Long-term medical risks to the living kidney donor

Ngan N. Lam, Krista L. Lentine, Andrew S. Levey, Bertram L. Kasiske and Amit X. Garg

Abstract | Living kidney donation benefits recipients and society but carries short-term and long-term risks for the donor. This Review summarizes the studies that underlie our current understanding of these risks in the first decade after donation, with a view to improving the informed consent process. Two studies report a higher risk of end-stage renal disease (ESRD) among donors than among healthy nondonors; however, the absolute 15-year incidence of ESRD is <1%. All-cause mortality and the risk of cardiovascular events are similar among donors and healthy nondonors, although one study provides evidence for a 5% increase in all-cause mortality after 25 years that is attributable to donation. Some evidence suggests that the 20-year incidence of gout is slightly higher among donors than among healthy nondonors. The risks of gestational hypertension or pre-eclampsia seem to be 6% higher in pregnancies among donors than in pregnancies among healthy nondonors. The incidences of acute kidney injury, kidney stones that require surgical intervention, gastrointestinal bleeding and fractures seem no higher among donors than among healthy nondonors, although some of these conclusions are based on a small number of events. Future studies must clarify the lifetime incidence of long-term outcomes, particularly in relation to a donor's age, race, and history of comorbidities.

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Introduction

Living kidney donation is highly beneficial to transplant recipients, and over 27,000 donations are completed worldwide every year.[1] Nevertheless, living donors exhibit a reduction of 25–40% in glomerular filtration rate (GFR) soon after nephrectomy.[2] Debate exists as to whether this reduction in GFR results in long-term adverse clinical outcomes that are similar to those observed in patients with mild to moderate chronic kidney disease (CKD), for example, increased risks of end-stage renal disease (ESRD) and cardiovascular disease.[3–7]

Living kidney donors with reduced GFR might experience different outcomes to those of patients with CKD because donors are otherwise healthy and without systemic vascular disease, whereas CKD is associated with comorbid conditions such as diabetes and hypertension. Studies have reported reassuringly safe and acceptable long-term outcomes for living kidney donors, although limitations of these studies include short follow-up durations (only a few studies have monitored a large number of donors for more than 20 years), high loss to follow-up, and limited racial diversity.[8,9] Furthermore, most studies have compared donors with the unscreened general population; such comparisons are valid, but a clear understanding of the limitations of these comparisons relative to alternative study designs is critical for drawing inferences (Box 1). For example, living kidney donors are thoroughly screened for kidney disease, hypertension and other conditions before being allowed to proceed with donation, so are inherently healthier at baseline than the general population.[10,11] Controls with similar baseline health to that of accepted donors are, therefore, required to estimate the risks that are attributable to kidney donation.

Outcomes for living kidney donors, such as perioperative complications,[12–14] psychosocial health,[15–17] and economic and insurability consequences,[18–21] are described elsewhere, as are outcomes for kidney recipients in relation to donor characteristics.[22,23] In this Review, we summarize studies that examine long-term medical outcomes for living kidney donors within the decade after donation, focusing on outcomes that can plausibly be associated with a reduction in GFR. These studies include many with a median follow-up period of 8 years (maximum 20 years), and compare donors with selected healthy nondonors, so allow assessment of outcomes that are attributable to donation (Table 1); no studies with longer follow-up periods make similar comparisons. An understanding of the current evidence and its limitations will improve the informed consent process for potential donors and recipients, and guide the development of recommendations for follow-up procedures.

Renal outcomes for kidney donors

The loss of renal mass from uninephrectomy in living kidney donors is associated with compensatory changes in the remaining kidney. Nevertheless, studies suggest

Department of Medicine, Division of Nephrology, Western University, London Health Sciences Centre, 800 Commissioners Road East, London, ON N6A 4G5, Canada (**N.N.L.**, **A.X.G.**). Department of Internal Medicine, Division of Nephrology, Saint Louis University, 3635 Vista at Grand Boulevard, St. Louis, MO 63110, USA (**K.L.L.**). Division of Nephrology, Tufts Medical Center, 800 Washington Street, Boston, MA 02111, USA (**A.S.L.**). Department of Medicine, Hennepin County Medical Center, 701 Park Avenue, Minneapolis, MN 55414, USA (**B.L.K.**).

