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More than a decade after live donor nephrectomy: a prospective cohort study

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Summary

Previously reported short-term results after live kidney donation show no negative consequences for the donor. The incidence of new-onset morbidity takes years to emerge, making it highly likely that this will be missed during short-term follow-up. Therefore, evidence on long-term outcome is essential. A 10-year follow-up on renal function, hypertension, quality of life (QOL), fatigue, and survival was performed of a prospective cohort of 100 donors. After a median follow-up time of 10 years, clinical data were available for 97 donors and QOL data for 74 donors. Nine donors died during follow-up of unrelated causes to donation, and one donor was lost to follow-up. There was a significant decrease in kidney function of 12.9 ml/min ($P < 0.001$) at follow-up. QOL showed significant clinically relevant decreases of 10-year follow-up scores in SF-36 dimensions of physical function ($P < 0.001$), bodily pain ($P = 0.001$), and general health ($P < 0.001$). MFI-20 scores were significantly higher for general fatigue ($P < 0.001$), physical fatigue ($P < 0.001$), reduced activity ($P = 0.019$), and reduced motivation ($P = 0.030$). New-onset hypertension was present in 25.6% of the donors. Donor outcomes are excellent 10 years post-donation. Kidney function appears stable, and hypertension does not seem to occur more frequently compared to the general population.

Introduction

In the last two decades, live donors have rapidly become a major source of kidney transplants. The benefits for the recipients of live kidney donor transplantation are clear and include superior transplant quality and timing of the transplantation. While the donor is not the patient, he or she is willingly exposed to harm of the surgical procedure to improve the well-being of another individual. Laparoscopic donor nephrectomy has become the standard of care for live kidney donors [1–3]. This approach has proven to limit discomfort, shorten length of hospital stay, and enable faster recovery with less fatigue and better quality of life (QOL) up to 1 year after donation [4]. As opposed to recipients, donors are often discharged from further follow-up within months after the operation. Data on kidney function are scarce. However, it is unlikely that the donors' kidney function will differ from the kidney function of patients who underwent nephrectomy for other indications. Reports on quality of life show a significant difference 1 year post-donation between different surgical techniques [4]. However, long-term results are rare. Most studies lack baseline data, have a retrospective design, and do not have a prospective long-term follow-up. To establish the surgical

standard of care in this era, we conducted a randomized controlled trial comparing laparoscopic and mini-incision open donor nephrectomy (MIDN) between 2001 and 2004. We previously reported short-term results 3–5 years after donation, demonstrating no difference between different surgical techniques in kidney function, quality of life, and mortality [5]. However, the occurrence of, for example, cardiovascular diseases takes years to emerge. With donors being a group of selected healthy individuals, it is highly likely that this will be missed during a short-term follow-up of less than 10 years. Recent studies demonstrated an increased risk in end-stage renal disease [6] and mortality [7] compared to nondonors. Therefore, evidence on long-term outcome is essential. We now present the prospective data of aforementioned donors who have been followed up annually, with a long-term follow-up of over a decade after donation to evaluate their kidney function, the incidence of new-onset hypertension, mortality, and quality of life.

Patients and methods

Study population

All 100 donors of our randomized trial comparing laparoscopic and mini-incision open live donor nephrectomy were included [4,5]. All donors have preoperatively been screened by a nephrologist, surgeon, social worker, and an anesthesiologist, and underwent imaging by angiography, MRI, or ultrasonography to evaluate the vascular anatomy of both kidneys. If both kidneys were deemed suitable, the right kidney was procured for transplantation. The pre-, intra-, and post-operative procedures were described previously [4]. An amendment to the protocol was written and approved by the internal medical ethics committee to evaluate the 10-year follow-up data of all donors, and a description of the ethical guidelines was followed. Donor survival was checked in the Municipal Registry; 10 years after donation, all donors who were still alive were contacted by mail and telephone to fill out questionnaires on their quality of life and fatigue. Of the deceased donors, the date and cause of death were recorded. Other outcomes were derived from current medical records (Fig. 1).

