LIVE KIDNEY DONATION

LONG-TERM HEALTH-RELATED OUTCOME

Shiromani Janki

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Chapter 1

General introduction

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The kidneys are two bean shaped organs, each about 10cm in length, located under the diaphragm at the rear of the abdominal cavity in the retroperitoneal space behind the intestines. Blood supply is received from direct branches of the abdominal aorta, the left and right renal artery and after filtration the blood drains into the left and renal vein respectively, which connect with the inferior vena cava. Each kidney contains up to a million functioning units called nephrons (Figure 1). A nephron consists of a filtering unit of tiny blood vessels called a glomerulus attached to tubules. When blood enters the glomerulus, it is filtered and the remaining fluid then passes along the tubules. In the tubules, chemicals and water are either added to or removed from this filtered fluid according to the body's need, the final product is the urine we excrete. The kidney is an essential organ, which plays a pivotal role in acid/base balance, sodium/potassium balance, calcium metabolism, regulation of blood pressure, red blood cell synthesis, and excretion of metabolites.

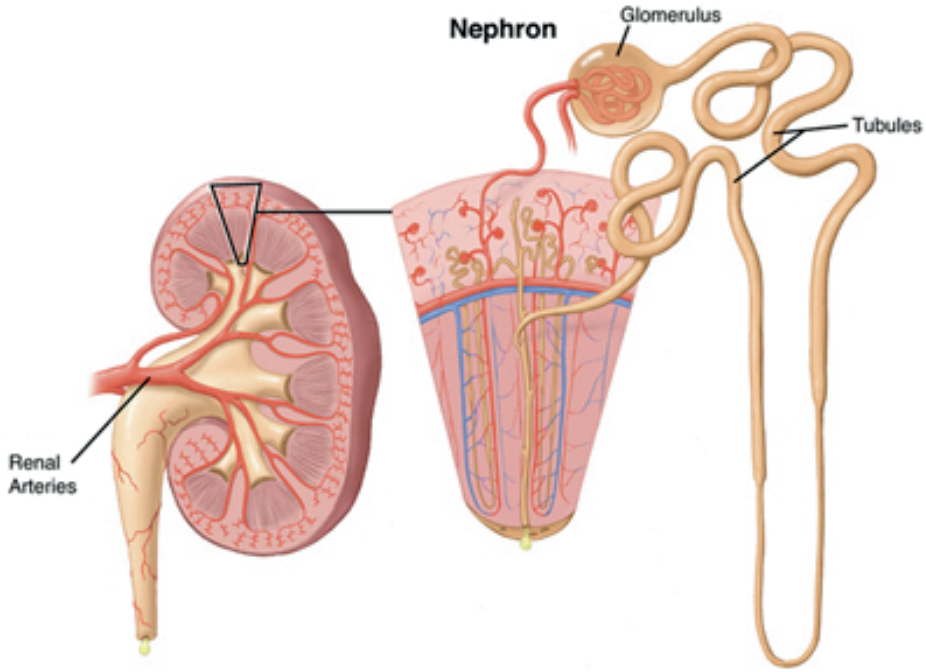

Figure 1. Kidney and nephron

A progressive loss in kidney function could ultimately lead to end-stage renal disease (ESRD), where kidneys are no longer able to remove waste and excess water from the body and patients require renal replacement therapy to survive. Renal replacement therapy may consist of maintenance dialysis or renal transplantation. Renal transplantation offers a better prognosis and long-term benefit to patients with ESRD compared with other renal replacement therapies[1].

In the early 1950s, Rene Kuss and Joseph Murray performed the first successful kidney transplantations using identical twins as live donors in France and the United States, respectively[2,3]. The invention of adequate immunosuppressive therapy in the 1960s enabled deceased donor kidney transplantation, preventing risky operations performed on healthy individuals. As enough deceased donors were present at that time, live kidney donor transplantation was pushed into the background. In the late 1980s and 1990s, a discrepancy between deceased organ demand and supply occurred due to an increasing number of patients suffering from ESRD and a stagnating number of transplants. This prompted renewed interest in live donor kidney transplantation as an alternative. With the increase in the number of live kidney donor transplantations significant benefits over kidney transplantation from a deceased donor were demonstrated: superior organ quality, increased graft survival and the possibility of pre-emptive transplantation[1]. Live kidney donation has been proven to be a safe surgical procedure[4-7] with a very low mortality rate[8,9]. Justified by all these excellent results a significant increase in live kidney donations was observed. Thus, live donor kidney transplantation has helped to narrow the gap between deceased organ shortage and the number of ESRD patients on the transplant waiting list[10]. Nevertheless, a shortage in donor kidneys still remains, and against this background an extension of the donor acceptance criteria was observed in recent years; donors with comorbidities such as cardiovascular disease, obesity and higher age are no longer denied for donation[11,12]. As a result, nearly 30,000 transplants from live kidney donors are annually performed worldwide, and this number has remained stable over the past decade[13,14].

With the extension of donor acceptance criteria we must be attentive to the potential effect on the donor's health, as any harm to the donor has to be prevented. Live kidney donation is possible because of the capacity of the remnant kidney to physiologically compensate for the decrease in kidney function by hyperfiltration and increase in kidney volume[15-21]. Increase in volume of the remnant kidney can be considered as the physiological response to adapt for the decrease in kidney function. To assess which individuals are suitable for live kidney donation potential donors are exhaustively screened by a multidisciplinary team of nephrologists, transplant surgeons and anesthesiologists prior to donation. Medical suitability of the donor is assessed by using criteria defined by the Amsterdam Forum, a group of experts that developed an international standard of care on live donor evaluation in 2004. They set forth a list of all the (relative) contra-indications to live kidney donation. Donors must have sufficient renal function (GFR more than 80 ml/min), no hypertension (less than 140/90), no obesity (BMI less than 35 kg/m^2), negative urine analysis for protein (less than 300mg/24 hours), no diabetes, no kidney stone disease, no malignancy or recurrent urinary tract infections, no or at most a minor cardiovascular or pulmonary risk, no smoking, and no alcohol[22]. In addition to providing

detailed information on the donor's medical history, imaging is of utmost importance in selecting donors. The decision which kidney can safely be donated is largely dependent on imaging results. The guiding principle for this choice is that the donor should remain with the "best" kidney, i.e. the kidney with the lowest long-term risk for the donor. This requires diagnostic imaging by CT or MRI to determine kidney size, vascular anatomy, ureter anatomy, renal cysts or other abnormalities in both kidneys. If there is a significant mismatch in size a renal split function using excretion scintigraphy is indicated.

Live kidney donors are individuals who willingly undergo major surgery to improve the well-being of someone else. Over the years, the discomfort of the operation has been reduced significantly by using minimal invasive procedures resulting in an excellent quality of life after donation. In the past, all live donor kidneys were procured by a 15 to 25 cm flank incision with transection of all abdominal wall muscles[23]. This procedure markedly injured the abdominal wall, resulting in significant postoperative pain, an average hospital stay of one week and prolonged recovery time. Fortunately, renewed interest in live kidney donation occurred in an era in which minimally invasive surgery was gradually replacing conventional surgery. In 1995, Ratner and colleagues performed the first laparoscopic donor nephrectomy[24]. Various alternatives to the laparoscopic approach have been presented since, including hand-assisted laparoscopic donor nephrectomy[4,5], retroperitoneoscopic donor nephrectomy, robot-assisted donor nephrectomy[7], laparo-endoscopic single-site and natural orifice transluminal endoscopic donor nephrectomy. Laparoscopic donor nephrectomy is now considered the gold standard[25].

Studies on short-term follow-up show excellent results regarding kidney function, mortality and morbidity[8,26-28]. It is pivotal to minimize risks and maximize donor safety on short as well as long-term. Three renowned research groups in the field of living kidney donation recently reported unfavourable long-term outcomes for live kidney donors following donation compared to non-donors, including an increased risk for cardiovascular and overall mortality[29], increased risk for ESRD[29,30], and increased risk for gestational hypertension and preeclampsia[31]. However, it should be stressed that the number of events and absolute risks are low, but with the inclusion of more extended donor acceptance criteria the observation may be very relevant. Previous publications from these research groups did not demonstrate unfavourable outcomes detrimental to live kidney donors, as they reported a lower risk of long-term cardiovascular[32] and overall mortality[28,32,33] and lower risk of cardiovascular events[33]. To uncover these contradictory results, the study design and analysis of the three most recent studies and the previous studies from the same research groups were compared in **Chapter 2**.

In 2015, the 1500th live donor kidney transplantation was performed at the Erasmus MC, University Medical Center, Rotterdam, The Netherlands. With the availability of large prospective databases of these donors we have the unique opportunity to study long-term outcome. This donor population consists of prospective cohorts included in three randomized controlled trials on surgical techniques between 2001-2004, 2008-2010, and 2011-2012[4-6]. One hundred donors of the first cohort were included in a randomized controlled trial between 2001 and 2004 in which mini-incision open donor nephrectomy and laparoscopic donor nephrectomy were compared. Laparoscopic donor nephrectomy resulted in faster recovery, less fatigue and a better quality of life compared with mini-incision open donor nephrectomy up to one year after the donation. However, the procedures were equal safe with no difference in graft function[6]. The difference in fatigue and quality of life scores one year after donation warranted longer follow-up and physical and psychosocial outcomes were analysed 3 to 5 years after donor nephrectomy. The results of this study demonstrated no difference between mini-incision open donor nephrectomy and laparoscopic donor nephrectomy in kidney function, quality of life, and mortality[34]. However, the occurrence of, for example, cardiovascular diseases take 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 ten years. Recent studies demonstrated an increased risk for ESRD[29,30] and mortality[29] compared to non-donors. Therefore, evidence on long-term outcome is essential. In **Chapter 3** we present the ten-year follow-up of our previous conducted randomized controlled trial comparing mini-incision open donor nephrectomy and laparoscopic donor nephrectomy.

Driven by its success the acceptance criteria of the living donation program have been extended in the past decade and older donors and donors with minor comorbidities such as hypertension and obesity have become eligible for live kidney donation[14,35-37]. Previous donation outcome studies report on cohorts including low numbers of donors with minor comorbidities. Therefore, these studies do not apply for donors under the current donor acceptance criteria. The second prospective cohort of 190 live kidney donors were included in a randomized controlled trial between 2008 and 2010 in which left-sided laparoscopic donor nephrectomy and hand-assisted donor nephrectomy were compared. This period represents the extension of the living kidney donor acceptance criteria. In **Chapter 4** we present the five-year follow-up of this previous prospective cohort, including live kidney donors who donated with pre-existing minor comorbidities.

The aforementioned two chapters study a selection of the entire Erasmus MC donor population and do not include a matched comparison cohort of non-donors. Studies on long-term outcomes should uncover risk estimates for potential donors and how these risks would change if an individual becomes a live kidney donor. Therefore, comparison

studies with non-donors are important to uncover potential risks additional to donation. Till date there are nine studies in which long-term outcomes are compared between donors and selected non-donors with an average follow-up of ten or more years[29,31-33,38-42]. These studies on long-term follow-up of live kidney donors compared with non-donors demonstrate that the morbidity and mortality increases with the duration of follow-up and subsequent aging. However, these long-term studies have contradictory outcomes regarding kidney function, incidence of hypertension, ESRD and mortality detriment to donors. These inconsistencies represent the differences in the methodology of these studies questioning the comparability of donors and the selected non-donors. Live kidney donors are exhaustively screened prior to donation, resulting in a population that is inherently healthier than the general population. Therefore, selecting non-donors with health similar to accepted donors is difficult and may affect estimates of any potential risks additional to donation. Furthermore, the occurrence of some comorbidities takes years to emerge and might be missed during a short-term follow-up. Thus, in addition to the problem of adequate selection, an extended follow-up period for live kidney donors is important to demonstrate the risks of donation on long-term health[29,30]. Therefore, high quality research is needed.

To increase the sample size of our previous studies and taking in consideration the strengths and limitations of the current literature we designed a comparative follow-up study with individual level patient data that comprises the entire Erasmus MC donor population from 1981 through 2010. Donors are compared with non-donors derived from population-based cohort studies. The aim of this study is to evaluate long-term effects after live kidney donation for the donor regarding kidney function, kidney size **(Chapter 5)**, the incidence of hypertension, the incidence of diabetes mellitus, the incidence of cardiovascular events, cardiovascular and overall mortality, and quality of life when compared to non-donors. The preliminary results of this study are presented in **Chapter 6**. Determining the long-term impact of living donation is an essential part of evaluating the current donor eligibility criteria and further developing and expanding the live kidney donation program.

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LOVE

Chapter 2

Live kidney donation

Are concerns about long-term safety justified? A methodological review

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ABSTRACT

Live kidney donors are exhaustively screened pre-donation, creating a cohort inherently healthier at baseline than the general population. In recent years, three renowned research groups reported unfavourable outcomes for live kidney donors post-donation that contradicted their previous studies. Here, we compared the study design and analysis of the most recent and previous studies to determine whether the different outcomes were due to methodological design or reflect a real potential disadvantage for living kidney donors. All six studies on long-term risk after live kidney donation were thoroughly screened for the selection of study population, controls, data quality, and statistical analysis. Our detailed review of the methodology revealed key differences with respect to selection of donors and compared non-donors, data quality, follow-up duration, and statistical analysis. In all studies, the comparison group of non-donors was healthier than the donors due to more extensive exclusion criteria for non-donors. Five of the studies used both restriction and matching to address potential confounding. Different matching strategies and statistical analyses were used in the more recent studies compared to previous studies and follow-up was longer. Recently published papers still face bias. Strong points compared to initial analyses are the extended follow-up time, large sample sizes and better analysis, hence increasing the reliability to estimate potential risks for living kidney donors on the long-term. Future studies should focus on equal selection criteria for donors and non-donors, and in the analysis, follow-up duration, matched sets, and low absolute risks among donors should be accounted for when choosing the statistical technique.

INTRODUCTION

Live donor kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD). The benefits of this treatment include pre-emptive transplantation, superior organ quality, and increased graft survival[1] and have led to an increase in live kidney donations and consecutive transplants. Despite this increase, the growing demand for donor kidneys cannot be matched, which has led to an increase in the number of extended-criteria live donors with minor comorbidities, such as well-regulated hypertension or higher body mass index (BMI)[2]. As a result, more than 20,000 transplants from live kidney donors are performed annually worldwide, and this number has remained stable over the past decade[3,4].