Correspondence to: N.N.L. nlam5@uwo.ca

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Key points

- Transplantation of kidneys from living donors is an important treatment for kidney failure, but the long-term risks to kidney donors are unclear; understanding the risks could improve the informed consent process
- Studies suggest that living kidney donors are at increased risk of developing end-stage renal disease relative to healthy nondonors, but the 15-year cumulative incidence remains <1%
- All-cause mortality in the first decade after nephrectomy seems to be lower or no different among donors than among healthy nondonors; one study suggests that over 25 years, the incidence might increase by 5%
- The absolute incidence of gout might increase by <2% in the first decade after donation among donors compared with healthy matched nondonors
- Women should be informed that complications of pregnancy are more likely after donation than before donation and that their risk of gestational hypertension and pre-eclampsia is 6% higher than that in nondonors
- Risks of acute kidney injury, cardiovascular events, kidney stones requiring surgical intervention, major gastrointestinal bleeding and skeletal fractures do not seem to be increased in the decade after kidney donation

that the loss of GFR over time following donor nephrectomy occurs no faster than that observed with healthy ageing.[2] Outcome studies have considered the long-term risk of developing ESRD and acute kidney injury (AKI) in living kidney donors.

End-stage renal disease

Some centres worldwide have reported on the risk of ESRD in living kidney donors. In this context, ESRD has typically been defined as the receipt of chronic dialysis or kidney transplantation.[10,24–33]

The overall incidence of ESRD among living kidney donors during the first 10 years after donation is low, at 0.2–0.5%.[10,34,35] Many single-centre studies that have reported ESRD outcomes are limited by a high loss to follow-up and/or short follow-up periods.[24] In the few studies that have compared outcomes of living kidney donors with those of the general population, the incidence of ESRD seems to be lower in donors or no different. For example, a national American study observed 134 cases of ESRD per million person-years in donors and 354 cases of ESRD per million person-years in the unscreened general population.[34]

Box 1 | Perspectives of risk in living kidney donors

Descriptive risk
- Frequency of events after donation

Comparative risk

Within-donor
- Relative outcomes in donor subgroups

Donor versus general nondonors
- Relative outcomes in donors versus general experience (often demographically matched but not screened for baseline health status)

Attributable risk

Donor versus highly selected nondonors
- Relative outcomes in donors versus persons who would otherwise meet donor criteria (designed to simulate counter-factual experience of life without donation)

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Two studies published since 2014 have compared the risk of ESRD in donors with that in selected healthy nondonors to better quantify the proportion of the risk that is attributable to donation.[36,37] The first included 1,901 white living kidney donors who donated between 1963 and 2007 at a single centre in Norway.[36] The median follow-up period was 15 years (range 1.5–44 years), with no reported loss to follow-up. Donors aged >70 years and those with hypertension or obesity were excluded. The mean estimated GFR (eGFR) before donation was 105 ml/min/1.73 m^2 (SD 14 ml/min/1.73 m^2). The nondonor control group included 32,621 individuals who were selected on the basis of a population-based survey (the Health Study of Nord-Trøndelag) that was conducted between 1984 and 1987 (median follow-up period 25 years, range 0.1–26 years). The exclusion criteria were similar to that for the donors, except that information on renal function was unavailable. In this study, 0.47% of donors and 0.07% of nondonors developed ESRD. All affected donors were biologically related to their recipient; in total, 85% of donors in the study were biologically related to their recipient. The relative risk of ESRD was higher among living kidney donors than among healthy nondonors (Table 1).

Limitations of that study included different accrual periods and differences in baseline characteristics between donors and nondonors.[38,39] For example, donors were older than nondonors at baseline (46 years versus 38 years); after matching, however, the mean age of both groups at baseline was 46 years and all analyses were adjusted to account for this difference.[40] Subsequent concerns have also been raised about whether the control group is representative of the Norwegian population, as the survey was conducted in the rural county of Nord-Trøndelag, where life expectancy exceeds the national average.[41] Despite these limitations, this study was the first to report an 11-fold increase in the relative risk of ESRD among living kidney donors compared with that among healthy nondonors. Reassuringly, and most importantly, the absolute incidence of ESRD in living kidney donors during the follow-up period was low.