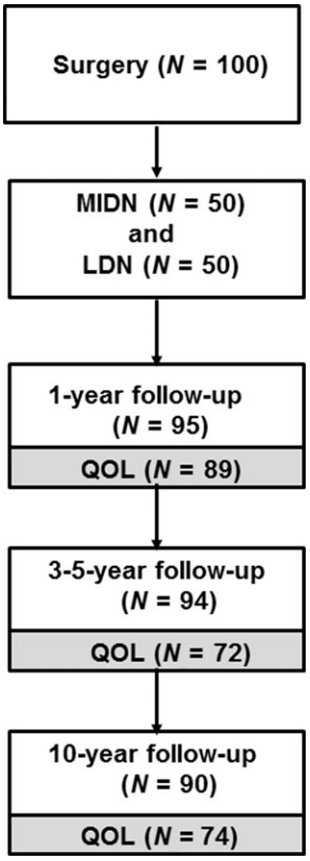

Figure 1 Flowchart of follow-up of 100 randomized live kidney donors. The follow-up boxes correspond with the number of donors of whom annual data on their kidney function and blood pressure were available. The quality of life (QOL) boxes represent the number of donors with available data on quality of life.

Surgical procedures

Donors were operated in two Dutch tertiary referral centers of which 50 were randomized to MIDN and 50 to laparoscopic donor nephrectomy (LDN). Both techniques have been described previously [4].

Data collection

After discharge, the donors visited the outpatient clinic for a follow-up at 3 weeks, 2 months, 3 months, and 1 year. Thereafter, a yearly visit to the outpatient clinic was advised to evaluate kidney function. All donors have prospectively been followed since donation. Data on serum creatinine, blood pressure, weight, used medication, and medical history were collected from the medical records. Hypertension was defined according to the World Health Organization definitions: For donors aged <45: systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg; for donors aged >45: systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg; and/or for both age groups, the use of antihypertensive medication [8]. The estimated glomerular filtration rate (eGFR) was measured according to the Cockcroft-Gault formula [9] .

To evaluate the physical and psychosocial outcome among the donors, they were asked to fill out validated questionnaires on QOL (short form-36; SF-36) and fatigue (multidimensional fatigue inventory-20; MFI-20). Previously, these questionnaires had been conducted preoperatively, at 1 month, 3 months, 6 months, 1 year, and once

between 3 to 5 years [4,5]. For the current study, questionnaires to all donors were sent between 2011–2014 at 10 years after donor nephrectomy. The SF-36 is a validated and commonly used scale to measure health-related QOL in eight health domains: physical function, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Scores for each of these domains range from 0 to 100, with higher scores indicating better QOL [10]. The MFI-20 includes 20 items ranging from one to five, which are divided into five scales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. The total score per scale ranges from 4 (no fatigue) to 20 (exhausted) [11,12].

Statistical analysis

Continuous variables were compared with the Mann–Whitney *U*-test, categorical variables with the chi-square test, repeated variables of the SF-36 and MFI-20 with SPSS mixed models, and other repeated continuous variables (including between-group analysis) with the paired-samples *t*-test. Repeated measures of the SF-36 and MFI-20 were adjusted for baseline values and donor's gender and age. A five-point difference between baseline and follow-up on any health concept of the SF-36 [13] and a ten-point difference between baseline and follow-up of the MFI-20 [14] were considered minimal clinically relevant difference. Survival was analyzed with a Kaplan–Meier analysis, and between-group analysis was performed with a log-rank test. All analyses were conducted using SPSS (version 22, SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 (two-sided) was considered statistically significant.

Results

Between November 2001 and February 2004, donors were randomly selected into two groups: 50 for MIDN and 50 for LDN. The follow-up period was between November 2011 and February 2014. Ninety-four percent of the donors were alive at 10-year follow-up. Donor response rates with regard to the forms increased from 72% at 3–5 years post-donation to 80% at 10 years post-donation. One donor lives abroad and was lost to follow-up. Therefore, annual data on kidney function and blood pressure were available in 90% of the donors. Median follow-up of the population was 10 years (range 2–11 years). Baseline characteristics of the responders are shown in Table 1.

Table 1. Long-term outcomes of donor and recipient. Categorical data are given as numbers (%) and continuous variables as median (range).

