to reimburse all donors for their non-medical expenses such as lost income, lost days of sick-leave and travel expenses.

Reimbursement programs are sparse across Asia. However, in Singapore, an amendment to the Human Organ Transplant Act, allowing reimbursement of reasonable expenses in relation to organ donation, was recently passed. The new law allows recipients to reimburse donors for their incurred medical and non-medical expenses. In addition, in India, living donor benefits have been recommended by the Transplant of Human Organs Act (THOA) review committee. Existing THOA law permits compensation for the loss of wages but it is not practiced since the same could be interpreted as sale or purchase of organs. The National Organ Transplant Program is in the process of being implemented; coverage of medical expenses and medical insurance for the donor, as well as travel concessions on Indian railways, are under consideration for the program.

Discussion

This is the first comprehensive review of global legislation and procedures to reimburse living organ donors for their financial costs. Living organ donor reimbursement programs have recently been introduced in many countries, in some cases as a pilot project. In other countries *de novo* programs are under development. Many programs differ in their operation, funding source and expenses reimbursed. We described existing programs, funding sources, eligibility criteria and categories of donor cost that are reimbursed.

In most reimbursement programs, non-medical expenses are paid directly or indirectly (via health care) from government sources. Some programs rely on charities and employers; very few programs rely on the recipient (either through direct payment or through health care insurance). Almost half of the reimbursement programs are comprehensive in that they cover the 5 major types of non-medical expenses (travel, accommodation, meals, lost income and childcare). For the countries with comprehensive reimbursement, donors in 8 countries can apply through one source to receive reimbursement. Of the 6 programs that were initiated in the last 5 years, 2 are comprehensive. We were unable to determine if all costs incurred by living donors were reimbursed through existing programs.

Limitations of our review merit discussion. As for all reviews of this type, the accuracy of the results is highly dependant on the quality of the data collected. We compiled data from 40 of the 72 countries eligible for review. Despite repeated attempts we were unable to obtain information for 32 of the 72 countries that practice living

donation, such as Columbia, Cyprus and Georgia. However, this may not materially impact the results presented, as we believe it is reasonable to assume such countries do not have reimbursement programs.

We did not collect information on monetary values for reimbursement. A paper focusing solely on program details would be the ideal setting in which to collect and present such data.

The data acquired from the 40 countries were derived from a variety of sources, as a single source for international legislation and information on reimbursement programs does not exist. Information obtained for this review was at risk for being outdated, biased or untranslatable. To address these deficiencies, we undertook the additional step of contacting country representatives to confirm the accuracy of the data. Information obtained from country representatives, however, may be subject to bias and is directly limited by the individual's experience in living organ donation. In some countries, multiple complex opportunities for reimbursement exist, including programs beyond the sphere of transplantation (18). We provided generalizations of these opportunities to allow for broader comparisons across countries. We could not determine whether donors had difficulties accessing current programs, nor to what extent programs reimbursed incurred donor costs. The degree to which reimbursement programs improve satisfaction with the transplant process, and transplant rates, remains the subject of further research.

In summary, this review provides a comprehensive overview of legislation and practices of living organ donor reimbursement worldwide. Many programs have recently been enacted, and several nations are considering implementing *de novo* reimbursement programs. Despite this, most living organ donors worldwide lack organized programs to defray the costs of the donation process. This summary will allow decision makers and transplant professionals to frame current programs in the global context, and will aid development and refinement of optimal reimbursement policies. Given the emerging practice of living organ donor reimbursement, it may be prudent for countries that expressly prohibit reimbursement to reassess current legislation in light of global practices and current international recommendations. It is our hope that the information presented here can be used to assist those countries yet to develop local programs, and refine existing programs.

Acknowledgments

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Supporting Information

The following supporting information is available for this article online:

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Appendix A is a table including information on country legislation name, availability, details and source of legislation. Appendix B is a table with information on sources of country-specific data; these sources include online references and country representatives.

Appendix A. Table of country legislation name, availability, details and source.

Appendix B. Sources of country-specific information: online references and country representatives.

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Economic Consequences Incurred by Living Kidney Donors: A Canadian Multi-Center Prospective Study

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Some living kidney donors incur economic consequences as a result of donation; however, these costs are poorly quantified. We developed a framework to comprehensively assess economic consequences from the donor perspective including out-of-pocket cost, lost wages and home productivity loss. We prospectively enrolled 100 living kidney donors from seven Canadian centers between 2004 and 2008 and collected and valued economic consequences ($CAD 2008) at 3 months and 1 year after donation. Almost all (96%) donors experienced economic consequences, with 94% reporting travel costs and 47% reporting lost pay. The average and median costs of lost pay were $2144 (SD 4167) and $0 (25th–75th percentile 0, 2794), respectively. For other expenses (travel, accommodation, medication and medical), mean and median costs were $1780 (SD 2504) and $821 (25th–75th percentile 242, 2271), respectively. From the donor perspective, mean cost was $3268 (SD 4704); one-third of donors incurred cost >$3000, and 15% >$8000. The majority of donors (83%) reported inability to perform usual household activities for an average duration of 33 days; 8% reported out-of-pocket costs for assistance with these activities. The economic impact of living kidney donation for some individuals is large. We advocate for programs to reimburse living donors for their legitimate costs.

Introduction

Transplantation is the preferred treatment for patients with kidney failure, given the reduced risk of death (1), improved quality of life and reduced healthcare costs (2) compared with dialysis. Each kidney transplanted into a patient with end-stage renal disease is estimated to provide an additional 2–3.5 quality-adjusted life years, direct healthcare savings of $100 000 (3) and economic value of approximately $300 000 (4). Despite strategies to increase organs available for transplantation for both living and deceased donation (5–7), the need for kidneys continues to exceed their supply (8). Potential living donors and their intended recipients are concerned about economic consequences of donation (9). It has been recognized that living donors experience economic consequences during workup, surgery and convalescence. These economic consequences may be considered unfair and act as a disincentive for some donors. It has been suggested that living donors be reimbursed for their incurred expenses in jurisdictions where this is feasible (10,11).

We published a comprehensive, critical review of the existing 35 studies describing the frequency and magnitude

of expenses incurred by living donors (12); however, an accurate estimate of costs was not possible given the multiple methodological issues in existing studies, including the retrospective nature of most reports, lengthy time frames for patient recall, low response rates and incomplete capture of all relevant costs. As such the true extent and magnitude of the economic burden to living kidney donors are uncertain, highlighting the need for prospective and accurate determination of these costs (13). Given the poor health outcomes for patients on dialysis, limited supply of deceased donor organs and high costs of dialysis therapy, it is imperative that all barriers to living organ donation be identified, fully characterized and definitively addressed. Better knowledge of the economic consequences experienced by living kidney donors also informs the feasibility and conduct of emerging and existing reimbursement programs.

As part of a larger prospective multi-center study designed to determine the medical and psychosocial consequences of living kidney donation, we conducted a rigorous prospective costing study to obtain precise estimates of the expenses incurred by Canadian living kidney donors.

Methods

Economic consequences incurred were determined from participants enrolled in a multi-center prospective study designed to determine long-term outcomes in living donors. Briefly, subjects ≥18 years of age deemed eligible to donate a kidney to a relative or friend at one of seven Canadian transplant centers, who verbally communicated in English or French, and provided consent, were recruited prior to donation and followed post–kidney donation. This economic sub-study examined the first 100 living kidney donors enrolled who proceeded with donation and had follow-up for at least 1 year.

The three-step micro-costing approach of identification, measurement and valuation of resources (14) was followed. Identification of potential economic consequences was determined through systematic review of existing literature (12) and iterative consultation with healthcare professionals in transplantation to identify categories and details of potential costs (Figure S1; Table S1). Measurement of resources consumed by donors was performed through two mail self-administered surveys at 3 and 12 months after kidney donation, based on the observation that the majority of costs due to donation are encountered within the first 3 months of donation, and almost all within the first 12 months. A 90-day period for self-reported productivity impairment has an intraclass correlation coefficient of over 0.80 with actual records (15), indicating that participants are likely to accurately recall expenses occurring in the 3 months postdonation. Donors reported for the predonation (including donor evaluation), donation and postdonation time periods. Follow-up telephone calls to participants were made by the central data-coordinating center for missing or discrepant data.

We identified the major cost categories relevant to living donors, including direct costs defined as resources consumed in the donation process even where a direct monetary transaction does not occur, and productivity costs including days off work with (and without) lost income, lost home productivity, as well as caregiver for convalescent or dependent care (Table S1). Workforce productivity was valued using province-specific average wage rates (Table S2). We developed a comprehensive instrument using accepted techniques to capture units of resources consumed as a result of living donation (14–16). This instrument quantified the number of units consumed in each category by donors for a full accounting of resource utilization. Collecting units consumed (e.g. capturing distance traveled instead of out-of-pocket fuel costs) facilitates portability of the results to alternate settings, as the monetary value per unit may vary depending on setting and region. Finally, we assigned each resource unit a cost using conventional costing techniques and relevant Canadian estimates (Table S1 and Supplemental Methods).

The cost incurred for living kidney donors was calculated by each cost category and in total using the average and standard deviation as well as median and range (given that cost data are frequently skewed). We determined the frequency distribution of total costs incurred by each donor. The value of lost workforce productivity where the donor did not incur lost wages was determined but was not included in total cost in the primary analysis.

Results

Among donors with at least 1 year of follow-up postdonation, 85% had complete 1-year data at the time of this analysis. The 100 living kidney donors enrolled had an average age of 45.2 years, and 64% were Caucasian women (Table 1). They were enrolled from 2004 to 2008, and all costs are expressed in Canadian dollars for this period of time. The most frequently reported household annual income category was ≥$80 000; at this time, the average household income in Canada was $71 600–$78 500 (17). The majority of donors were from four transplantation centers in Ontario. Direct out-of-pocket costs were incurred by 94 of the 100 subjects, with highest proportion reporting cost for ground travel (94%) and nonhospital accommodation (49%) (Table 2). For donors who reported resource use in cost category of interest, the greatest average costs were observed for ground travel, accommodation and air travel ($897, $1759 and $1480, respectively). When considering all donors (including those who incurred no resource use), the largest costs were for ground travel and accommodation ($852 and $862, respectively). In all 100 donors, average direct cost was $1780 (SD 2504), and median cost was $821 (25th–75th percentile 242–2271).

Work and home productivity losses occurred in over 80% of subjects (Table 3), and lost wages was reported by 47% of donors. In those who experienced loss of pay, the average number of days and income lost were 20 and $4567, respectively; for all donors average lost wage was $2144. Total workforce productivity loss that includes time off work with and without pay (i.e. vacation, sick leave, employment insurance) for all donors was $6729 (Table 4).

Approximately 45% of donors directly experienced economic consequences attributable to living kidney donation (out-of-pocket costs, lost pay, but excluding home productivity costs) that were less than $1000 (Figure 1). However, 20% incurred costs between $1000 and $3000, 34%

Table 1: Characteristics of living kidney donors

Variable	N = 100 donors
Age at time of donation, mean (SD)	45.2 (9.5)
Female, n	71
Race/ethnicity, n	
Caucasian	90
Asian	3
African Canadian/American, Black	2
Other	4
Married prior to donation, n	74
Family income prior to donation (CAD), n	
<15 000	2
15 000–29 999	6
30 000–49 999	22
50 000–79 999	21
≥80 000	48
Relationship to recipient	
Sibling	38
Parent	16
Son/daughter	14
Spouse/partner	12
Friend	4
Other	15
Transplant center, n	
Edmonton	11
Halifax	8
Hamilton	11
London	34
Toronto (St. Michael's)	12
Vancouver	11
Winnipeg	13
Province of residence, n	
Alberta	11
British Columbia	11
Manitoba	12
Nova Scotia	4
Ontario	59
Prince Edward Island	1
Out of country (USA)	1

One donor is missing age, gender, race and annual household income.
All respondents were English speaking.

experienced costs >$3000, with 15% of those incurring costs >$8000. The average out-of-pocket costs and lost wages for living donors was $3268 (median $1282) (Table 4). In sensitivity analysis, mean home productivity cost was estimated at $5521.

Interpretation

To our knowledge, this is the first study to prospectively and comprehensively capture and value the economic consequences experienced by living kidney donors. While there is considerable variation between donors in what costs are encountered and their magnitude, the vast majority of living kidney donors directly experienced substantial economic consequences, with an estimated average value of costs of $3268 for all 100 Canadian living

Table 2: Direct economic costs for 100 Canadian living kidney donors

Cost type	Cost category	Description	Units	Number of patients (n=100)	Median (25th–75th percentile) units[1]	Costs $ (in patients reporting outcome)[1] Average (SD)	Median (25th–75th percentile)	Costs $ (all patients)[2] Average (SD)	Median (25th–75th percentile)
Direct								1780 (2504)	821 (242–2271)
	Travel	Ground travel	# Return trips	94	10 (6–16)	897 (1048)	512 (216–1187)	852 (1040)	486 (194–1080)
	Travel	Air travel	# Return trips	3	3 (1–4)	1480 (1108)	2065 (203–2173)	44 (299)	0 (0–0)
	Accommodation	Nonhospital accommodation	# Overnight stays	49	6 (3–11)	1759 (2567)	1094 (547–2007)	862 (1995)	0 (0–1090)
	Medication[3]	Pain medication or antibiotics	Drugs taken (yes/no)	4	N/A	40 (28)	40 (20–60)	1 (6)	0 (0–0)
	Medical	Out-of-pocket medical expenses related to tests, appointments or hospital stays	Expenses incurred (yes/no)	22	N/A	152 (247)	60 (40–150)	30 (123)	0 (0–0)

[1] Considers only those donors who reported the resource use.
[2] Considers all donors (n = 100) in denominator (one donor experienced exceptional circumstances [out of country donor with 3-month stay] and these costs were excluded).
[3] Medication includes only patients who paid for medication out of pocket, and some or all of the cost of medication was not reimbursed. Note that 30 out of 100 donors reported requiring medication. Two out of four donors are missing cost of medication.

Table 3: Economic outcomes for 100 Canadian living kidney donors

Cost type	Cost category	Description	Number of donors reporting the outcome	Number of days (in donors reporting outcome) Median (25th–75th percentile)	Number of days (all donors) Median (25th–75th percentile)	Costs $ (in donors reporting outcome)[1] Average (SD)	Costs $ (in donors reporting outcome)[1] Median (25th–75th percentile)	Costs $ (all donors)[2] Average (SD)	Costs $ (all donors)[2] Median (25th–75th percentile) Cost	Costs $ (all donors)[2] Average (SD)	Costs $ (all donors)[2] Median (25th–75th percentile)
Indirect	Lost wages	Time spent away from work (with loss of pay)	47	20 (5–44)	0 (0–14)	4567 (5111)	3273 (850–7484)	2144 (4167)	0 (0–2794)	6729 (6259)	6572 (1048–9081)
		Time spent away from work (without loss of pay)	68	38 (14–53)	15 (0–46)	6898 (5448)	6659 (2288–8522)	4558 (5753)	2517 (0–7816)		
	Housework and dependent care	Days unable to perform usual household activities (estimated cost)	83	33 (14–60)	23 (6–56)	6597 (5053)	5763 (2445–9780)	5453 (5231)	3977 (1116–9014)	5233 (5196)	3345 (838–8557)
		Number of days requiring assistance or care (reported out-of-pocket cost)	8	7 (6–12)	0 (0–0)	372 (800)	53 (0–125)	23 (202)	0 (0–0)		

[1] Considers only those donors who reported the resource use.
[2] Considers all donors (n = 100) in denominator.

Table 4: Total costs incurred for living kidney donors

Scenario	Average cost $ (SD)	Median cost $ (25th–75th percentile)
Donor costs[1]	3268 (4704)	1282 (205–4619)
Estimated home productivity cost[2]	5521 (5287)	4462 (1222–9014)
Total workforce productivity cost[3]	6729 (6259)	6572 (1048–9081)

Considers all donors (n = 100) in denominator.
[1]Donor costs = out-of-pocket costs + lost wages.
[2]Home productivity determined using provincial wage rates.
[3]Includes time off work with and without pay.

donors in this study. We also identified a wide variation in costs incurred in both overall costs as well as costs in the categories examined. While a large proportion incurred costs valued at <$1000, one-third of donors experienced a large economic burden in excess of $5000 or $10 000 as a result of donation.

We (10), as well as others (18), have advocated for reimbursement of incurred expenses on both the principle of fairness, as well as eliminating a potential barrier or disincentive to living kidney donation. The economic consequences enumerated here are not trivial, and the context in which they occur is worth noting. Biological relatives and spouses make up the majority of living donors, who may be burdened financially by the burden of the chronic illness of end-stage renal disease. Further, living kidney donation leads not only to better quality and quantity of life for recipients but also to substantial net healthcare cost savings estimated at $100 000 (3). It is counterintuitive to allow economic penalties to occur to living kidney donors when programs are attempting to heavily promote this activity that results in health improvements and healthcare resource savings.
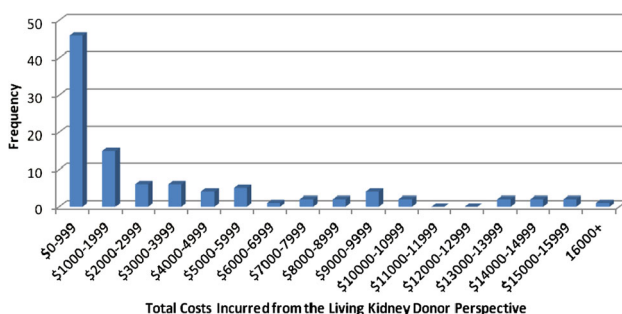
Figure 1: Frequency distribution of total costs incurred from the living kidney donor perspective. 25th percentile: $205; median: $1282; 75th percentile: $4619. Average (SD): $3268 (4704). Five donors incurred 0 costs. Excludes home productivity costs and time off work where no pay was lost. One donor experienced exceptional circumstances (out-of-country donor with 3-month stay) and these costs were excluded.

Several living donor reimbursement programs have emerged in Canada since our study began, and while this is an important step forward, the conduct of new and existing programs can be informed by this study. We are aware that many of these programs have caps in place for reimbursement by cost category and overall in an attempt to maintain sustainability, with caps often of ~$5500 per donor. While our data indicate that this is sufficient for the majority of donors, there are a proportion of donors who experience costs that exceed these caps. While sustainability is a critical consideration, it is not equitable that donors who incur higher costs should be penalized. Examples of these scenarios encountered in this cohort include individuals unable to obtain time off work with pay, or an out-of-country donor who was required to stay near the transplant center for almost 3 months postdonation and incurred high costs due to this. We would argue that all reasonable costs as a result of living kidney donation be reimbursed, without penalizing those in whom circumstances lead to a greater magnitude of these costs.

There are limitations of this study. First, there may be recall bias for participants. We attempted to minimize this by utilizing a short recall time frame of 3 months (15) during the time when most losses would occur, and requesting identification of units of resources to minimize the cognitive burden of calculating costs. This also allows portability of results to different jurisdictions where the cost per unit (hotel night, airline travel) may differ. Second, these data are reflective of participants enrolled in a larger observational study, and it is not clear that results would be generalizable to all donors. For example, it is surprising that donors traveling by air would have a median of three round trips, although air travel was reported by only three donors. Further, Canada is geographically large and many donors may travel longer than in more densely populated areas. However, study inclusion criteria are broad, and donor characteristics are similar to typical living kidney donors in Canada. Third, economic consequences may be greater for living donor paired exchange, where travel distances may be greater and the donor frequently brings a support person; this practice was nonexistent in Canada during the study enrollment period. Finally, medical costs were not considered as Canada has a single payer universal healthcare system. Incurred costs may be higher in other jurisdictions, which may be a critically important consideration (19) given the recommendations of lifelong medical surveillance of living kidney donors for adverse medical consequences, such as hypertension. Currently in Canada recommended practice is follow-up at 4–12 weeks and 1 year, followed by annual follow-up with a medical practitioner (20); other jurisdictions such as the Organ Procurement and Transplantation Network mandate follow-up for 2 years. While we do not have data from our study on these costs beyond 1 year (or other cost related to disability or death that rarely occur with living donation), we support provision of short-term and long-term medical insurance for living kidney donors.