Live kidney donors are individuals who willingly undergo major surgery to improve the well-being of someone else. It is of the utmost importance to minimize risks, such as the intra-operative risk of bleeding[5,6] and mortality[7], and maximize donor safety during and after donation as well as in the long-term. Live kidney donors are exhaustively screened by a multidisciplinary team of transplant professionals and anaesthesiologists prior to donation, resulting in a cohort that is inherently healthier at baseline than the general population. Therefore, selecting non-donors with baseline health similar to accepted donors is difficult and may affect estimates of any potential risks additional to donation. In addition to the problem of adequate selection, an extended follow-up period for live kidney donors is important for revealing the risks of donation on their long-term health[8,9].

Three renowned research groups recently uncovered unfavourable outcomes for live kidney donors following donation compared to non-donors, including an increased risk of cardiovascular and overall mortality[8], increased risk of ESRD[8,9], and increased risk of gestational hypertension and preeclampsia[10]. The number of events and absolute risks are low. Previous publications from these research groups Oslo University Hospital, Johns Hopkins Medical Institutions, and the Donor Nephrectomy Outcomes Research (DONOR) Network did not demonstrate unfavourable outcomes detrimental to live kidney donors, as they reported a lower risk of long-term cardiovascular[11] and overall mortality[11–13] and lower risk of cardiovascular events[13]. This is remarkable because studies from the same research group largely included the same donor population. We compared the study design and analysis of the three most recent studies and the previous studies from the same research groups.

MATERIALS AND METHODS

Literature search

We searched for studies that reported negative outcomes following live kidney donation using MEDLINE, Embase, CENTRAL (the Cochrane Library 2013), OvidSP, and Google Scholar.

Literature screening

We selected studies published in the last 5 years with an impact factor >15 or high citation rate >20. We found three studies by three different research groups[8–10]. Previously, studies from these research groups reported favourable outcomes following live kidney donation[11–13] in the same donor cohort. The discrepancies in outcomes of these studies have been highly debated within the transplant community.

Outcome

In light of the impact of these studies on the transplant community, we compared the methodology used in the studies and the likely impact on outcomes. The six studies were thoroughly screened by two authors (SJ and JNMI) in regard to the selection of the study population, data quality, and statistical analysis.

RESULTS

Outcome and selection of study population

The Norwegian studies by Mjoen et al. were published in 2012[11] and 2014[8] and report on a single centre experience with contradictory results (Table 1). They studied a consecutive cohort of 2269 donors who donated between 1963 and 2007 at a single centre in Oslo, Norway, where all kidney transplantations in Norway are performed. However, there were important differences in the selection and comparability of donors and non-donors (Tables 2, 3). In the 2014 study, 368 donors were excluded based on antihypertensive medication, blood pressure >140/90 mmHg, BMI >30 kg/m^2, age >70 years or <20 years, macroalbuminuria, or eGFR <70 ml/min per 1.73 m^2. This selection left only the healthiest donors. In the 2012 study, comparison data on non-donors were obtained from the Norwegian background population as provided by Statistics Norway. The 2014 study derived the comparison group from a Norwegian population-based cohort study (Helseundersøkelsene i Nord-Trøndelag, HUNT 1) carried out between 1984 and 1987[14]. However, data on kidney function was not available for non-donors, while donors with low renal function were excluded from the analysis. Though similar donor and non-donor groups were studied, the other two research groups from the US and

Canada reported on different outcomes, including long-term mortality[12], ESRD[9], death and major cardiovascular events[13], and gestational hypertension and preeclampsia[10]. The previous US analysis selected a donor cohort from the mandated national Organ Procurement and Transplantation Network (OPTN) registry. A total of 80,347 donors between 1994 and 2009 with a median follow-up of 6.3 years (maximum 12 years) were included in this study, excluding 36 donors for whom age was not recorded or were <18 years old. For the more recent US analysis the selection period was extended to 2011, increasing the donor cohort by 15,870 donors to a total of 96,217 donors with a median follow-up of 7.6 years (maximum 15 years). Both studies derived their comparison group of non-donors from National Health and Nutrition Examination Survey (NHANES) III participants[12]. NHANES participants were matched 1:1 to live donors with replacement to a predetermined maximum permissible radius. If information on the live donor's BMI or systolic blood pressure was not available, a match was selected with healthy BMI (20–30 kg/m^2) or systolic blood pressure (100–140 mmHg). Sampling with replacement was performed when a matched participant was the only fit despite ideal and radius matching. In the 2012 Canadian analysis, a donor cohort was selected from live kidney donors who donated between 1992 and 2009 in Ontario, Canada, and were permanent residents of Ontario[13]. The 2015 study included female live kidney donors who donated a kidney between July 1, 1992, and April 30, 2010, and who had at least one pregnancy

Table 1. Results of studies comparing live kidney donors to non-donors

Study	Year	Average follow-up, years	Outcome	Risk for donor	Overall results, donors versus non-donors	p-value
Mjoen et al.[11]	2012	14.7	Overall mortality	↓	-	<0.001
			Cardiovascular mortality	↓	-	0.004
Mjoen et al.[8]	2014	15.1	All cause death	↑	HR 1.30 (95% CI 1.11-1.52)	0.001
			Cardiovascular death	↑	HR 1.40 (95% CI 1.03-1.91)	0.030
			End-stage renal disease	↑	302 cases per million; HR 11.38 (95% CI 4.37-29.6)	0.001
Segev et al.[12]	2010	6.3	Long-term mortality	↓	1.5% versus 2.9%	0.001
Muzaale et al.[9]	2014	7.6	End-stage renal disease	↑	30.8 per 10,000 (95% CI 24.3-38.5) versus 3.9 per 10,000 (95% CI 0.8-8.9)	0.001
Garg et al.[13]	2012	6.8	Death or major cardiovascular event	↓	2.8 versus 4.1 events per 1000 person years; HR 0.66 (95% CI 0.48-0.90)	0.010
			Major cardiovascular event	↓	1.7 versus 2.0 events per 1000 person years; HR 0.85 (95% CI 0.57-1.27)	-
Garg et al.[10]	2015	11.0	Gestational hypertension and preeclampsia	↑	11% versus 5%; OR 2.4 (95% CI 1.2-5.0)	0.010

HR, hazard ratio; CI, confidence interval; OR, odds ratio

with a gestation of at least 20 weeks during follow-up. The study population comprised only 88 donors. The non-donor comparison group for both studies was derived from the adult general population of Ontario in the Ontario Registered Persons Database, which contains demographic and vital status information for all Ontario residents. The starting date for follow-up was the date of nephrectomy and assigned as the index date. The donor index dates were randomly assigned to all adult residents of Ontario. Residents were excluded if any medical conditions that could preclude donation were known. For the 2015 study, in addition to previous restrictions depicted in Table 3, women with a previous diagnosis of gestational hypertension or preeclampsia were excluded from the analysis. Furthermore, the index data was extended to ±2 years to account for era effects. Each non-donor could be selected only once, resulting in 380,955 potential female non-donors (52 % of the original sample), though matched sets could be found for only 85 donors.

Data quality

Data for donors and non-donors were collected from pre-existing registries or databases (Table 2). Data were collected prospectively in national registries for live kidney donors in Norway, the US, and Ontario. In addition, the Canadian studies verified the donor data from Ontario's central organ and tissue donation agency, the Trillium Gift of Life, with donor medical records from five major transplant centres. The Canadian studies did not state if there was any discrepancy between the donor registry and medical records. The outcomes were derived from registries in all six studies (Table 2). The Norwegian and Canadian studies, as well as the first US study in 2010, linked both the donor and non-donor data with the registries containing their studied outcomes. All outcomes were specifically coded within the registries. The recent US study in 2014 identified the outcome of ESRD differently for donors and non-donors, potentially leading to information bias. ESRD was defined as the initiation of maintenance dialysis, receipt of a living or deceased donor kidney transplant, or placement on the deceased waiting list. The outcome was ascertained by linkage to medical evidence Form 2728 for the Centers for Medicare and Medicaid Services (CMS). Donors were also linked to the transplant network's kidney waiting list.

Statistical analysis

All studies used both restriction and matching to address potential confounding except for the 2012 analysis by Mjoen et al.[11] (Table 3). The Norwegian research group added restriction and altered their matching method for their 2014 study. Mjoen et al. used Kaplan–Meier analysis without adjustment of confounders in 2012. In 2014, Mjoen et al.[8], reported 31 ESRD events in 9 donors and 22 in non-donors. A majority of the donors who developed ESRD were immediate family members of the recipient. The Cox regres-

Table 2. Selection of live kidney donors and non-donors

Study	Year	Donors (n)	Donor participation (%)	Data collection	Non-donors (n)	Derived from	Average follow-up, years	Data collection
Mjoen et al.[11]	2012	2,269	100	Norwegian Living Donor registry	6,807	Norwegian background population	n.a.	Statistics Norway database
Mjoen et al.[8]	2014	1,901	84	Norwegian Living Donor registry, Statistics Norway, Norwegian Renal Registry	32,621	HUNT 1 1984-1987	24.9	Survey database, Statistics Norway database, Norwegian Renal Registry
Segev et al.[12]	2010	80,347	100	OPTN registry, Social Security Death Master File	80,347	NHANES III	12.0	Survey database, Social Security Death Master File
Muzaale et al.[9]	2014	96,217	100	OPTN registry, CMS, deceased waitlist	96,217	NHANES III	15.0	Survey database, CMS
Garg et al.[13]	2012	2,028	100	Medical records, Trillium database, CIHI-DAD, OHIP database, RPDB	20,280	General Canadian population	6.4	CIHI-DAD, OHIP database, RPDB
Garg et al.[10]	2015	85	97	Medical records, Trillium database, CIHI-DAD, OHIP database, RPDB	510	General Canadian population	10.9	CIHI-DAD, OHIP database, RPDB

OPTN, Organ Procurement and Transplantation Network; CMS, Centers for Medicare & Medicaid Services; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; OHIP, Ontario Health Insurance Plan; RPDB, Ontario Registered Persons Database

Table 3. Comparability of live kidney donors to non-donors

Study	Year	Matched by	Statistics
Mjoen et al.[11]	2012	Restriction: Not performed Matching: 1:3 age, gender, and year of birth	Kaplan Meier analysis
Mjoen et al.[8]	2014	Restriction: Only inclusion of donors with a blood pressure ≤140/90 mmHg, BMI B30 kg/m^2, no antihypertensive medication, age 20–70 years, no macroalbuminuria, and eGFR >69 ml/min per 1.73 m^2. Only inclusion of non-donors with a blood pressure ≤140/90 mmHg, BMI ≤30 kg/m^2, no diabetes or cardiovascular disease, no use of antihypertensive medication, and if participants rated their own health as "good" or "excellent" Matching: By age, gender, year of inclusion, blood pressure, BMI, smoking	Multiple imputation, Coarsed exact matching, Cox regression
Segev et al.[12]	2010	Restriction: Recorded kidney disease, diabetes, heart disease, and hypertension, and who had missing data on any of the four aforementioned criteria were excluded. The excluded participants also included those who answered positively to survey questions regarding "if doctors had told them that they had" heart disease, lupus, cancer, kidney stones or (pre)diabetes; difficulty independently performing physical activities or chest/leg pain while performing physical activities; or no health insurance because of poor health, illness, or age Matching: 1:1 with replacement by gender, ethnicity, and history of cigarette smoking, and radius matching was done on age at donation, educational background, pre-operative BMI, and pre-operative systolic blood pressure	Kaplan Meier analysis; log-rank test between group analysis
Muzaale et al.[9]	2014	Restriction: No change in design Matching: No change in design	Kaplan Meier analysis; log-rank test within group analysis, bootstrap methods between group analysis
Garg et al.[13]	2012	Restriction: Evidence of diagnostic, procedural, or visit codes for genitourinary disease, diabetes, hypertension, cancer, cardiovascular disease, pulmonary disease, liver disease, rheumatological conditions, or chronic infections, a history of nephrology consultation, evidence of frequent physician visits (more than four visits in the previous two years), or any person who failed to see a physician at least once in the two years before the index date Matching: 1:10 fashion on age (within two years), sex, index date (within six months), rural (population less than 10,000) or urban residence, and income (categorized into fifths of average neighbourhood income on the index date)	Log-rank test, Cox regression
Garg et al.[10]	2015	Restriction: Only inclusion of donors who had at least one pregnancy with a gestation of at least 20 weeks during follow-up. No change in design for non-donors. Matching: 1:6 fashion on age (within two years), sex, index date (within ±2 years), rural (population less than 10,000) or urban residence, and income (categorized into fifths of average neighbourhood income on the index date), the number of pregnancies carried to at least 20 weeks of gestation before index date (0, 1, or ≥2), and the time to the first birth after the index date	Generalized linear mixed model

sion analyses for all outcomes including ESRD were adjusted for six confounders: age, gender, year of inclusion, blood pressure, BMI, and smoking. A second adjusted model was created after multiple imputation of blood pressure, BMI, and smoking. This latter model was used for the primary analyses. In contrast, the US and Canadian research groups did not alter the restriction and matching methods for their recent analyses. Although all outcomes were reported differently, as percentages, hazard ratios, or odds ratios depending on the statistical methods used. The US research group performed a Kaplan–Meier analysis in both studies but used a bootstrap method to properly estimate the variance of repeated sampling of nondonors in their most recent study[9]. The crude incidence of ESRD was 9 out of 1901 donors and 17 out of 32,621 non-donors, resulting in 36 cases of ESRD in the nondonor group after matching with replacement. Persons aged ≥65 years, African Americans, and Mexican Americans had an increased risk of ESRD, whereas Caucasian non-donors had no risk of ESRD. In the 2012 study by the Canadian research group[13], differences in baseline characteristics between donors and non-donors were assessed using standardized differences. If these differences were >10 % they would reflect a meaningful imbalance. A two-sided log-rank test stratified on matched sets was used to compare differences in death and cardiovascular outcomes between donors and non-donors. Furthermore, a Cox regression stratified on matched sets was used to estimate hazard ratios with 95 % confidence intervals. In the 2015 study by Garg et al.[10], generalized linear models with generalized linear estimating equations were used to compare the characteristics of donors and non-donors at the index date, and generalized linear mixed models with a random intercept and random effects logistic regression models were used to compare pregnancy characteristics and outcomes. These methods account for the correlation structure within matched sets and in women with more than one pregnancy during follow-up.

Table 4. Overview of bias in selection of study population, data quality, and statistical analysis

	Selection bias			Information bias				
Study	Donors	Non-donors	Risk of donation	Donors	Non-donors	Risk of donation	Confounding	Risk of donation
Mjoen et al.[11]	-	+	Underestimation	+	-	Overestimation	-	n/a
Mjoen et al.[8]	+	+	Overestimation	+	+	Overestimation	+	Overestimation
Segev et al.[12]	-	+	Unclear	+	+	Overestimation	-	n/a
Muzaale et al.[9]	-	+	Overestimation	+	+	Overestimation	+	Overestimation
Garg et al.[13]	-	+	Underestimation	+	-	Overestimation	-	n/a
Garg et al.[10]	-	+	No effect	+	-	Overestimation	-	n/a

+/-, bias present/not present in study

DISCUSSION

Our detailed review of the methodology of the different studies on long-term risk after live kidney donation revealed key differences with respect to the comparability of donors and non-donors in regard to selection, data quality, follow-up, and statistical analysis (Table 4).