Donor	
Female (%)	37 (50%)
Age at baseline (years)	49.0 (20–77)
eGFR (ml/min)	*P* = <0.001
Baseline	89.5 (29.3)
Follow-up	76.6 (26.6)
Hypertension (%)	
Baseline	9 (9%)
New onset	23 (26%)
BMI (kg/m^2)	*P* = <0.001
Baseline	25.9 (4.0)
Follow-up	27.2 (4.3)

Kidney function

As expected, the 10-year follow-up measurements of eGFR were significantly lower compared to the baseline measurements, median 76.6 and 89.5 ml/min, respectively ($P < 0.001$), resulting in a median eGFR loss of 14%. However, the 10-year follow-up measurements of the eGFR of all donors were not significantly different compared to the 1-year measurements, median 76.4 and 76.1 ml/min, respectively ($P = 0.858$). Seventeen donors (18.8%) had an eGFR between 30 and 60 ml/min. Within this group, eGFR at baseline was significantly lower when compared to donors with an eGFR of 60 ml/min or more, a median of 60 and 94 ml/min, respectively ($P < 0.001$). Also, age at follow-up was significantly higher in this group, a median of 75 and 57 years, respectively ($P < 0.001$). No significant differences with regard to body mass index (BMI), gender, and pre-existent or new-onset hypertension were observed within this group.

After 10 years, 35 donors (38%) lost over 6–34% of their creatinine levels as compared to their 1-year follow-up. Within this group, creatinine at follow-up was significantly lower when compared to donors who lost less than the expected 5% of their creatinine, a median of 98.5 and 112.5 ml/min, respectively ($P = 0.004$). None of the donors developed end-stage renal disease (ESRD) or required renal replacement therapy.

Incidence of hypertension

The median systolic blood pressure at follow-up was 130 mmHg compared to 128 mmHg before donation ($P = 0.622$). Donors who did not develop hypertension had a median systolic blood pressure of 125 mmHg at follow-up, which was not statistically significantly different as compared to their systolic blood pressure of 124 mmHg at baseline ($P = 0.359$).

Hypertension pre-existed in nine donors, who were all treated medically, and of which, four donors were involved in a living-related kidney transplantation ($P = 0.064$). These donors had well-regulated hypertension at follow-up. Their median systolic pressure at follow-up was

133 mmHg, which had not increased compared to their systolic blood pressure of 140 mmHg at baseline ($P = 0.307$). One donor still had the same medication, three donors received one additional antihypertensive drug, two donors received two additional antihypertensive drugs, and the other three had switched to other antihypertensive drugs. These donors had a median eGFR of 69.0 ml/min at follow-up.

Twenty-three donors (25.6%) developed high blood pressure 10 years (818 person-years) post-donation, of whom 13 donors were involved in a living-related kidney transplantation ($P = 0.708$). The recipients of six of these donors (46%) were treated for hypertension. There was no significant difference between the incidence and prevalence of hypertension among recipients compared to donors with pre-existing hypertension ($P = 0.682$). Hypertension of all 23 aforementioned donors was adequately treated with medication. Their median systolic pressure was 135 mmHg, which was not different compared to their systolic blood pressure of 133 mmHg at baseline ($P = 0.826$). Ten donors were treated with one antihypertensive drug, 10 donors with two antihypertensive drugs, and two donors with three antihypertensive drugs. Data were missing in one case. These donors had a median eGFR at follow-up of 68.7 ml/min, and the median eGFR in the group of donors without hypertension was 79.9 ml/min ($P = 0.109$). Donors who developed hypertension were significantly older at time of donation when compared with donors who did not develop hypertension, mean age of 57 vs. 45 years, respectively ($P = 0.001$). No significant differences with regard to eGFR at baseline or 1 year after donation and BMI at baseline or follow-up were observed.