While uncertainty exists regarding the optimal method of valuing and reimbursing lost home or workforce productivity, we adhered to accepted practice. First, we used average provincial wage rates to determine cost, not actual wage rates. For reimbursement purposes, it is not clear if actual wages should be reimbursed, or if a standard wage rate or set stipend should be provided. Potential benefits of a stipend are that it would compensate home productivity losses without requiring measurement, may mitigate unfairly undercompensating nonemployed donors (which in our sample were primarily female—the predominant gender of donors), and may particularly serve those with little or no home productivity support. Due to poor response we do not have actual wages, and argue that the main purpose of reimbursing lost wages is to prevent financial hardship in a sustainable fashion. As some donors may have a very high income, reimbursing actual income may not be feasible or desirable. From an economic perspective nonpaid labor (such as home productivity) has real value, which a set stipend may address, if allowable by interpretation of existing legislation. Second, we examined the value of time off work that did not result in a loss of wages to the donor in scenario analysis. We are aware of many donors who use sick leave, vacation time or employment insurance to avoid lost wages. Arguably donors should not have to utilize these privileges, which have quantifiable economic value, for the act of donation, but retain them for their intended use or to utilize when required at a future date (e.g. retain the ability to take future sick leave due to unrelated reasons). Finally, we did not include the value of home productivity, as the true economic value of this activity is not clear. If lost home productivity is valued in the same manner as workforce productivity, the mean and median values are $5233 and $3345, respectively. However, if these activities are assumed by other household members, this may be an overestimate. Further, from a strictly economic perspective, this has a nonzero value; it is not commonly used or advocated for in donor reimbursement programs, despite the fact that is of real value.

In conclusion, we present the first high-quality comprehensive prospective assessment of the economic consequences in 100 Canadian living kidney donors from seven centers. Economic consequences are frequent and nontrivial, with a sizable proportion of donors experiencing significant costs. These results further support the development of donor reimbursement programs and can be used to guide their implementation.

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Donor Nephrectomy Outcome Research (DONOR) Network Investigators

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1: Cost categories for living kidney donors.

Table S1: Direct and indirect costs incurred by kidney donors, unit of measurement, valuation method and valuation sources.

Table S2: Average wage rate per Canadian province (July 2008).

Supplemental Methods

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The Cost of Organ Donation: Potential Living Kidney Donors' Perspectives

Beatriz Cuesta-Briand, Natalie Wray, and Neil Boudville

Living kidney transplantation is a treatment option for some people with end-stage kidney disease. The procedure has low complication rates and positive outcomes; despite this evidence, the number of living kidney donations has decreased in recent years, and the causes are not well understood. This qualitative study sought to explore the experiences of potential living kidney donors before the transplantation. A total of 19 semistructured interviews were conducted with potential living kidney donors in Perth, Western Australia. Results reported here relate to participants' experience of the employment and financial implications of living kidney donation. Participants incurred direct and indirect costs during the time leading up to the transplantation, and many had concerns about the potential financial impact during the recovery period. Employment status, occupation type, and financial commitments affected participants' experiences, and financial concerns were exacerbated for those who were donating to their partners. Results suggest that potential living kidney donors would benefit from tailored financial planning advice to help them prepare for the time of the surgery and the recovery period.

KEY WORDS: *economic costs; financial implications; potential living kidney donors; work implications*

Following a worldwide trend (Jha et al., 2013), the incidence of end-stage kidney disease (ESKD) is on the rise in Australia, with the annual number of new ESKD cases increasing by 29 percent between 2000 and 2010 (ANZDATA, 2011). An increase in the number of people affected by ESKD who require a kidney a transplant has resulted in a shortage of kidneys and longer waiting lists (Mathew, Faull, & Snelling, 2005). With improvements in medical treatments, a growing demand for kidney donors, and an unchanging number of deceased kidney donors available, living kidney donation is increasingly considered as an alternative, cost–effective source for kidney transplantations (National Health and Medical Research Council [NHMRC], 2007). Living kidney donation has an extremely low surgical complication rate, positive outcomes for the donor, and excellent survival rate for the recipient (Johnson et al., 1999; Johnson et al., 1997).

Despite this evidence, the number of living kidney transplants (LKTs) has decreased in recent years (Rodrigue, Schold, & Maldenbrot, 2013). Australian data show a downward trend in the number of LKTs, both in absolute terms and as a proportion of the total number of kidney transplants (ANZDATA, 2011, 2013). The reasons behind this decline are not clear, and may include an increase in medical unsuitability, shifting practice patterns, public policies, and financial disincentives (Rodrigue et al., 2013). There is evidence that some populations' beliefs may be incongruent with organ donation (Alvaro et al., 2008; Fahrenwald & Stabnow, 2005). In addition, multilevel influences contributing to barriers to living kidney donation have been identified; among these are the economic costs associated with the transplant evaluation and the availability of mandated sick leave and donor reimbursement (Purnell, Hall, & Boulware, 2012). Living kidney donors (LKDs) incur both direct and indirect costs; direct costs include travel, accommodation, long-distance phone calls, and medical expenses, whereas indirect costs include lost income, dependent care (child, elder, and spousal), cost for domestic help hired to undertake housework, and other miscellaneous services (Clarke, Klarenback, Vlaicu, Yang, & Garg, 2006). Furthermore, evidence shows that it takes approximately five weeks for LKDs to be able to return to work after the operation (Tooher, Boult, Maddern, & Rao, 2004), which may exacerbate any income loss experienced during the work-up (that is, the assessment of kidney donor suitability).

Although this research informs our understanding of some emerging issues, there is scarce qualitative evidence on the financial implications of living kidney donation. In a review of living donors' and recipients' experience of donation, Ummel and colleagues found 15 qualitative studies conducted with donors and/or recipients (Ummel, Achille, & Mekkelholt, 2011). However, their metasummary of results did not report on any data related to the financial cost of living kidney donation. Qualitative research conducted among African Americans has shown that LKDs have financial concerns related to having to take time off work (Adams-Leander, 2011; Lunsford et al., 2007), and a study conducted in Western Australia found that donors perceived support from work as essential, as they needed to take time away before, during, and after the surgery (Williams, Colefax, & O'Driscoll, 2010). More recently, a qualitative study conducted in Queensland explored the financial impact of transplantation on LKDs and found that donors living outside the metropolitan area incurred greater economic costs related to testing, hospitalization, and surgery (McGrath & Holewa, 2012). This finding suggests that the LKD's place of residence may exacerbate the financial losses experienced and is a salient factor in Australia, where 31 percent of people live in regional and remote areas (Baxter, Gray, & Hayes, 2011).

A strategy to address these financial barriers consists of establishing provisions for the remuneration of donors' out-of-pocket expenses. Countries such as Belgium, Canada, France, Spain, and the United States have legislation allowing donors to receive reimbursement for expenses and lost income; in contrast, other countries such as Portugal and Turkey have legislation that expressly forbids any compensation to donors (Klarenbach et al., 2006). Seeking to alleviate some of the financial burden incurred by LKDs, in 2013 the Australian government introduced a pilot initiative designed to support living donors by providing a payment of up to six weeks at up to the National Minimum Wage, which was $16.37 per hour as of July 1, 2013 (Australian Government Department of Health, 2013).

The results reported here are part of a broader study exploring the experiences of potential LKDs (PLKDs) before the transplant. This article discusses PLKDs' reports of the costs incurred during the work-up process, and their expectations of the financial and work implications of the transplant operation.

METHOD

The study adopted a qualitative methodology and, insofar as it was interested in participants' lived experiences, it was informed by the principles of phenomenology (Starks & Trinidad, 2007) and naturalistic inquiry (Lincoln & Guba, 1985).

Sample and Recruitment

The work-up is conducted in stages and includes medical and immunological testing, as well as psychological and social screening (NHMRC, 2007). This study sought to explore the experiences of PLKDs as they undergo the work-up, regardless of the outcome of the assessment; thus, both those who had been deemed suitable to donate and those assessed as unsuitable were eligible to participate. Study participants were recruited from a renal transplant unit of a public teaching hospital in Perth, Western Australia. Recruitment occurred once the assessment process had been completed and a minimum of two weeks before the transplant operation. One of the principal investigators—a nephrology consultant who had no further involvement in data collection—contacted potential participants by telephone and obtained verbal consent for their contact details to be forwarded to the study coordinator. The study coordinator followed up with a telephone call, explained the aim of the study to potential participants, mailed an information sheet describing the study and a consent form to those interested in taking part in the study, and gained written consent prior to the interviews.

Data Collection

Data were collected through in-depth interviews, which have widely been used to explore the experiences of PLKDs (Sanner, 2005; Tong et al., 2012; Williams, Colefax, O'Driscoll, & Dawson, 2009). The interviews adopted a semistructured format to capitalize on the richness of participants' responses while ensuring a complete understanding of the topic (Inglish, Ball, & Crawford, 2005). The interview schedule comprised a series of open-ended questions designed to trigger conversation, providing a framework within which participants could express their experiences in their own terms (Patton, 2002). The interviews were conducted at participants' convenience, either at home or at the hospital. Interviews with participants living outside the metropolitan area were conducted over the telephone. The interviews

had an average duration of 45 minutes and were audio-recorded.

Data Analysis

All interviews were transcribed verbatim, and the resulting transcripts were imported into NVivo 10 (QSR International, 2014) and subjected to thematic analysis. An inductive approach was adopted to develop an initial list of coding categories; this list was subsequently reviewed by the research team until consensus was reached. In addition, the transcripts were periodically reviewed to identify any additional category. Once the coding of the data was completed, connections between categories and patterns were identified, ultimately leading to a theoretical explanation (Green et al., 2007). Member checking, coding validation, and peer debriefing were used to attain trustworthiness (Morse, Barrett, Mayan, Olson, & Spiers, 2002). In addition, using NVivo 10 enhanced the rigor of the data analysis by adding transparency to the data analysis process (Siccama & Penna, 2008).

RESULTS
Sample

A total of 19 participants took part in the study. Their characteristics are shown in Table 1. All participants were either genetically or emotionally related to the potential recipient. The majority ($n = 13$) were going to donate directly to the recipient, and the remainder ($n = 6$) were part of a paired kidney exchange program whereby potential donor–recipient pairs who are incompatible with each other can be matched with other incompatible pairs (NHMRC, 2007).

The results are presented in two sections: The first discusses participants' reports of any economic costs incurred during the time leading up to the transplant; the second discusses participants' expectations of the likely employment and financial impact at the time of transplant surgery and during the recovery period. All quotes are contextualized by a pseudonym and an indication of the participant's employment status. Given that participants were recruited from a small pool, for confidentiality reasons, no further demographic information is provided.

Employment and Financial Implications of the Work-Up

Most participants in our study ($n = 16$) were employed at the time of the interview. Participants who worked full-time had to take time off work during the work-up to undergo tests and attend hospital

Table 1: Selected Characteristics of Study Participants ($N = 19$)	
Characteristic	**Participants *n* (%)**
Gender	
Female	9 (47.4)
Male	10 (52.6)
Age group	
25–34	3 (15.8)
35–44	3 (15.8)
45–54	9 (47.4)
55–64	3 (15.8)
65+	1 (5.3)
Country of birth	
Australia	7 (36.8)
Overseas	12 (63.2)
Recipient	
Partner	7 (36.8)
Parent	4 (21.1)
Sibling	3 (15.8)
Other relative	3 (15.8)
Friend	2 (10.5)
Donation type	
Direct	13 (68.4)
Paired exchange	6 (31.6)
Suitability status	
Suitable	17 (89.5)
Unsuitable	2 (10.5)
Employment	
Casual work	2 (10.5)
Full-time work	9 (47.4)
Part-time work	5 (26.3)
Retired/no longer in workforce	3 (15.8)
Location of residence	
Metropolitan area	15 (78.9)
Outside metropolitan area	4 (21.1)

appointments; however, most reported having supportive and flexible employers who had allowed them to take time off as needed. The impact on work was minimized for those working shifts, as they reported being able to swap shifts if needed. Working part time and being self-employed also mitigated any impact on work, as participants reported being able to fit their appointments around their work schedule.

Participants reported incurring some direct costs related to travel, such as fuel, public transport, and parking fees. Although four participants lived outside of the metropolitan area requiring a two- to four-hour drive (one way) to attend their hospital appointments, travel expenses were not reported as a major concern. Only one participant reported having accessed the Patient Assisted Travel Scheme, an Australian government initiative that provides travel

subsidies to patients living outside the metropolitan areas (Government of Western Australia, 2011).

There were a few reports of out-of-pocket medical expenses related to some medical tests, although most participants reported having had all tests fully covered by Medicare, Australia's publicly funded universal health care system. It is noteworthy that, regardless of their private insurance status, all participants in our study underwent all major medical tests at the public tertiary hospital where the transplant surgery was due to take place, and were thus covered by Medicare. Participants were appreciative of this: Molly, for example, described it as "a shock" to find out that Medicare would cover the cost of all the testing, as she expected she would incur out-of-pocket expenses, and Stan reflected,

> Years ago we used to think, oh, when this comes around, you know, we'll be up for thousands like, you know, like if it was a wedding or something [chuckles]. . . . It was nice to know that it's pretty much cost-free, yeah. That's good.

The most significant financial impact associated with the work-up was the indirect cost related to loss of income reported by two participants who were employed in casual work (a form of employment characterized by lack of access to certain rights and benefits) and contract work, respectively. Tony, a single father of two young children, described his situation as he spoke of his experience:

> It was actually frustrating to me because I'm a casual worker and every time I went to book up for a test it would cost me about four or five hundred dollars in lost work, just to make that particular test. Because it would always happen on a Thursday or a Friday, or even a Wednesday, and I'd have to book off work for it, and it cost me thousands. . . . I don't care about the fuel driving up or anything like that, that was nothing, or parking or whatever, it was just that it couldn't all be done on a particular day or squeezed into like a two- or three-day block, the whole process.

Tony estimated the loss of income incurred throughout the work-up at "five or six grand," and this was exacerbated by the fact that, because of the nature of his work, he was unable to schedule his shifts in advance, and thus had to forego any shifts that clashed with his tests and appointments. Similarly, Greg, a full-time contract worker, explained,

> I only have certain days that I can do tests. I can't . . . and I'm a contractor doing this, so when I take a day off work, I don't get paid. . . I can't take sick leave or anything like that.

Greg's account revealed his frustration at what he described as a process lacking in flexibility and unable to accommodate his work and personal circumstances. This perception was shared by Tony and other participants, and although for most it was just an inconvenience, for Tony and Greg this lack of flexibility had major financial implications. It has to be noted that throughout the interview, Greg was very critical of the work-up process, and his account was punctuated by reports of lack of flexibility and communication issues that marred his experience.

There was also evidence of further work and financial impact for PLKDs who were donating to their partners. Financial difficulties were compounded when the intended recipient was too unwell to remain in the workplace or had to transition from full-time to part-time work. Elizabeth, who was donating to her husband following a first kidney rejection, became emotional while discussing financial issues. Her husband had lost his job twice because of his kidney condition, first when he became too unwell to work before the first transplant, and more recently when his body had rejected the kidney. This had compounded their financial difficulties. Elizabeth, who was self-employed, reflected on the protracted nature of the work-up:

> Especially if [the recipients] lose their job or they can't work, you know, it's. . . when they say it can be anything from six to twelve months in the work-up, that's a long time out of people's lives to, you know, try and get through, and, you know, if the person's not working for twelve months, you know, it'd be a big strain on people.

Similarly, Claire reported that her husband was unable to work full-time following recent health complications; however, she reported that her husband's workplace had been very supportive, allowing him to adopt a work schedule that suited him.

Donors whose surgeries were delayed because the intended recipients were stable also reported additional stresses. Mary reported feeling "slightly frustrated"

about not knowing when the surgery would take place, especially as she had just returned to work and felt that she had to keep her employers informed of what lay ahead. Similarly, Leyla spoke of the "waiting game" until the surgery would take place and the impact on her work:

I'm happy doing my casual hours and stuff, but when I look online and look at jobs and stuff, I think, "Oh, full-time permanent, should I go for it?" you know? And you go, I don't want to start a job and having to say, you know, "I need time off,"'cause that's not the person I am, I don't like doing that, you know, you commit to something and you wanna finish it, so yeah, that plays on my mind as well, 'cause it's a waiting game.

Leyla reported that she had quit her job and was now doing casual work. She explained,

I made the decision to leave my full-time job, not because of the testing process, but because I wasn't happy in it, so, it's worked out now that I can do my testing and doing work at the same time, so that was good.

Expectations of Posttransplant Employment and Financial Impact

Participants who were still in the workforce had the expectation that becoming an LKD would have an impact on their finances at the time of the surgery and during the recovery period. This perception was a source of concern to participants and was influenced by their understanding of the recovery time, the nature of their work, and whether they had adequate sick leave to cover their living expenses during the recovery time.

Participants reported having been advised that it might take them up to six weeks to get back to their normal routine after the transplant surgery. However, consistent with their perception of themselves as "fit and healthy"—a common feature in our sample—many appeared to expect that they would recover more quickly. For example, Daniel, a shift worker, thought he would "probably be OK after a week," although he had given himself two weeks before returning to work; similarly, Joe, an office worker, hoped to be "up and about" doing his "normal things" within a couple of weeks.

Participants' expectations of the financial impact of donation were influenced by the nature of the

work and whether it involved manual labor. Thus, participants perceived that those employed in office work would be more likely to return to work sooner, and the ability to work from home during the recovery time was also seen as mitigating the financial impact of donation. In contrast, those working in more physically demanding jobs expected that it would take them longer to be fit enough to return to work. Jim, a full-time worker whose job required him to use machinery and climb ladders, reflected,

I have heard of people saying that they were back at work in three weeks' time after donating a kidney, but those might, you know, their jobs are fairly different to mine, and everyone is different, people recover in different ways.

Similarly, Jacinta had a physically demanding full-time job; however, she believed that her employers—who had been very supportive throughout the work-up—would be willing to allocate her other tasks when she returned to work. She explained,

My job is easy anyway, so I can go back and if there's any hard work that I can't do, they'll just say, "OK, don't do it; we'll get other carers to do the hard work."

A total of 14 participants had been deemed suitable to donate and were still in the workforce. The narratives of seven of these participants suggested that the operation would have a significant impact on their finances because they had either inadequate or no sick leave. Mary, for example, explained that as a part-time worker she was not entitled to any sick leave, while Daniel spoke of having less than two weeks' paid leave. As a contractor, Greg was not entitled to sick leave, and although he had income protection insurance, this would not go into effect until 10 weeks after he stopped earning an income and would, thus, not apply in this instance. Similarly, Jim, a full-time maintenance worker, reported that he was unsure whether a living donation was covered by his income protection insurance. He understood that his policy covered sickness or injury, but not a voluntary procedure such as an organ donation. Reflecting on what the financial impact of the transplant surgery would be if he was not covered, Jim noted,

It would have a very negative effect on me, 'cause I would run out of money quite quickly, I would

think, and I would have many questions asked by, you know, I've got payments, I've got food to provide for my family, and the money is not an endless pit, it will run out eventually and I'm sure . . . you know, the banks they're not interested in how my health is going, they're only interested in what they're owed.

The financial impact of the transplant was a strong theme throughout Jim's interview. He was supportive of providing financial assistance to living donors to alleviate the cost of the donation, and at the time of the interview he was seeking clarification on his situation through his employer. Asked whether he had contacted the hospital's social worker to seek advice on this matter, Jim replied,

I'm not that concerned about myself, I know I'm going to be . . . financially I'm going to be fine, but for the others, I mean, I know this study is all about trying to make things better for others and that sort of stuff, so . . . I'm just speaking on behalf of the next person, they might not be in the position I'm in, and they might find that they really want to help, whether it's a mother or a father or a brother or a sister, whatever, they might say, look I would be interested but being off work would make things awfully hard for my family or . . . or whatever, you know.