The second study included 96,217 living kidney donors who donated a kidney in the USA between 1994 and 2011.[37] The median follow-up period was 8 years (interquartile range [IQR] 4–12 years, maximum 15 years). At baseline, 4.2% of donors were aged ≥60 years, 9.0% had hypertension, 25.2% were obese, and 22.1% had an eGFR before donation <80 ml/min/1.73 m^2. The mean eGFR before donation was 101 ml/min/1.73 m^2 (SD 24 ml/min/1.73 m^2). Members of the nondonor control group were selected from 20,024 participants of the Third National Health and Nutrition Examination Survey (NHANES III), who were enrolled between 1988 and 1994. The median follow-up period for the matched nondonors was 15 years (IQR 14–15 years, maximum 15 years). Participants with medical conditions that could preclude donation (for example, hypertension or diabetes) were excluded, leaving 9,364 healthy nondonors to serve as controls. These nondonors were then matched to donors with replacement (that is, nondonors

Table 1 | Studies that quantified long-term outcomes in living kidney donors compared with selected healthy controls

Study	*n*		Median donor follow-up time (years)	Donor age at donation (years)*	Incidence (%)		HR (95% CI)	*P* value
	Living kidney donors	Healthy matched nondonors			Donors	Nondonors		
End-stage renal disease								
Mjøen *et al*. (2014)[36]	1,901	32,621‡	15.1	46 (11)	0.47	0.067	11.38 (4.37–29.63)	<0.001
Muzaale *et al*. (2014)[37]	96,217	96,217	7.6	40 (11)	0.10	0.037	NR	<0.001
Acute kidney injury treated with dialysis								
Lam *et al*. (2012)[43]	2,027	20,270	6.9	43 [34–50]	0.05	0.07	0.58 (0.08–4.47)	0.61
All-cause mortality								
Mjøen *et al*. (2014)[36]	1,901	32,621	15.1	46 (11)	11.8	7.4	1.30 (1.11–1.52)	0.001
Segev *et al*. (2010)[12]	80,347	80,347	6.3	NR	1.5	2.9	NR	<0.001
Reese *et al*. (2014)[46]	3,368	3,368	7.8	59 (NR)	3.4	4.5	0.90 (0.71–1.15)	0.21
Death or major cardiovascular event								
Reese *et al*. (2014)[46]	1,312	1,312	NR	NR	NR	NR	1.02 (0.87–1.20)	0.70
Garg *et al*. (2012)[44]	2,028	20,280	6.8	43 [34–50]	2.1	3.0	0.66 (0.48–0.90)	0.01
Major cardiovascular events								
Garg *et al*. (2012)[44]	2,028	20,280	6.8	43 [34–50]	1.3	1.4	0.85 (0.57–1.27)	0.43
Cardiovascular mortality								
Mjøen *et al*. (2014)[36]	1,901	32,621	15.1	46 (11)	3.6	2.1	1.40 (1.03–1.91)	0.03
Kidney stones with surgical intervention								
Thomas *et al*. (2013)[48]	2,019	20,190	8.8	43 [34–50]	0.79	0.89	0.85 (0.47–1.53)§	0.58
Major gastrointestinal bleeding								
Thomas *et al*. (2014)[51]	2,009	20,090	8.8	42 [34–50]	1.6	1.3	1.24 (0.85–1.81)§	0.26
Skeletal fractures								
Garg *et al*. (2012)[56]	2,015	20,150	6.9	43 [34–50]	1.2	1.3	0.88 (0.58–1.32)§	0.50
Gout								
Lam *et al*. (2015)[60]	1,988	19,880	8.8	43 [35–51]	3.4	2.0	1.6 (1.2–2.1)	<0.001
Gestational hypertension or pre-eclampsia								
Garg *et al*. (2015)[63]	85‖	510‖	11.0	29 [26–32]	11.5	4.8	2.4 (1.2–5.0)¶	0.01

*Data presented as mean (standard deviation) or median [interquartile range]. ‡Living kidney donors were not matched to healthy nondonors in the comparison for end-stage renal disease risk. §Presented risk estimate is a rate ratio rather than a hazard ratio. ‖In 85 donors, there were 131 pregnancies in follow-up. In 510 nondonors, there were 788 pregnancies in follow-up. ¶Presented risk estimate is an odds ratio rather than a hazard ratio. Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported.

could be selected more than once), resulting in a cohort of 96,217 healthy matched nondonors.