Selection of the study population

Donors are a pre-screened healthy selection of the population. This is a key issue to account for when selecting the comparison group of non-donors. Furthermore, the extended donor selection criteria during the past decade[2] complicate restriction rules when including non-donors. Both Norwegian studies are a good example of choosing a more appropriate comparison group when studying the same donor population. In the 2012 study by Mjoen et al.[11], the full Norwegian background population was a comparison group without restriction according to the live kidney donor selection criteria. Therefore, the risk attributable to donation could be underestimated despite matching 1:3 on age, gender, and year of birth to account for confounding. In their 2014 study, Mjoen et al.[8], used the healthiest donors from the earlier study. In addition, more healthy non-donors were derived from a Norwegian population-based cohort study[14]. The restriction rules for donors and non-donors did not entirely lead to a match on renal function, cardiovascular disease, and subjective perception of health, leading to the possible overestimation of risk detrimental to donors because of healthier non-donors.

The US studies used more extensive restriction rules and matching for NHANES III participants compared to the healthier donors. NHANES III participants were derived from 81 counties in the US based on geography and the proportions of minority populations using probability proportionate to size sampling. Young children, persons aged ≥65 years, African Americans, and Mexican Americans were subgroups that were oversampled and were not representative of the donor population, the majority of which is Caucasian (75 %). Both studies used a similar restriction and matching strategy. The entire NHANES III cohort comprised 20,024 adult participants. The excluded group (n=10,660) also contained participants who would be eligible for living donation, presumably making the non-donor group somewhat healthier than the donor population. The 9364 eligible NHANES III participants were significantly younger, more educated, had a higher proportion of women and Caucasians, and had a lower proportion of smokers than the donor population. This difference may have led to an overestimation of risk attributable to donation, which was however not demonstrated in the study by Segev et al.[12]. The 2014 study by Mjoen et al. did demonstrate an increased mortality risk for donors. In the more recent US study, the strict selection of healthier non-donors made them less likely

to develop ESRD. The donor population had significantly higher systolic blood pressure, BMI, and fraction of smokers at baseline, which are all factors associated with an increased risk of ESRD[15]. Thus, the risk attributable to donation was likely overestimated. In a recent study by Grams et al.[16], a proportion of the same aforementioned US donor population consisting of 52,998 live kidney donors was analysed based on their 15-year projected risk of ESRD, which was previously reported by Muzaale et al.[9]. In this recent study, the risk of ESRD among live kidney donors was compared to a meta-analysis of 4,933,314 participants in seven general population cohorts who would be eligible for living kidney donation according to 10 demographic and health characteristics. The average follow-up for these cohorts was 6.4 years and their 15-year risk projections for ESRD were compared among US live kidney donors. The donors had a 3.5–5.3-times higher projected 15-year risk than non-donors. As pointed out by Steiner[17], the previous US study by Muzaale et al.[9] reported an 8-times higher incidence of ESRD among donors than non-donors. This finding supports the notion that the risk attributable to donation was overestimated in that study.

Both Canadian studies used a similar restriction and matching strategy. The extended live donor eligibility criteria over the years have caused the broad exclusion criteria to encompass participants who would be eligible for living donation, making the non-donor group healthier. Furthermore, any person who failed to see a physician at least once in the 2 years before the index date was not included in the analysis in order to ensure that everyone who was included in the analysis had access to health care. This restriction could have led to the exclusion of the healthiest non-donors who did not require any medical attention in the past years and who would be highly eligible for living donation. Nevertheless, this exclusion criterion of healthier non-donors in the Garg et al.[10] study had no effect on the study results in a sensitivity analysis.

Data quality

The strength of the data collection in all studies was that all data were collected mostly from national prospective registries. The Canadian studies even verified donor data with the donors' medical records. However, there were some limitations in the data collection in regard to donor and non-donor medical outcomes and missing additional information on outcomes. Donors could be more aware of their health than non-donors, leading to differential misclassification because all outcomes except for death could have been registered earlier. This could have led to more registered outcomes among donors and an overestimated risk attributable to donation. Non-donor data from the population-based studies included data from surveys, giving a subjective rating of HUNT 1 and NHANES III participants' health. These non-donor data were not verified with medical records, but were used for restriction, which could have led to an underestimation of risk

among non-donors. The 2014 US study prioritized live kidney donors who developed ESRD on the deceased donor transplant waiting list[18]. Pre-emptively placing live kidney donors on the deceased waiting list possibly resulted in more registered donors with ESRD. This was seen in the higher crude incidence of ESRD among donors (99 out of 96,217) compared to non-donors (crude incidence 17 out of 9364). Non-donors who registered pre-emptively on the deceased waiting list were not identified as having ESRD, which caused a delay in the registration of ESRD for non-donors. However, their follow-up was longer than that of donors, and most non-donors would either receive a transplant or initiate dialysis shortly thereafter. Errors in the estimation of outcomes occurred in donors who emigrated; given the large sample sizes in both US studies, this is accepted to have had no material effect on the outcomes of the studies. Moreover, it will not affect the other studies given the high donor participation.

In the Garg et al. 2012 study, data on blood pressure is lacking[19], though previously the same authors demonstrated an increase in blood pressure[20], which increases the risk of cardiovascular events and mortality[21]. Lely et al.[22] pointed out that the severity and gestational age at which preeclampsia and gestational hypertension were diagnosed was not provided in Garg et al.'s 2015 study. Given that the rate of premature birth was not increased, only mild or at-term preeclampsia likely occurred[22]. Although there is an increased risk of preeclampsia and gestational hypertension in donors, the absolute risk is low and the severity of the complications, such as premature birth, are less than expected from a gynaecological point of view.

Follow-up and statistical analysis

Differences between donors and non-donors in regard to comparability and follow-up should be accounted for during the analysis to overcome confounding. Restriction and matching is the first step, but matched sets and comparability should also be taken into consideration during the analysis. In Mjoen et al.'s 2014 study, the starting date of the follow-up for donors occurred decades earlier, causing an increased duration of follow-up, as pointed out by Boudville et al.[23], leading to a maximum follow-up time of 43.9 years for donors compared to a maximum of 24.9 years for non-donors. Boudville et al. suggested that secular changes in individuals' health and health care made the baseline characteristics not fully comparable between the groups and could have resulted in a higher incidence of ESRD among donors. The authors tried to correct for this bias by adjusting for year of inclusion. Furthermore, Boudville et al.[23] raised some concerns about statistical overfitting of the models used. For Cox proportional hazard models, a rule of thumb is to have at least 10 events per added confounder[24]. For the outcome ESRD, there were 31 reported events, but the primary analysis adjusted for six confounders. Both factors could have led to an overestimated risk attributable to

donation. Furthermore, what stands out in the baseline characteristics of the donors and non-donors before any matching or adjustments were performed, as pointed out by Kaplan et al.[25], was the mean age difference of 46.0±11.5 versus 37.6±11.7 years, respectively. The higher age of donors could have been a plausible explanation for their increased risk of mortality. The Norwegian authors later replied that this difference was corrected by using coarsened exact matching in the survival analysis, which created strata of the potential confounders:age, gender, year of inclusion, blood pressure, BMI, and smoking. Donors and non-donors were matched based on these strata, after which the analysis was performed on non-coarsened data. After this matching the mean age of donors and non-donors was 46.0 versus 45.7 years, respectively[26]. For both US studies, Matuchansky[27] pointed out that a different NHANES cohort should have been selected instead of the participants from NHANES III; they proposed that participants in the "continuous NHANES" cohort beyond 1994, up to 2006, would have been a better chronological fit for their study cohort[27]. The US authors replied that the strength of NHANES III lies in its larger sample size, greater number of geographic areas, and availability of mortality linkage beyond 10 years. Furthermore, a limitation of "continuous NHANES" is that it cannot be used for survival comparisons[27, 28]. By using their specific bootstrap, the authors stated that this technique does not lead to bias, and differences in follow-up were accounted for by their use of survival analysis[29]. As pointed out by Gill et al.[30], in an editorial accompanying the study by Muzaale et al.[9], the crude incidence of ESRD was extremely low for NHANES participants: 17 out of 9364. Taken together with the longer follow-up of non-donors, replacement of non-donors with long event-free survival in matched analysis may have underestimated the risk of ESRD in non-donors[30]. The matching technique was also discussed by Matas et al.[15], who stated that matching with replacement could magnify any differences between donors and non-donors[15]. Furthermore, how many times each control was used was not stated. The authors replied that this technique has been established and that a specifically designed bootstrap was created to estimate the variance[31].

Future perspectives

Live kidney donors are individuals who are not patients themselves, and submitting them to a surgical procedure stretches the Hippocratic oath taken by physicians. Although the absolute risks for donors following donation are very low, increased risks seem to exist among live kidney donors compared to non-donors. Risks both during and after donation are taken for granted by live kidney donors to help patients with ESRD[32]. Reduced risk of lifetime dialysis, improved quality of life, and prolonged survival are gained by the recipients[1]. Furthermore, transplantation is far more cost-effective than dialysis[33,34]. Nevertheless, these benefits for kidney transplant recipients should not outweigh the risks for live donors after donation. Therefore, future studies should focus

on long-term outcomes following donation in which the risks for donors are taken into consideration against the risks for comparable non-donors.

CONCLUSION

We conclude that recently published papers still face bias that could have led to a potential overestimation of risk additional to donation. Even if risks are elevated among live kidney donors compared to non-donors, the absolute risks for donors following donation are very low and should therefore not discourage potential donors. Strong points of recent analyses compared to initial analyses are the extended time of follow up after donation, large sample sizes and better analysis, hence increasing the reliability to estimate potential risks for living kidney donors on the long-term. Key problems remain such as that donors are a pre-screened healthy selection of the general population, making it difficult to find an equal healthy unscreened comparison group. Specifically, not all required clinically relevant data are available for potential comparison groups. Selecting a healthier comparison group overestimates the risk additional to donation. Future studies should focus on equal inclusion criteria for donors and non-donors, and in the analysis, follow-up duration, matched sets, and low absolute risks among donors should be accounted for when choosing the statistical technique. Ideally, long-term outcomes should uncover risk estimates for potential donors and how these risks would change if an individual becomes a live kidney donor.

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LOVE

Chapter 3

More than a decade after live donor nephrectomy - A prospective cohort study

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ABSTRACT

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 take 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 non-donors. 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).

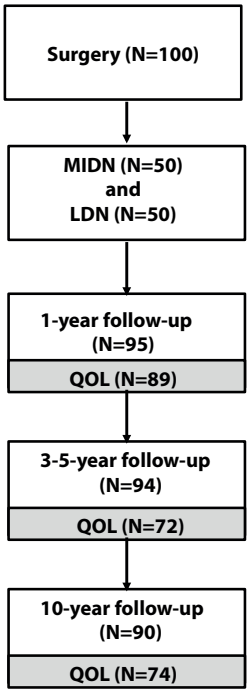

Figure 1. Flowchart of follow-up of100 randomized live kidney donors. The follow-up boxes correspond with thenumber of donors of whom annual data on their kidney function and bloodpressure were available. The quality of life (QOL) boxes represent the numberof donors with available data on quality of 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 years: systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg; for donors aged >45 years: 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 ten 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 percent of the initial cohort was 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

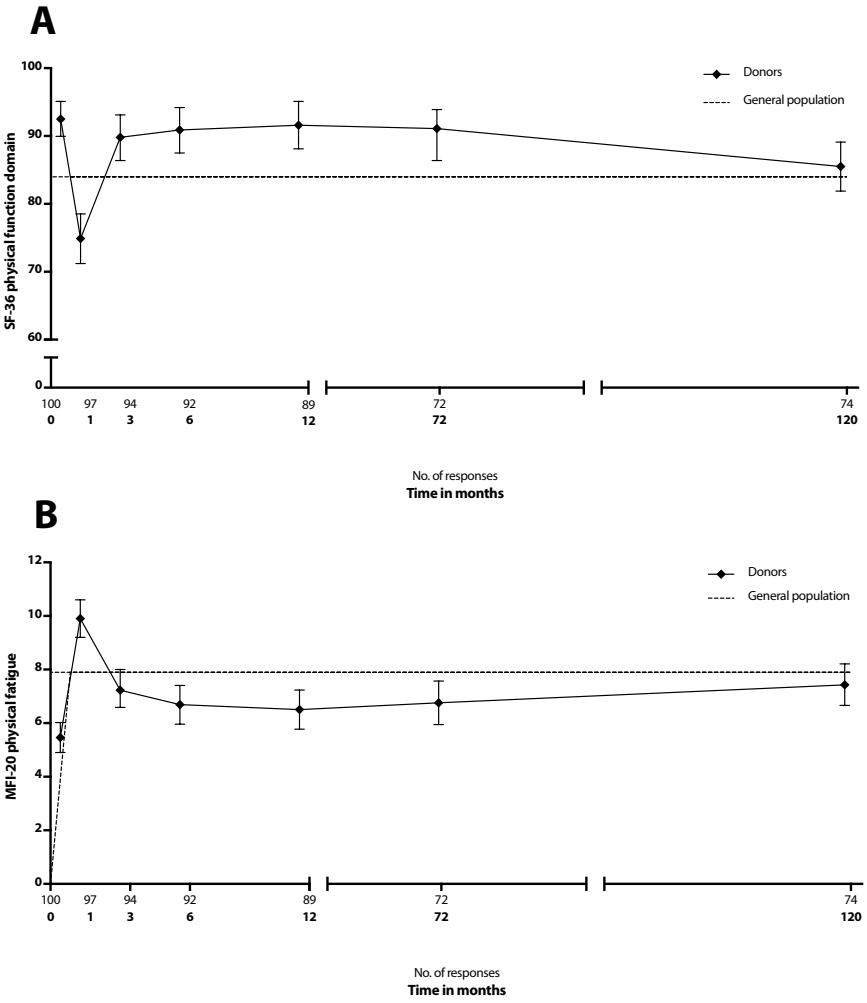

Figure 2. SF-36 physical function dimension of donors and general Dutch population (A) and MFI-20 physical fatigue of donors and general population (B) development during 10 years of follow-up. Points indicate estimate with 95% confidence interval.

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.

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

Dimension	baseline	ten-year follow-up	general population	Estimated difference[1]	95 % Confidence	p-value[1]
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

[1] Baseline compared with ten-year follow-up

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 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.