This response is revealing, at it appears to contradict Jim's previous statements and suggests that he found it easier to reflect on potential financial stress by deflecting the discussion to what "the next person" might experience rather than focusing on his own circumstances. This was not unique to Jim, as participants tended to speak about what difficulties others might experience rather than disclosing their own.

Faced with no or inadequate sick leave, participants were forced to take time off without leave. Some participants spoke of their planned strategies, including putting money aside, and working more hours during the time leading up to the operation "to compensate for later." Molly reported that a relative had offered financial support, while Mary shared the following:

We've inherited not a huge amount of money, but it's a substantial amount of money . . . my husband doesn't want to spend any money on getting a new shed or anything like that until after the operation to make sure everything's OK.

In Mary's case, the financial cost of donation was aggravated by the fact that her husband would need to take time off to care for her and their children at the time of the operation. Because Mary's husband was self-employed, he would stop earning an income until he went back to work, compounding the financial impact on their family because, as a part-time worker, Mary was not eligible for sick leave. Similarly, Greg and his wife were both contract workers, and they faced a significant combined loss of income as Greg's wife would need to take some time off to care for him as he recovered from the operation.

Finally, for those living outside the metropolitan area, the financial impact of donation was aggravated by accommodation costs at the time of the operation. In our study, of the four donors who lived outside the metropolitan area, two were donating to their spouses, and these couples were planning to relocate to Perth for several weeks to be close to the hospital during the recovery time.

At the time of the interviews, the Australian government was about to implement a pilot scheme aimed at providing financial support to living donors. Participants in our study were aware of the scheme, and although they supported it, the payment was widely perceived as inadequate. Jim summed up this sentiment, when he reflected on how quickly that six weeks' pay would be spent:

In all honesty, the minimum wage, and the way the price of living is at the moment, is not enough, it's far from enough. I know how much I have to pay with my wife and two kids, and that wouldn't cover it a week.

DISCUSSION

Consistent with existing evidence (Adams-Leander, 2011; Clarke et al., 2006; Klarenbach et al., 2006; McGrath & Holewa, 2012), our findings showed that there are direct and indirect economic costs associated with the assessment for donor suitability. In contrast with other Australian evidence (McGrath & Holewa, 2012), participants in our study did not incur significant direct costs related to the work-up. Our participants did not report significant medical expenses, and travel costs were not reported as being of concern, including among those living outside the metropolitan area. Two participants reported a significant loss of income incurred during the assessment, and the employment and financial implications of the

work-up were aggravated for those whose surgeries were on hold and those donating to their partner.

Participants in our study had financial concerns relating to the time of the surgery and the recovery time. These financial worries may add to what is already a stressful period in donors' lives (Sanner, 2005), and they are of concern because pretransplant life stress has been associated with delayed wound healing in donors (Maple et al., 2015). Somewhat in contrast with findings from research conducted in the United States (Lunsford et al., 2007), participants were concerned about the time away from work at the time of the surgery, and many reported not having adequate sick leave. In this context, and consistent with findings from Williams et al. (2010), support from work was seen to be essential in mitigating the financial impact posttransplant. Our findings also suggest that donors may have somewhat unrealistic expectations about recovery time and side effects of the operation. This is of concern as there is evidence that donors may experience physical and emotional discomfort after the transplant (Andersen et al., 2007; Heck, Schweitzer, & Seidel-Wiesel, 2004; Williams et al., 2009), and on average, donors return to work five weeks after undergoing laparoscopic nephrectomy (Tooher et al., 2004).

In addition, our findings show that some donors may be at higher risk of financial stress; these include contract and casual workers, those employed in physically demanding jobs, and those intending to donate to their partners. Our finding on the financial vulnerability of contract and casual workers is of particular salience in Australia, a country characterized by the prominence of its casual (Campbell, 2004) and part-time workforce (Burgess, 2005). Casual work is common in Australia, with 20 percent of the Australian workforce (approximately 2 million employees) having no paid leave entitlements (Australian Bureau of Statistics, 2008).

Other studies have limited their exploration of financial barriers to donations to disadvantaged minority groups (Adams-Leander, 2011; Purnell et al., 2012). Our study shows that there are financial considerations that operate not only at the recipient–donor level (direct and indirect costs incurred during the work-up), but also at the community level (availability of sick leave from work and donor reimbursement) (Purnell et al., 2012), which may be barriers to living kidney donation across the population. Furthermore, our results lend support to the view that living kidney donation does not occur in isolation,

but rather in the context of "myriad sets of everyday family obligations" (Crombie & Franklin, 2006, p. 206). We acknowledge that our study does not provide evidence on actual economic costs after donation, given that we interviewed potential donor prior to transplantation. Further research is warranted to explore how actual costs match potential donors' expectations.

Participants reported having limited information on the financial implications of donation, and our findings suggest that discussing financial matters was a sensitive issue. Our results suggest that PLKDs would benefit from tailored practical and financial advice relating to the economic implications of donation, especially regarding the loss of income associated with the recovery time. Our participants were aware of and supported the new government Supporting Leave for Living Organ Donors pilot program; however, the payment was widely perceived as inadequate. This pilot program was evaluated in 2014 and has been extended until June 30, 2017 (ACIL Allen Consulting, 2014). Further qualitative research is warranted to examine donors' perspectives on the implementation of the program.

The role of social workers in the decision-making process and pretransplant preparation of living donors has been noted (Brown et al., 2008a, 2008b). Social workers play an important role in the psychosocial care of donors, helping to minimize the risk of negative outcomes, including financial issues (van Hardeveld & Tong, 2010). Results from this study suggest that social workers may play an important role in providing tailored practical and financial advice to PLKDs. However, at the time of the interviews, the psychosocial assessment protocol at the renal unit where we recruited our participants had been amended so that a screening questionnaire flagged at-risk donors, and only those had a formal session with a social worker. This is of concern, as PLKDs who could benefit from discussing employment, financial, and legal matters with a social worker might lose that opportunity.

In conclusion, our study sheds light on ways in which potential economic barriers to living kidney donation operate, and provides new evidence regarding donors who may be at higher risk of financial stress. Our results support the need for tailored practical and financial advice for donors that takes into account donors' individual contextual circumstances and is responsive to the current employment landscape. **HSW**

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Donors at risk: impaired glucose tolerance

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **All potential living kidney donors should have a fasting plasma glucose level performed on at least two occasions. If the levels are:**
  - **≥7 mmol/L on both occasions then the potential donor is diabetic and this is an absolute contraindication for living kidney donation,**
  - **6.1–6.9 mmol/L on at least one occasion then this patient should have a 2 h oral glucose tolerance test (OGTT),**
  - **<6.1 mmol/L then this is normal and not a contraindication to donation.**
- **Patients at high risk for the development of type 2 diabetes mellitus (i.e. family history, age > 45 years, Aboriginal or Torres Strait Islander (ATSI) or obesity) should be screened with a 2 h OGTT.**
- **If the 2 h glucose of an OGTT results are:**
  - **≥11.1 mmol/L then the patient is diabetic and this is an absolute contra-indication to living kidney donation,**
  - **7.8–11.0 mmol/L then this patient has impaired glucose tolerance and this is an absolute contraindication to living kidney donation,**
  - **<7.8 mmol/L is normal and not a contraindication to donation.**
- **A past history of gestational diabetes is an absolute contraindication to living kidney donation.**

IMPLEMENTATION AND AUDIT

Short- and long-term living kidney donor outcomes need to be closely monitored.

BACKGROUND

The aim of this guideline is to review the available literature on the potential long-term risks of donating a kidney in the presence of pre-donation impaired glucose tolerance and develop suggestions for the management of these potential donors.

The justification for performing living kidney donation is based on the benefits of the procedure on the recipient's health and on the psyche of the donor through the act of altruism, outweighing the short- and long-term adverse outcomes on the donor. In the medical assessment of the potential donor, a critical estimation is made of their future risk of kidney failure and cardiovascular disease. If the risk is predicted to be too great then the living kidney donation should not proceed.

There is no direct evidence quantifying the outcome of patients with impaired glucose tolerance who proceed to donate a kidney for transplantation. This is primarily related to the traditional practice of not using patients with diabetes mellitus or impaired glucose tolerance as living kidney donors. Many of these recommendations are extrapolated from the documented natural history of patients with impaired glucose tolerance.

The following definitions of impaired glucose tolerance have been proposed:[1,2]

A fasting plasma glucose on two occasions of –
≥7 mmol/L indicates diabetes mellitus
6.1–6.9 mmol/L indicates impaired fasting glucose
<6.1 is normal

A standard 2 h OGTT with a 2 h glucose concentration of –
≥11.1 mmol/L indicates diabetes mellitus
7.8–11.0 mmol/L indicates impaired glucose tolerance
<7.8 mmol/L is normal.

The presence of diabetes mellitus is a contraindication for living kidney donation due to the 25–51% long-term risk of the individual developing diabetic nephropathy.[3,4] Despite the common practice of avoiding people with diabetes mellitus and impaired glucose tolerance as living kidney donors, the development of type 2 diabetes mellitus in living kidney donors is documented. Due to the lack of suitable controls, however, it is unclear if this is at an increased rate compared with normal ageing. In the event that diabetic nephropathy does develop, the reduced renal reserve in a donor will lead to a more rapid onset of end-stage kidney disease.

Chronic kidney disease does increase the risk of cardiovascular events and all cause mortality.[5] It is unclear if a similar increased risk is associated with chronic kidney

disease that has resulted from donor nephrectomy, although a rise in blood pressure seems to occur.[6] Concern would be raised as to the possibility that the chronic kidney disease that results from donor nephrectomy may have an additive or synergistic effect with impaired glucose tolerance or diabetes to increase the cardiovascular risk, adding further weight to avoiding the use of diabetics as living kidney donors.

Patients with impaired glucose tolerance have a 5-year risk of developing type 2 diabetes mellitus of 30% if they have a family history of type 2 diabetes (parent or sibling) and 10% if there is no family history.[7] This risk may be higher with certain ethnic groups (e.g. ATSI, South East Asians).[8] In addition, impaired glucose tolerance induces an increased risk of cardiovascular events even in the absence of overt diabetes mellitus, especially in the context of the metabolic syndrome.[9,10]

Patients with a history of gestational diabetes have a high risk of subsequently developing Type 2 diabetes mellitus and this is therefore a contraindication to living kidney donation.[11]

Patients with a family history of diabetes, age > 45 years, ATSI and obesity are at an increased risk for the future development of diabetes and as such consideration for screening all high-risk patients with a 2 h OGTT rather than just two fasting plasma glucose measurements should be made.[12]

SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for living donor and combined with MeSH terms and text words for glucose intolerance. The search was carried out in Medline (1950–July Week 3, 2008). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.
Date of searches: 24 July 2008.

WHAT IS THE EVIDENCE?

Outcome of living kidney donors with pre-donation impaired glucose tolerance

There are no published studies that could be located that quantify the risk to donors with impaired glucose tolerance prior to transplant nephrectomy. This likely reflects the common practice of avoiding these donors.

Incidence of diabetes in 'healthy' living kidney donors

Due to the lack of information on the outcome in living kidney donors with pre-donation impaired glucose tolerance we commenced our review by examining the incidence of type 2 diabetes mellitus in healthy living kidney donors (i.e. normal blood pressure, glomerular filtration rate > 80 mL/min and normal amount of proteinuria pre-donation). There are 11 studies that describe the development of diabetes

mellitus following living kidney donation in donors.[13–23] These studies describe an incidence of 1.5–7.4% with a follow up of more than 20 years in some studies. All of the studies suffer with the following methodological problems:
1. cross-sectional – none were designed to follow donors prospectively from the time of transplant and most examine donors cross-sectionally post transplant,
2. sampling bias – the selection of participants was primarily convenience based rather than random or complete,
3. lack of suitable controls – living donors being a healthy group of people should have better long-term outcomes than the general population and therefore should be compared with an equally healthy group of non-donors, and
4. lack of baseline information – most studies did not provide detailed blood glucose results prior to donor nephrectomy to accurately classify the donor's baseline status.

Fehrman-Ekholm *et al.* described 348 Swedish living kidney donors at a mean of 12 years post-donation. They represented 87% of the total living donors from Stockholm between 1964 and 1995 who were still alive. Despite normal OGTT for all donors at baseline, six developed type 2 diabetes mellitus.[13]

In another study, the authors were able to obtain information on 33% (256/773) of living kidney donors over 20 years post-donation. Of these, 19 developed type 2 diabetes mellitus, despite the 10 with a positive family history having negative baseline OGTT.[14]

It is unclear the effect donation has on the incidence of developing diabetes mellitus due to the lack of suitable controls.

The risk of developing diabetic nephropathy in patients with diabetes mellitus

Diabetic nephropathy is currently the most common cause of end-stage kidney disease in developed countries. The risk of developing diabetic nephropathy varies between studies, with one study documenting a prevalence of 25.4% for microalbuminuria and <10% for macroalbuminuria or end-stage kidney disease in 27 805 type 1 diabetic patients.[24] A similar prevalence was observed in type 2 diabetes.[3,4,25] The prevalence also seems to differ with ethnicity.[8]

The risk of developing diabetes mellitus in patients with impaired glucose tolerance

In a meta-analysis of six prospective studies, the incidence of type 2 diabetes mellitus in people with impaired glucose tolerance was 57.2 per 1000 person years.[26] The incidence however, varied considerably, depending on the ethnicity of the individual, being increased in Mexican–Americans, Hispanics and Pima Indians. This has been supported by other publications.[27]

Impaired glucose tolerance and risk of cardiovascular disease and mortality

Even in the absence of frank diabetes mellitus, impaired glucose tolerance is associated with an increased risk of

death. In a systematic review and meta-analysis performed using MEDLINE until 1996, the results of 95 783 people were collated. A fasting plasma glucose level of 6.1 mmol/L and a 2 h OGTT glucose level of 7.8 mmol/L was associated with an increased relative risk of cardiovascular events of 1.33 (95% confidence interval (CI): 1.06–1.67) and 1.58 (95% CI: 1.19–2.10), respectively, compared with a fasting plasma glucose level of 4.2 mmol/L.[9]

More recently, the Diabetes Epidemiology: Collabarotive Analysis of Diagnostic Criteria in Europe (DECODE) investigators examined 22 cohorts in Europe, totalling 29 714 people followed up for 11 years.[10] This group demonstrated that elevated fasting plasma glucose levels and 2 h plasma glucose levels were associated with a graded increased risk of mortality.

SUMMARY OF THE EVIDENCE

There is no direct evidence documenting the outcome of people with impaired glucose tolerance who subsequently donate a kidney. Diabetes mellitus is a contraindication to living kidney donation due to the high risk of the development of nephropathy and cardiovascular disease. In line with this logic, impaired glucose tolerance is in addition a contraindication to living kidney donation. This is based on the high risk of the development of diabetes mellitus in people with impaired glucose tolerance and the inherent risk of cardiovascular disease even without the development of diabetes mellitus.

WHAT DO THE OTHER GUIDELINES SAY?

INTERNATIONAL GUIDELINES:
The Amsterdam Forum on the Care of the Living Kidney Donor (2006)
. . . individuals with a history of diabetes or fasting blood glucose ≥ 7 mmol/L on at least two occasions (or 2 h glucose with OGTT ≥ 11.1 mmol/L should not donate.
The Canadian Council for Donation and Transplantation (2006)
We recommend . . . to refer to existing guidelines regarding the assessment and eligibility of potential living kidney donors (e.g. Amsterdam Forum).
European Renal Association-European Dialysis and Transplant Association (2000)
. . . exclusion criteria: . . . Diabetes mellitus . . .
UK Guidelines for Living Donor Kidney Transplantation (2005)
Diabetes mellitus is an absolute contraindication to living donation. Prospective donors with an increased risk of type 2 diabetes mellitus because of family history, ethnicity or obesity should undergo a glucose tolerance test and only be considered further as donors if this is normal.

SUGGESTIONS FOR FUTURE RESEARCH

1. Conduct prospective, controlled studies on long-term living kidney donor outcomes. Include an assessment of the incidence of impaired glucose tolerance and diabetes in donors with normal glucose tolerance pre-donation compared with controls. Assess the effect of impaired glucose tolerance on cardiovascular events, renal outcomes and mortality.
2. Set up a registry for living kidney donors. Include practice patterns of living kidney donors.

CONFLICT OF INTEREST

Neil Boudville has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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Donors at risk: hypertension

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

• **Potential living kidney donors should have their blood pressure (BP) measured on at least three occasions with a level less than 140/90 mmHg on all three occasions.**
• **If one or more office BP measurements are elevated, white-coat hypertension may be excluded by:**
  – **12 home BP measurements with an average less than 135/85 mmHg or**
  – **24 h ambulatory blood pressure measurement (ABPM) with an average less than 135/85 mmHg.**
• **An elevated BP on the above definitions is a relative contraindication to donation.**
• **Donors with:**
  – **evidence of end-organ damage related to hypertension (e.g. retinopathy, left ventricular hypertrophy, proteinuria), or**
  – **poorly controlled BP (e.g. requiring more than two medications or BP still elevated), or**
  – **other cardiovascular risk factors (e.g. elevated cholesterol, overweight, smoker, family history of cardiovascular disease) should not be considered for donation.**

IMPLEMENTATION AND AUDIT

Short- and long-term live donor outcomes need to be closely monitored.

BACKGROUND

The aim of this guideline is to review the available literature in relation to live donor effects on BP and in the setting of pre-existing hypertension in the living donor. In particular, the following issues need to be considered:
(i) the effect of unilateral nephrectomy on BP in healthy, normotensive individuals, and
(ii) the long-term risks of donating a kidney if the donor has pre-existing hypertension.
Hypertension is a common disorder that is often found incidentally on routine medical examination. In many individuals, it has often been present for several years before it is eventually diagnosed. Even when considering a clearly nor-

motensive individual, one must still consider the lifetime risk of developing hypertension in that individual. An additional factor to consider is that BP is known to rise with ageing.

The definition of hypertension has changed over time with the acceptable 'treatable limits' gradually falling over the past few decades. In addition, it is now accepted that the relationship between BP and cardiovascular risk does not have an absolute cut-off.[1] The risk is continuous and is apparent in the normal range of BP (i.e. subjects with a higher normal BP have an increased cardiovascular risk compared with those with a lower normal BP. As an example, the cardiovascular risk is higher for a subject with a normal BP of 135/80 mmHg, when compared with an age- and gender-matched individual with a BP of 115/70 mmHg).

Individuals with hypertension or on antihypertensive therapy have been commonly excluded as kidney donors in the past. As a result, there is relatively little information available regarding the effects of donation on the long-term outcome in this group of live donors. At the present time due to a lack of appropriate data, it is difficult to clearly present conclusive information regarding the long-term effects of kidney donation in hypertensive individuals.

In practice, it is generally accepted that kidney donation is contraindicated in those with hypertensive end-organ damage, poorly controlled hypertension and hypertension that requires multiple medications to achieve adequate control. Many units accept kidney donors with well-controlled hypertension and without any evidence of end-organ damage but other factors such as the donor's age and other medical factors are usually considered simultaneously. On the basis that uninephrectomy may increase BP some units choose to completely exclude hypertensive individuals even when their BP is well controlled on minimal medication. This would be particularly the case in younger donors who face their individual risks for a longer time after they donate.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text

words for living donor, and combined with MeSH terms and text words for hypertension. The search was carried out in Medline (1950–July Week 3, 2008). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 24 July 2008.

WHAT IS THE EVIDENCE?