In this study, 0.10% of living kidney donors and 0.04% of healthy matched nondonors developed ESRD during follow-up; ESRD was defined as the receipt of chronic dialysis or a kidney transplant for both groups, and/or placement on the transplant waiting list for donors. The total number of ESRD events in the healthy matched nondonors (36) represented multiple selection of 17 individuals from the healthy nondonor pool during matching. The crude incidence of ESRD was, therefore, higher in this pool of 9,364 nondonors (0.18%) than in donors, but these results cannot be compared, as NHANES III oversampled for African American, Hispanic and older participants.[39]

The estimated cumulative incidence of ESRD in the 15 years after donation was higher among living kidney donors than among healthy matched nondonors (30.8 cases per 10,000 people among donors, 95% CI 24.3–38.5, versus 3.9 cases per 10,000 people among nondonors, 95% CI 0.8–8.9, $P<0.001$). Analysis of subgroups of donors showed the cumulative incidence of ESRD in the 15 years after donation to be higher among donors who were aged ≥60 years than among those aged 18–39 years at the time of donation, and higher among African American donors than among white donors, but not significantly different between donors who were biologically related to recipients and donors who were unrelated to recipients ($P=0.15$).

This study has three limitations.[39,42] First, the repeated use of healthy nondonors in the matching process might have resulted in underestimation of the incidence of ESRD in nondonors. Second, small imbalances in the measured traits between the two groups remained after matching. Third, the definition of ESRD included addition to the transplant waiting list for donors but not for nondonors; however, this factor would only be a concern if a large proportion of donors who developed ESRD were placed on the waiting list for pre-emptive transplantation but never subsequently received transplantation or dialysis.

Despite their limitations, which should be considered when discussing the above findings with potential donors, these studies have improved our understanding of how donor nephrectomy affects the risk of ESRD. Although these studies had different follow-up periods and potential differences between cohorts, they consistently found an approximately 10-fold relative increase in ESRD among donors, although the absolute risks were <1%. During the informed consent process, physicians can emphasize the low (<1%) absolute expected incidence of ESRD in the 15 years following nephrectomy, while recognizing that for certain donors—such as young male African American donors—the lifetime incidence of ESRD and low eGFR (<30 ml/min/1.73 m^2) might be higher than currently appreciated and requires clarification.

Acute kidney injury

Many patients who develop severe AKI die before they develop ESRD. Few studies have reported AKI among living kidney donors. A study in Sweden reported on one donor (of 451 donors) who developed AKI and subsequently died from heart failure.[35] Another study in Japan described two donors (of 1,519 donors) who developed AKI.[28] One of these donors had acute pyelonephritis and acute tubular necrosis (proven by biopsy) at 11 years after donation, and developed CKD, but did not require dialysis. The other donor developed AKI that was treated with dialysis after a car accident and subsequent cardiogenic shock at 10 months after donation. Although this donor recovered sufficient renal function to stop dialysis, progressive loss of GFR resulted in reintroduction of dialysis 4 years after donation.

Similarly, just one living kidney donor developed AKI that was treated with dialysis in a matched cohort study of 2,027 living kidney donors in Ontario, Canada, who donated between 1992 and 2009 and were monitored for a median of 7 years (maximum 18 years).[43] In this study, information from predonation medical charts was linked to health care administrative databases, ensuring loss to follow-up was <3%. 35% of living kidney donors were siblings of their recipients, 19% were spouses, 14% parents, and 13% children; 13% of donors were unrelated to recipients. The median eGFR before donation was 98 ml/min/1.73 m^2 (IQR 86–109 ml/min/1.73 m^2). A healthy subset of the general population was selected as the comparison group; individuals were excluded if they showed evidence of any medical condition that could preclude donation (for example, hypertension or diabetes). The remaining healthy adults were matched to the donors in a ratio of 10 nondonors to each donor on the basis of age, sex, index date (defined for donors as the date of donation and for nondonors as a randomly assigned date based on the distribution of index dates for donors), rural or urban residence, and income.