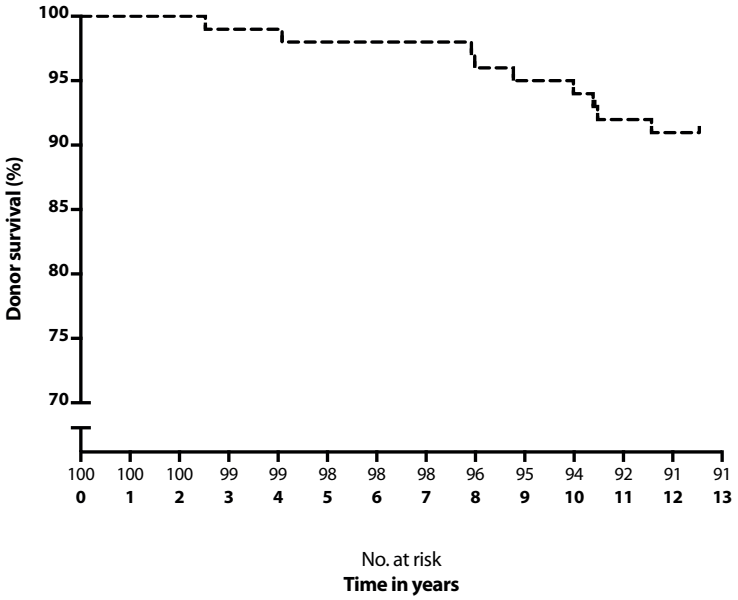

Figure 3. Longest follow-up survival of donors. The numbers at risk are shown on the x-axis.

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 participating 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 pre-nephrectomy values[23]. Donors with low pre-operative 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 non-donors. 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 non-donors 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 non-donors 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 non-donors 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 non-donors 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 non-donors 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.

CONCLUSION

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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LOVE

Chapter 4

Five-year follow-up after live donor nephrectomy - Analysis of a prospective cohort within the era of extended donor criteria

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ABSTRACT

To establish the outcome of live kidney donors five years after donation we investigated the risk for progressive renal function decline and quality of life (QoL). Data on estimated glomerular filtration rate (eGFR), creatinine, hypertension, QoL, and survival were assessed in a prospective cohort of 190 donors, who donated between 2008-2010. Data was available for >90%. The mean age pre-donation was 52.8±11.5years, 30 donors having pre-existent hypertension. The mean follow-up was 5.1±0.9 years. Eight donors had died due to non-donation related causes. After five years the mean eGFR was 60.2 (95%CI 58.7-62.7) ml/min/1.73m^2, with a median serum creatinine of 105.1 (95%CI 102.5-107.8) µmol/L. eGFR decreased 33.6%; and was longitudinally lower among men than women and declining with age ($p<0.001$), without any association on QoL. Donors with pre-existent and new-onset hypertension demonstrated no progressive decline of renal function overtime compared to non-hypertensives. No donors were found with proteinuria, microalbuminuria or at risk for end-stage renal disease. After an initial decline post-donation, renal function remained unchanged overtime. Men and ageing seem to affect renal function overtime, while decreased renal function did not affect QoL. These data support further stimulation of living kidney donation programs as seen from the perspective of donor safety.

INTRODUCTION

Renal transplantation offers a better prognosis and long-term benefit to patients with chronic kidney failure compared with other renal replacement therapies[1, 2]. The benefits of live kidney donation have been well-described[3-6] and the surgical procedure has been proven to be safe[7-13] with a very low mortality rate[13, 14]. In addition, health related quality of life of donors after the procedure has proven to be better than of the general population[7, 8, 10, 15, 16]. Driven by its success the inclusion criteria of the living donation program gradually have been extended and older donors and donors with minor co-morbidities such as hypertension and obesity have become eligible for donation[17-20].

However, it must be noted that live donor nephrectomy is performed on people considered to be healthy individuals who do not need any intervention. Therefore, seeking after optimal donor safety remains priority in living kidney donation for the short as well as the long-term. It has been documented that renal function usually may decline directly after donation and recovers within the first year. Previous studies suggest that renal function reached at one year post-donation remains stable at least for over the next decade[16, 21, 22], but then declines with ageing[21]. These studies report on cohorts including low numbers of donors with minor co-morbidities, such as hypertension and obesity. Therefore, the outcome of these studies may not apply for donors under the donor eligibility criteria used at present.

Previously, we have reported on the one year follow-up of a donor cohort from a randomized study on hand-assisted or laparoscopic donor nephrectomy [10]. Donors were included with hypertension and overweight. We now present data of five-year follow-up and analyzed the effect of potential factors associated with accelerated decline of renal function. In addition, we longitudinally studied the effect of renal function on health related quality of life of live kidney donors.

PATIENTS AND METHODS

Study population

All 190 donors of a randomized controlled trial comparing left-sided hand-assisted and laparoscopic donor nephrectomy conducted between July 2008 and September 2010 at the Radboud University Medical Center, Nijmegen and the Erasmus University Medical Center, Rotterdam were selected[10, 23]. The pre-, intra- and post-surgery procedures were described previously[10, 23]. An amendment to the protocol[23] was written and approved

by the internal medical ethics committee to evaluate the five-year follow-up data of all donors (MEC-2015-653), and a description of the ethical guidelines were followed.

Surgical procedures

Donors were operated in two Dutch tertiary referral centers of which 95 were randomized to hand-assisted and 95 to laparoscopic donor nephrectomy. Both surgical techniques have been described previously[23].

Data collection

Yearly visits to the outpatient clinic or the general practitioner were scheduled. All donors have prospectively been followed since donation. For this study, data were collected from medical records five years after the randomized controlled trial had ended. The data collection included serum creatinine, proteinuria, microalbuminuria, blood pressure, weight, hypertension, medication, and donor survival. A creatinine based estimated glomerular filtration rate (eGFR) was measured with the CKD-EPI equation[24]. Proteinuria was defined as a protein-creatinine ratio of >45 mg/mmol[25] and microalbuminuria as an albumin-creatinine ratio of >30mg/mmol[26]. Blood pressure was manually measured in an upright position in the exam room on one arm. Hypertension was defined as listed as diagnosis in medical records, the use of antihypertensive medication or repeated high blood pressure measurements. Donor survival was checked in the Municipal Registry up to November 13th, 2015 and, if applicable, the date and reason of death was recorded.

Quality of life measures

We used a physical and mental instrument to assess the quality of life, both represented in the Short Form health questionnaire, a validated and commonly used tool to measure health related quality of life. It contains questions on physical performance and well-being, and mental functioning and emotional well-being, resulting in the physical (PCS) and mental component score (MCS) respectively. The SF-12 can be extracted from a SF-36[27, 28]. The component scores are computed by normative comparison and standardized to the Dutch population[29, 30]. Scores below 50 indicates inferior QoL compared to the general Dutch population and scores above 50 indicates superior QoL. The EQ-5D records QoL in five dimensions: mobility, self-care, daily activities, pain or discomfort, and anxiety/depression. The responses on the five dimensions combine to a score between -0.59 (worst imaginable health state) and 1.00 (best imaginable health state)[31]. The SF-36 and EQ-5D questionnaires had been conducted preoperatively at one, three and six months, and one year[10]. For the current study SF-12 and EQ-5D questionnaires were sent to all donors who were still alive five years after the trial had ended.

Statistical analysis

The difference between baseline and follow-up were compared with paired T-tests for continuous normally distributed variables, Wilcoxon's tests for abnormally distributed variables and the Chi-square tests for categorical variables.

Mixed modeling, also referred to as multilevel regression analysis, was applied for longitudinal analyses of renal function and health related QoL. Multilevel regression analysis can efficiently handle data with unbalanced time points and corrects for selective dropout when the dropout is dependent on aspects that are included in the model[32]. First, saturated models were postulated for each of the dependent variables eGFR, creatinine, PCS, MCS, and EQ-5D. The saturated models included age, gender, BMI, pre-existent hypertension, new-onset hypertension, PCS, MCS, and EQ-5D, time, linear, and logarithmic and all interactions with time as fixed effects. The time variables were entered as continuous variables. The deviance statistic[33] using restricted maximum likelihood[34] was applied to determine the most parsimonious covariance structure (unstructured, variance components or intercept only). The saturated model was subsequently reduced by eliminating insignificant fixed effects, taking into account that interaction effects ought to be nested under their respective main effects[35]. The significance of the difference between the saturated model and the parsimonious final model was determined with the deviance statistic using ordinary likelihood. Effect sizes (Cohen's d) were computed by dividing the difference between the estimate at time point t and the baseline score by the estimated baseline standard deviation. An effect size between 0.20 and 0.50 was considered a small effect, between 0.50 and 0.80 a medium effect and above 0.80 a large effect[36]. All analyses were conducted using SPSS (version 22, SPSS Inc., Chicago, USA). Two sided p-values <0.05 were considered statistically significant.

RESULTS

Population characteristics

The living kidney donation procedures were conducted in 93 (48.9%) living-related and 97 (51.1%) non-related donor-recipient combinations. Thirty-two percent of the donors (n=61) had (multiple) extended eligibility criteria: pre-existent hypertension (n=30), age >70 years (n=10), and BMI >30 kg/m^2 (n=26). The follow-up examinations were performed between November 2015 and January 2016. Eight donors had passed away due to non-donation related causes; three out of these eight donors had completed a 5-year follow-up. Five donors were lost to follow-up: one donor lives abroad and four donors were not willing to visit the outpatient clinic for the annual follow-up. Thus, follow-up

data was available in more than 90.0% of donors. Mean follow-up of the population was 5.1±0.9 years. Population characteristics are shown in Table 1.

Table 1. Population characteristics pre-donation and at 5-year follow-up

	Pre-donation (N=190)		5-year (N=176)		
	N	mean±s.d./ median [IQ-range]/ frequencies (%)	N	mean±s.d./ median [IQ-range] frequencies (%)	p-value
Age (years)	190	52.8±11.5	176	58.0±11.1	-
Gender (male)	190	92 (48.4%)	176	82 (46.6%)	-
Caucasian	190	183 (96.3%)	176	170 (96.6%)	-
Creatinine (µmol/L)	190	74 [64 - 83]	173	104 [91 - 118]	p <0.001
eGFR (ml/min/1.73m^2)	190	91.9±15.0	173	60.2±12.1	p <0.001
BMI (kg/m^2)	190	25.9 [23.8 - 28.5]	157	26.7 [24.5 - 30.1]	p <0.001
Systolic blood pressure (mmHg)	189	130 [120 - 144]	167	134 [120 - 145]	p =0.407
Diastolic blood pressure (mmHg)	189	79 [73 - 85]	167	80 [75 - 85]	p =0.005
Hypertension*	170	30 (17.6%)	169	59 (34.7%)	p <0.001
Physical component score (PCS)	178	58.4 [55.8 - 59.8]	169	52.3 [48.3 - 55.5]	p <0.001
Mental component score (MCS)	178	54.4 [52.1 - 56.4]	169	44.2 [40.0 - 49.0]	p <0.001
EQ-5D score	188	1.00 [1.00 - 1.00]	167	1.00 [0.84 - 1.00]	p =0.350

*defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication

Renal function

Only gender and age turned out to have significant effect on eGFR (Table 2). After one year, eGFR values for women decreased significantly with 31.8%, and thereafter remained stable during five years after donation (Table 3). Men had at baseline a small but significantly higher eGFR than women, which decreased with 32.5% after one year, and decreased further to 35.1% after five years. Older patients (e.g. age 10 years older) had lower baseline values, but recovered slightly at the one and five year follow-up. Overall, the five-year follow-up measurements of eGFR compared with the pre-donation measurements, demonstrated a mean decline in eGFR of 33.6%. Longitudinal analysis showed no effect of new-onset hypertension and BMI on eGFR (data not shown). Furthermore, no different outcome in eGFR (p=0.479) or eGFR decline (p=0.159) was found in donors with extended eligibility criteria (n=61) as compared with donors without these criteria.

Table 2. Parsimonious mixed models predicting renal function and quality of life measures

Model	Intercept or main effect		Time linear		Time logarithmic	
	estimate	standard error	estimate	standard error	estimate	standard error
eGFR(ml/1.73m^2)	90.26 ***	1.06	18.70 ***	0.66	-68.40 ***	1.94
men	1.99 *	0.66			-1.86*	0.83
age	-0.83 ***	0.07	-0.13 *	0.06	0.48 **	0.17
Creatinine (umol/L)	67.57 ***	1.25	-19.41 ***	1.18	67.61 ***	3.33
men	15.42 ***	1.81	-5.74 ***	1.67	22.70 ***	4.75
age	0.16 *	0.07			0.15**	0.05
Physical component score	57.02 ***	0.52	-2.43 **	0.75	2.69	2.08
men	0.00	0.74	2.71 *	1.08	-6.71 *	3.02
age	-0.10 ***	0.03				
BMI	-0.40 ***	0.09				
new-onset hypertension	2.30 *	0.89				
Mental component score	52.37 ***	0.58	-3.39 ***	0.58	4.34 **	1.60
men	1.80 *	0.80				
EQ-5D	0.947 ***	0.009	-0.023 *	0.011	0.063 *	0.031
pre-existent hypertension	0.003	0.020	-0.013 *	0.006		
BMI	0.005 *				-0.007 ***	0.002

All models included age, gender, BMI, and pre-existent and new-onset hypertension for all models. In addition, PCS, MCS, and EQ-5D for outcome renal function, and eGFR and creatinine for outcome QoL. Only significant effects are mentioned.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Also for creatinine gender and age were found to have significant effects on renal function (Table 2). After one year, creatinine values for women increased significantly with 40.6%, but this reduced to 35.7% five years after donation (Table 3). Men had at baseline a small but significantly higher creatinine level than women, which increased with 45.1% after one year, and remained stable (43.5%) after five years. Older patients had lower baseline values, and these increased slightly at one and five-year follow-up. Overall, the five-year follow-up measurements of creatinine compared with the pre-donation measurements, resulted in a mean increase of 39.4%. Longitudinal analysis demonstrated no effect of pre-existent and new-onset hypertension, or BMI on creatinine.

The five-year follow-up mean eGFR of men and women are plotted against age categories (n=±20), as depicted in Figure 1 (See Supplement A for corresponding values). The eGFR of the donors are matched to the eGFR of corresponding age categories of the general population[37]. All age categories for men and women demonstrated significant differences in eGFR.