Definition of hypertension

Assessment of living donors' BP should consider the long-term cardiovascular risk and the presence of hypertension as a surrogate marker of underlying renal disease. The definition of hypertension and how BP should be measured requires some consideration. There is a well-established relationship between cardiovascular risk and degree of hypertension, however, the threshold for concern has been progressively lowered in more recent years. The definition of 'hypertension' as a threshold of measurement has been generally considered to be 140/90 mmHg, however, the most recent Joint National Committee now defines increased cardiovascular risk for individuals previously considered to be in the 'normal' range, and define a group of patients as 'pre-hypertension' with BP readings 120–140 systolic/80–90 diastolic.[1] The implication of this redefinition of risk for these patients previously considered to be in the normal range has not been evaluated for living donors.

The method of BP measurement is an additional variable that needs further consideration. Assessment of live donors should include serial manual BP measurements on at least three separate outpatient visits as a minimum evaluation. The majority of studies evaluating BP measurement in the general population relating measurement to cardiovascular risk and morbidity have relied on manual measurement. The role of ABPM continues to be evaluated and has been shown to correlate with end-organ damage[2] and predict cardiovascular risk better than manual BP measurement in some studies.[3,4] If elevated manual BP is detected, then it may be worthwhile performing home self-BP measurements or ABPM, since 10–20% of patients with elevated manual measurements have normal BP by ABPM.[5–7] A normal BP on home BP measurements or ABPM is an average of less than 135/85 mmHg.

Hypertensive potential living kidney donors

If hypertension is detected evidence of end-organ disease should be excluded by echocardiogram and ophthalmology assessment. Patients with evidence of end-organ damage should not be considered as donors, including potential donors with poorly controlled BP or those taking multiple antihypertensives.

In addition to detecting patients with 'white-coat' hypertension, ABPM may also improve the detection of hypertension. Ozdemir *et al.* studied renal donors and demonstrated that ABPM was more sensitive at detecting hypertensive patients than manual BP.[5] Textor *et al.* also

reported that ABPM is useful in the diagnosis of hypertension in renal donors, particularly the elderly.[6] Although the use of ABPM may provide valuable clinical information in selected potential donors, the value of routinely using ABPM in the assessment of donors requires further study.

The effect of donor nephrectomy on BP in a healthy donor

A further issue relates to whether or not nephrectomy increases the risk of developing hypertension in the long term. An increase in BP is commonly observed following nephrectomy, however, an increase in BP into the hypertensive range in previously normotensive individuals, remains to be determined.[8,9] Studies examining this possibility are varied and have often used different control groups. Most commonly, the general population is used, and this may not be the most appropriate group to compare with healthy donors.

A number of studies report an incidence of hypertension following nephrectomy ranging from 9% to 48%.[9–19] It is important to note that the definition of hypertension varies between these studies. Additionally, there are no studies that compare age- and gender-matched individuals in a prospective manner for individuals who either undergo nephrectomy or are followed without a nephrectomy.

Torres *et al.*[10] followed patients post-nephrectomy for 10 years and defined hypertension as a systolic/diastolic BP of ≥160/95 mmHg. Ten of 66 patients (15%) who were previously normotensive became hypertensive and 9/24 (38%) of patients who had borderline hypertension developed hypertension according to the study definition. Clearly, the level of BP used to define hypertension here, is much higher than is generally used now and the relevance of the data from this study remains unclear.

Another study of 250 patients followed long-term for up to 10 years or more, demonstrated that 'borderline hypertension' (defined as 150–159/90–94 mmHg) developed in 8.8% and definite hypertension (160/95 mmHg or greater) developed in 5.6% of patients. The investigators compared the incidence of hypertension with the general population and concluded that this was lower than that seen in age-matched individuals.[16]

Some small studies comparing BP in donors to control groups have suggested an increase in the risk of developing hypertension.[19–21] However, most of the larger studies have not confirmed this. Goldfarb *et al.*[22] studied 70 donors followed for a mean time of 25 years and found no increase in the risk of developing hypertension compared with age-matched individuals. Two larger studies, one of 402 donors with a mean follow up of 12 years[23] and another of 733 donors with a follow up of up to 30 years or more,[24] showed that the age-matched incidence of hypertension was not increased. Grossman *et al.*[25] followed 152 donors with a mean time after uninephrectomy of 11 ± 7 (range: 1–28) years with a 93% retrieval rate. BP increased from 125 ± 15/79 ± 11 to 134 ± 19/81 ± 9 mmHg ($P < 0.01$) but remained in the normotensive range.

A large meta-analysis by Kasiske *et al.*[26] of the long-term effects of reduced renal mass in humans examined mostly nephrectomy for renal donation, however, the group of patients was not uniform. The analysis examined 48 studies with 3124 patients and 1703 controls. Nephrectomy did not affect the incidence of hypertension, but an increase in systolic BP (2.4 mmHg, $P > 0.05$) was observed, which increased further with follow up (1.1 mmHg/decade). Diastolic BP increased after nephrectomy (3.1 mmHg), but this increment did not change with duration of follow up.[26]

Another large meta-analysis by Boudville *et al.*[27] examined results from 48 studies with a total of 5145 donors (Fig. 1). They concluded that kidney donors have an increase in BP of approximately 5 mmHg systolic and 4 mmHg diastolic, above that expected with normal ageing, within 5–10 years of donation.

In the general population, every 10 mmHg increase in systolic BP and 5 mmHg increase in diastolic BP is associated with a 1.5-fold increase in mortality from both ischaemic heart disease and stroke.[28]

Boudville *et al.*[27] also reviewed the risk of developing hypertension in donors. Six studies were assessed (total of 249 donors comparing results against 161 control participants), however, results could not be pooled due to heterogeneity in the groups. Only one of the six studies (Watnick *et al.*[20]) showed an increase in the risk of developing hypertension (relative risk: 1.9 (confidence interval: 1.1–3.5)). All others showed no difference. It must be noted that none of these studies were adequately powered to detect a meaningful difference between the study and the control groups (less than 80% chance of detecting a 1.5-fold increase in the risk of hypertension). The donor population in each individual study ranged from 15 to 50 patients whereas the control population ranged from only 0 to 10 patients.

In summary, there is no conclusive evidence that kidney donation increases the risk of developing hypertension in normal individuals. The studies examining this, however, are very limited. Studies do show that kidney donation is associated with a small increase in BP within the normal range. Since reduced glomerular filtration rate (GFR) and hypertension are both important cardiovascular risk factors, it is very important to explain this potential added risk and also aggressively treat other cardiovascular risk factors such as smoking, hyperlipidaemia, obesity, metabolic syndrome and diabetes during follow up.

The effect of donor nephrectomy on donors with pre-donation hypertension

The presence of established hypertension in potential live kidney donors has been considered to be a contraindication to proceeding with donation. Conclusive recommendations regarding the routine use of hypertensive donors cannot be made at this stage since only short-term cohort studies have been reported. Textor *et al.*[29] showed that 58 donors with normal renal function and controlled hypertension on 1–2 medications showed no increased risk of renal deterioration, microalbuminuria or poor BP control at 12 months. A

follow-up study by the same investigators examined 148 living kidney donors before and 6–12 months after nephrectomy.[7] Patients who were normotensive donors had no change in awake ABPM results. Of the 148 live donors, 24 were hypertensive (ABPM > 135/85 mmHg and clinic BP > 140/90 mmHg) before donation. The group concluded that patients with moderate, essential hypertension and normal kidney function have no adverse outcomes with respect to BP, renal function or urinary protein excretion in the first year after living kidney donation.

Young *et al.* performed a systematic review and meta-analysis and identified six studies on 125 hypertensive donors (Fig. 2).[30] A number of methodological issues restrict the external validity of all of these studies. Follow up was for a median of 2.6 years, with two having a mean follow up of over 5 years. One study described a 14 μmol/L greater rise in serum creatinine in hypertensive donors compared with donors who were normotensive pre-donation. Two studies described conflicting results on the change in renal function using radioisotope or inulin GFR between 62 hypertensive donors and 527 normotensive donors. One study demonstrated that BP in hypertensive donors at 1 year decreased by 5 mmHg systolic and 6 mmHg diastolic compared with normotensive donors. An additional study found that mean arterial BP following donation decreased more often in hypertensive donors.

SUMMARY OF THE EVIDENCE

Please refer to Table 1 – Characteristics of included studies (Appendices).

There is a lack of prospective controlled long-term data regarding the effects of nephrectomy in both normal and hypertensive donors. More precise information is required and this would ideally be collected prospectively using a live donor registry.

On the basis of limited studies, nephrectomy appears to lead to a small increase in BP but there is no evidence of an increased risk of developing hypertension. However, to better assess whether there is an alteration in the risk of developing hypertension, it is acknowledged that prospective studies of age- and sex-matched individuals with and without nephrectomy would need to be performed.

The recommendation to exclude from donation individuals with poorly controlled hypertension or with known hypertensive end-organ damage (e.g. retinopathy, left ventricular hypertrophy, stroke, proteinuria and renal impairment) is based on the known natural history of these disorders. No study has been performed comparing the outcome in these subjects who donate, compared with those who do not.

WHAT DO THE OTHER GUIDELINES SAY?

British Transplant Society/British Renal Association:
An extensive, 100-page document has been produced outlining similar issues to those discussed here.[31] The full version of these British Live Donor Guidelines is available

at: http://www.bts.org.uk/transplantation/standards-and-guidelines/

– Prospective donors should not be precluded from further evaluation if their office (casual) BP recordings are below 140/90 mmHg.

– Evidence of hypertensive end-organ damage is an absolute contraindication to kidney donation.

– If a prospective donor is on treatment for hypertension it may still be reasonable to consider proceeding if their BP is well controlled (less than 140/85 mmHg). They should be warned of the possibility that nephrectomy may increase their BP and subsequent cardiovascular risk and appropriate follow up should be arranged.

– Smoking, obesity and/or raised cholesterol in the context of hypertension place the donor at additional risk.

The Amsterdam Forum:

A short manuscript outlining similar issues to those discussed here.[32]

Hypertension has been considered to be a contraindication in potential renal transplant donors. However, the precise risk to donors who have borderline elevation in BP (BP) and those with a family history of hypertension has not been conclusively determined.

The following consensus guidelines regarding hypertensive donors were adopted:

– Patients with a BP of 140/90 by ABPM are generally not acceptable as donors.

– BP should preferably be measured by ABPM, particularly among older donors (50 years) and/or those with high office BP readings.

– Some patients with easily controlled hypertension who meet other defined criteria (e.g. 50 years of age, GFR 80 mL/min and urinary albumin excretion < 30 mg/day) may represent a low-risk group for development of kidney disease after donation and may be acceptable as kidney donors.

– Donors with hypertension should be regularly followed by a physician.

European Renal Association-European Dialysis and Transplant Association:

Exclusion criteria include: 'Reduced GFR (in comparison to normal range for age), proteinuria of >300 mg/day, microhematuria (except when an urologic evaluation and a possible kidney biopsy are normal), . . . or hypertension without good control'.[33]

The Canadian Council for Donation and Transplantation:[34]

It would appear that BP increases by ~5 mmHg after donating a kidney above the natural increase which occurs with normal aging. Most studies have not suggested an increased rate of hypertension following donation. To date no study using appropriate controls has examined whether donating a kidney increases the risk of premature death or cardiovascular disease over the long-term. This concern has been raised due to the observation that renal insufficiency is an independent risk factor for cardiovascular disease in the general population.

Not unexpectedly, there is considerable variability in practice particularly when it comes to accepting a poten-

tial living donor with hypertension or mildly abnormal renal function. In the case scenario involving a 50-year-old male with well-controlled hypertension on a single antihypertensive agent, 5 of 14 centres responded that they would never accept such an individual as a kidney donor. However, other centres would rarely ($n = 2$), sometimes ($n = 5$) and usually ($n = 2$) accept this individual as a living kidney donor.

Reference is also made to recommendations from the Amsterdam Forum, the British Renal Association and the European Renal Association-European Dialysis and Transplant Association.

SUGGESTIONS FOR FUTURE RESEARCH

1. Further prospective studies with appropriate control groups are required in order to determine whether uninephrectomy in normotensive individuals increases the long-term risk of developing hypertension.

2. Further studies are needed to confirm long-term safety for potential donors with existing hypertension. These patients should form part of a study group or registry.

CONFLICTS OF INTEREST

Frank Ierino has received Educational Grants and fees for attendance at Conferences/Transplant Symposia from Wyeth, Roche, Janssen-Cilag and Novartis. He has also received an Unrestricted Research Grant from Roche and Novartis, has been a member of the medical advisory boards for Roche and Novartis and a member of the Drug Trial Safety Monitoring Board for Novartis. John Kanellis and Neil Boudville has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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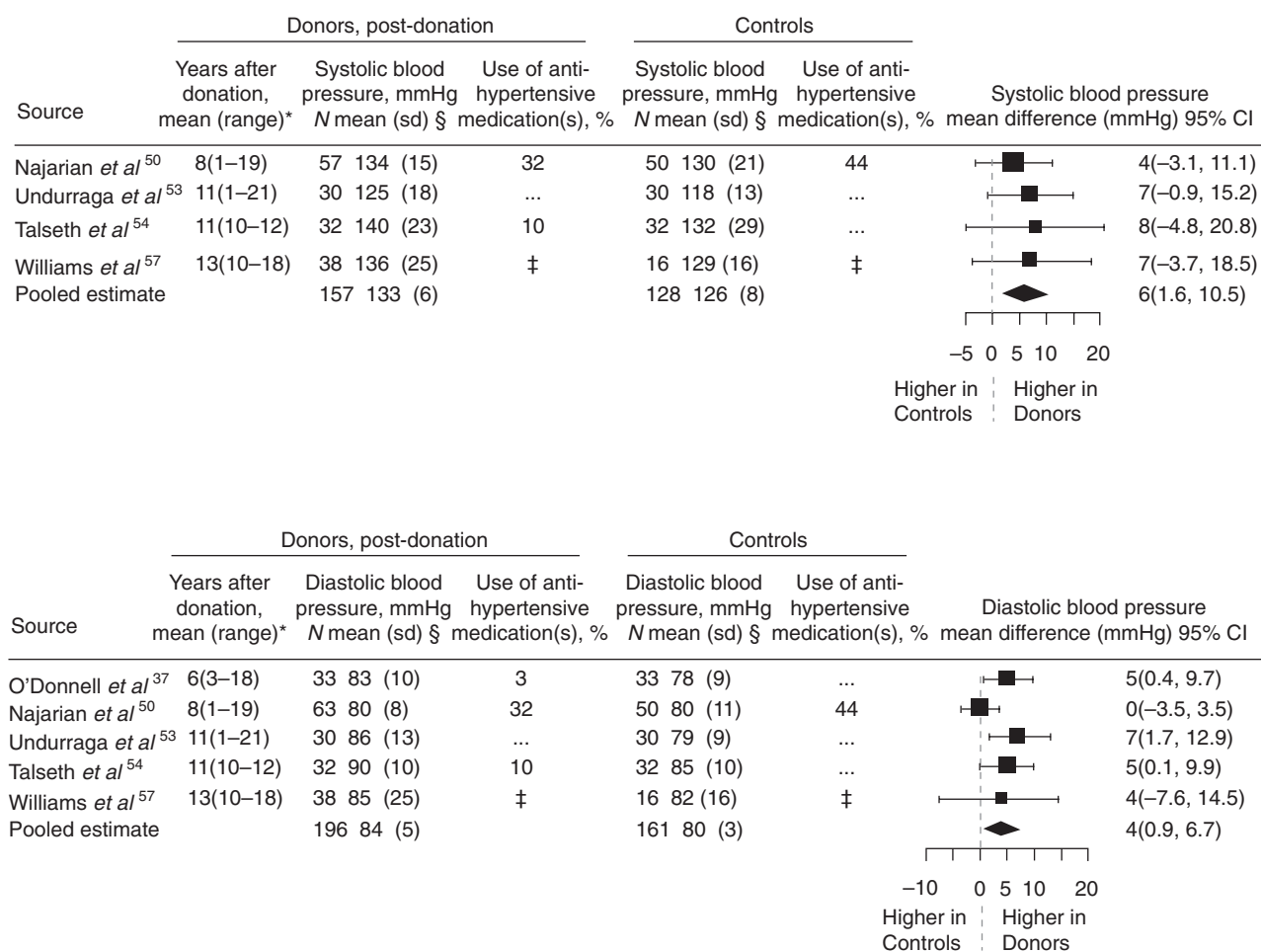
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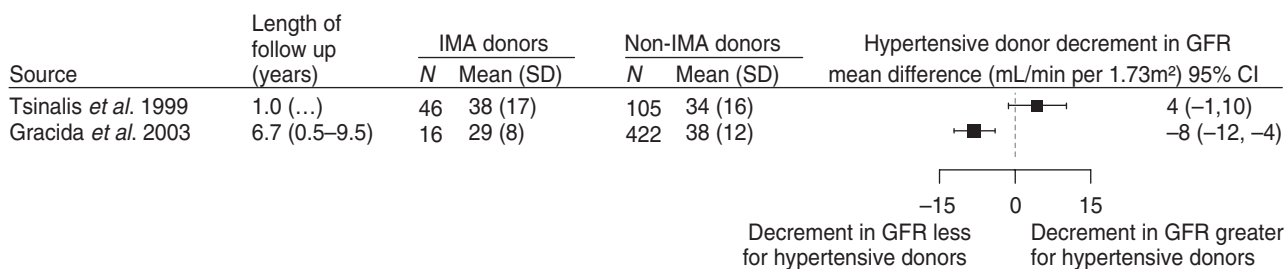
APPENDICES

Table 1 Characteristics of included studies

Study ID	N	Study methods	Results	Conclusions
Boudville et al. (2006)[27]	–	Meta-analysis, data sources included Medline, Embase, Science Citation Index	48 studies included 5145 donors.	Kidney donors may have 5 mmHg increase in BP 5–10 years after donation over anticipated normal aging.
Dunn et al. (1986)[16]	314	Prospective follow-up data, 1970–1984	Major late complications were seen in 50 (20.0%) of 250 patients followed for 6 to 175 months (mean 53.1 months). These included definite hypertension (5.6%).	While the risk of hypertension appears to increase as the interval from donation increases, no cases of renal failure after donation were observed.
Goldfarb et al. (2001)[22]	70	Follow-up data, 1963–1975	SBP after donation were significantly increased but within normal range, overall incidence of hypertension was comparable to that expected in the age-matched general population.	No gender differences were noted in BP.
Kasiske et al. (1995)[26]	–	Meta-analysis	48 studies included 3124 patients and 1703 controls; unilateral nephrectomy decreased GFR but improved with each 10 years follow up. Patient with single kidneys had small progressive increases in proteinuria, but negligible after nephrectomy for trauma or kidney donation. Nephrectomy did not affect the prevalence of hypertension, but there was a small increase in SBP which increased with duration of follow up. Diastolic blood pressure higher after nephrectomy, which did not change with duration of follow up.	In normal individuals, unilateral nephrectomy does not cause progressive kidney function but may be associated with small increase in BP.
Ramcharan et al. (2002)[24]	464	Follow-up data, 1963–1979	The rate of proteinuria and hypertension was similar to the age-matched general population.	Most kidney donors have normal renal function 20–37 years post donation. However, some do develop renal dysfunction and some develop renal failure.
Textor et al. (2004)[7]	148	Prospective follow up before and 6–12 months after nephrectomy	Normotensive donors had no change in awake ABPM pressure, in hypertensive donors BP decreased with therapy.	White participants with moderate, essential hypertension and normal kidney function have no adverse effects (BP, GFR, urinary protein) during the first year after donation.
Torres et al. (1987)[10]	99 living related kidney donors, 50 recipients	Follow-up data	Borderline and definite hypertension were present in 22.2% and 4.0% of donors prior to donation, in 14.4% and 21.1% of donors at follow up, and in 2.0% and 18.0% of the 50 recipients at follow up. Age, relative weight and MAP prior to donation were the key variables in predicting the follow-up ranked MAP of the donors. CPAH prior to donation was inversely correlated with the age of the donors and, indirectly, with the follow-up MAP. Donor CPAH prior to donation was significantly correlated with the renal allograft function of the recipients but not with the recipient ranked MAP at follow up. No correlation of the ranked MAP or BP outcome categories between donors and recipients was found.	Donation of one kidney can accelerate the development of hypertension in those donors with predisposition to develop hypertension. The predisposition of donors to develop hypertension and their age, within the range observed in the study, does not significantly influence the long-term BP of the recipient.
Williams et al. (1986).[23]	38	Evaluation of renal function in donors and their siblings	No statistically significant difference was found between the prevalence of hypertension in donors and siblings.	With the exception of mild proteinuria of unknown clinical significance, unilateral nephrectomy is not associated with adverse effects on kidney function.