The incidence of AKI that was treated with dialysis among donors was statistically no different to that among healthy matched nondonors (Table 1). Neither the incidence of AKI based on laboratory serum creatinine values nor the incidence of nondialysis-requiring AKI could be obtained accurately from the data sources.

This study concluded that AKI that was treated with dialysis was rare among living kidney donors and seemed to occur no more frequently than in healthy matched nondonors. However, the incremental risk of AKI that is attributable to donation could not be precisely defined, given the limited number of events observed.

Nonrenal outcomes for kidney donors

All-cause mortality

At least eight studies have assessed the risk of all-cause mortality among donors compared with that among controls to evaluate whether donation affects long-term survival.[10–12,14,36,44–46] Some have shown that mortality is lower among living kidney donors than among the unscreened general population.[10,11,14,45] One study in Japan reported a 20-year cumulative survival rate of 86% among living kidney donors and 82% among the age-matched and sex-matched general population.[14] Similarly, a study in Sweden reported a 20-year cumulative survival rate of 83% among donors and 79% among the age-matched and sex-matched general population.[45] Although these results are reassuring, they might also be expected given the rigorous screening and selection of donors to ensure good health before donation.

To overcome this selection bias, one study compared long-term survival among 80,347 living kidney donors in the USA with that of an age-matched and comorbidity-matched cohort of 9,364 participants of NHANES III who did not have comorbidities that preclude donation.[12] The median follow-up period was 6 years (IQR 3–10 years). Mortality during the decade after kidney donation was lower among living kidney donors than among the healthy matched nondonors (Table 1).

Use of a longer follow-up period in a different study conducted in Norway showed that the risk of all-cause mortality in the first decade after donation was similar among living kidney donors and healthy matched nondonors, but that the survival curves subsequently diverged.[36] At 25 years after donation, the cumulative all-cause mortality was approximately 18% among donors and 13% among healthy nondonors matched by age, sex, systolic blood pressure, body mass index, and smoking status (adjusted HR 1.3, 95% CI 1.1–1.5, P<0.001).

A study published in 2014 compared mortality among 3,368 donors aged ≥55 years who underwent donor nephrectomy in the USA between 1996 and 2006 with that of healthy matched nondonors selected from participants of the Health and Retirement Study.[46] The median follow-up period was 8 years (IQR 5–10 years). The risk of all-cause mortality did not differ between the living kidney donors and the healthy matched nondonors (Table 1). The same study also found no difference for the composite outcome of death or cardiovascular disease defined as ischaemic cardiac disease, congestive heart failure, stroke or peripheral vascular disease (Table 1).

Cardiovascular disease

Cardiovascular disease is a leading cause of morbidity and mortality for individuals with low GFR in the general population,[4,5] and is the main cause of death

among living kidney donors, accounting for approximately 30–40% of all deaths.[11,36] A study published in 2012 compared the risk of cardiovascular events among 2,028 living kidney donors who underwent donor nephrectomy in Ontario, Canada, between 1992 and 2009 with that of 20,280 healthy nondonors who were matched with similar restriction and matching techniques as those described for the study of AKI that was treated with dialysis.[44] The primary outcome was death or a major cardiovascular event, defined as myocardial infarction, stroke, coronary angioplasty, coronary bypass surgery, carotid endarterectomy, abdominal aortic aneurysm surgery or peripheral vascular bypass surgery.