Table 3. Longitudinal analysis of renal function and quality of life

Model	Estimates			Effect sizes (Cohen's d)		
	Baseline	1 year	5 years	Baseline - 1 year	Baseline - 5 years	1 year - 5 years
eGFR (ml/min/1.73m2)						
women	90.3	61.6	61.2	-2.68***	-2 71 ***	-0.03
men	92.2	62.3	59.9	-2.80***	-3.02***	-0.22**
age 10 years older, additional effect[11]	-8.3	-6.4	-6.4	0.18**	0.18***	-0.00
Creatinine (nmol/L)						
women	67.6	95.0	91.7	2.15***	1.89***	-0.26*
men	83.0	120.4	119.1	2.93***	2.82***	-0.11
age + 10 years[1,]	1.6	2.6	4.2	0.08**	0.21**	0.13**
Physical component score						
women	57.0	56.5	49.7	-0.11	-1.45***	-1.34***
men	57.0	54.5	51.2	-0.50**	-1.15***	-0.65***
age 10 years older, additional effect[11]	-1.0	-1.0	-1.0			
BMI 5 kg/m^2 higher, additional effect[11]	-2.0	-2.0	-2.0			
new-onset hypertension[1,]	2.3	2.3	2.3			
Mental component score						
women	52.4	52.0	43.2			
men	54.2	53.8	45.0	-0.06	-1.51***	-1.45***
EQ-5D						
no pre-existent hypertension	0.95	0.97	0.95	0.18	0.02	-0.19
pre-existent hypertension	0.94	0.95	0.88	0.07	-0.55*	-0.62**
BMI 5 kg/m^2 higher, additional effect[11]	0.03	0.00	-0.04	-0.21***	-0.54***	-0.33***

All models included age, gender, BMI, pre-existent, new-onset hypertension for all models. In addition, PCS, MCS, and EQ-5D for outcome renal function, and eGFR and creatinine for outcome QoL. Only significant effects are mentioned.

[1)] This value must be added to the estimate reported above e.g. the eGFR estimate for women at mean age (52.3 years) at baseline is 90.3, and the estimate for 10 years older women (i.e. 62.3 years) is 90.3 - 8.3 = 82.0.

* p<0.05; ** p<0.01; *** p<0.001 Non-significant effects are deleted

Ninety-three donors had an eGFR <60 ml/min/1.73m^2 at five-year follow-up without proteinuria (mean protein-creatinine ratio of 11.3±6.9 mg/mmol) or microalbuminuria (mean albumin-creatinine ratio of 2.5±4.5 mg/mmol). These donors were older at the time of donation (mean 58.3±8.6 versus 47.5±10.6 years, p<0.001) and had a lower eGFR pre-donation (mean 82.3±11.5 versus 101.0±10.7 ml/min/1.73m^2, p<0.001) than donors with a current eGFR of ≥60 ml/min/1.73m^2. In addition, their eGFR decline was higher at five-year follow-up, mean 36.9±8.6 versus 30.0±7.8 % (p<0.001) respectively. However, there were no differences at five-year follow-up in gender (p=0.152) or BMI (p=0.920).

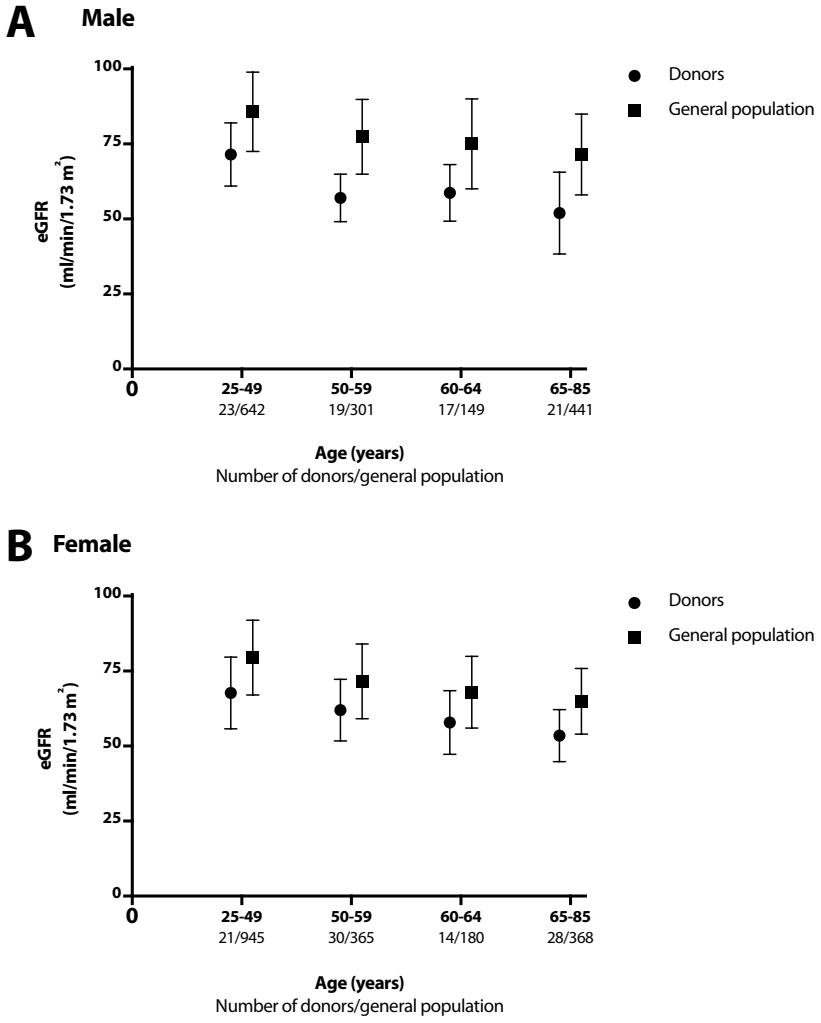

Figure 1. Overview of mean eGFR values at 5-year follow-up after live kidney donation of male (A) and female (B) donors with corresponding eGFR of the general population.

At follow-up none of the donors had proteinuria or microalbuminuria; mean protein-creatinine ratio was 13.5±24.6 mg/mmol and mean albumin-creatinine ratio 2.0±3.6 mg/mmol. No donors were found at risk for end-stage renal disease or renal replacement therapy. Among the 93 living-related donations, 14.7% of the recipients (n=10) had a hereditary renal disease (e.g. Joubert syndrome, polycystic kidney disease). No significant differences in eGFR or protein-creatinine ratio were found among living-related donors with recipients with a hereditary renal disease and other living-related donors, p=0.408 and p=0.490 respectively.

Effect of hypertension on renal function

Blood and urine renal function measures among non-hypertensive and hypertensive donors are depicted in Table 4. The eGFR overtime for non-hypertensive and hypertensive donors is depicted in Figure 2.

Table 4. Effect of hypertension on renal function of live kidney donors

Renal function		Non-hypertensives N=111	Pre-existent hypertensives N=30	New-onset hypertensives N=29
		mean±s.d/medians [IQ-range]	mean±s.d/medians [IQ-range]	mean±s.d/medians [IQ-range]
Blood				
eGFR (ml/min/1.73m^2)	Baseline	94.1 ± 14.8	85.4 ± 12.1	85.9 ± 13.0
	1 year	60.7 ± 11.6	54.4 ± 11.3	53.2 ± 10.2
	5 year	62.3 ± 12.2	57.6 ± 12.2	54.2 ± 9.7
Creatinine (µmol/L)	Baseline	74 [56-92]	76 [58 – 104]	73 [45 – 101]
	1 year	106 [81 – 131]	112 [94 – 130]	112 [84 – 130]
	5 year	102 [75 – 129]	103 [73 – 134]	119[84- 153]
Urine				
Protein-creatinine ratio	5 year	8.7 [2.7 – 14.7]	11.8 [1.8 – 21.8]	8.5 [5.2 – 11.8]
Albumin-creatinine ratio	5 year	0.9 [-0.5 – 2.3]	1.9 [-4.3 - 6.3]	1.4 [0.1 – 2.7]

Thirty donors (17.6%) had pre-existent hypertension compared with 59 donors at follow-up. The five-year eGFR and serum creatinine of donors with pre-existent hypertension was not significantly different from these values of non-hypertensive donors, p=0.062 and p=0.533 respectively. Donors with pre-existent hypertension were adequately treated after donation and showed no abnormalities at follow-up, having a mean systolic blood pressure of 138.9±17.6 mmHg and a mean diastolic blood pressure of 83.5±9.2 mmHg. Treatment consisted of beta blockers (n=16), diuretics (n=12), calcium chain blockers (n=5), ACE inhibitors (n=5), ATI inhibitors (n=5), and other (n=1). Ten donors used one medication to regulate blood pressure. During follow-up of donors antihypertensive medication was unchanged in nine, dose adaptation or combined drug treatment in eight, complete drug substitution in five, cessation of medication in three, and dose reduction in two Of two donors it is unknown if the medication has altered compared to pre-donation use, and of one donor the use of medication is unknown.

Twenty-nine donors developed new-onset hypertension with a mean systolic blood pressure of 141.7±17.3 and a mean diastolic blood pressure of 83.1±7.9 mmHg. They were mostly treated with medication, including beta blockers (n=7), diuretics (n=5), calcium chain blockers (n=3), ACE inhibitors (n=10), and ATI inhibitors (n=7). One donor used three medications, eight donors used two medications, fifteen donors used one

medication, four donors did not use medication, and of one donor the number of medications is unknown. The five-year eGFR and serum creatinine of new-onset hypertensive donors were significantly different compared to non-hypertensive donors, p=0.001 and p=0.015 respectively, while the eGFR decline was not significantly different 36.6 versus 33.4 % (p=0.073), respectively. New-onset hypertensive donors were older at the time of donation (59.0±8.7 versus 50.4±11.2 years, p<0.001) with a higher BMI (27.6±3.7 versus 25.9±3.4, p=0.021), and lower eGFR before donation (85.9±13.0 versus 94.1±14.8 years, p=0.007) compared with non-hypertensive donors. Furthermore, there were more donors with an eGFR <60 ml/min/1.73m^2 with new-onset hypertension compared with non-hypertensive donors, 79.3 versus 43.5% (p=0.001), respectively.

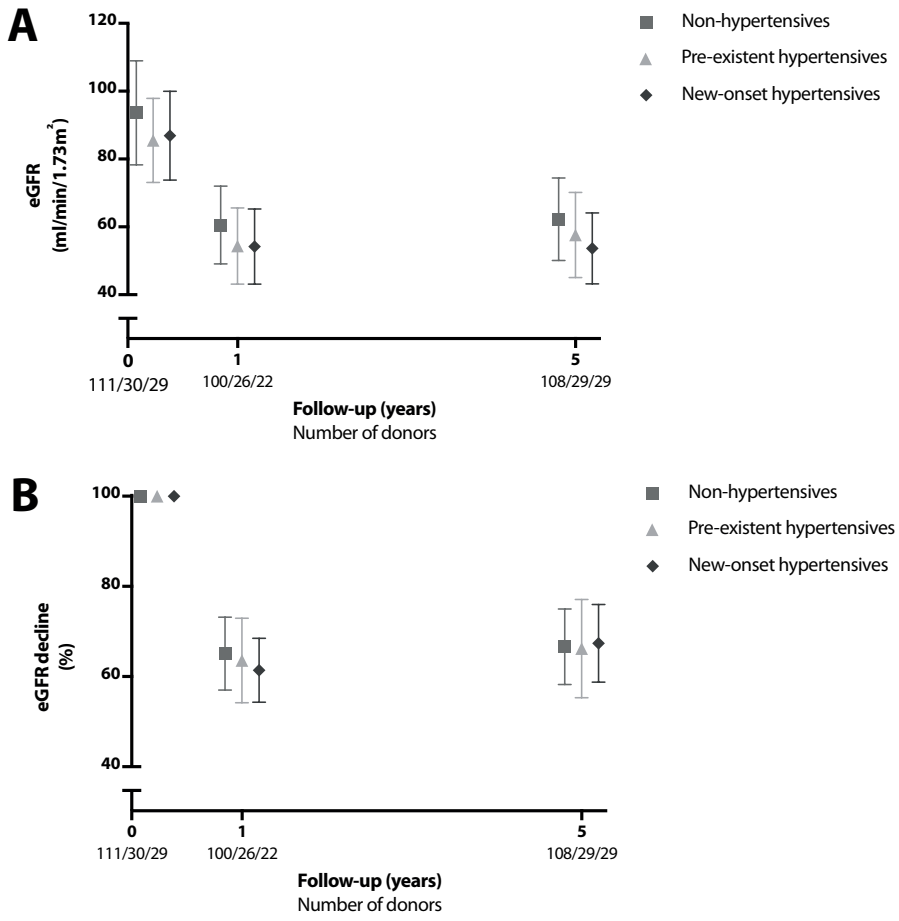

Figure 2. Renal function (A, eGFR overtime; B, eGFR decline) during follow-up of non-hypertensive, preexistent hypertensive, and new-onsethypertensive donors overtime.

Health related quality of life

Donor response with regard to the quality of life questionnaires was almost 90% of the original cohort. PCS and EQ-5D follow-up scores were higher compared with the general Dutch population[29, 30]. MCS scores were lower (Table 1). There were no significant differences in PCS, MCS and EQ-5D score at five-year follow-up between donors with an eGFR <60 ml/min/1.73m^2 compared with an eGFR ≥60 ml/min/1.73m^2, p=0.993, p=0.754, and p=0.242 respectively. There was also no significant difference in MCS at five-year follow-up among living-related donors for recipient (p=0.837) or graft survival (p=0.894).

Longitudinal analysis of health related quality of life

No change in PCS was observed in women after one year, but they had a large decrease five years after donation. Men had a medium decrease at one-year with a further reduction at five-year. Older donors and donors with a higher BMI had lower PCS over the whole period. Donors who developed new-onset hypertension had higher PCS pre-donation and during follow-up. In all donors a large decrease in MSC was observed after five years. MCS scores remained stable at one-year follow-up, but showed a large decrease at five-year follow-up. Men had slightly higher MCS than women pre-donation and during follow-up. Donors had a small decrease in EQ-5D values after one year, but this difference was not significant at the five-year follow-up. Donors with a pre-existent hypertension had a medium decrease at one and five-year follow-up. Donors with e.g. 5 kg/m^2 higher BMI had relatively lower baseline EQ-5D scores, which reduced further to a medium decrease at five-year follow-up (Table 3). No significant effect of age or gender on EQ-5D scores was found.

Survival

Eight donors died due to non-donation related causes. One donor suddenly died at home within one year after donation due to an unknown reason after coughing up blood (age 75, unrelated donation); four donors died after 4 years of follow-up, one for unknown reason (negative findings at autopsy; age 24, related donation), one due to sudden cardiac arrest (age 62, unrelated donation), one due to a malignant mesothelioma (age 67, unrelated donation), and one due to a brain tumor (age 65, unrelated donation); two died after 5 years of follow-up, one due to lung cancer (age 56, related donation) and one due to sepsis (age 63, related donation); finally one died after 6 years of follow-up due to decompensated alcoholic liver cirrhosis (age 66, related donation).