ABPM, ambulatory blood pressure measurement; BP, blood pressure; CPAH, clearance of para-amino hippurate; GFR, glomerular filtration rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

Source	Donors, post-donation			Controls		Systolic blood pressure mean difference (mmHg) 95% CI	
	Years after donation, mean (range)*	Systolic blood pressure, mmHg N mean (sd) §	Use of anti-hypertensive medication(s), %	Systolic blood pressure, mmHg N mean (sd) §	Use of anti-hypertensive medication(s), %		
Najarian et al [50]	8(1–19)	57 134 (15)	32	50 130 (21)	44		4(−3.1, 11.1)
Undurraga et al [53]	11(1–21)	30 125 (18)	...	30 118 (13)	...		7(−0.9, 15.2)
Talseth et al [54]	11(10–12)	32 140 (23)	10	32 132 (29)	...		8(−4.8, 20.8)
Williams et al [57]	13(10–18)	38 136 (25)	‡	16 129 (16)	‡		7(−3.7, 18.5)
Pooled estimate		157 133 (6)		128 126 (8)			6(1.6, 10.5)

−5 0 5 10 20

Higher in Controls | Higher in Donors

Source	Donors, post-donation			Controls		Diastolic blood pressure mean difference (mmHg) 95% CI	
	Years after donation, mean (range)*	Diastolic blood pressure, mmHg N mean (sd) §	Use of anti-hypertensive medication(s), %	Diastolic blood pressure, mmHg N mean (sd) §	Use of anti-hypertensive medication(s), %		
O'Donnell et al [37]	6(3–18)	33 83 (10)	3	33 78 (9)	...		5(0.4, 9.7)
Najarian et al [50]	8(1–19)	63 80 (8)	32	50 80 (11)	44		0(−3.5, 3.5)
Undurraga et al [53]	11(1–21)	30 86 (13)	...	30 79 (9)	...		7(1.7, 12.9)
Talseth et al [54]	11(10–12)	32 90 (10)	10	32 85 (10)	...		5(0.1, 9.9)
Williams et al [57]	13(10–18)	38 85 (25)	‡	16 82 (16)	‡		4(−7.6, 14.5)
Pooled estimate		196 84 (5)		161 80 (3)			4(0.9, 6.7)

−10 0 5 10 20

Higher in Controls | Higher in Donors

Fig. 1 Meta-analysis of controlled studies of systolic blood pressure and diastolic blood pressure at least 5 years after kidney donation. The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years after donation. §A summary of various methods to assess blood pressure are presented in the Results section. ‡Study reported that a percentage of donors were taking antihypertensive medication but did not quantify the amount. NR, not reported.
Source: Boudville N, Prasad GV, Knoll G et al. Donor Nephrectomy Outcomes Research (DONOR) Network. Meta-analysis: Risk for hypertension in living kidney donors. *Ann. Intern. Med.* 2006; **145**: 185–96. © 2006 American College of Physicians.

Source	Length of follow up (years)	IMA donors		Non-IMA donors		Hypertensive donor decrement in GFR mean difference (mL/min per 1.73m²) 95% CI	
		N	Mean (SD)	N	Mean (SD)		
Tsinalis et al. 1999	1.0 (...)	46	38 (17)	105	34 (16)		4 (−1,10)
Gracida et al. 2003	6.7 (0.5–9.5)	16	29 (8)	422	38 (12)		−8 (−12, −4)

−15 0 15

Decrement in GFR less for hypertensive donors | Decrement in GFR greater for hypertensive donors

Fig. 2 Meta-analyses of long-term medical outcomes for hypertensive donors. Decrement in glomerular filtration rate (mL/min per 1.73 m²).
Graphed results are the difference between isolated medical abnormalities (IMA) and non-IMA donors on the change in outcome from before donation to after donation. (. . .) indicates missing value. Results were not pooled for I² > 50%.
Source: Young A, Storsley L, Garg AX et al. Health outcomes for living kidney donors with isolated medical abnormalities: A systematic review. *Am. J. Transplant.* 2008; **8**: 1878–90. © 2008 The American Society of Transplantation and the American Society of Transplant Surgeons; published by Wiley Periodicals Inc.

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Donors at risk: proteinuria

Date written: Jan 2008
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Author: Neil Boudville, John Kanellis

GUIDELINES
No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

• **Potential living donors should have their urinary protein excretion measured using either a 24-hour urine collection (daily excretion) or a spot urine sample (protein/creatinine ratio).**
• **A urine protein excretion of >300 mg/day (24 hour collection) or of >30 mg/mmol (spot urine protein/ creatinine ratio) is usually a contraindication to live donation.**
• **Further investigations are warranted when urine protein excretion is >150 mg/day but less than <300 mg/ day (corresponds approximately with spot urinary protein/ creatinine of >15 mg/mmol but <30 mg/mmol). Repeat urinary protein estimation, as well as measurement of urinary albumin excretion may help in further assessing potential living donors.**
• **Although overt proteinuria may be absent, the presence of microalbuminuria (urinary albumin excretion of >30 mg/day or >20 μg/min; albumin/creatinine ratio >2.5 mg/mmol) should be considered a relative contraindication to live donation.**
• **Microalbuminuria or mild proteinuria (<300 mg/day) occurring in the presence of another associated clinical or laboratory abnormality (e.g. hypertension, obesity, glucose intolerance, glomerular haematuria) should be considered a relative contraindication to live donation.**
• **In potential living donors with minor degrees of proteinuria or albuminuria, a renal biopsy may help in further assessing the donor's risk of developing progressive renal disease following donation (Opinion).**
• **Donors should have their urinary protein excretion measured as part of their routine, follow-up care. It is recommended that this be performed at least once a year along with blood pressure and serum creatinine measurement (Opinion).**

IMPLEMENTATION AND AUDIT

Short- and long-term living kidney donor outcomes need to be closely monitored.

BACKGROUND

The aim of this guideline is to review the available literature on the potential long-term risks of donating a kidney in the presence of pre-donation proteinuria and to develop suggestions for management of these potential donors.

The justification for performing living kidney donation is based on the benefits of the procedure on the recipient's health and on the psyche of the donor through the act of altruism, outweighing the short- and long-term adverse outcomes on the donor. In the medical assessment of the potential donor, a critical estimation is made of their future risk of kidney failure and cardiovascular disease. If the risk is predicted to be too great then the living kidney donation does not proceed.

A normal amount of urinary protein excretion is dependent on the local laboratory but is typically <150 mg/24 hours or a spot urine protein to creatinine ratio of <15 mg/ mmol. In some laboratories, the upper limit of normal may be as high as 300 mg/24 hours. Increased levels of proteinuria are a sensitive marker in the general population of an increased risk of kidney failure and cardiovascular disease.[1–6] The theoretical incremental increase in the risk of future kidney failure with the combination of proteinuria and a nephrectomy has resulted in this factor being examined critically in all potential donors.

In living kidney donors who had a normal amount of proteinuria prior to the nephrectomy, studies to date have consistently demonstrated the development of proteinuria post-nephrectomy in up to 41% of donors.[7] In a meta-analysis, the pooled incidence of proteinuria was 10% after 7 years post-nephrectomy.[7] One of the difficulties in interpreting adverse long-term outcomes in living kidney donors is teasing apart the relative contribution of the nephrectomy to the adverse event from the ageing process and the development of other comorbidities in the donor. In all 3 studies that compared the development of proteinuria in healthy donors to control patients, the incidence of proteinuria was increased in the donors.[8–10] A meta-analysis of these studies demonstrated that donors had a statistically significant 66 mg/24 hour increase in proteinuria compared with non-donor controls, an average of 11 years post-nephrectomy.[7] However, none of these

studies meet strict methodological criteria to accurately assess the long-term risk of proteinuria in healthy living kidney donors.[7,11]

To date, there has only been one publication that assesses the long-term risk for donors who already have increased levels of proteinuria pre-donation.[12] The results of this study are inconclusive however, due to its small sample size, short follow-up and lack of non-donor controls. As such, it is not possible to directly estimate the effect of proteinuria pre-donation on the long-term outcomes of a living kidney donor. Estimates must therefore be made through extrapolation of results from the general population and the assumption that it will be at least as great as that seen in healthy donors.

The mechanism through which a living donor develops proteinuria is different to that for members of the general population who have proteinuria. As such, the relative significance of the degree of proteinuria in donors' post-nephrectomy compared to that seen in the general population is also uncertain.

Measurement of urinary albumin excretion, through a 24-hour urine collection or a spot urine albumin to creatinine ratio has been shown to be a sensitive and specific marker of proteinuria.[13] Elevated levels of urinary albumin excretion are a risk factor in diabetic and non-diabetic patients of kidney failure and cardiovascular disease.[1–4] The relative strengths of albuminuria versus proteinuria are uncertain in the general population. Studies in living kidney donors to date are lacking, and so the interpretation of the effect of the degree of urinary albumin excretion on long-term outcomes in addition to the determination of a well-accepted cut-off level is uncertain.

In a single study of donors who had a 24-hour urine protein excretion between 150 mg and 300 mg, the simultaneous estimation of urinary albumin excretion was normal in all individuals.[14] No follow-up, however, was provided to determine which factor proved to be the superior risk marker.

The effect of the addition of proteinuria with other renal and cardiovascular risk factors is uncertain. There is limited literature on this topic but it is assumed that there would be an incremental rise in the adverse long-term outcome of living kidney donors with every additional risk factor. The size of this incremental rise is unknown.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for living donor and with MeSH terms and text words for hematuria, proteinuria, and albuminuria, combined with the Cochrane highly sensitive search strategy for prognosis questions. The search was carried out in Medline (1966 – January Week 2, 2008). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.
Date of search/es: 15 January 2008.

WHAT IS THE EVIDENCE?

Due to the limited information on the outcome in living kidney donors with pre-donation proteinuria, we commenced our review by examining the effect of donation on proteinuria in healthy living kidney donors (i.e. normal blood pressure, GFR > 80 mL/min and normal amount of proteinuria pre-donation). There are more than 40 studies that describe the development of proteinuria following living kidney donation in donors who had 'normal' levels of proteinuria pre-operatively.[7] The key studies include a study that followed 70, out of a possible 180 donors, over 20 years following nephrectomy.[15] These authors discovered 19% of donors had a protein excretion of over 150 mg/24 hours and 7% had greater than 800 mg/24 hours.

Fehrman-Ekholm *et al.* described 348 Swedish living kidney donors a mean of 12 years post-donation.[16] They detected 'slight' proteinuria (<1.0 g/L) in 9% and 'significant' proteinuria (≥1.0 g/L) in 3% of donors. There was a significant association between proteinuria and increased blood pressure (P < 0.01) and lower glomerular filtration rate (P < 0.05).

There are 3 published articles that examined the long-term outcome of proteinuria in donors compared with controls.[8–10] They compared a total of 129 donors with 83 control subjects, with a mean follow-up of 11 years after donation. Two of the 3 papers detected a statistically significant increase in proteinuria in the donors compared with the control. On pooling the results, the weighted average increase in proteinuria in living kidney donors was 66 mg/24 hours compared with controls (95% CI: 24 mg/24 hours, 108 mg/24 hours).[7]

Four studies measured 24-hour urine albumin excretion in donors compared with controls [8–10,17]. In 2 of the 4 studies, there was a statistically significant increase in albuminuria of about 50 mg/24 hours compared with controls, at a mean of 14 years post-donation.[10,17] In the 2 studies that examined the risk of developing microalbuminuria in a total of 67 donors and 51 controls, there was a 3.9-fold increased relative risk of microalbuminuria with donation.[7,17,18]

There is only one study that has been published (in abstract form only) that examines the long-term outcomes of living kidney donors with elevated levels of proteinuria prior to donation.[12] This study prospectively examined 8 donors who pre-donation had a spot urine albumin to creatinine concentration over 10 mg/mmol and/or a spot urine protein to creatinine ratio over 20 mg/mmol. At 1 year post-donation, there was no significant difference in creatinine, blood pressure and inulin clearance compared with 'normal' living kidney donors.

SUMMARY OF THE EVIDENCE

Studies to date in healthy donors suggest that there is an increased risk of developing proteinuria following living kidney donation. However, the literature is limited by the lack of appropriate control groups, retrospective nature of most published articles, large loss to follow-up of donors,

and small sample sizes. The external validity of their findings is therefore questionable.

There is only one study that examined the outcomes of living kidney donors who had elevated levels of proteinuria pre-donation. This study included a small sample size and had a follow-up of only 1 year. In addition, the controls they used were healthy donors rather than healthy non-donors.

The suggestions for clinical care are therefore based on the assumption that a potential donor who has proteinuria prior to donating their kidney is likely to develop an increase in the level of proteinuria at least equal to that seen in healthy donors. We also know that proteinuria is a risk factor for the development of kidney failure in the general population and assume that it represents a similar risk in this patient group.

As the degree of pre-donation proteinuria that is a risk factor is unknown, we have limited our recommendations to any abnormal amount of proteinuria but have opted to take the upper limit of normal (i.e. 300 mg/24 hours).

WHAT DO THE OTHER GUIDELINES SAY?

INTERNATIONAL GUIDELINES:
The Amsterdam Forum on the Care of the Living Kidney Donor (2006):
A 24 hour urine protein of >300 mg is a contraindication to donation.

Microalbuminuria determination may be a more reliable marker of renal disease, but its value as an international standard of evaluation for kidney donors has not been determined.
The Canadian Council for Donation and Transplantation (2006):
We recommend . . . to refer to existing guidelines regarding the assessment and eligibility of potential living kidney donors (e.g. Amsterdam Forum).
European Renal Association-European Dialysis and Transplant Association (2000):
Exclusion criteria of donor proteinuria >300 mg/day.
UK Guidelines for Living Donor Kidney Transplantation (2005):
The presence of proteinuria is a strong independent predictor of future end stage renal disease in the general population.

Urine protein excretion should be quantified by analysis of a 24-hour urine collection or spot urine protein : creatinine ratio. Increased urine protein excretion usually excludes further consideration as a kidney donor.
American Society of Transplantation Position Statement on the Medical Evaluation of Living Kidney Donors (2007):
The following reasons will typically exclude a living donor candidate from donating . . . ≥300 mg/day of proteinuria.

SUGGESTIONS FOR FUTURE RESEARCH

1. Conduct prospective, controlled studies on long-term living kidney donor outcomes. Include an assessment of the utility of urinary protein excretion compared with urinary albumin excretion; and outcomes of donors with isolated medical abnormalities.
2. Set up a registry for living kidney donors. Include practice patterns of living kidney donors.
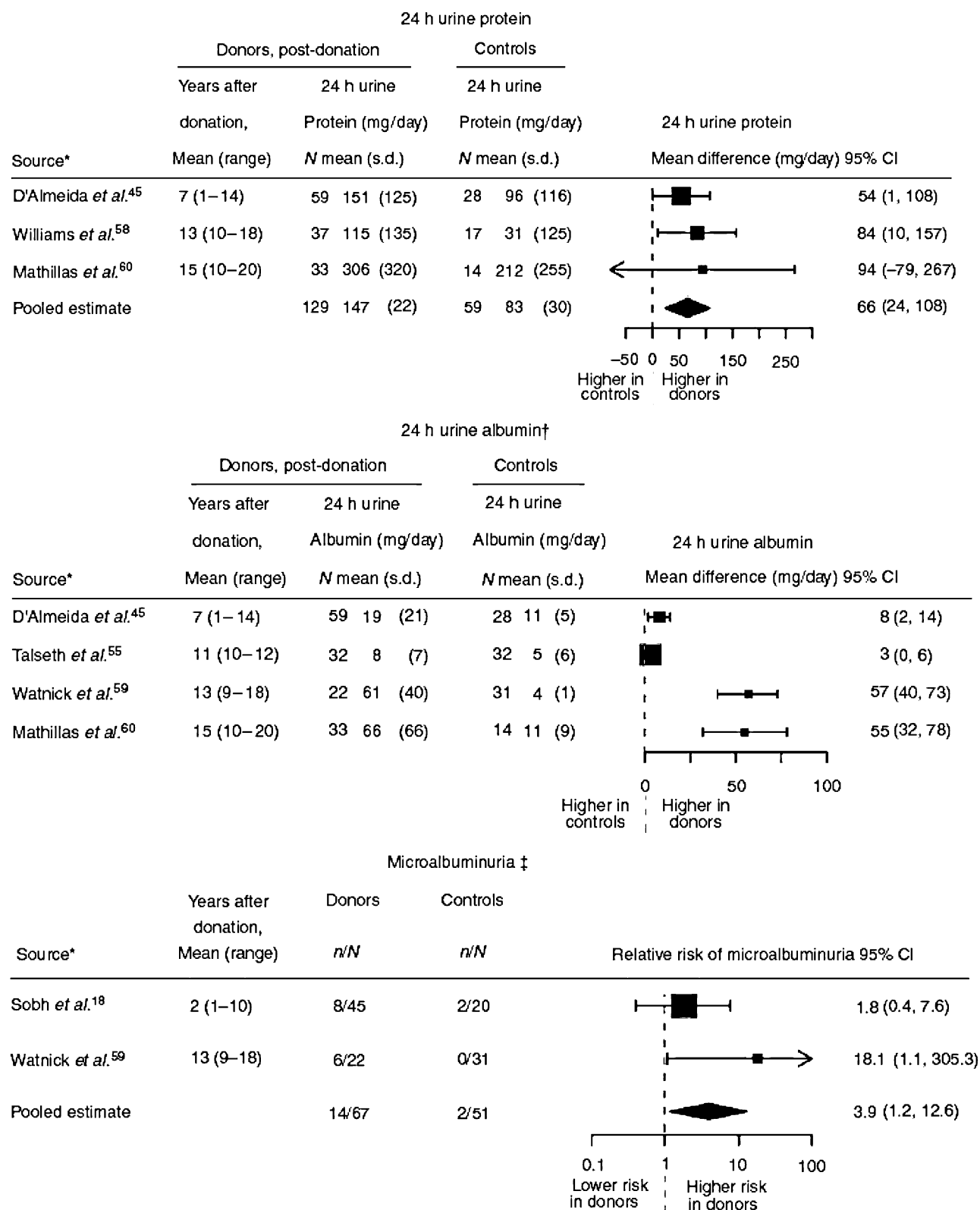
CONFLICT OF INTEREST

Both of the authors have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDIX

24 h urine protein

Source*	Donors, post-donation		Controls	24 h urine protein	
	Years after donation, Mean (range)	24 h urine Protein (mg/day) N mean (s.d.)	24 h urine Protein (mg/day) N mean (s.d.)	Mean difference (mg/day) 95% CI	
D'Almeida et al.[45]	7 (1–14)	59 151 (125)	28 96 (116)		54 (1, 108)
Williams et al.[58]	13 (10–18)	37 115 (135)	17 31 (125)		84 (10, 157)
Mathillas et al.[60]	15 (10–20)	33 306 (320)	14 212 (255)		94 (–79, 267)
Pooled estimate		129 147 (22)	59 83 (30)		66 (24, 108)

–50 0 50 150 250
Higher in controls   Higher in donors

24 h urine albumin†

Source*	Donors, post-donation		Controls	24 h urine albumin	
	Years after donation, Mean (range)	24 h urine Albumin (mg/day) N mean (s.d.)	24 h urine Albumin (mg/day) N mean (s.d.)	Mean difference (mg/day) 95% CI	
D'Almeida et al.[45]	7 (1–14)	59 19 (21)	28 11 (5)		8 (2, 14)
Talseth et al.[55]	11 (10–12)	32 8 (7)	32 5 (6)		3 (0, 6)
Watnick et al.[59]	13 (9–18)	22 61 (40)	31 4 (1)		57 (40, 73)
Mathillas et al.[60]	15 (10–20)	33 66 (66)	14 11 (9)		55 (32, 78)

0 50 100
Higher in controls   Higher in donors

Microalbuminuria ‡

Source*	Years after donation, Mean (range)	Donors n/N	Controls n/N	Relative risk of microalbuminuria 95% CI	
Sobh et al.[18]	2 (1–10)	8/45	2/20		1.8 (0.4, 7.6)
Watnick et al.[59]	13 (9–18)	6/22	0/31		18.1 (1.1, 305.3)
Pooled estimate		14/67	2/51		3.9 (1.2, 12.6)

0.1 1 10 100
Lower risk in donors   Higher risk in donors

Fig. 1 **Controlled studies of proteinuria after kidney donation.** The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years after donation. ‡Microalbuminuria was assessed by 24 h urine. Reprinted with permission from Macmillan Publishers Ltd. Garg AX, Muirhead N, Knoll G, *et al.* Proteinuria and reduced kidney function in living kidney donors: A systematic review, meta-analysis, and meta-regression. *Kidney International.* 2006; **70**: 1801–10.