Donors were at lower risk of death or major cardiovascular events than were nondonors (Table 1). The risk of major cardiovascular events (censoring the observation period for death) was similar among donors and nondonors (Table 1). The follow-up period in this study was relatively short (median 7 years, maximum 18 years). In a subsequent independent study conducted in Norway, a longer follow-up period of 15 years demonstrated a higher risk of cardiovascular death among living kidney donors than among healthy nondonors (Table 1).[36]

Kidney stones

Individuals with a history of kidney stones and a high probability of kidney stone recurrence are often ineligible for kidney donation.[47] Donors would be expected to have a similar incidence of kidney stones as healthy nondonors, but development of a kidney stone after donation might be expected to have more serious consequences than in nondonors, and to require surgical intervention (such as shock-wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy). However, one study of kidney stones in donors suggests otherwise.[48] This study compared the long-term risk of developing kidney stones that were treated with surgical intervention among 2,019 living kidney donors who donated between 1992 and 2009 in Ontario, Canada, with that of 20,190 healthy matched nondonors. The median follow-up time for the donors was 9 years (maximum 20 years). The risk of kidney stones that required surgical intervention did not differ between donors and healthy matched nondonors, and the incidence was below 1% in both groups (Table 1). The risk of hospitalization with a kidney stone also did not differ between donors and healthy matched nondonors (12.1 versus 16.1 events per 10,000 person-years, RR 0.75, 95% CI 0.45–1.24, $P = 0.27$). The development of kidney stones that did not result in hospitalization or surgical intervention was not assessed in this study.

Gastrointestinal bleeding

Patients with moderate to severe CKD are at increased risk of bleeding, particularly gastrointestinal bleeding.[49,50] One study has examined the long-term risk of major bleeding in living kidney donors.[51] This study monitored 2,009 living kidney donors in Ontario, Canada, who underwent donor nephrectomy between 1992 and 2009; the median follow-up period was 9 years (maximum 20 years). In comparison with 20,090 selected healthy matched nondonors, no significant increase in hospitalization for gastrointestinal bleeding was observed among donors (Table 1). Information on the use of medications that increase the risk of bleeding, such as NSAIDs and anticoagulants, was not available, but low usage is expected in the donor population given their general good health. Reassuringly, 98% of donors did not experience a major gastrointestinal bleed in the first decade after donation.

Fractures

Patients with CKD can develop bone and mineral disorders owing to impaired calcium and phosphate regulation, thereby increasing their risk of skeletal fractures.[52,53] In comparison with healthy nondonors, living kidney donors have higher levels of plasma parathyroid hormone, higher fractional urinary excretion of phosphate, lower serum phosphate, lower serum calcitriol levels, and similar serum calcium levels.[54,55] These biochemical changes are similar to those observed in patients with CKD-related bone and mineral disorders.

A retrospective matched cohort study aimed to determine whether the biochemical changes seen after nephrectomy increase the risk of skeletal fractures.[56] In this study, 2,015 living kidney donors from Ontario, Canada, who donated between 1992 and 2009 (median follow-up period 7 years, maximum 18 years) were compared with 20,150 healthy matched nondonors. The incidence of fragility fractures was similar among living kidney donors and healthy matched nondonors (Table 1). The study also found that donors were more likely to receive bone mineral density testing than were nondonors (648 versus 405 tests per 10,000 person-years, $P < 0.001$), although the results of these tests were unavailable. Furthermore, the median age of donors and nondonors in this study was 43 years (IQR 34–50); given that most fractures occur in old age, the duration of follow-up might have been insufficient to detect an increased risk of fracture.

Gout

Reduced renal function is associated with reduced excretion of uric acid, which can result in increased serum levels of uric acid, a potent risk factor for gout.[57–59] As early as 6 months after nephrectomy, serum uric acid levels are 8% higher in living kidney donors than in nondonor controls (mean 315 μmol/l versus 290 μmol/l, $P < 0.001$).[54]

One study examined the risk of gout following living donor nephrectomy by comparing 1,988 living kidney donors from Ontario, Canada, with 19,880 healthy matched nondonors over a median follow-up period of 9 years (maximum 21 years).[60] Living kidney donors were more likely to be diagnosed with gout than were healthy matched nondonors (Table 1). However, the increase in the absolute incidence of gout over 9 years was modest, at just 1.4%. At 20 years, the estimated cumulative incidence of gout was 2% higher in donors than in nondonors (6.8% versus 4.9%). In the same study, prescription records showed that donors were

more likely than nondonors to receive a prescription for allopurinol or colchicine, two medications typically used for the treatment of gout (OR 3.2, 95% CI 1.5–6.7, $P = 0.002$). Ascertainment of gout events was based on administrative database codes; information about serum uric acid and serum creatinine levels were unavailable.