DISCUSSION

This study reports on a prospective cohort of 190 donors that were followed annually after living kidney donation up to five years after the randomized trial had ended. Data were available of more than 90% of donors. This study demonstrates a stable renal function five years after donation with no progressive decline in function. Also, donors with pre-existent and new-onset hypertension do not have a progressive decline during follow-up. Furthermore, no proteinuria or albuminuria was observed in any of the donors, not even in donors with an eGFR <60 ml/min/1.73 m^2. This supports the assumption that live kidney donors are a highly selected group of healthy individuals who may safely proceed in life with one kidney and the values on eGFR and creatinine outside the normal range for individuals with two kidneys do not indicate any physiological dysfunction, since secondary signs of kidney disease such as proteinuria are not present. These findings support the recommendation of Matas et al. that kidney donors with an eGFR <60 ml/min/1.73m^2 should not be classified as having chronic kidney disease, especially if there are no other signs of kidney disease present[38].

Renal function

Our study demonstrates that lower eGFR after donation is longitudinally associated with older age and male gender, and cross-sectionally with lower pre-donation eGFR levels. All three factors can easily be explained. The CKD-EPI equation[24] used to calculate the eGFR, has age and gender embedded in the equation. Therefore, ageing will result in a lower eGFR, while the serum creatinine remains stable. This is comparable to the findings in the general population. Second, muscle mass, which is different between males and females, influences serum creatinine levels and is therefore responsible for the difference in eGFR. Last, there is an expected decline in eGFR levels among donors after donation, therefore lower pre-donation eGFR levels will result in lower post-donation levels. Thus, by definition donors with a lower eGFR levels will have lower eGFR levels at follow-up. In our study no donors had any signs of glomerular dysfunction such as proteinuria or microalbuminuria, not even donors with an eGFR <60 ml/min/1.73m^2.

Other studies reporting on renal function following donation also reported on a stable renal function after one year[39-44], with a decline in renal function of 31-40%[43, 44]. Despite that our cohort is older compared with most studies and has included a higher number of hypertensive donors with a higher pre-donation eGFR, the decline fits the lower range. The renal function of the general population age categories[37] was found to be higher than our donor cohort. It should be noted that hypertensives were excluded from their analysis, which could have led to a higher renal function among the general popu-

lation. Furthermore, the renal function was calculated using the MDRD[45]. Nowadays the CKD-EPI equation is used, which is more accurate compared with the MDRD equation[24].

Effect of hypertension on renal function

Ageing and hypertension are reported to be associated with progressive decline in renal function in the general population[46-50]. These factors are part of the extended eligibility criteria of live kidney donors indicating that they would even have an increased risk with just one kidney and no renal reserve left. Our study demonstrated that in cross-sectional analysis new-onset hypertensive donors have a significant lower eGFR and higher serum creatinine at five-year follow-up than non-hypertensive donors, while eGFR decline was similar. More importantly, longitudinal analysis demonstrated no effect of new-onset hypertension on eGFR. Furthermore, the incidence of hypertension is known to increase with age[51], which is supported by our finding that hypertensives were significantly older compared to non-hypertensives. The used definition of hypertension embeds the use of antihypertensive medication[52], which could include donors who were prescribed antihypertensive medication for a different indication than hypertension, such as a cardiac condition (beta blockers, diuretics, or ACE-inhibitors). The use of antihypertensive medication can influence the renal function, such as ACE-inhibitors, which could decrease or remove proteinuria, or increase serum creatinine, and diuretics, which could increase the serum creatinine, resulting in a lower eGFR. This could have affected our renal function results among hypertensive donors. Reassuringly, as in previous studies[40-44, 47, 53], we found no evidence of further decline in renal function after one year, no proteinuria or albuminuria, and no donors at risk for end-stage renal disease.

Health related quality of life

EQ-5D scores remained at the same level after five years of follow-up. Physical and mental component scores decreased after five years, but the PCS remained higher than the general population scores[30], the MCS at five-year follow-up was lower. The overall decrease in all measures overtime is a phenomenon that has also been observed in the general population[30]. It has been established that quality of life depends on both age and gender[30, 54]. This was true for the PCS where differences were found in age and gender, but also in BMI. The latter is known to be associated with a decreased quality of life among the general population[55, 56]. Reassuringly, the PCS was not affected by a decreased eGFR <60 ml/min/1.73m^2, which is known to decrease physical functioning[57]. Unfortunately, the overall decrease for MCS was larger overtime compared to the general population[30]. This could not be explained by age or BMI. MCS was not affected by recipient or graft survival among living related donors. However, some respondents did report to have mental difficulties due to problems at work, or death of a partner or family member. This might explain the lower MCS for some donors, but this was not a sufficient explanation

for the overall lower MCS at five-year follow-up. This may be explained by assuming that donors are mentally affected by other (medical) conditions not related to donation or life events. It must be noted that while donors are a pre-selected group of individuals, their quality of life follow-up scores are within the range of the general population.

Strengths and limitations

The strength of this study is the extensive pre-donation and follow-up data from a prospective cohort of live kidney donors, who annually visited a physician and whose changes in medical condition were recorded. Only 2.6% of the donors were lost to follow-up. Previous studies[58, 59] have indicated that donors lost to follow-up are healthier than donors attending timed control visits. The quality of life questionnaire response was more than 90%, and it seems unlikely that donors who were not satisfied with the results of the donation were less likely to respond to the questionnaire. Therefore, both limitations could not have influenced the outcome of this study in a major way. A limitation that should be mentioned is the lack of a matched control group of non-donors limiting the statements of the decline in renal function, incidence of hypertension, and quality of life to population-based studies. Furthermore, the relatively small number of donors in our cohort limits us to perform subgroup analysis. Finally, the eGFR used as a measurement for renal function is merely an estimation and could underestimate the renal function for leaner or bigger persons. Furthermore, the eGFR is less accurate in the higher renal function levels. The better the kidney function, the less accurate the predictive value of the eGFR. Also, the eGFR is not validated for individuals with a mono kidney. A GFR from a 24hrs urine sample would be more accurate.

Future perspectives

Of course, it is possible for donors to develop a medical condition that could cause deterioration of the renal function to ESRD[11, 12, 60]. Two recent studies reported that donors have an increased risk for ESRD than non-donors[61, 62]. While their follow-up was longer than our study, the establishment of the results and more importantly the subsequent limitations of these studies should be taken into consideration by transplant professionals before indiscriminately repeating these results to the next potential donor in the consulting room. Especially, considering the impact of these studies[61, 62] among the transplant community. Selection criteria for non-donors were not equal to donors leading to a healthier group of non-donors. Furthermore, due to the low incidence of ESRD, both analyses overadjusted for potential confounders. Both limitations could have led to an overestimation of risk additional to donation[63]. Reassuringly, both studies reported low absolute risks for ESRD among donors, which should be the main message for potential new donors. One should bear in mind that donors with a decreased renal function are no patients with renal insufficiency. Individuals are categorized as having

chronic kidney disease if the eGFR is below 60 ml/min/1.73m^2. Furthermore, among these individuals secondary signs of kidney disease such as proteinuria are usually present. It is unfair to categorize donors within this group, unless other signs of kidney disease are present. Annual follow-up of live kidney donors is recommended to detect any loss of renal function. Future studies are indicated to identify those individuals at risk for a progressive loss of renal function after kidney donation[64].

In conclusion, we report a stable renal function after five years of follow-up among live kidney donors in the era of extended live kidney donation eligibility criteria, which seems to be maintained after an initial decline post-donation. Ageing, gender and hypertension seem to be associated with a lower renal function among donors, which is similar for the general population. There was no evidence for end-stage renal disease among donors or other additional signs of renal dysfunction. These results reassure the current practice of live kidney donation and a conscientious follow-up of live kidney donors should be maintained after donation. Future studies are indicated to identify those individuals at risk for a progressive loss of renal function after kidney donation.

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Supplement A. The 5-year follow-up mean eGFR of male and female donors with the eGFR of corresponding age categories of the general population

Age (years)	Donors		General population			
Male	N	Mean ±s.d.*	N	Mean ±s.d.*	$t_{(df)}$	p-value
25-49	23	71.5 ±10.5	642	85.7 ±13.2	$6.33_{(24.6)}$	<0.001
50-59	19	57.0 ±7.9	301	77.4 ±12.5	$10.41_{(24.1)}$	<0.001
60-64	17	58.7 ±9.4	149	75.0 ±15.0	$6.29_{(26.4)}$	<0.001
65-85	21	52.0 ±13.7	441	71.5 ±13.5	$6.39_{(21.9)}$	<0.001
Female						
25-49	21	67.7 ±12.0	945	79.5 ±12.5	$4.45_{(21.0)}$	<0.001
50-59	30	62.0 ±10.3	365	71.6 ±12.5	$4.80_{(36.4)}$	<0.001
60-64	14	57.9 ±10.6	180	68.0 ±12.0	$3.40_{(15.7)}$	0.004
65-85	28	53.5 ±8.7	368	64.9 ±11.0	$6.55_{(33.8)}$	<0.001

* eGFR (ml/min/1.73 m^2)


LOVE

Chapter 5

Follow-up after living kidney donation: validation of ultrasonographic kidney volume measurements

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ABSTRACT

To investigate the kidney selection procedure prior to donation to maximize donor safety, we investigated whether ultrasound measurements for kidney volume are comparable with CT measurements. Pre-donation volume and increase in kidney size may be an important indicator for renal function after donation and subsequent loss of function. Consecutive donors, with a pre-donation CT-scan, were approached preoperatively for additional ultrasound examination. Measurements were independently performed by two ultrasonographists (US-1; US-2) and considered accurate when the mean differences between both ultrasonographists for length, width and thickness of the kidneys were <5 mm. Ultrasound volumes were calculated with the ellipsoid equation (length x width x thickness x $\pi/6$) and an adjusted equation (length x width x thickness x 0.674), and CT volumes with the voxel count method, which is considered the gold standard. One hundred kidneys were measured. The mean differences between US-1 and US-2 for similar measurements were <5 mm. The ellipsoid equation underestimated the volume for US-1 with 16.9% and for US-2 with 14.8%, while the adjusted equation overestimated the volume with 6.8% and 9.5% respectively. The correlation between CT and ultrasound volume with the adjusted equation is strong for both US-1 (r 0.76, $p<0.001$) and US-2 (r 0.80, $p<0.001$). Ultrasound measurements for kidney volume are comparable with CT measurements. Therefore, ultrasonography is a reliable modality for live kidney donor follow-up monitoring kidney size adaption post-donation.

INTRODUCTION

Live kidney donation has proven to be the best treatment for patients with end-stage renal disease. Live kidney donors are individuals who undergo major surgery for the benefit of someone else and it is of utmost importance to minimize the risks of the procedure and to maximize donor safety on short as well as long term[1]. The benefits of a living kidney donation program are pre-emptive transplantation, superior organ quality and increased graft survival[2]. These superior results have led to an increase in the number of live kidney donations[3, 4].

Live kidney donation is possible because of the capacity of the remnant kidney to physiologically compensate for kidney function by hyperfiltration and subsequent increase in kidney volume[5-11]. Increase in volume of the remnant kidney can be considered as the physiological response to adapt for the decrease in kidney function. The most accurate measurement for kidney volume, that does not deviate from the actual kidney size, is the voxel count method[12]. Nevertheless, this method always requires the need of a dedicated workstation with three-dimensional image processing abilities to generate the images, which is currently not widely available[13]. This raises the question whether kidney size estimation after donation or for research purposes would be possible with ultrasonography. This would be less time-consuming for health care professionals, and would be less harmful and expensive for (study) patients. Furthermore, ultrasonography is the first diagnostic imaging modality of choice after donation.

Recently, long-term safety of live kidney donors has been debated[14-17]. Therefore, follow-up of kidney size after donation may become an important indicator in the near future. To measure kidney volume with ultrasonography the volumetric ellipsoid equation is used: length x width x thickness x $\pi/6$[18]. Nevertheless, this equation is debated because it has proven to underestimate the kidney volume[19-22]. This has led to the proposed adjusted equation by Zakhari et al.[22]: length x width x thickness x 0.674. To validate ultrasound kidney volume measurements for the monitoring of kidney function adaption after donation, we investigated if these ultrasound measurements for kidney size are comparable with the voxel count method as measured on CT, and which volumetric equation is more accurate.

MATERIALS AND METHODS

Donor selection

Between November 2013 and June 2014 all consecutive live kidney donors who were approved by a multidisciplinary team of surgeons, nephrologists and anesthesists were approached for ultrasound examination one day prior to donor nephrectomy. The choice for the side of donation is based on the principal that the donor should be left behind with his/her best kidney, which is generally determined by size. A pre-donation CT scan is performed to determine kidney size and the vascular anatomy. Donors were included when a pre-donation CT-scan of kidneys and ultrasonography of both ultrasonographists (US-1, SJ; US-2, HK) were present. In addition, both CT scan and ultrasonography acquired images should be conform study protocol and deemed of sufficient quality. The study protocol was approved by our local institutional review board (MEC-2012-519) and written informed consent was obtained from all included study participants. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Ultrasonography

The ultrasound examination was performed using a commercially available system (Hitachi HI VISION Avius®, with a EUP-C715 transducer; Hitachi Medical Systems, Zug, Switzerland). All ultrasound measurements included length, width, and thickness of the kidney performed independently by two trained ultrasonographists. The ultrasonographists, a surgeon and a physician - research fellow, were exclusively involved in live donor kidney imaging program since 2012. Both ultrasonographists were trained and supervised by an experienced radiologist (RD) with 10 years of clinical experience in abdominal imaging. The image quality was deemed adequate when clear margins of the kidney were visible to perform all measurements (Figs. 1a and 1b). Image quality was assessed by the supervising radiologist (RD). The maximum length of the kidney was measured in the coronal axis of the kidney with clear vision of the hilum ($length_{us}$, Fig. 1a). In this same image the maximum width was measured perpendicular to this plane at the renal hilum ($width_{us}$, Fig. 1a). The transducer was then turned 90° with clear vision of the hilum, including identification of the main renal artery and vein . The maximum thickness (medial-lateral diameter) of the kidney was measured from the lateral margin of the kidney to the renal sinus ($thickness_{us}$, Fig. 1b). All measurements were performed three times by each ultrasonographist. A mean difference of < 5 mm between similar mean measurements of both ultrasonographists was accepted as normal[23-25] and only then defined as an accurate measurement. The kidney volume ($volume_{us}$) was calculated according to the commonly used volumetric ellipsoid equation (length in cm x width in