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Risk-Factor Profile of Living Kidney Donors: The Australia and New Zealand Dialysis and Transplant Living Kidney Donor Registry 2004-2012

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Background. Recent literature suggests that living kidney donation may be associated with an excess risk of end-stage kidney disease and death. Efforts to maximize access to transplantation may result in acceptance of donors who do not fit within current guidelines, potentially placing them at risk of adverse long-term outcomes. **Methods.** We studied the risk profile of Australian and New Zealand living kidney donors using data from the Australia and New Zealand Dialysis and Transplant Living Kidney Donor Registry over 2004 to 2012. We compared their predonation profile against national guidelines for donor acceptance. **Results.** The analysis included 2,932 donors (mean age 48.8 ± 11.2 years, range 18–81), 58% female and 87% Caucasian. Forty (1%) had measured glomerular filtration rate less than 80 mL/min; 32 (1%) had proteinuria >300 mg/day; 589 (20%) were hypertensive; 495 (18%) obese; 9 (0.3%) were diabetic while a further 55 (2%) had impaired glucose tolerance; and 218 (7%) were current smokers. Overall 767 donors (26%) had at least one relative contraindication to donation and 268 (9%) had at least one absolute contraindication according to national guidelines. **Conclusions.** Divergence of current clinical practice from national guidelines has occurred. In the context of recent evidence demonstrating elevated long-term donor risk, rigorous follow-up and reporting of outcomes are now mandated to ensure safety and document any change in risk associated with such a divergence.

(*Transplantation* 2016;100: 1278–1283)

Kidney transplantation is the optimal treatment for the majority of patients with end-stage kidney disease (ESKD), affording improved survival[1,2] and quality of life[3] compared with dialysis at reduced cost.[4] Compared with deceased donor transplantation, living donor transplantation reduces waiting time, allows elective rather than emergency surgery, and is associated with superior patient and graft survival.[5,6] Living donor transplantation is therefore the preferred treatment for ESKD in many centers.

Acceptance of living kidney donation as an ethical practice is contingent on knowledge and comprehension of risks by donors.[7] The short- and long-term outcomes of kidney donation have been reported in a large number of studies which provided reassurance of long-term safety.[8-13] However, those studies were generally based on historical cohorts of donors, from a single center or from a small group of centers, with incomplete follow-up. Significant variation in donor assessment and acceptance criteria among US transplant centers has been reported, suggesting such studies may not be representative of all donors.[14]

More recently, in 2 long-term population-based studies, donors were found to be over 10 times more likely to develop ESKD than healthy nondonors.[15,16] One of these studies also reported increased cardiovascular and all-cause mortality in donors.[15] These reports suggest the need to monitor donor acceptance patterns and long-term donor outcomes. Since 2004, the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry has prospectively collected data on all living kidney donors in Australia and New Zealand. We analyzed these data to determine the baseline characteristics of contemporary Australian and New Zealand living kidney donors.

MATERIALS AND METHODS

The ANZDATA Registry collects data on all patients receiving renal replacement therapy in Australia and New Zealand.

Details of its collection methods are available on its website http://www.anzdata.org.au. In 2004, ANZDATA began collecting data on living kidney donors in Australia and New Zealand through the creation of the ANZDATA Living Kidney Donor Registry. Data are collected at baseline and then annually postdonation. Baseline data are reported by the transplant hospital, and follow-up data are reported either by the transplant hospital or by the current treating nephrologist depending on local practice. In this article, we report the baseline characteristics of donors.

We included all living kidney donors in Australia and New Zealand over 2004 to 2012 apart from pathologic donors (nondirected donors after surgical management of a pathological process, typically tumor nephrectomy). We determined the renal and cardiovascular risk profile of the donors. We defined renal risk factors as reported measured glomerular filtration rate (GFR) less than 80 mL/min per 1.73 m^2 by nuclear isotope dilution, and/or proteinuria greater than 300 mg/day assessed by 24-hour collection. In donors without a reported 24-hour urine protein measurement, we considered a spot urine albumin:creatinine ratio (ACR) less than 2.5 mg/mmol (men) or less than 3.5 mg/mmol (women), or a spot urine protein:creatinine ratio (PCR) less than 20 mg/mmol to be normal. Estimated GFR (eGFR) was calculated using the 4-variable MDRD equation.[17] We defined cardiovascular risk factors as: (1) overweight or obesity, defined as body mass index (BMI) 25 to 29.9 kg/m^2 or greater than 30 kg/m^2, respectively; (2) diabetes, defined as use of hypoglycaemic medication, fasting blood glucose greater than 7.0 mmol/L or 2-hour blood glucose greater than 11.0 mmol/L after a standard 75 g oral glucose load; (3) hypertension as defined by blood pressure of 140/90 mm Hg or greater or use of antihypertensive medication; and (4) currently smoking.

We compared the risk factor profile of donors with the local Caring for Australasians with Renal Impairment (CARI) Guidelines for donor acceptance.[18-21] These guidelines suggest relative and absolute contraindications to donation based on renal and cardiovascular risk factors (among other considerations); a summary of these is shown in Table 1. It should be noted that these suggestions were only published in 2010 and were therefore not available when the majority of donors in this study were assessed.

Finally, we explored the variation in donor acceptance patterns between different transplant hospitals and between different age groups. All analyses were conducted using State/IC version 13.1 (StataCorp, College Station, TX).

RESULTS

There were 3012 living kidney donors in Australia and New Zealand in the 9-year period of 2004 to 2012. Eighty (3%) were donors after nephrectomy performed primarily because of a pathologic process, typically a renal cell carcinoma less than 3 cm in diameter, and were excluded, leaving 2932 donors in the study.

The baseline characteristics of the donors are shown in Table 2. One thousand seven hundred forty-three (59%) donors were biologically related to the recipient, including 792 parents, 654 siblings, 134 children, and 163 other relatives. The 1189 (41%) unrelated donors included 737 spouses/partners, 219 friends, and 233 other unrelated donors.

Glomerular filtration rate was measured by radionuclide scanning in 1565 (53%) donors, timed creatinine clearance in 505 (17%), iohexol/iothalamate clearance in 81 (3%), "other" methods (predominantly eGFR using a creatinine-based estimation formula) in 347 (12%) and was not reported in 434 (15%). Forty (1%) donors had a GFR measured by radionuclide scanning or iohexol/iothalamate clearance less than 80 mL/min per 1.73 m^2. In addition, GFR less than 80 mL/min per 1.73 m^2 was recorded for 15 (3%) of those assessed by creatinine clearance and 112 (41%) in those assessed by eGFR, although these methods have poor accuracy compared with measured GFR in potential donors.[22]

Twenty-four–hour urine protein excretion was reported in 2273 (78%), among whom 32 (1%) excreted greater than 300 mg daily. Of the remaining 659 (22%) donors, ACR or PCR was reported for 300 (10%), of whom 14 had an ACR or PCR between 1 and 3 times the upper limit of normal.

Cardiovascular risk factors were common. Hypertension was reported in 294 (10%) donors, of whom 55 were taking 2 antihypertensive drugs and 10 were taking more than 2 drugs. A further 295 (10%) donors had a reported systolic blood pressure of 140 mm Hg or greater and/or diastolic blood pressure of 90 mm Hg or greater, such that in total 589 (20%) donors were classified as hypertensive. Donors included current (218, 7%) and former (947, 32%) smokers.

Nine donors were reported to be diabetic. Of the 2878 donors reported to be nondiabetic, an oral glucose tolerance test result was reported for 1499 (52%) donors. Two donors met criteria for diabetes and 65 had impaired glucose tolerance or impaired fasting glucose. An additional 4 donors had a history of gestational diabetes. The Registry does not currently collect donor hemoglobin A1c. Donor BMI ranged from 16.4 to 46.6 kg/m^2 with a mean of 26.5 kg/m^2. One thousand two hundred sixty-one (45%) donors were overweight (BMI, 26-30 kg/m^2) with a further 495 (18%) deemed obese (BMI, >30 kg/m^2). Of the 1429 (49%) donors who did not undergo an oral glucose tolerance test, 59% were overweight or obese.

The presence of multiple cardiovascular risk factors within individual donors was common (Table 3). One thousand six hundred eighty-nine (58%) donors had no reported

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TABLE 1.

CARI suggestions for acceptance of living kidney donors (abbreviated)

Renal function
Glomerular filtration rate <80 mL/min/1.73 m^2 relative contraindication

Proteinuria
>300 mg/day relative contraindication

Hypertension
Blood pressure ≥140/90 mmHg relative contraindication; absolute contraindication if treated with >2 drugs, presence or end-organ damage or other cardiovascular risk factors

Obesity
Body mass index >30 kg/m^2 relative contraindication; absolute contraindication in the presence of an additional cardiovascular risk factor

Glucose metabolism
Diabetes mellitus, impaired glucose tolerance or history of gestational diabetes all absolute contraindications

TABLE 2.

Baseline characteristics of donors (n = 2932)

Characteristic	Value
Age: mean ± SD, y	48.8 ± 11.2
Sex	
Female	1692 (58%)
Male	1240 (42%)
Race	
White	2546 (87%)
Australian indigenous	14 (<1%)
Asian	200 (7%)
Māori or Pacific Islander	91 (4%)
Other	44 (2%)
Not reported	23 (<1%)
Measured GFR[a], mL/min	
<80	40 (2%)
80–99	484 (29%)
≥100	1130 (68%)
Not reported	1278 (44%)
24 h urinary protein excretion	
≤300 mg	2241 (77%)
>300 mg	32 (1%)
Not reported	659 (22%)
Glucose metabolic status[b]	
Normal	2811 (96%)
Impaired fasting glucose	10 (<1%)
Impaired glucose tolerance	55 (2%)
Diabetes	11 (<1%)
Unknown	45 (2%)
Body mass index, kg/m^2	
<18.5 (underweight)	17 (<1%)
18.5–24.9 (normal)	1044 (36%)
25–29.9 (overweight)	1263 (43%)
≥30 (obese)	493 (17%)
Not reported	115 (4%)
Hypertension[c]	589 (20%)
Cigarette smoking	
Current	218 (7%)
Former	947 (32%)
Never	1737 (59%)
Not reported	29 (1%)

[a] Glomerular filtration rate measured by radionuclide scanning or iothalamate clearance.
[b] Glucose metabolic status as determined by standard oral glucose tolerance test (n = 1499, 52%) or self-report.
[c] Hypertension was defined as reported blood pressure ≥140/90 mmHg or use of antihypertensive medication.

cardiovascular risk factors. One hundred eighty-eight (6%) donors had 2 cardiovascular risk factors and 3 (<1%) had 3 risk factors. If overweight was considered a cardiovascular risk factor, the majority of donors had at least 1 risk factor.

Based on the CARI suggestions for donor acceptance, 767 (26%) donors had at least 1 relative contraindication to donation and 268 (9%) at least 1 absolute contraindication (Table 4). The majority of these contraindications were due to donor hypertension or obesity in combination with another cardiovascular risk factor. There was significant variation between transplant hospitals in acceptance patterns (Figure 1). All hospitals accepted donors with 1 or more relative contraindications, and all but 6 hospitals accepted donors with one or more absolute contraindications.

TABLE 3.

Cardiovascular risk factors

Cardiovascular Risk Factors	N	%
None	1689	58
Unable to be determined[a]	176	6
Smoking	162	6
Smoking + diabetes	1	<1
Diabetes	2	<1
Obesity	315	11
Obesity + smoking	29	1
Obesity + diabetes	2	<1
Hypertension	397	14
Hypertension + smoking	16	<1
Hypertension + diabetes	4	<1
Hypertension + obesity	136	5
Hypertension + obesity + diabetes	1	<1
Hypertension + obesity + smoking	2	<1

[a] Missing data in 1 or more fields prevented categorization.
A BMI of ≥25 kg/m^2 was considered high.

Older donors were more likely to have relative or absolute contraindications to donation (Table 4 and Figure 2), although even in donors who were younger than 40 years, a significant minority had contraindications to donation. There was no clear association between donor relationship to recipient, recipient sensitization or waiting time and the risk profile of

TABLE 4.

Implications of baseline factors

Contraindication Status (%)[a]					
Characteristics	None	Relative	Absolute	Unclear	Total
All donors	1063 (36)	767 (26)	268 (9)	834 (28)	2932
Donor age, y					
18–24	23 (43)	6 (11)	4 (8)	20 (38)	53
25–34	131 (49)	33 (12)	18 (7)	86 (32)	268
35–44	290 (42)	133 (19)	41 (6)	229 (33)	693
45–54	365 (38)	253 (26)	75 (8)	269 (28)	962
55–64	218 (29)	250 (34)	93 (13)	182 (24)	743
65–74	34 (17)	85 (42)	37 (18)	45 (22)	201
75–84	2 (20)	7 (70)	0 (0)	1 (10)	10
Donor relationship to recipient					
Sibling	250 (38)	139 (21)	52 (8)	213 (33)	654
Parent	253 (32)	250 (32)	88 (11)	201 (25)	792
Child	61 (46)	23 (17)	7 (5)	43 (32)	134
Spouse/partner	260 (35)	209 (28)	72 (10)	196 (27)	737
Other related	63 (39)	44 (27)	14 (9)	42 (26)	163
Friend	90 (41)	47 (21)	20 (9)	62 (28)	219
Other unrelated	86 (37)	55 (24)	15 (6)	77 (33)	233
Recipient peak PRA (%)					
0–49	972 (36)	713 (27)	246 (9)	740 (28)	2671
50–79	41 (32)	23 (18)	14 (11)	50 (39)	128
80–100	34 (36)	25 (26)	7 (7)	29 (31)	95
Recipient years on dialysis					
<6 mo	491 (37)	317 (24)	111 (8)	394 (30)	1313
6 mo to 1 y	154 (37)	120 (29)	40 (10)	105 (25)	419
1 to 4 y	364 (35)	290 (28)	108 (10)	291 (28)	1053
≥5 y	54 (37)	40 (27)	9 (6)	44 (30)	147

[a] According to CARI recommendations.

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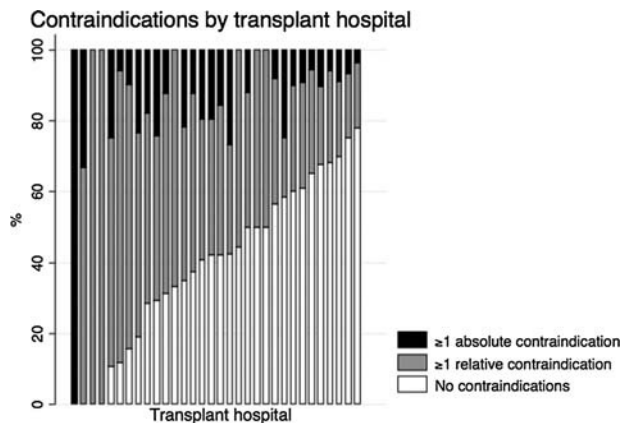
FIGURE 1. Proportion of donors with absolute, relative, or no contraindications by transplant hospital. Donors who could not be classified due to missing data are excluded.
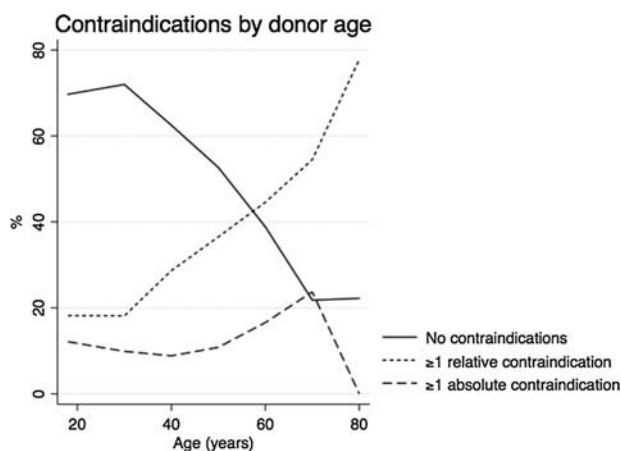

FIGURE 3. Proportion of donors with absolute, relative, or no contraindications by year of donation. Donors who could not be classified due to missing data are excluded.

donors, with approximately 10% of each subgroup studied having a contraindication (Table 4). However, parental donors were the donor group least likely to have no contraindications (32%). There was no clear change in donor risk profile over time (Figure 3).

DISCUSSION

One third of all living kidney donors in Australia and New Zealand during the past 9 years had a relative or absolute contraindication to donation, according to local and international guidelines.[7,23] This was due to the presence of one or more renal or cardiovascular risk factors identified before donation, most commonly obesity, hypertension, or smoking.

Many studies have reported on the long-term outcomes of kidney donation and provided reassuring results. For example, the Donor Nephrectomy Outcomes Research Network has reported that donors are not at increased risk of cardiovascular disease,[8] need for acute dialysis,[9] fracture risk,[10] or reduction in quality of life.[24] Analyses of administrative datasets in the United States have demonstrated acceptably low risk of postdonation death,[11] depression,[12] and cancer,[13] which compare favourably with nondonor controls.

However, a recent population-based study comparing US donors with healthy matched controls from the National

FIGURE 2. Proportion of donors with absolute, relative, or no contraindications by donor age. Donors who could not be classified due to missing data are excluded.

Health and Nutrition Examination Survey reported a substantially increased risk of ESKD in donors.[16] The rate of ESKD in donors was estimated at 30.8 per 10 000 patient-years compared with 3.9 per 10 000 patient-years in matched nondonors. A similar study in the Norwegian population produced similar findings, with a hazard ratio for ESKD of 11.38 (95% confidence interval, 4.4-29.6) compared with nondonors.[15] The latter study also reported increased all-cause and cardiovascular mortality, with hazard ratios of 1.30 and 1.40, respectively. It can be argued that both studies had less than perfect control groups.[25,26] Importantly, absolute risks of excess ESKD and mortality were low. Nevertheless, these studies clearly define the risk of ESKD in patients deemed acceptable for living kidney donation.