Complications in pregnancy

To date, three main studies have assessed the long-term outcomes for the mother and fetus after kidney donation. The first, published in 2009, used registry data in Norway to identify 326 donors among whom 726 pregnancies were reported, 106 of which were after donation in 69 donors.[61] The analyses, which were adjusted for maternal age, birth order, and year of birth, showed that pre-eclampsia was more common in pregnancies after donation than in those before donation (5.7% versus 2.6%). The incidence of pre-eclampsia among donors was also higher than that among a random sample of the general population from the Norwegian Birth Registry (5.7% versus 3.1%), although the mean maternal age among donors was 5 years older than among nondonors; the comparison of pre-eclampsia among donors and nondonors did not take into account such between-group differences.

The second study reported on 1,085 American living kidney donors, among whom a total of 3,213 pregnancies were reported; 490 pregnancies occurred after donation in 239 donors.[62] The incidences of fetal loss, gestational diabetes, gestational hypertension and pre-eclampsia were higher among women who had pregnancies after donation than among women who had pregnancies before donation.

An important consideration in the interpretation of these two studies is that the risk of complications in pregnancy increases with maternal age. Comparisons between the outcomes of pregnancies before and after donation, even with statistical adjustment, might not clearly delineate the incremental risk that is attributable to donation.

The third study, published in 2015, assessed the risk of gestational hypertension or pre-eclampsia, as well as other maternal and fetal outcomes, in living kidney donors.[63] 85 donors from Ontario, Canada, who underwent nephrectomy between 1992 and 2009, and among whom 131 pregnancies were reported, were compared with 510 healthy matched nondonors, among whom 788 pregnancies were reported. Donors and nondonors were matched according to risk factors for gestational hypertension or pre-eclampsia: age, index date, rural versus urban residency, income, number of childbirths before the index date, and time to the first pregnancy after the index date. The median follow-up time was 11 years (maximum 20 years), and the cohort was similar to cohorts in previous Donor Nephrectomy Outcomes Research Network studies. Living kidney donors were more likely to develop gestational hypertension or pre-eclampsia than were healthy matched nondonors (Table 1). For each independent outcome, the absolute increase in risk for donors compared with nondonors was 3%. No significant difference between the two groups was seen for the incidences of caesarean section, post-partum haemorrhage, preterm birth or low birth weight.

Reassuringly, these studies show that the incidence of severe maternal and fetal outcomes among living kidney donors is low: <1% for maternal and fetal death and <10% for pre-eclampsia and preterm birth before 37 weeks of gestation. Most living kidney donors in these studies had uncomplicated pregnancies after donation.

Risks in unique donor populations

Many of the studies described above report long-term risks for patient populations that mainly consisted of white participants who were sampled from the USA, Canada or Scandinavia. The effects of specific donor characteristics at baseline, such as age at donation, race, and pre-existing comorbidities, warrant further investigation.

Age

As described above, living kidney donors aged ≥55 years do not seem to be at increased risk of death or cardiovascular disease,[46] and a systematic review published in 2015[64] concluded that age alone should not preclude donation, as few adverse donor or recipient outcomes have been associated with age up to 70 years. The review proposes that renal function, comorbidities and overall health should determine the suitability of an older living kidney donor.

The lifetime medical risks for younger donors are less clear.[38,65] Approximately half of ESRD cases occur after age 65 years, and risk factors for kidney disease, such as hypertension and diabetes, can take years to manifest; a higher lifetime incidence of ESRD is expected among young healthy donors than among older donors, as they live with one kidney for longer.[66] However, in a comparison of 39 American adolescent living kidney donors (aged <18 years, mean follow-up period 32 years) with 128 matched adult donors (aged 18–30 years, mean follow-up period 29 years), adolescent donors had similar outcomes to adult donors with respect to survival, reduction in GFR, hypertension, diabetes and proteinuria.[67]