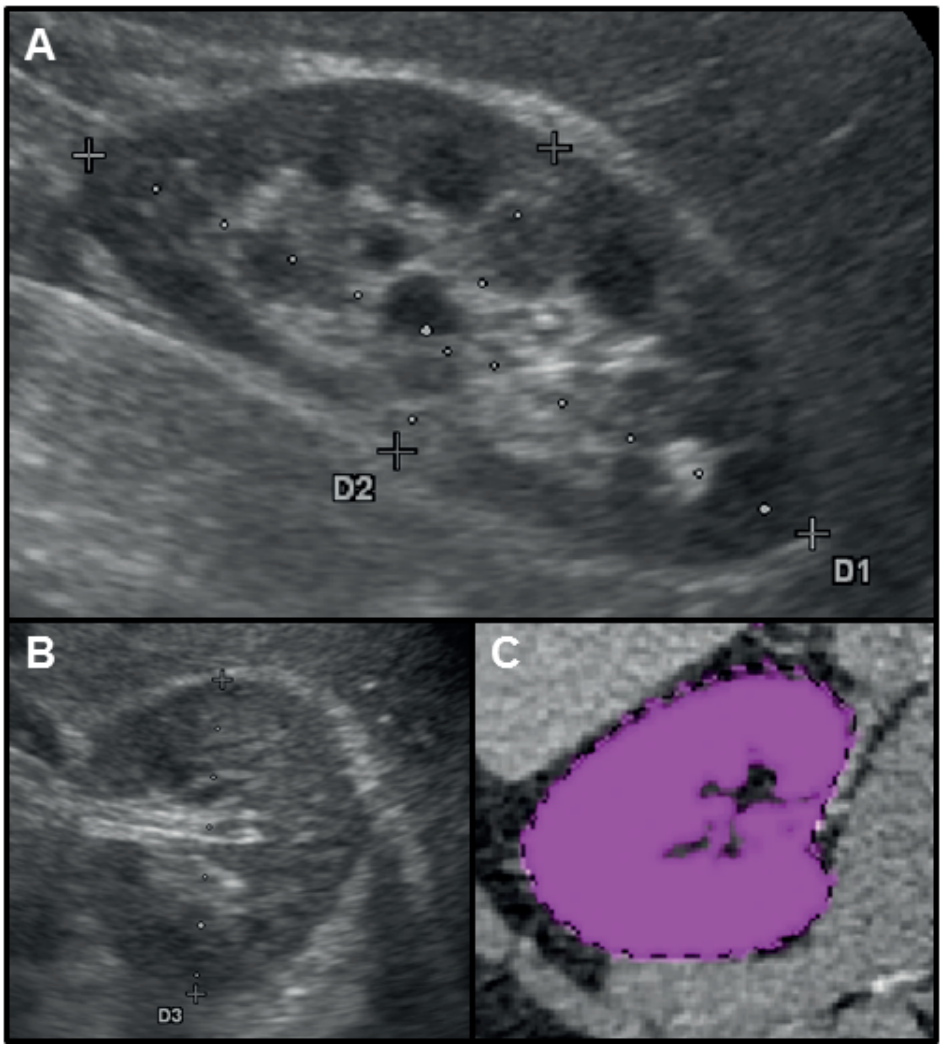

Figure 1. Measurement of the maximum length of the kidney (D1, A), the maximum width (D2, A), the maximum thickness (D3, B) by the ultrasonagraphists, and CT volume by a specialized radiological assistant(C).

cm x thickness in cm x π/6), however, in previous studies this equation has demonstrated to underestimate the kidney volume[19-22]. Therefore, also a more accurate deemed volumetric ellipsoid equation was used with 0.674 as an correction factor instead of π/6[22].

Computed tomography

The CT scans were performed on a 128-multislice CT Systems (Siemens Healthcare, Erlangen, Germany). A standardized CT scan protocol was used in which a triple split contrast bolus was injected to achieve an arterial, venous and excretion phase in a single

scan acquisition. The maximum length of the kidney on the CT ($length_{ct}$) was determined by manual measurements on oblique multiplanar reformats parallel to the longitudinal axis of the kidney, reconstructed from 0.75 mm slices with 0.5 mm increment in 3D software (AquariusNet, TeraRecon, Inc. Foster City, USA). All kidney volumes ($volume_{ct}$, Fig. 1c) were measured by the voxel count method by a specialized radiological assistant. For the voxel count method, the axial CT images (0.75 mm thickness and 0.5 mm increment) were transferred to a dedicated CT volume measurement software (Syngo Volume Calculation, Siemens Healthcare, Erlangen, Germany). On each axial image, contouring of the kidney was manually traced. A manual Hounsfield threshold adjusted to the density of the excretion contrast was set to also include the renal collecting system. The areas that were circumscribed by the manual contour on each slice were multiplied by the slice thickness and systematically summed to obtain kidney volume.

Statistical analysis

The inter-observer variability between both ultrasonographists and CT was determined by the Bland-Altman method[26]. The mean $length_{us}$, $width_{us}$ and $thickness_{us}$ were calculated by the mean of the three measurements for each ultrasonographist. The $length_{ct}$ as reported by the radiologist and $volume_{ct}$ as calculated by the voxel count method were deemed as the accurate measurements. A paired sample T-test was used to determine the mean difference between CT and ultrasound measurements for length and volume. The relationship between CT and ultrasound was evaluated by linear regression analysis (Pearson correlation coefficient, r). All analyses were carried out using SPSS 22.0 for windows.

RESULTS

Fifty consecutive donors were approached to participate in this study and all met the inclusion criteria. Acquired images of all 100 kidneys were deemed adequate to guarantee accuracy of the measurements. Thus, no donors were excluded from this consecutive series. The mean age of the included population was 51.6 ± 15.7 years, with a mean BMI of 25.4 ± 4.8 kg/m^2 (range 18.5-37.0), and 36% was male.

Accuracy of ultrasound measurements

In Table 1 the mean length and volume of CT, US-1 and US-2 of 100 kidneys are presented. The mean $length_{ct}$ of the left kidney was 111.0 ± 10.3 mm and the mean $length_{ct}$ of the right kidney was 108.7 ± 10.5 mm (P =0.284). The mean difference in $length_{us}$ between US-1 and US-2 for the left kidney was 1.5 ± 0.8 mm (P =0.062) and 2.0 ± 5.3 (P = 0.011) mm for the right kidney. The inter-observer variability between CT, US-1 and US-2

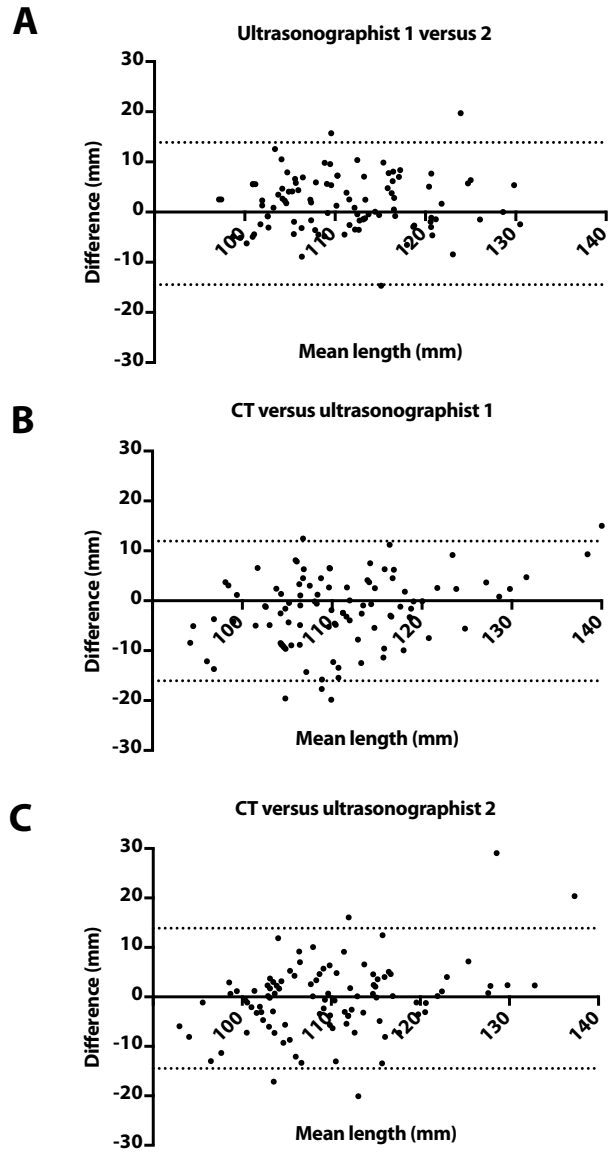

Figure 2. Bland-Altman plot of kidney length of ultrasonographist 1 versus ultrasonographist 2 (A), CT versus ultrasonographist 1 (B), and CT versus ultrasonographist 2 (C).

for length is depicted in Bland-Altman plots in Figs. 2a-c. The mean difference between $length_{ct}$ and $length_{us}$ for US-1 was 2.0± 7.1 mm (P = 0.057) for the left kidney and 2.1± 7.3 mm (P = 0.041) for the right kidney, and for US-2 the mean difference was 0.4± 7.0 mm (P = 0.678) for the left kidney and 0.2± 7.5 mm (P = 0.862) for the right kidney. There is a strong relation between $length_{ct}$ and $length_{us}$ for both US-1 and US-2 as well as for

the left (correlation coefficient 0.73 and 0.73 respectively) and right kidney (correlation coefficient 0.72 and 0.70 respectively) (P <0.001). In addition to $length_{us}$, the $volume_{us}$ is calculated by the $width_{us}$ and $thickness_{us}$ of the kidney. The mean difference in $width_{us}$ of the left and right kidney between US-1 and US-2 was 0.9 ± 5.0 mm (P =0.203) and 1.7 ± 6.7 mm (P = 0.082) respectively, and the mean difference in $thickness_{us}$ of the left and right kidney between US-1 and US-2 was 3.0 ± 4.5 mm (P <0.001) and 1.5 ± 5.2 mm (P = 0.040) respectively. The mean differences for all measurements for both kidneys between US-1 and US-2 were ≤ 5 mm. Therefore, all measurements of both ultrasonographists were deemed accurate.

Table 1. Mean length and volume of CT, ultrasonographist 1, and ultrasonographist 2.

	Mean
Length left kidney (mm)	
CT	111.0 ± 10.3
ultrasonographist 1	112.9 ± 7.9
ultrasonographist 2	111.4 ± 7.8
Length right kidney (mm)	
CT	108.7 ± 10.5
ultrasonographist 1	110.9 ± 8.5
ultrasonographist 2	108.9 ± 8.3
Volume left kidney (cm^3)	
CT	183.3 ± 43.4
*Ellipsoid equation**	
ultrasonographist 1	150.6 ± 30.1
ultrasonographist 2	155.3 ± 37.2
Adjusted volume equation†	
ultrasonographist 1	193.7 ± 38.7
ultrasonographist 2	199.8 ± 47.9
Volume right kidney (cm^3)	
CT	177.4 ± 45.9
*Ellipsoid equation**	
ultrasonographist 1	146.6 ± 44.4
ultrasonographist 2	149.7 ± 39.8
Adjusted volume equation†	
ultrasonographist 1	188.5 ± 57.2
ultrasonographist 2	192.6 ± 51.2

*mean $length_{us}$ (cm) x mean $width_{us}$ (cm) x mean $thickness_{us}$ (cm) x $\pi/6$
†mean $length_{us}$ (cm) x mean $width_{us}$ (cm) x mean $thickness_{us}$ (cm) x 0.674

Difference in kidney volume

The mean $volume_{ct}$ of the left kidney was 183.3 ± 43.4 cm^3 and the mean $volume_{ct}$ of the right kidney was 177.4 ± 45.9 cm^3 (P =0.511). The inter-observer variability between $volume_{ct}$ and $volume_{us}$ for US-1 and US-2 for both volumetric ellipsoid equations are depicted in Bland-Altman plots in Figs. 3a-d. The mean difference between $volume_{ct}$ and $volume_{us}$, calculated with the common ellipsoid equation, for the left and right kidney measured by US-1 was 32.7 ± 34.5 cm^3 and 30.8 ± 22.7 cm^3 respectively (P <0.001), and for US-2 28.0 ± 27.2 cm^3 and 27.7 ± 26.8 cm^3 respectively (P <0.001). The mean difference between $volume_{ct}$ and $volume_{us}$, calculated with the adjusted ellipsoid equation, for the left and right kidney measured by US-1 was -10.4 ± 36.4 cm^3 (P =0.048) and -11.1 ± 28.1 cm^3 (P =0.007) respectively, and for US-2 -16.5 ± 30.3 cm^3 (P <0.001) and -15.2 ± 30.1 cm^3 (P =0.001) respectively. The common ellipsoid equation underestimated the kidney volume for US-1 with 16.9% and for US-2 with 14.8%, while the adjusted ellipsoid equation overestimated the kidney volume for US-1 with 6.8% and for US-2 with 9.5%. The relation between volumect and volumeus calculated with the adjusted volumetric ellipsoid equation is strong for both US-1 (correlation coefficient 0.76) and US-2 (correlation coefficient 0.80) (both P <0.001). The calculated personalized correction factor for the left and right kidney for US-1 was 0.634 and 0.663, and for US-2 was 0.589 and 0.678.

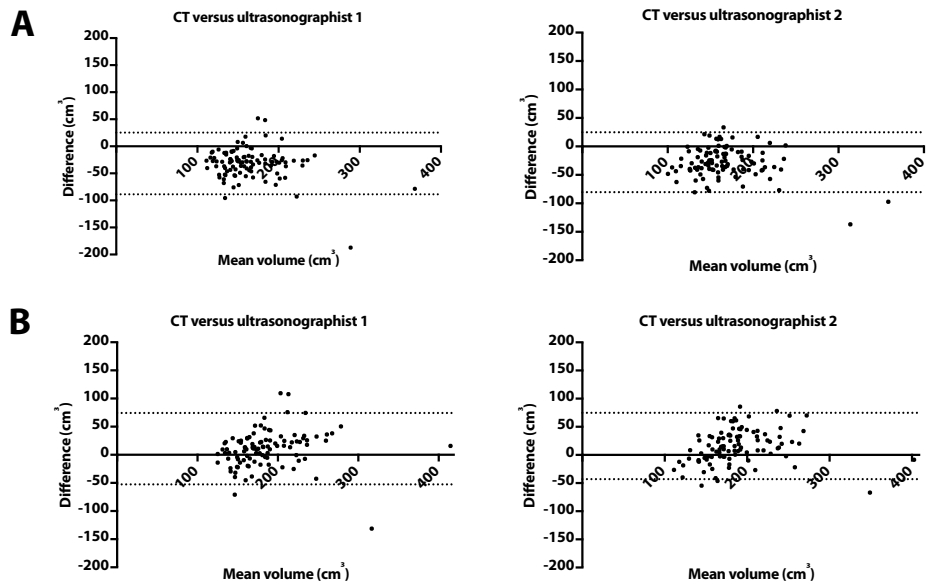

Figure 3. Bland-Altman plot of kidney volume of CT versus both ultrasonographists calculated with mean length x mean width x mean thickness x π/6 (A) and calculated with mean length x mean width x mean thickness x 0.674 (B).