There is strong biologic plausibility for an excess of renal and cardiovascular risk after kidney donation. Living donors are at increased risk of hypertension, with a mean increase in blood pressure of 6/4 mm Hg[27] and a 1.4 times increase in hypertension diagnoses.[28] Donors also commonly experience low-grade proteinuria.[29] The reduction in GFR caused by nephrectomy is partially compensated by the remaining kidney, and average long-term kidney function has been reported to approximate 70% of predonation GFR.[29-31] Among the general population, low eGFR has been associated with increased cardiovascular and all-cause mortality,[32] with risk logarithmically related to magnitude of reduction in eGFR below 70 mL/min. It is worth noting that with a lower GFR threshold of 80 mL/min for kidney donation, many donors would be expected to have a postdonation GFR less than 70 mL/min. Whether donors whose eGFR falls below 70 mL/min postdonation incur cardiovascular and mortality risks similar to those seen in the general population remains to be seen; it is plausible that a reduced GFR due to surgical reduction in nephron mass has different implications from a reduced GFR due to an underlying disease process.

Evidence for the impact of donor obesity on outcomes is limited. In the short-term, obese donors are likely to have a longer length of hospital stay.[33] In the long-term, obesity in the general population is a risk factor for the development of chronic kidney disease,[34,35] diabetes,[36] and ESKD,[37] and in nondonors undergoing nephrectomy, obesity is associated with the development of proteinuria and renal insufficiency.[38]

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Donors with metabolic syndrome are more likely to have abnormal histologic findings on implantation biopsy and have a protracted recovery of renal function after donation, raising concerns about inferior long-term kidney health.[39] Clinical practice guidelines on donor acceptance suggest different BMI cutoffs, reflecting the lack of strong evidence in this area.[23]

A large proportion of Australian and New Zealand donors were hypertensive. Hypertension was reported in 10%, and reported blood pressure was consistent with a diagnosis of hypertension in a further 10%. These numbers are substantially higher than the US data.[11,33] This is concerning given that hypertension is a well-established complication of kidney donation,[27,28,40] and an established risk factor for chronic kidney disease progression,[41] short-term donor complications,[33] and donor mortality.[11] Furthermore, the majority of hypertensive donors in our study had additional cardiovascular risk factors.

A history of smoking was also common in this cohort, with 7% of donors current and 32% former smokers. ANZDATA collects neither cumulative exposure nor duration of abstinence in former smokers, so it is not possible to determine magnitude of smoking-associated risk or risk of return to smoking postdonation. As with hypertension, the majority of currently smoking donors also had additional cardiovascular risk factors, particular overweight or obesity.

Living kidney donors who proceed to donation in Australasia appear to have a relatively high-risk profile which, in the majority of cases, represents either relative or absolute contraindications to donation according to local CARI guidelines.[7] In terms of guideline adherence, the guidelines were published in 2010, postdating acceptance of many donors in this study, and provide "suggestions for clinical care" rather than direct recommendations due to perceived limitations of the existing literature. Similar variations between guidelines and practice in donor acceptance criteria have been well documented elsewhere.[42,43] Consistent with these reports, we found substantial variability between centers, suggesting differences in assessment and/or tolerance of risk. Variability by center exhibited a gradation of risk factor acceptance, rather than clear polarisation into centers with either low or high thresholds. It is unlikely that such variation can be explained by unmeasured donor factors. It is unclear why centers accept so many donors with relative and absolute contraindications. Possibilities include uncertainties in the evidence base underpinning the CARI recommendations, availability of additional data not reported to ANZDATA (eg ambulatory blood pressure measurement), or the use of discretion in donors considered unlikely to develop long-term complications despite the presence of risk factors.

Older donors have a lower life expectancy than younger ones. Younger donors therefore have potential to develop and be exposed to renal and cardiovascular risk factors for a longer period of time than older donors, resulting in an increased lifetime risk of developing ESKD or premature mortality.[44] It may therefore be reasonable to have a lower threshold for acceptance of older donors. Accordingly, we found that older donors were more likely to have risk factors than younger donors. Similar findings were reported in the RELIVE retrospective study of donors from three major US transplant centers.[45] However, even young donors in our study frequently had risk factors, with around one-third of donors under 40 having at least one relative or absolute contraindication to donation.

A key strength of our study is that the data were collected prospectively and represent all living donors in both Australia and New Zealand over 2004 to 2012. This provides a comprehensive survey of donor acceptance patterns across both countries, avoiding the selection bias that may occur in single- or multicenter studies (in which high performing units are typically overrepresented) and retrospective studies (in which donors with poor outcomes may be more likely to be lost to follow-up). Our study also has a number of limitations. We have analyzed registry data that had some missing data (especially for measured GFR and proteinuria), and we cannot determine whether these factors were not measured or simply not reported to ANZDATA. Several important aspects of cardiovascular risk assessment are not captured, including lipids, quantification of smoking exposure, family history of vascular disease, more sophisticated assessment of hypertension (24-hour monitoring), measurement of left ventricular mass or stress testing for ischemia, some or all of which may have been performed and used to inform the decision to proceed to donation. No information was available on weight loss counselling in overweight and obese donors. Although psychological assessments are routine in donor assessment in Australasia, the Registry does not capture either psychological acceptability or motivation to donate, both of which may impact appetite for risk and outcome.

As the first publication from this Registry, we included only predonation data and have not analyzed outcome data after donation. Although annual follow-up data are sought for all donors, complete data are available for a minority of donors at present. We plan to increase capture of follow-up data in the future, and to link the Registry with hospitalization and mortality data sets. However, these projects are beyond the scope of the current analysis.

In summary, we have reported the baseline characteristics of 2932 living kidney donors in Australia & New Zealand over 2004 to 2012. These donors exhibit a higher prevalence of renal and cardiovascular risk factors than that recommended by local and international guidelines. Given these risk factors, along with recent studies suggesting elevated long-term donor risk, we believe our findings mandate tight follow-up of this cohort and justify the ongoing collection of both baseline and follow-up donor data in Australian and New Zealand and in other countries. Such data are required to define donor profile and donor outcomes to provide potential donors and clinicians with accurate, contemporary estimates of risk associated with living kidney donation.

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Living kidney donation: outcomes, ethics, and uncertainty

Peter P Reese, Neil Boudville, Amit X Garg

Since the first living-donor kidney transplantation in 1954, more than half a million living kidney donations have occurred and research has advanced knowledge about long-term donor outcomes. Donors in developed countries have a similar life expectancy and quality of life as healthy non-donors. Living kidney donation is associated with an increased risk of end-stage renal disease, although this outcome is uncommon (<0·5% increase in incidence at 15 years). Kidney donation seems to elevate the risks of gestational hypertension and pre-eclampsia. Many donors incur financial expenses due to factors such as lost wages, need for sick days, and travel expenses. Yet, most donors have no regrets about donation. Living kidney donation is practised ethically when informed consent incorporates information about risks, uncertainty about outcomes is acknowledged when it exists, and a donor's risks are proportional to benefits for the donor and recipient. Future research should determine whether outcomes are similar for donors from developing countries and donors with pre-existing conditions such as obesity.

Introduction

The first successful kidney transplantation from a living donor was 60 years ago between identical twins. More than 27000 living-donor kidney transplants are now done each year across developed and developing countries.[1] In practice, a perioperative death or major complication from kidney transplantation is a rare event.[2,3] At the time of nephrectomy, kidney donors typically only spend a short time in hospital.[4] Yet, living with one kidney has lifelong implications. Research has advanced knowledge about donor life expectancy, quality of life, costs (donor-related and health-care system), and the risks of end-stage renal disease, hypertension, and adverse pregnancy outcomes. This new information creates the need for important revisions to the processes of informed consent and decision making about living kidney donation, particularly for donors in North America, Europe, Australia, and New Zealand, where most of the research originated. For transplant professionals, improved strategies are needed to communicate risks to donors, especially when adverse health outcomes such as end-stage renal disease are uncommon or unlikely to occur in the first few years after donation. Additionally, helping donors balance considerations of risk in the presence of strong emotions around the decision to donate is a difficult task.

In this Review, we provide a perspective on living kidney donation with data about long-term donor outcomes. We describe ethical implications and challenges related to decision making for donors. The Review does not address the practice of illegal and unregulated living kidney donation (eg, transplant tourism).

Epidemiology of living kidney donation

Worldwide trends in living kidney donation

Since 1954, we estimate that more than half a million living-donor kidney transplantations have been done worldwide. The highest number of living kidney donations happened in the USA (5600–6600 annually) and India (an estimated >6000 annually, although India does not have a formal registry). Brazil, Iran, Mexico, and Japan each do almost 1500 living-donor kidney transplantations annually.[1] About 60% of donors are women,[5–7] and the average age at the time of donation is between 40 and 45 years.[8–11]

Living-donor kidney transplantation has recently stagnated in the USA, Canada, Australia and New Zealand, and Brazil, but has continued to grow substantially in other countries such as Japan and South Korea (figure 1).[1] In the USA, the annual number of living kidney donors reduced by 10%, from 6647 to 5989, between the years 2004 and 2013. Declines in donation disproportionately took place in male, black, genetically related donors, and donors younger than 50 years.[3,12,13] In Canada, the number of living kidney donations rose steadily until 2006, remaining stable since then at 454–491 annually.[14] The number of living kidney donations in Australia and New Zealand peaked at 423 in the year 2008 and declined by 31% to 292 in the year 2012.[15] The rate of growth in living kidney donor transplantation has slowed considerably in Europe.[16] These declines in donation are not easily explained, but seem temporally associated with the economic recession, drawing attention to the financial risks of kidney donation for individuals with little savings or income.

Unequal access to living-donor kidney transplantation

Unlike deceased-donor organs, living-donor organs are not usually treated as a public resource. Living kidney donation generally takes place as a directed gift between individuals after careful assessment by the transplant


Search strategy and selection criteria

Comprehensive searches of PubMed Plus, EBSCO MegaFILE, JSTOR, and PsycINFO were done with the keyword terms "live kidney donor(s)", "living kidney donor(s)", or "living kidney donation" for all articles published in English from Aug 1, 1989 to Sept 3, 2014. We also searched for guidelines from professional societies focused on the care of living kidney donors. Results of this literature search are displayed in the appendix.

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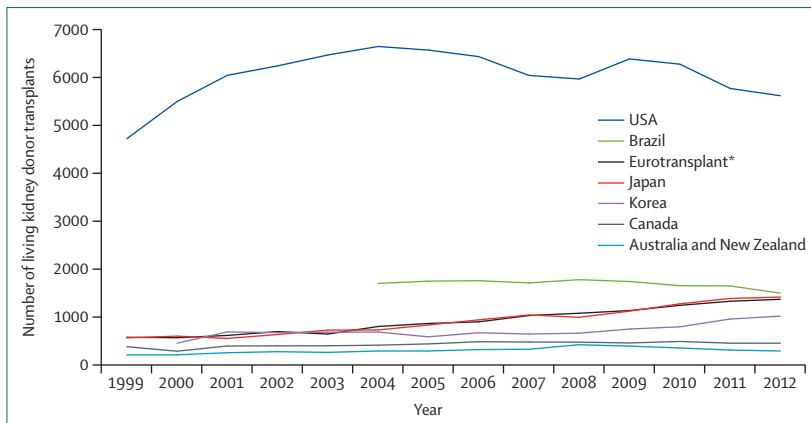
Figure 1: Temporal trends in the annual number of living kidney donation transplants
*Eurotransplant membership has changed over time; to show temporal trends, we restricted the counts to living-donor transplants in original member countries of Germany, Austria, Luxembourg, Belgium, and the Netherlands.

team. In the USA and Australia, patients with kidney failure are much more likely to receive a living-donor kidney transplant, if they are white, young, wealthy, privately insured, and well educated.[12,17–19] These disparities in access to transplants might be partly explained by high rates of contraindications to donation such as obesity in some minority populations and great difficulties in the management of donation costs.[20]

In many countries, living kidney donation is the only affordable treatment for kidney failure. This is evident across large regions of India and Pakistan, for example, where chronic dialysis is rationed in units supported by government or community donations, or is only available with payments that are prohibitive for most patients. In this respect, chronic dialysis is viewed as a bridge to a life-saving kidney transplant from a living donor. In many developing countries, the infrastructure to procure deceased-donor organs does not exist.[21–23]

Unrelated and incompatible donors

Living kidney donation in unrelated donors (eg, friends, spouses, or distant relatives of the recipient) are becoming more common.[3,12] In the USA, the proportion of living kidney donations from unrelated donors increased from 30% to 57% between 1999 and 2013. Similar trends are evident in Europe, Australia, and New Zealand.[16]

This rise in unrelated living kidney donation is largely associated with a declining emphasis on close HLA matches between donor–recipient pairs.[24] With advances in immunosuppressive therapy, the longevity and function of the transplanted organ is now less dependent on the genetic donor–recipient relationship than in the past. The rise in unrelated donors has also been helped by so-called kidney paired donation, a strategy used to overcome donor–recipient incompatibility if the transplant candidate has antibodies to the donor's blood or HLA type. Such antibodies greatly increase the risk of donated-organ rejection and, in the case of

anti-HLA antibodies, might develop because of previous pregnancies, blood transfusions, or transplants.[25] As shown in figure 2, registries of incompatible donor–recipient pairs have enabled transplantation to proceed through paired exchanges, or donation chains in which each donor provides a kidney to an unrelated compatible recipient. Paired exchange has been helped by the transportation of living-donor kidneys between centres and by non-synchronous transplants, in which one or more donors wait to donate until new pairs enter the chain.[26,27] In some cases, a transplantation chain begins when an individual with no relationship to any recipient donates a kidney (termed non-directed donation). In 2012, this type of altruistic donation enabled a 30-transplant chain to proceed.[28]

Disadvantages of kidney paired exchange include the logistical demands of coordinating transplants across multiple centres. Additionally, pairs without a blood type O donor might face prolonged delays to transplantation because it is more difficult to find matches in the available pool of donors. Despite these difficulties, paired exchange is an important pathway to transplantation for an increasing number of patients. In 2013, 10% of living kidney donations in the USA were paired exchanges.[5]

Desensitisation protocols offer an alternative approach to enable living kidney donation between incompatible pairs. The recipient undergoes intensive pretransplant immunosuppression, which typically includes plasmapheresis and intravenous immunoglobulin to reduce antidonor antibody titres.[29] Although desensitised recipients might have an increased risk of infections and antibody mediated rejection, life expectancy is still improved compared with dialysis.[30]

Chronic kidney disease

To meet the demand for kidneys, transplant teams are increasingly allowing older individuals than previously allowed and individuals with health conditions such as obesity, prediabetes, kidney stones, or hypertension, to become living kidney donors.[31] Prominent guidelines do not stipulate an upper age limit for living donors, and donation in older adults is increasing.[20,32–36] Between 2002 and 2009, the number of living kidney donors aged 55 years or older in the USA nearly doubled, increasing from 407 to 726. During that period, the percentage of donors aged 55 years or older in Australia and New Zealand increased from 27% to 38%. This trend is not surprising since, in many countries, the median age of patients on the kidney transplant waiting list is rising and these patients might attract donors in the same age group.

About 25% of living donors in the USA, Canada, Australia, and New Zealand have a body-mass index (BMI) of 30 kg/m² or higher. On trend with the general population, the proportion of living kidney donors with obesity in the USA has increased steadily over time.[37]

By contrast, donors who meet contemporary definitions of prediabetes and hypertension—but whose blood pressure and glucose tolerance were deemed to be normal at the time of donation—have been accepted for several decades.[38] Unfortunately, long-term outcomes for donors with these pre-existing conditions have not been well defined.

Assessment and selection of living kidney donors

Psychosocial assessment

As shown in table 1, the assessment includes an in-depth health and psychosocial assessment. The process is guided by ethical principles to protect the donor. To provide informed consent, donors should be free from coercion, have the capacity to make the donation decision, have all relevant information disclosed, and have sufficient comprehension of potential outcomes.[34] The transplant team should understand the donor's motives, commitment, and views on the trade-off between the risks and non-medical benefits of donation.

### Contraindications to living kidney donation

Many major guidelines identify evidence of kidney disease and diabetes as absolute contraindications to living kidney donation.[33,34,39,40] Some guidelines list active malignancy, hypertension with end-organ damage, and uncontrolled psychiatric conditions as contraindications.[33]

Relative contraindications to living kidney donation include obesity (BMI≥35 kg/m²), hypertension, prediabetes, recent nephrolithiasis, vascular disease such as fibromuscular dysplasia, substantial proteinuria, and haematuria caused by conditions such as thin basement membrane disease.[33,35,36,40] The risk posed by these conditions might plausibly depend on the donor's age at donation, race, lifestyle, and the availability of postoperative health care. However, reliable data on the lifetime chance of complications for individuals who differ in age, baseline kidney function, or race, are not available, nor is clear information on risks attributable to donation versus other baseline factors such as genetics (in cases in which the donor is related to the recipient). Perhaps as a result, substantial practice variation exists with respect to these risk factors.[41] For example, in a survey of US transplant centre policies, 10% of centres excluded donors based on a cutoff of BMI of more than 30 kg/m², 52% excluded donors with a BMI more than 35 kg/m², and 20% excluded donors with a BMI more than 40 kg/m², while 12% had no policy and 6% would exclude donors on the basis of BMI only if other cardiovascular risk factors were present.[42]

Health outcomes after living kidney donation

Outcomes for organ recipients

Although this Review focuses on donors, the excellent outcomes for recipients provide the main motivation for
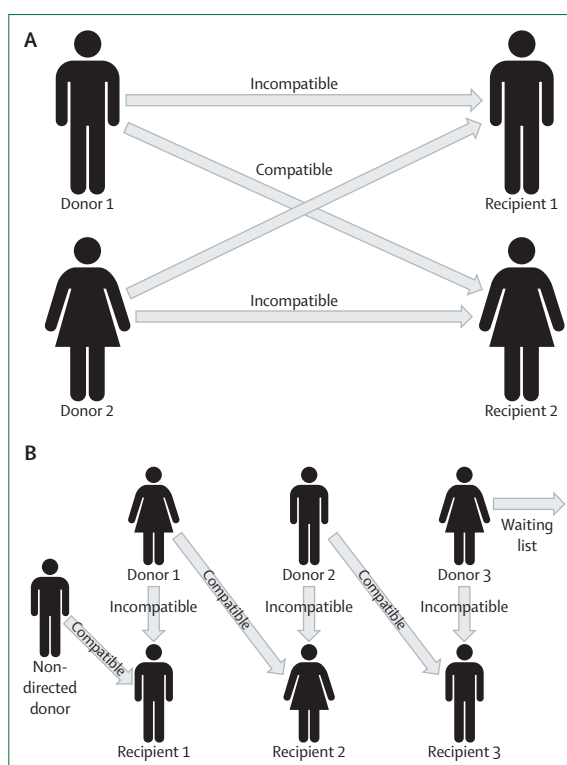
Figure 2: **Kidney paired donation**
(A) Donation across two pairs and (B) open chain paired donation.

living kidney donation and merit brief consideration. Recipients of living kidney donation have a better quality of life and a much longer survival versus chronic dialysis treatment. Compared with recipients of deceased-donor kidneys, recipients of living-donor kidneys wait less time for transplantation, have a lower risk of rejection, and have better allograft survival and longer life (although outcomes might depend on donor age and predonation kidney function).[3,12,43] Unlike deceased-donor transplantation, living kidney donation can be scheduled when the recipient's health is optimum, and the kidney avoids injury from donor brain death, prolonged transport, or associated events.

Assessment of outcomes for donors

Randomised trials could generate very reliable estimates of the risks for donors; however, randomised trials of organ donation are not ethical. Living kidney donors undergo extensive medical and psychosocial assessment and are therefore healthier than the general population. However, in many observational studies, donor outcomes were compared with general population controls, which could mask any increased risk attributable to donation. Historically, the validity of many studies of donor outcomes was also limited by high rates of loss to follow-up, recall bias, and inadequate sample sizes to detect clinically important risks.