QOL and Fatigue

Previous follow-up results showed that all dimensions of QOL had returned to baseline [5]; however, 10-year follow-up scores of the following dimensions were significantly decreased compared to baseline: physical function domain (-7.0, $P < 0.001$), bodily pain (-7.0, $P = 0.001$), general health (-7.1, $P < 0.001$), and vitality (-4.1, $P = 0.028$) (Table 2). However, the latter was not clinically relevant [13]. The SF-36 physical functioning development during 10 years of follow-up of the donors in comparison with the psychical functioning of the general Dutch population of 41–60 years [15] is shown in Fig. 2a. After 10 years of follow-up, the donors had a physical functioning score above the average of the general Dutch population. Compared to the 5-year follow-up, the scores for general health and social functioning at 10-year follow-up showed a statistical difference of -5.1 ($P = 0.013$) and -4.9 ($P = 0.036$), respectively.

On average, donors did not return to baseline during 10-year follow-up for any dimension of the MFI-20: general fatigue ($+2.2$, $P < 0.001$), physical fatigue ($+2.0$, $P < 0.001$), reduced activity ($+1.0$, $P = 0.019$), and reduced motivation ($+0.8$, $P = 0.030$), with the exception of mental fatigue ($+0.1$, $P = 0.807$) (Table 2). However, none of these differences were clinically relevant [14]. The MFI-20 physical fatigue development during 10 years of follow-up is shown in Fig. 2b. Compared to the 5-year follow-up, the

Table 2. Quality of life of 74 live kidney donors after 10 years past donation. Raw data at baseline and 10-year follow-up [estimate (SD)]. Estimated adjusted difference between baseline and 10-year follow-up, 95% confidence intervals and *P*-values for the dimensions of the SF-36 and MFI-20 scales during 10-year follow-up. For the SF-36 dimensions overall scores from the general population with similar age are provided [estimate (SD)].

	Baseline	Ten-year follow-up	General population	Estimated difference*	95% Confidence interval*	*P*-value*
Dimension						
SF-36						
Physical function	92.5 (13.1)	85.5 (16.0)	84.0 (19.6)	−7.0	−10.9 to −3.2	<0.001
Role physical	91.1 (24.7)	89.0 (30.1)	74.5 (36.8)	−1.4	−9.6 to 6.7	0.728
Bodily pain	95.0 (13.6)	88.0 (16.7)	71.8 (24.1)	−7.0	−11.3 to −2.8	0.001
General health	85.1 (13.7)	78.2 (15.5)	69.7 (20.6)	−7.1	−10.8 to −3.4	<0.001
Vitality	79.9 (15.0)	75.8 (17.0)	68.6 (20.2)	−4.1	−7.8 to −0.5	0.028
Social functioning	90.0 (15.6)	89.2 (17.3)	83.5 (22.1)	−0.8	−4.9 to 3.4	0.716
Role emotional	90.0 (24.1)	91.8 (27.8)	81.6 (33.2)	2.4	−5.2 to 10.0	0.539
Mental health	81.1 (13.2)	82.4 (13.8)	75.6 (18.5)	1.3	−1.5 to 4.1	0.345
MFI-20						
General fatigue	6.0 (3.0)	8.3 (3.9)	8.4 (3.4)	2.2	1.4 to 3.1	<0.001
Physical fatigue	5.5 (2.5)	7.4 (3.4)	7.9 (3.7)	2.0	1.2 to 2.8	<0.001
Reduced activities	6.8 (3.1)	7.8 (3.6)	7.9 (3.5)	1.0	0.2 to 1.8	0.019
Reduced motivation	6.3 (2.5)	7.2 (3.3)	7.8 (3.1)	0.8	0.1 to 1.5	0.030
Mental fatigue	7.4 (4.0)	7.5 (3.9)	7.5 (3.2)	0.1	−0.7 to 0.9	0.807

*Baseline compared with 10-year follow-up.