Race

Some comparative data exist on long-term donor outcomes associated with race. One study reported that the absolute increase in the estimated incidence of ESRD in the 15 years following donation, relative to that in healthy controls, was greater among African American donors (an increase of 51 cases per 10,000 people) than among white donors (an increase of 23 cases per 10,000 people).[37] Other studies reported that African American donors were also more likely to be diagnosed with hypertension, diabetes, proteinuria and CKD than were white donors.[68,69] In two other studies, indigenous donors in Australia and Canada were more likely to develop hypertension, diabetes, proteinuria and a reduction in GFR after nephrectomy than were white donors.[70,71]

Pre-existing comorbidities

Some transplantation centres are increasingly accepting donors with pre-existing comorbidities, such as hypertension, obesity, prediabetes and lower eGFR, despite limited availability of data on the long-term medical outcomes for these donors; acceptance practices vary considerably by centre.[72,73] A systematic review that assessed health outcomes of living kidney donors with pre-existing medical conditions found that most studies monitored small numbers of donors, did not include a comparison group, and few reported outcomes beyond 1 year after donation.[74] For example, six studies have monitored donors with pre-existing hypertension ($n = 125$, median follow-up period 2.6 years),[75–80] 10 studies have monitored obese donors ($n = 484$, median follow-up period 2.4 months),[79,81–89] and only one study has monitored donors with a low GFR before donation ($n = 16$, GFR <70 ml/min/1.73 m^3 as measured by inulin clearance, mean follow-up period 1 year).[76]

Two major studies have been published that assessed the risks for living kidney donors with prediabetes at the time of donation. One monitored 444 donors in Japan (mean follow-up period 10 years) and reported that 9.8% of donors (4 of 41 for whom information was available) with prediabetes developed diabetes mellitus compared with 2.4% (8 of 330) of donors without prediabetes.[90] After a mean follow-up period of 7 years, no severe diabetic complications were reported in either group.

The second study matched 45 American living kidney donors who had prediabetes before donation (mean follow-up period 10 years) with 45 donors without prediabetes (follow-up period 10 years);[91] the donors and nondonors were matched according to age, sex, race and year of donation. At follow-up, 16% (7 of 45) of donors with prediabetes developed diabetes mellitus compared with 2% (1 of 45) of donors in the control group without prediabetes (RR 7.0, 95% CI 0.9–54.6, $P = 0.06$). 58% of the donors with prediabetes reverted to normal fasting glucose levels during the follow-up period. Renal function and albuminuria were similar in the two groups.

Conclusions

We strongly support living kidney donation, which is an important option for the treatment of kidney failure that benefits many people with ESRD, their families and society. In this Review, we summarize our current understanding of the long-term medical risks to living kidney donors. Information about the estimated risks of donation, as well as remaining uncertainties, should be shared with potential donors and recipients during the informed consent process. When possible, discussion of the risks should be tailored to the characteristics of individuals.

Overall, living kidney donors have a similar or lower risk of adverse long-term outcomes such as ESRD and mortality in relation to the unscreened general population.[10,11] Although these patterns are an expected consequence of donor selection, such comparisons offer reassurance that donor evaluation and selection is effective.

Similarly, in the first decade after donor nephrectomy, the incidence of all-cause mortality and cardiovascular events among donors seems to be similar to that among healthy matched nondonors,[12,44] as do the risks of AKI that requires dialysis, kidney stones that require surgical intervention, gastrointestinal bleeding, and skeletal fractures.[43,48,51,56] However, evidence suggests that living kidney donors are at greater risk of ESRD than are selected healthy nondonors, although the absolute incidence after 15 years is low. Donors also seem to be at higher risk of gout than are healthy matched nondonors, and female donors might be at increased risk of gestational hypertension or pre-eclampsia, although many women have healthy pregnancies after donation.

Currently, communication of long-term medical risks to potential donors and their recipients varies with transplantation practices,[92] and publicly available information, for example that on the Internet, is inconsistent.[93] We hope that the results from studies highlighted in this Review are used to improve the informed consent process.

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N.N.L. and A.X.G. researched data for the article. N.N.L., K.L.L. and A.X.G. wrote the article. All authors contributed to discussion of the content and reviewed and/or edited the manuscript before submission.