	Testing	Main purpose	Related absolute contraindications
Kidney structure and function	Assessment of filtration function; screening for present or previous proteinuria or haematuria, or both; imaging, typically with contrast enhancement	To estimate whether postdonation renal function will be sufficient; to screen for kidney disease, including kidney stones, and to characterise the kidney's structure and vascular anatomy	Evidence of chronic kidney disease
Haematological or oncological assessments	Blood typing; coagulation; review of age-appropriate cancer screening, and any family history of cancer	To ensure blood type compatibility with recipient; to assess bleeding risk; to confirm overall donor health, and in some rare cases, prevent cancer transmission to the recipient	Blood type incompatibility needs recipient desensitisation or donor exchange; untreated malignancy
Cardiovascular function	Blood pressure; lipid screening; preoperative stress testing, per clinician judgment	To determine whether blood pressure postdonation is likely to be sufficiently controlled to protect the remaining kidney; cardiovascular health assessment; operative risk assessment	Transplant team might decline donor if findings show risk of future poor health
Infectious disease risk	Screening for HIV, hepatitis B and C, syphilis, tuberculosis; where appropriate, infections endemic to specific regions	To identify diseases that might impair the donor's future health or harm the immunosuppressed recipient if infection transmitted through donated organ	Transplant team might decline donor if findings show risk of future poor health
Endocrine function	Assessment of glycaemic abnormalities, often with oral glucose tolerance testing in high-risk patients; body-mass index	To confirm absence of diabetes and low risk of future diabetes	Diabetes
Other health aspects (gastrointestinal, pulmonary, dermatological, and rheumatological)	Interview; physical assessment; routine laboratory assessment; chest radiograph	General health assessment	Transplant team might decline donor if findings show risk of future poor health
Family history	Renal disease; diabetes; cancer	Assessment for genetic predisposition to kidney disease (eg, polycystic kidney disease); to confirm low risk of future diabetes; general health assessment	Transplant team might decline donor if findings show risk of future poor health
Histocompatibility	HLA typing; donor and recipient tissue cross-matching	Ensure HLA compatibility of donor organ with recipient's immune system	High levels of recipient antibodies against donor antigens needs desensitisation or paired kidney exchange
Psychosocial assessments	Interview to determine capacity for decision making; mental health history; substance misuse history; social support, financial resources; detailed assessment of donor's motives, values, and understanding	To assess donor's capacity for decision making; to assess donor's risks for future health problems; where relevant (eg, injection drug use), to assess risks of acquiring blood-borne infections; to assess support and resources for donor during surgical recovery period; to assess whether coercion or financial inducements are present; understanding of risks and benefits; and whether decision is consistent with the donor's values	Inability to understand or little insight into risks and benefits because of mental illness or other reasons; evidence of coercion
Counselling by an independent donor advocate	Additional assessment of the elements of informed consent	Assessment by a professional whose judgment should be independent from the needs of the recipient or the centre	Processes of informed consent not satisfied

Table represents synthesis of guidelines from multiple countries.

Table 1: Elements of the extensive health and psychosocial assessment for potential living kidney donors

More recent studies[9,11,44] have succeeded in assembling comparator groups that have undergone some health assessment, and matched these comparators to donors with key baseline characteristics such as demographics, comorbidities, and health habits (table 2).

Mortality and cardiovascular disease outcomes

Many studies, including cohorts from Sweden, Japan, and the USA, have showed that living kidney donors have similar or better life expectancy than the general population.[2,45–47,66] Four large studies have also compared mortality in living kidney donors with healthy matched controls who did not have evidence of chronic diseases that would preclude kidney donation at many transplant centres.[2,10,11,44] Segev and colleagues[2] matched 80 347 living kidney donors to a smaller group of healthy non-donors selected from the third US National Health and Nutrition Examination Survey and found similar survival during median follow-up of 6·3 years. By contrast, Mjøen and colleagues[10] reported an increased risk of death in 1901 Norwegian kidney donors with median follow-up of 15·1 years compared with healthy matched comparators from a regional population survey. The cumulative incidence of mortality at 25 years was about 18% in donors versus 13% in healthy non-donors (adjusted hazard ratio 1·30, 95% CI 1·11–1·52). The Segev and Mjøen studies were limited by the use of comparator cohorts from different time periods than when the donations took place. This approach creates the potential for bias because of changes in medical care or mortality trends across eras.

Cohorts of Canadian living kidney donors, US living kidney donors aged 55 years or older, and healthy controls, were assessed for death or major cardiovascular events by use of claims data and death registries.[44] Neither study found an increased risk of the outcome associated with kidney donation.[11,44] Together, the results from these two studies are generally

	Comparison group	Outcome for previous kidney donors*	Additional study information
Survival	Healthy matched non-donors	Most data show that donors have similar survival	Four studies: from the USA, Norway, Canada;[2,10,11,44] Norwegian cohort showed higher mortality associated with donation
Survival	General population	Longer-term survival than non-donors	Three studies from Sweden, and from single centres in the USA and Japan[45–47]
End-stage renal disease	Healthy matched non-donors; general population	Increased relative risk, but low cumulative incidence of end-stage renal disease; lower risk of end-stage renal disease (vs general population)	Two studies from the USA and Norway;[9,10] estimated cumulative incidence is less than 0·5% at 15 years; one study from Sweden[48]
Cardiovascular disease	Healthy matched non-donors	No increased risk of cardiovascular disease	Two studies from the USA and Canada[11,44]
Pre-eclampsia or gestational hypertension	Predonation and postdonation	Increased risk	Provincial cohort from Ontario, Canada;[49] single US centre;[50] national cohort from Norway[51]
Hypertension and elevated blood pressure	Healthy matched non-donors; predonation and postdonation	Increased blood pressure; increased systolic blood pressure of 4 mm Hg; increased diastolic blood pressure of 6 mm Hg at least 5 years postdonation	Two studies from the USA (black donors) and Canada;[52,53] various studies[54]
Quality of life	General population	Quality of life as good or better for living donors	Various studies from many countries[55–65]

Only the quality-of-life studies include donors from the developing world in the studies cited in the table. *Versus comparison group.

Table 2: **Summary of medium-term and long-term health outcomes after living kidney donation**

reassuring. However, concerns persist about whether the findings can be generalised to donors in the developing world. Some transplant leaders have also argued that, on the basis of present data, the lifetime risk of these complications or others cannot be accurately estimated in young donors (defined for this article as <30 years), who will spend many decades in a single-kidney state.[67]

End-stage renal disease

Evidence suggests that living kidney donation greatly elevates the relative risk of end-stage renal disease, although this outcome remains uncommon: less than 0·5% over 15 years.[10,68] Unfortunately, few data for long-term renal outcomes have been published outside North America and Europe.[69]

Immediately after nephrectomy, living kidney donors have a glomerular filtration rate of about 50% of predonation rate. Because of adaptive hyperfiltration in the remnant kidney, the glomerular filtration rate usually increases to 60–75% of predonation levels by a year after donation.[70] Kidney donors might also have small increases in concentration of serum uric acid, FGF-23, parathyroid hormone,[71,72] and non-albuminuric proteinuria.[73] Kidney donation might also cause blood pressure to increase.[52,54] These factors could contribute to an accelerated loss of renal function.

End-stage renal disease outcomes were investigated in the US donor cohort previously assembled by the group led by Segev.[2] 99 (0·1%) of 96 217 donors developed this disease with median follow-up of 7·6 years. The incidence of end-stage renal disease in donors was lower than in unscreened general population controls,

but higher than in matched healthy non-donors.[9,45] Muzaale and colleagues[9] extrapolated data to a longer time horizon and estimated that the 15-year cumulative incidence of end-stage renal disease was 0·31% in living kidney donors versus 0·03% (p<0·001) in healthy non-donors. Although the 15-year cumulative incidence of end-stage renal disease was twice as common in biologically related (0·34%) versus unrelated donors (0·15%), the difference was not significant.[9]

A concordant finding was identified in the cohort of Norwegian kidney donors, in which nine (0·47%) of 1901 donors developed end-stage renal disease (median follow-up time 15·1 years). Kidney donation was associated with a hazard ratio of 11·38 (95% CI 4·37–29·63) for this disease versus healthy non-donors.[10]

These studies have greatly expanded our understanding of postdonation renal outcomes; however, important gaps in knowledge remain. First, because comparison groups were not matched on family history, the extent to which the higher rate of end-stage renal disease in donors is attributable to genetic predisposition is unclear. However, all donors did not have substantial evidence of early kidney disease at the time of donation, which makes it less likely that genetics can fully explain the reported risk of this disease. Second, data do not enable precise estimates of the lifetime risk of developing end-stage renal disease.

Renal outcomes in black and Aboriginal donors

The very high rates of kidney disease in black individuals and Aboriginal communities have generated concern about outcomes for living kidney donors from these communities.[74,75] In the general population, black race is

associated with a four-times increased risk of end-stage renal disease.[76] An association of similar magnitude has been described in black versus white living kidney donors.[77] For example, Cherikh and colleagues[78] identified 126 US living kidney donors with end-stage renal disease and reported a relative risk of end-stage renal disease of 4·9 in black versus white donors.[78]

Fewer data are available about outcomes for Aboriginal donors. A case series reported outcomes of 22 indigenous kidney donors from the Northern Territory of Australia. From 16 with follow-up data, three (19%) had end-stage renal disease and two (12%) had died. A cohort of 38 Aboriginal living kidney donors from a Canadian centre noted that Aboriginal donors were much more likely to have hypertension (43% *vs* 19%, p=0·02) and diabetes (19% *vs* 2%) than randomly selected white donors.[79]

These findings and others have focused attention on the genetic versus social determinants of renal disease associated with race.[75] The G1 and G2 coding variants of the *APOL1* gene on chromosome 22 have a strong association with renal disease and are almost always inherited only by individuals with African ancestry.[80] The mechanism of disease associated with *APOL1* risk variants is not known. Screening for *APOL1* is not routinely done for black race donors at most centres. However, some transplant leaders have argued for taking race into account, for example by adopting more stringent criteria for blood pressure, when clinicians decide whether to accept black donors.[74]

Pregnancy after kidney donation
Some female living kidney donors are in their reproductive years. Because pregnancy leads to renal hyperfiltration and volume expansion, living kidney donors—whose remaining kidney is also subject to hyperfiltration—might be at increased risk of pregnancy complications.

Three retrospective cohort studies[49–51] from Canada, Norway, and the USA have examined pregnancy outcomes after kidney donation. The Canadian study ascertained postdonation pregnancies and proportion of pregnancy complications in 85 donors who were matched on relevant characteristics to non-donors. Gestational hypertension or pre-eclampsia were more common in kidney donors than matched non-donors (11% *vs* 5%). The incidence of pre-eclampsia (6% in donors) was similar across all three studies.[49] Reassuringly, in the Canadian study, most previous donors had uncomplicated pregnancies, and other important maternal and faetal outcomes did not differ significantly between the two groups.

Quality of life and decisional regret
Studies from many countries have generally shown good health-related quality of life after donation.[55] However, much of the data consist of generic quality of life instruments that might not capture donor-specific experiences. For example, some donors report difficulties including pain control during surgical recovery and a feeling of vulnerability to future health problems.[56,57]

The RELIVE cohort of 2455 US donors (mean follow-up of 17 years) showed that more than 80% had average or better self-rated health on the Medical Outcomes Study Short-Form 36.[58] Quality of life in the physical and mental component scores was similar to or more than norms for both black and white donors.[59] Generally, good health-related quality of life has been reported in donors in Canada, Australia, Scotland, Brazil, Taiwan, and several European countries.[56,60–63] Investigators have also asked donors whether they would make the donation decision the same way, in view of their experiences. Only a small minority of donors expressed regret about donation.[62–65] The RELIVE study revealed that predonation psychiatric diagnoses, younger age, a longer time to full recovery from surgery, and the feeling of having received inadequate attention from the transplant team were associated with worse mental health-related quality of life after donation.[58] Some donors also expressed regret or disappointment in the rare event that the donated kidney fails soon after surgery.[65,81] Notably, a randomised trial in potential kidney donors with use of motivational interviews to discuss the donation decision has suggested that this intervention might improve perceptions of postdonation recovery.[82]

Financial consequences of living kidney donation
Living kidney donation can be financially costly to donors, even in countries where the donor's medical expenses are paid by the recipient's insurance or the health-care system. Major costs can include transportation, child care, lost income (or holiday time) from missed work, and fees associated with medical care.[83] In a prospective follow-up of 100 Canadians, the mean cost associated with donation was CAN$3268. However, for 15% of donors, costs exceeded CAN$8000.[84]

In the USA, some donors have experienced difficulty in obtaining health or life insurance, although most data are self-reported.[85] A study of premiums for donors in Canada, on the basis of estimates provided directly by insurance representatives during the first stage of applications for life insurance, did not find increased rates.[86]

Ethical implications of new knowledge about donor outcomes
Informed consent process
Information about kidney-donor outcomes needs incorporation into the processes of informed consent. Transplant centres should ensure that potential donors understand that nephrectomy increases their risk of end-stage renal disease, but for most donors, the rate of this disease over 15 years is less than 1%. Estimates of the lifetime chance of end-stage renal disease are imprecise

particularly for young donors (younger than 30 years), and this uncertainty should be acknowledged. Female donors with childbearing potential should be counselled about future reproductive plans, with about 8–14% (*vs* 3–7% of women in the general population) of these women expected to have gestational hypertension or pre-eclampsia in a future pregnancy.[87] The informed consent process should include plans for financial consequences of donation. Consent should also incorporate information about good quality of life for donors, and any anticipated benefits to the recipient. Although most data suggest that live donors have excellent longevity, the informed consent process might also include discussion of a Norwegian study[10] that reported higher death rates in kidney donors versus healthy controls.

Some of these elements, particularly the contrast between relative and absolute rates of end-stage renal disease, might be difficult for donors to understand. To put rare outcomes into a familiar context, centres might need to develop more effective educational approaches, such as visual aids. The consent process should include serial meetings and diverse opportunities for potential donors to ask questions.[88]

Risk assessment and benefits from the donor's perspective

Transplant professionals should be guided by principles of beneficence and non-maleficence toward the donor, while taking the donor's autonomy into account.[89] Kidney donors often have a strong desire or duty to improve the life of the recipient.[57,90] Some individuals describe the donation experience as a morally meaningful act.[57] Many donors report making a rapid decision that does not change when shown the data about risks.[91] Many potential donors are already fully committed to the donation of a kidney by the time they contact the transplant programme. For a donor whose welfare is closely linked to the potential recipient (such as a spouse), the donor might hope that their mutual welfare will improve with transplantation. In summary, many donors describe non-medical benefits from donating.

For transplant professionals, helping a donor to achieve these benefits from donation is consistent with the principle of beneficence.[89] However, donors have a diversity of motives, expectations, and relationships to the recipient.[90] Some potential donors have reservations about the donation decision or expect few benefits. The assessment of potential non-medical outcomes (such as quality of life and psychological health) from donation needs members of the transplant team to understand the donor's perspective on how donation will affect many aspects of his or her life. Therefore, the transplant team needs the expertise to do a thorough psychosocial assessment.[33,92] In the USA, UK, Canada, and Australia, guidelines recommend or regulations mandate the use

of an independent donor advocate who verifies the donor's informed consent. The donor advocate should be an individual whose position in the health system offers some protection from any undue pressure to accept a donor.[20,33,34,36] For example, the advocate might not be directly employed by the transplant centre or might have a reporting structure to a leader outside transplantation.

The decision to accept a donor is generally made by an interdisciplinary committee. Although donor autonomy is an essential component, the committee members must also consider their own consciences and professional standards.[35] Transplant professionals might later encounter a donor who developed end-stage renal disease or another poor outcome. These professionals should feel comfortable that the decision making and informed consent processes were ethically sound.

For donors from the developing world, the processes of informed consent should include discussion of how outcomes data might not be generalisable to their situation. Transplant professionals should seek to confirm that donors will have the resources to obtain good preventive care and needed treatments if complications such as hypertension arise. Donation should not proceed until the team is satisfied with the follow-up plan.

Thresholds of acceptable absolute risk for adverse outcomes

The new data for donor outcomes draw attention to the unresolved problem of thresholds of acceptable risk for living kidney donors. By use of the end-stage renal disease example, the relative risk associated with kidney donation would lead to important differences in the expected absolute lifetime incidence of end-stage renal disease between donors without baseline risk factors for kidney disease (eg, a 45-year-old white donor with no health problems) versus donors with strong risk factors (eg, a 45-year-old black donor with family history of kidney disease).[93]

This scarcity of guidance about acceptable risk is, in part, because of the fact that each donor's risks must be weighed against the expected benefit to that donor and the intended recipient. Additionally, setting thresholds on the lifetime probability of complications such as end-stage renal disease might perpetuate or worsen disparities in access to kidney transplantation in minority groups that have a high baseline prevalence of end-stage renal disease, such as Aboriginal Australians.

Financial incentives for living kidney donation

New insights about donor outcomes could have implications for policy aimed to create financial incentives for live organ donation. First, evidence about financial costs has led to recommendations that donors receive financial counselling, and has fostered pro-grammes to reimburse donors for their legitimate

	Policy	Outcomes
Kidney donors might experience substantial financial costs of donation from mechanisms including lost wages, incurred travel and accommodation expenses, and, in some cases, barriers to obtaining affordable insurance	Health system provides appropriate reimbursement for donation-related expenses; laws protect donor's employment for a reasonable period after donation; elevated insurance premiums due to kidney donation prohibited	Remove financial risks to the donor; possible outcome of increased living kidney donation in interested potential donors who are financially vulnerable; treat donors fairly
Long-term health complications of kidney donation, such as end-stage renal disease	Transplant centre or health system provides medical care for complications, routine follow-up care, and payment for treatment; in countries with deceased donor transplantation, priority for former live organ kidney donors in allocation might be considered	Adverse health outcomes from kidney donation identified early and treated
Scarcity of thresholds of acceptable risk of complications for the acceptance of kidney donors	As research findings develop, clinical practice guidelines should incorporate input from stakeholders and identify a lifetime incidence of complications that precludes donation; because long-term risks are more difficult to predict in younger versus older donors, centres might preferentially recommend older donors when more than one donor is available	Standardisation and transparency related to the acceptance of kidney donors across centres

Table 3: Proposed policies and practice guidelines to protect living kidney donors from medical and financial risks

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Panel: **Key research needed to improve the informed consent process for living kidney donors**

1. Long-term outcomes for donors with pre-existing chronic health conditions, including obesity, hypertension, metabolic syndrome, and kidney stones
2. Outcomes for donors in developing countries
3. Genetic and social risk factors for end-stage renal disease in living kidney donors
4. Estimation of lifetime risks in young (eg, <30 years of age) kidney donors
5. Novel educational approaches to educate potential donors—particularly those with low numeracy—about the risks associated with kidney donation

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expenses.[94] Second, new data about donation-related complications might support the contention that donors deserve a financial reward to offset the acceptance of risk. Although societies of transplant professionals support reimbursement of expenses, regulated direct incentives for living kidney donation is a polarising issue, with many leaders in the transplant community providing compelling arguments for and against incentive programmes.[95]

Needed policy and research related to living kidney donor transplantation

New policies to address the medical and financial risks of living kidney donors are needed. Potential policies are described in table 3. Additionally, funding agencies should support research to determine long-term outcomes for living kidney donors, particularly for donors with predonation health conditions (panel). In particular, developing countries should consider investment in transplant registries that advance research into living-donor outcomes. New research is also needed to reduce disparities in access to living-donor

transplantation, and improve efficient evaluation procedures for motivated donors. For many transplant candidates, the option of living-donor kidney transplantation and the process of engagement with potential donors are not thoroughly explored by the transplant team. Yet, some research supports the idea that targeted education, counselling, or coaching transplant candidates might lead to increased access to living kidney donation—particularly in ethnic minorities and older patients who have historically had lower rates of living-donor kidney transplantation.[96–98,12]

Conclusion

Since 1954, more than half a million living-donor kidney transplants have been done worldwide. Recent studies have greatly clarified our understanding of the risks and benefits of kidney donation over the short and long term. Continuing efforts to resolve uncertainties related to living kidney donation, particularly in the developing world, are necessary to safeguard the ethical practice of living kidney donation for the future.

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