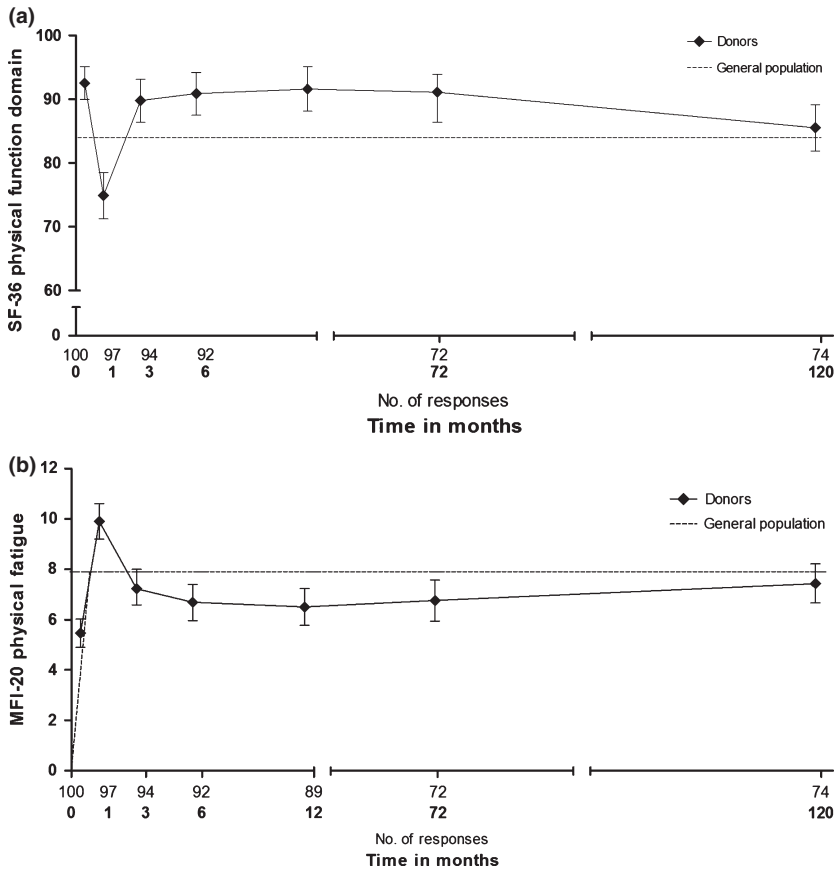

Figure 2 SF-36 physical function dimension of donors and general Dutch population (a) and MFI-20 physical fatigue of donors and general population (b) development during 10 years of follow-up. Points indicate estimate with 95% confidence interval.

reduced activity score shows a statistical difference of −1.2 ($P = 0.012$). All follow-up dimension scores are either better or similar as compared to the general population scores.

Mortality

Nine donors have died according to the longest follow-up. The overall donor survival is depicted in Fig. 3. One donor died after 2 years of follow-up due to a car accident, one died after 4 years of follow-up of metastasized colon cancer, two died after 7 years of follow-up of which one due to metastasized breast cancer and the other of metastasized lung cancer, one died after 8 years of follow-up due to a cerebral vascular incident, one died after 9 years of follow-up due to recurrence of breast cancer, two died after 10 years of follow-up of which one to an aspergillus infection during chemotherapy for acute myeloid leukemia and the other one of a cutaneous malignancy, and one died after 11 years of follow-up due to a ruptured aneurysm of the descending aorta. Of the six donors who died due to malignancies, three donors were related to their recipient. One donor donated to her brother and was diagnosed at age 48 with metastasized breast cancer, a second donor donated to his son and was diagnosed at age 60 with metastasized colon cancer, and the last donor also donated to his son and was diagnosed at age 68 with metastasized lung cancer. None of these donors were tested for genetic origin of their malignancies.

LDN versus MIDN

There was no significant difference between MIDN and LDN donors on the availability of their annual data of kidney function and blood pressure (46 vs. 44) or response rate (37 vs. 37). Neither baseline characteristics including gender, age, eGFR, pre-existent hypertension, and BMI nor long-term results of eGFR, new-onset hypertension, BMI, QOL, fatigue scores, and survival of recipient and graft were different between groups.

Discussion

This prospective study for which data have been gathered during regular, annual, long-term follow-up of donors par-

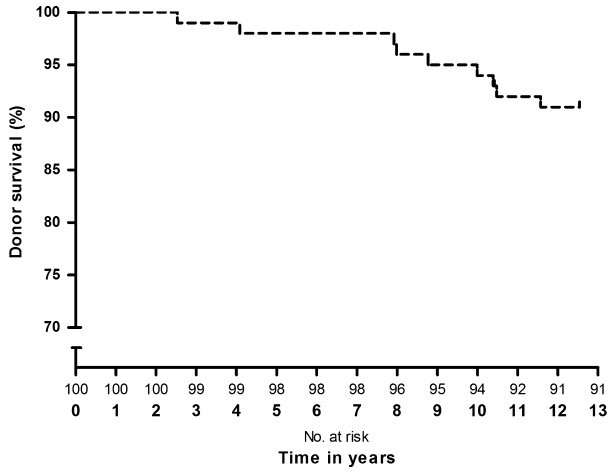

Figure 3 Longest follow-up survival of donors. The numbers at risk are shown on the *x*-axis.

