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

AX Garg[1,2,3], N Muirhead[1], G Knoll[4], RC Yang[1], GVR Prasad[5], H Thiessen-Philbrook[1], MP Rosas-Arellano[1], A Housawi[1] and N Boudville[1,6] for the Donor Nephrectomy Outcomes Research (DONOR) Network[7]

[1]Division of Nephrology, University of Western Ontario, London, Ontario, Canada; [2]Department of Epidemiology and Biostatistics, University of Western Ontario, London, Canada; [3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada; [4]Division of Nephrology, University of Ottawa, Ottawa, Ontario, Canada; [5]Division of Nephrology, University of Toronto, Toronto, Ontario, Canada and [6]Division of Nephrology, University of Western Australia, Perth, Western Australia, Australia

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.

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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]

Correspondence: *AX Garg, Division of Nephrology, London Kidney Clinical Research Unit, Room ELL-101, Westminster Tower, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario, Canada N6A 4G5. E-mail: amit.garg@lhsc.on.ca*

[7]Donor Nephrectomy Outcome Research (DONOR) Network Investigators: Neil Boudville, Larry Chan, Amit Garg, Colin Geddes, Eric Gibney, John Gill, Martin Karpinski, Scott Klarenbach, Greg Knoll, Norman Muirhead, Chirag Parikh, Ramesh Prasad, Leroy Storlsey, Sudha Tata, Darin Treleavan, and Robert Yang

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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

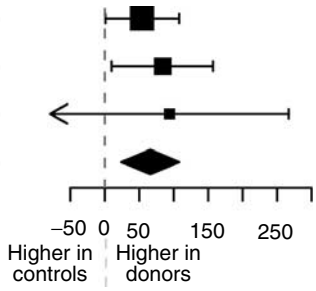
Among the 36 studies of 3529 donors which reported a post-donation serum creatinine or GFR with an estimate of variance, the average time after donation was 6 years, the average serum creatinine was 98 μmol/l (1.11 mg/dl, range 58–119 μmol/l), the average GFR was 86 ml/min (per 1.73 m^2) (range 64–117). 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

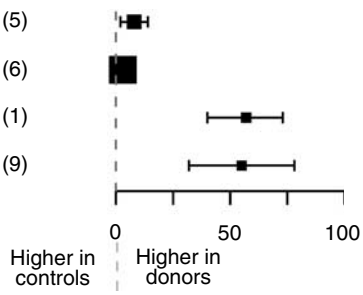
24 h urine protein

Source*	Donors, post-donation: Years after donation, Mean (range)	Donors, post-donation: 24 h urine Protein (mg/day) *N* mean (s.d.)	Controls: 24 h urine Protein (mg/day) *N* mean (s.d.)	24 h urine protein 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)



24 h urine albumin†

Source*	Donors, post-donation: Years after donation, Mean (range)	Donors, post-donation: 24 h urine Albumin (mg/day) *N* mean (s.d.)	Controls: 24 h urine Albumin (mg/day) *N* mean (s.d.)	24 h urine albumin 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)



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)

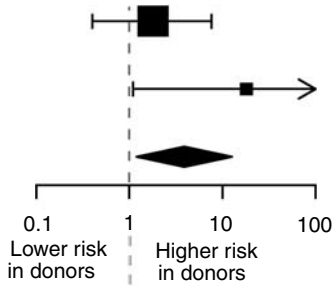


Figure 1 | Controlled studies of proteinuria after kidney donation. The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years after donation. ‡Microalbuminuria was assessed by 24 h urine. †Mathematically pooled results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

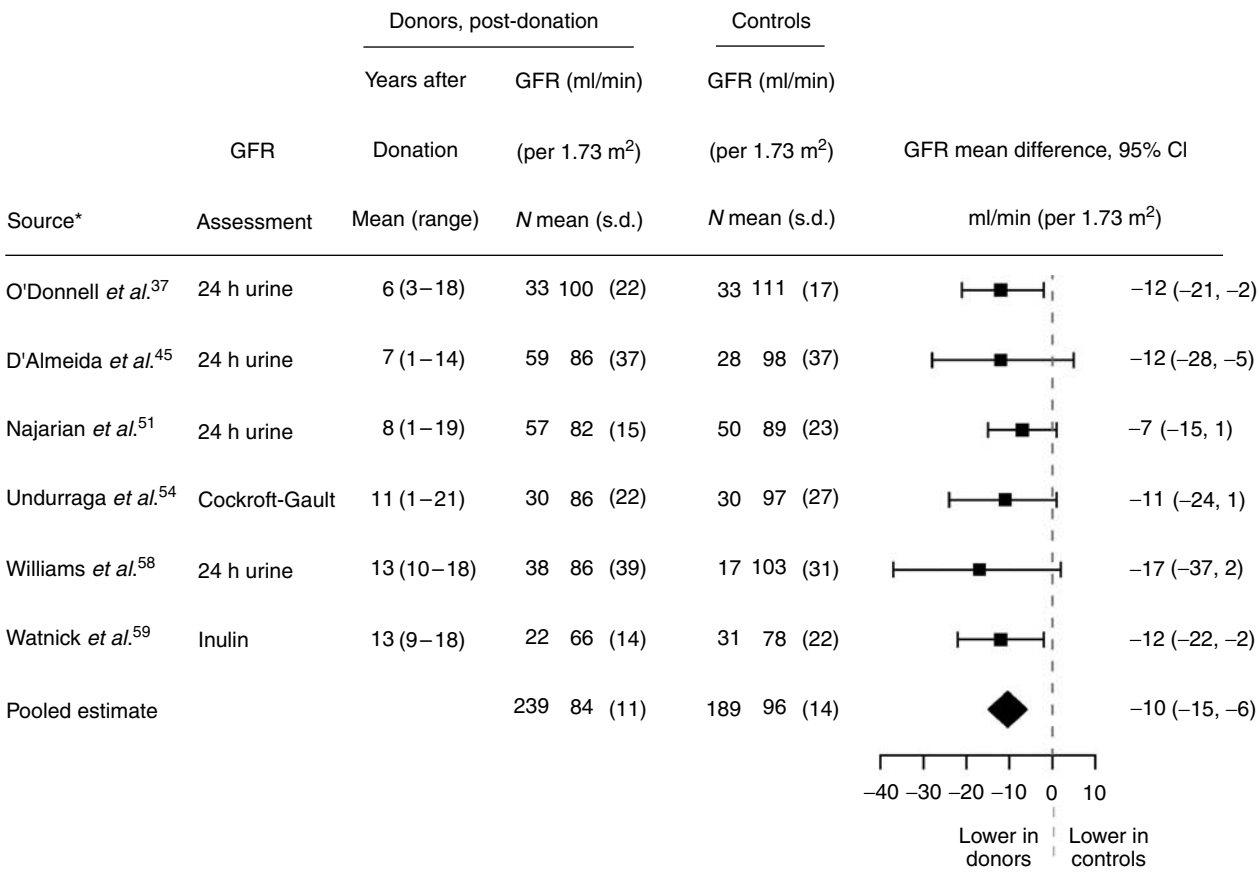


Figure 2 | Meta-analysis of controlled studies of kidney function at least 5 years after donation. GFR – glomerular filtration rate. The size of each square is inversely proportional to the variability of the study estimate. *Studies are arranged by the average number of years since donation.

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 m^2) 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 $SE_{\Delta} = \sqrt{SE^2_{pre} + SE^2_{post}(2 \times \rho_{\Delta} \times SE_{pre} \times SE_{post})}$, 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).

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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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