ticipating in a randomized controlled trial includes QOL and fatigue scores and data on renal function, hypertension, BMI, and survival. After 10 years of follow-up, we expected that surgical technique would not influence long-term outcomes. This hypothesis holds. Rather interesting is the outcome of the whole group. Long-term outcome of live donor nephrectomy is excellent from the perspectives of both donor and recipient. The donor retains good quality of life and sufficient kidney function. The recipient has a good chance of 10-year survival with a functioning graft. The response rate was excellent with 80 percent. As the cohort was randomized, baseline characteristics were not expected to significantly differ between groups. On average, live kidney donors have excellent life expectancy, do not have to fear further deterioration of kidney function or an increased risk of hypertension, and have a better quality of life than the general Dutch population [15]. To our knowledge, all other studies have been conducted with a retrospective design. QOL has been polled at different times from donation and analyzed without paired control data in particular.

The median eGFR 10 years after donation was 76.6 ml/min. These results are in line with other studies reporting on a median follow-up of approximately 10 years with similar age range of the donors on follow-up [16–21]. Of all donors, 18.8% have an eGFR between 30 and 60 ml/min, which is a higher percentage compared to a study by El-Agroudy *et al.* [22] of 0.9%. However, as baseline eGFR values were higher in the study by El-Agroudy *et al.*, post-donation values were expected to be higher and the mean age of their donors is less than our donors. Furthermore, the group of donors with an eGFR between 30 and 60 ml/min comprised significantly older donors and donors with an inferior eGFR at baseline. It has been established that nephrectomy will lead to a compensatory increase in eGFR in the remaining kidney to 70% of prenephrectomy values [23]. Donors with low preoperative eGFR before nephrectomy are associated with a low eGFR at follow-up [16,18,20,24]. Najarian *et al.* [25] showed a significant decline in creatinine clearance of live kidney donors after a mean follow-up of 16 years compared with baseline; however, these results did not significantly differ compared to the siblings of these donors. Therefore, the observed decrease in eGFR in our study was expected and in accordance with previous reports. Two studies reported an increased risk of ESRD for donors compared with nondonors. Mjoen *et al.* [7] reported an increased risk after a median follow-up of 15.1 years among 1.901 donors, which was likely caused by hereditary immunological kidney disease. Muzaale *et al.* [6] reported an increased risk of ESRD for donors compared with matched healthy nondonors after a median follow-up of 7.6 years. This study was performed in a much larger cohort of 96.217 donors. However, the increased risk was relatively small and the median follow-up was less than 10 years. Our donors have an annual follow-up on their kidney function, and as opposed to most other studies, we are able to report that eGFR is stable over time at various time points during follow-up. Most other studies did not include this continuous follow-up on eGFR and reported on a single time point. This might be a reason why the kidney function of our donors remains stable. Kidney function deterioration could be detected and monitored at an earlier stage, and if necessary, further investigation can be carried out.

Of all donors, 25.6% were diagnosed with new-onset hypertension. In the current literature, the hypertension rate among live kidney donors after approximately 10 years of follow-up ranges from 8.8% to 48.6% [19,20]. Our results are similar to the majority of the existing literature on live kidney donors [16,18,22,26,27]. Vasan *et al.* [28] showed that in their population-based study, the incidence of new-onset hypertension in their cohort with a mean age of 52 years was 19% after a follow-up of 4 years. Also, with age the incidence of hypertension increased, especially in elderly due to the longer exposure time to develop hypertension. These findings are similar to other concordant literature on population-based studies, where the incidence of new-onset hypertension ranged from 20% to 30% after a follow-up of 4 years [29–31]. Other studies with a longer follow-up up to 10 years showed an incidence of new-onset hypertension of 19–28% [32,33]. These results of nondonors are concordant with our findings. Donors with new-onset hypertension have a mean eGFR of 69.8 ml/min, which is relatively good. All donors had well-regulated hypertension. El-Agroudy *et al.* show a better mean eGFR in their hypertensive donors, in their cohort, but this cohort had higher baseline values and were of younger age. BMI of our donors at follow-up was 27.2 (4.3), which is

comparable with the current literature [17,22]. The existence of prevalent and incident hypertension of donors was not associated with the existence of prevalent hypertension among the recipients. In order to assess the incidence of decreased kidney function and hypertension after donation compared to the incidence in the general population, a matched study comparing live kidney donors and healthy nondonors is required.

Quality of life in general was excellent, and all SF-36 scores were above the average of the general Dutch population of 41–60 years [15]. Previous follow-up results showed that all dimensions of QOL had returned to baseline [5]. However, current results show that donors deviate from their baseline value for the dimensions on physical functioning, general health, bodily pain, and vitality of the SF-36. Most of the MFI-20 scores with the exception of mental fatigue also deviate from the baseline value. However, the average scores are similar to a sample of the general population of 40–59 years [34,35]. The question remains whether this may be considered a general effect of aging, as it has been established that QOL and fatigue depend on age and gender [10,34] or that the measured decrease is the result of living with one kidney. The first explanation might be most likely, as the entire cohort is 10 years older and one would expect all described changes to come with higher age. Although the latter explanation is unlikely, comparison with a matched control group that did not donate a kidney is necessary to provide a definite answer to this question.

Of all donors, 9% died within a range of 2–11 years after donation. All donors died of unrelated causes to donation. This percentage is comparable to previously published results and comparable to the mortality rate in the general population [17,18]. Mjoen *et al.* reported an increased cardiovascular and overall mortality among donors compared to nondonors after a median follow-up of 15.1 years. Only two donors in our cohort (2%) died of vascular causes due to a ruptured aortic aneurysm and a cerebral vascular incident with a kidney function of 135 and 108 ml/min within 1 week before their death, respectively. The majority of the donors (5%) died of malignancies, of which three donors were involved in a living-related kidney transplantation. These malignancies did not appear familial cancers based on family history and age of onset. Specific screening of recipients for these specific malignancies is currently not performed. In the Netherlands, there is a screening program for breast cancer and since a year for colorectal cancer. Therefore, it remains unknown whether their recipients are at risk to develop a malignancy. However, with regular follow-up of the recipients, early recognition of symptoms can be detected.

A possible limitation of this study could have been a response bias. Donors who are not satisfied with the results of the procedure are less likely to respond to a survey. However, as response rates were excellent, even higher than the response rate after 3–5 years of follow-up [5], it seems unlikely that these limitations have influenced the outcome of this study in a major way. Moreover, this cohort of 100 donors is too small to perform subgroup analyses on elderly donors and donors with minor comorbidity, and excess overall risk of donors. Larger databases should be generated to conduct these analyses. Last, there is no age-matched cohort of nondonors with whom the donor cohort can be compared with, which limits the statements on kidney function, QOL, and new-onset hypertension to population-based studies in the current literature.

In conclusion, donor outcomes including QOL and fatigue scores are excellent more than a decade after live kidney donation. Potential donors should not fear major negative changes at the long-term as kidney function appears stable and hypertension does not seem to occur more frequently compared to other live kidney donor studies and population-based studies. Recipient outcomes are excellent. These results are reassuring for the current practice of live kidney donation.

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Authorship

KWJK and SJ: contributed equally to this manuscript. KWJK, SJ, WW, JNMI and NFMK: responsible for the study design. KWJK, SJ, IMMD and NFMK: involved in the acquisition of data. KWJK, SJ, and NFMK: data analyzed. KWJK, SJ, IMMD, WW, JNMI and NFMK: involved in the interpretation of data. KWJK and SJ: drafted the article. IMMD, WW, JNMI, and NFMK: revised the work critically. KWJK, SJ, IMMD, WW, JNMI and NFMK: approved the final version of the manuscript for publication and agree to be accountable for all aspects of the work.

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