DISCUSSION

After live kidney donation adaptation of the remnant kidney is necessary to compensate for the loss of kidney function. Adaptation is associated with compensatory hypertrophy that can be monitored by measuring kidney volume[27]. We propose to use ultrasonography as it offers a less expensive and less time-consuming imaging modality. In this study we demonstrated that: [1] kidney size measurements of length and volume performed by ultrasonography of both kidneys are comparable with CT measurements, and [2] that the adjusted volumetric ellipsoid equation by Zakhari et al.[22] based on kidney ultrasound measurements of length, width and thickness demonstrated a more accurate volume estimation by a difference of less than 10% compared with the common volumetric ellipsoid equation[18]. This study has led to a feasible and accurate measurement for kidney volume. To our knowledge this is the first study to validate the adjusted volumetric ellipsoid equation by Zakhari et al.[22] for clinical use.

Our study demonstrates a strong correlation between kidney length measurements on ultrasonography and CT. While the mean difference between both ultrasonographists was significantly different for $length_{us}$ of the right kidney and $thickness_{us}$ of both kidneys, the difference of <5 mm is found acceptable between trained ultrasonographists[23-25]. These accurate ultrasound measurements have previously been confirmed by another study in 125 live kidney donors, which demonstrated a difference of 1.0-2.0 mm between all ultrasound and CT kidney length measurements[28]. In this study two measurements for CT length were used: the number of slices from top to bottom of the kidney times the thickness of the slices and length measurement in the coronal axis. While in our study CT length was measured on oblique multiplanar reformats parallel to the longitudinal axis of the kidney. In a study by Hwang et al.[21] the measurements between ultrasound and CT in 139 donors were more accurate (1 mm) for the right kidney as compared with the left kidney (5 mm). In our study a similar mean difference for either the left or right kidney was demonstrated, which is found in the difference between the personalized correction factors for both kidneys. All-over, the accuracy of ultrasound measurements is demonstrated to be highly comparable to CT measurements.

We compared the commonly used volumetric ellipsoid equation (length x width x thickness x $\pi/6$) with an adjusted volumetric ellipsoid equation in which 0.674 is used as an correction factor instead of 0.524 ($\pi/6$)[22]. Previous studies have demonstrated that the first equation underestimates the kidney volume compared with the voxel count method[19-22], the latter is considered the gold standard for volume measurement. This underestimation was similar for our study with a total volume underestimation of 15-17% on average for both kidneys, which is comparable with other studies (22-25%)[19, 22].

The adjusted volumetric ellipsoid equation proved to be more accurate with an overestimation of 7-10%. Though, this difference was slightly higher compared to the 100% accuracy found in the study that proposed the adjusted equation, despite that we both included the renal collecting system in our volume measurements. This difference might be due to the fact that this study was done in a slightly larger sample size of 79 donors or that the adjusted equation is based on the measurement differences of another individual who solely performed all ultrasound measurements in this study[22]. However, the adjusted correction factor came close to the personalized correction factor for both US-1 and US-2.

Our study has several limitations worth mentioning. First, ultrasound measurements can be variable[23-25], therefore only measurements performed by experienced ultrasonographists may be reliable. However, all our ultrasound measurements were independently performed by two ultrasonographists to achieve accuracy. Second, it should be noted that the sample size of 100 kidneys is relatively small for a validation study. However, due to the experienced ultrasonographists the variability of the ultrasound measurements of <5 mm difference has been accomplished. This strengthens the assumption that our US measurements are deemed accurate and reliable to be analysed. Last, this is the first study that has validated the Zakhari equation and an 100% accuracy is not accomplished. This indicates that a future study in a prospective cohort should be performed to validate the equation before it can be used for clinical purposes.

Pre-donation kidney volume is a significant predictor of volume increase in the remnant kidney, with lower pre-donation kidney volume being a significant predictor of delayed kidney function recovery[6]. The availability of a reliable technique to measure kidney volume pre-donation can enhance the kidney selection procedure prior to donation to maximize and maintain donor safety after donation. Furthermore, the degree of kidney function recovery can be reflected by measuring kidney volume after donation, which represents compensatory hyperfiltration. This study supports the feasibility and accuracy of a more cost-effective and approachable imaging modality; also to be used in less developed countries. Future studies should focus on the clinical implementation in a prospective cohort.

Ultrasound measurements for kidney size are comparable with CT measurements, allowing the reliable use of ultrasound examination as imaging modality to determine kidney size during follow-up of live donors to monitor kidney adaptation. The use of different equations to calculate the volume was demonstrated to achieve the most accurate ultrasound volume estimate of the kidney. Therefore, ultrasonography, having low costs,

being non-invasive and showing comparable outcome as CT, seems the technique to be recommended for follow-up examination after live kidney donation.

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LOVE

Chapter 6

Impact after live donor nephrectomy- A long-term comparative follow-up study

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ABSTRACT

Worldwide, tens of thousands of healthy individuals participate in living kidney donation programs to help patients with end-stage renal disease. Recently, unfavourable results emerged from donor versus non-donors studies. We conducted a follow-up study of 761 living kidney donors from The Netherlands who were propensity-score matched with 1522 non-donors from two Western population-based cohort studies on age, gender, BMI, ethnicity, kidney function, blood pressure, pre-existing co-morbidity, smoking, alcohol use and highest education degree. Live kidney donations occurred between 1981 through 2010 with follow-up until April 20th, 2016. The median follow-up time after donation was 8.0 years. The primary outcome was kidney function as defined by creatinine level and eGFR at follow-up. One-year median eGFR was 59.0 ml/min/1.73 m2 (IQR 50.5-68.6 ml/min/1.73 m2) and eGFR at follow-up was 59.9 ml/min/1.73 m2 (IQR 51.4-70.7 ml/min/1.73 m2). Donors were found to have an increased serum creatinine of 26.03 µmol/l (95%CI 24.17; 27.89), a decreased eGFR of 27.23 ml/min/1.73m^2 (95%CI -28.61; -25.85), and eGFR decline of 31.70% (95%CI 29.94-33.46) as compared to non-donors. There was no difference in outcome between both groups for microalbuminuria, BMI, incidence of diabetes or cardiovascular events, and cardiovascular mortality. A lower risk of new-onset hypertension (OR 0.45, 95%CI 0.33; 0.62) was found among donors. The EQ-5D health-related quality of life was higher among donors, while the SF-12 physical and mental component scores were lower. In conclusion, one year after donation live donors have a reduced renal function, remaining stable without any kidney-related morbidity or mortality to at least eight years of follow-up. However, the decline in renal function may be further compromised when unforeseen conditions would develop that additionally affect renal function. Having knowledge of this risk, albeit small, donors should be well-informed by the medical team and offered lifelong follow-up to monitor the remnant renal function.

INTRODUCTION

Each year, nearly 5000 healthy individuals in Europe and 6000 in the United States participate in a living kidney donation program to help patients with end-stage renal disease (ESRD).[1,2] Potential living donors are exhaustively screened by transplant professionals, who select only those whose health will not be compromised by donation. The surgical donation procedure has been demonstrated to be safe with a low risk of peri-operative morbidity and a very low risk of procedure-related mortality.[3,4] However, donors should be aware of the implications of donation in their future life. Compared to pre-donation levels, renal function initially decreases after donation[5] but seems to remain stable with no further progression after more than a decade.[6,7]

Previously, it was assumed that donors have no increased risk of mortality,[4,8-10] ESRD,[8,11-13] or gestational hypertension[8,14] compared to non-donors. However, recent single-center and national registry studies on long-term follow-up outcomes comparing donors to non-donors have reported an increased risk of mortality,[15] ESRD,[15-17] gestational hypertension, and pre-eclampsia[18] among donors. These conflicting results are mainly due to the incomparability of donors and non-donors because of limitations in the included study population and analysis.[19] Live kidney donors represent a screened and selected cohort of the population that is inherently healthier than the general population, which jeopardizes the comparability of donors and non-donors when studying outcomes. Furthermore, low absolute risk among donors creates uncertainty in estimates when adjusting for potential confounders.[19] Strengths of recent studies compared to previous studies are the extended time for follow-up after donation, large sample sizes, and better analysis,[15-18] increasing the reliability of estimating potential risks for living kidney donors in the long-term.

Determining the long-term impact of living donation is essential and criteria are needed to identify the donors at risk in the long-term. In the present study, we aim to evaluate the long-term consequences for live kidney donors compared to matched non-donors regarding kidney function, including hypertension, diabetes mellitus, cardiovascular events, survival, and quality of life.

METHODS

Study design

We performed a propensity-score matched follow-up study using individual level donor data from Erasmus University Medical Center, and comparison data from two popula-

tion-based follow-up studies. All eligible donors were invited for an extensive study visit that included self-reported medical history, and an interview-based questionnaire on quality of life, supplementary to their annual physical examination and laboratory tests. The study visits were conducted between August 19, 2013, and December 31, 2014. To increase the response among donors, the visits were also conducted at another academic university medical center and one district hospital located in different provinces of the Netherlands. Donors were included in the study if they were alive during the inclusion period, lived in the Netherlands, and visited one of the study hospitals or filled out self-report forms. All questionnaire-related interviews were conducted by three investigators. Non-participants were asked to fill out self-report forms on their medical history and quality of life and permission requested for access to their medical records in order to analyze potential selection bias. The conduct and reporting of the study followed guidelines for observational studies[20] (Supplemental Table S1). The study was designed by the authors[21] and approval obtained by the medical ethics committee of Erasmus University Medical Center, Rotterdam, the Netherlands (MEC-2012-519). Informed consent was obtained from all study participants.

Data sources

All data were obtained from self-reporting, interview-based questionnaires, physical examination, and laboratory tests. To ensure the accuracy and completeness of the donor data, we manually reviewed the pre-donation and annual follow-up medical records in the hospital's electronic patient database. We also obtained information from two linked databases containing the municipal administration records on vital status and demographic characteristics for all inhabitants. Outcome data were complete for all variables in this study except for quality of life scores among non-donors.

Population

Donors

We included all individuals who donated a kidney from 1981 through 2010 at the Department of Surgery of Erasmus University Medical Center or who had their full medical work-up performed at the Erasmus University Medical Center prior to donation but donated at another transplant center because of their participation in the national kidney exchange transplant program.[22] We identified 1092 study-eligible donors (See Supplemental Figure S1 for an overview of the number of donations per year).

Non-donors

Inhabitants of Western Europe have similar donation and transplantation legislation, lifestyles, and healthcare systems and access.[23-25] Therefore, non-donors were selected from the Study of Health in Pomerania (SHIP)[26] in Germany, a population-based cohort

study with participants aged 20-70 years, and the Rotterdam Study[27] in the Netherlands, a population-based cohort study with participants aged 45 years and older. SHIP is a population-based cohort study initiated in 1997 among inhabitants of West Pomerania in the north-east of Germany. Two main objectives of this study were first to assess prevalence and incidence of common risk factors, subclinical disorders and clinical diseases, and second to investigate the complex associations amongst these. The Rotterdam Study is a prospective cohort study that started in 1990 in Ommoord, a district of the city of Rotterdam, the Netherlands. The study targets cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric and respiratory diseases. Both population-based studies were selected to cover the whole age range of our donors. Participants from the SHIP-0 cohort who enrolled between 1997 and 2001 (n=4308) were selected on sufficient follow-up time. Participants from the Rotterdam Study II and III cohorts who enrolled between 2000 and 2001 or 2006 and 2008, respectively (n=6943), were selected to ensure the presence of studied outcomes compared to cohort I. Data were taken from the latest follow-up examinations of both cohorts, 2012 for the SHIP and 2015 for the Rotterdam Study.

Restriction, multiple imputation, and matching were used to select a cohort of non-donors that was just as healthy as the donors (Supplemental Methods). We restricted the sample of all Rotterdam Study and SHIP participants (n=11,251) to eligible non-donors without identified contraindications for donation (n= 9270) at the time of enrollment in the population-based cohort studies, including pre-existing diabetes, an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 (defined by blood or urine analysis), and BMI > 40 kg/m^2. To account for the fact that the data on covariates at baseline were not complete for all subjects, a multiple imputation approach was utilized to impute missing covariate values based on the method of chained equations.[28] Using this procedure, 20 complete data sets were created. For each imputed data set, non-donors were matched to donors with replacement using propensity score matching.[29,30] Balance between the donor and non-donor groups was checked with summary measures of Q-Q plots comparing the covariates in the matched groups.[31] Initially, a 4:1 match was targeted,[21] but the ratio was reduced to 2:1 to strive for optimal balance. Matching was based on baseline characteristics of age (years), gender, year of donation/enrollment in the population-based cohort study, weight (kg), height (cm), ethnicity, eGFR (ml/min/1.73 m^2), systolic and diastolic blood pressure (mmHg), pre-existing hypertension, pre-existing cardiovascular events, serum glucose level (mmol/l), current smoking, alcohol use, and education level.

Study outcomes

All study subjects were followed until death, emigration out of the country, or the end of the examination period (April 20, 2016, for donors, and December 31, 2015, for non-donors). The primary outcome was defined as kidney function based on serum creatinine (μmol/l) and eGFR (ml/min/1.73 m^2; calculated using the CKD-EPI formula[32]), and measured at baseline, one year after donation (donors only), and at long term follow-up[32]. Secondary outcomes were incidence of hypertension (defined as use of antihypertensive medication, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg), incidence of diabetes (defined as use of antidiabetic medication or glucose ≥ 7 with diet), BMI (kg/m^2), incidence of cardiovascular events (defined as myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, or cerebral vascular accident), cardiovascular mortality (defined as death by cardiovascular event), mortality (censor date April 20, 2016, for donors; December 31, 2012 for the SHIP; and December 31, 2015, for the Rotterdam Study), and quality of life measured by ShortForm-12 (SF-12)[33] and EuroQoL (EQ-5D)[34]. The Short Form health questionnaire is a validated and commonly used tool to measure health related quality of life ranging from a score between 0-100. It contains questions on physical performance and well-being, and mental functioning and emotional well-being, resulting in the physical (PCS) and mental component score (MCS) respectively. The EQ-5D records quality of life in five dimensions: mobility, self-care, daily activities, pain or discomfort, and anxiety/depression. The responses on the five dimensions combine to a score according to Dutch tariff[35] between -0.59 (worst imaginable health state) and 1.00 (best imaginable health state).

Statistical analysis

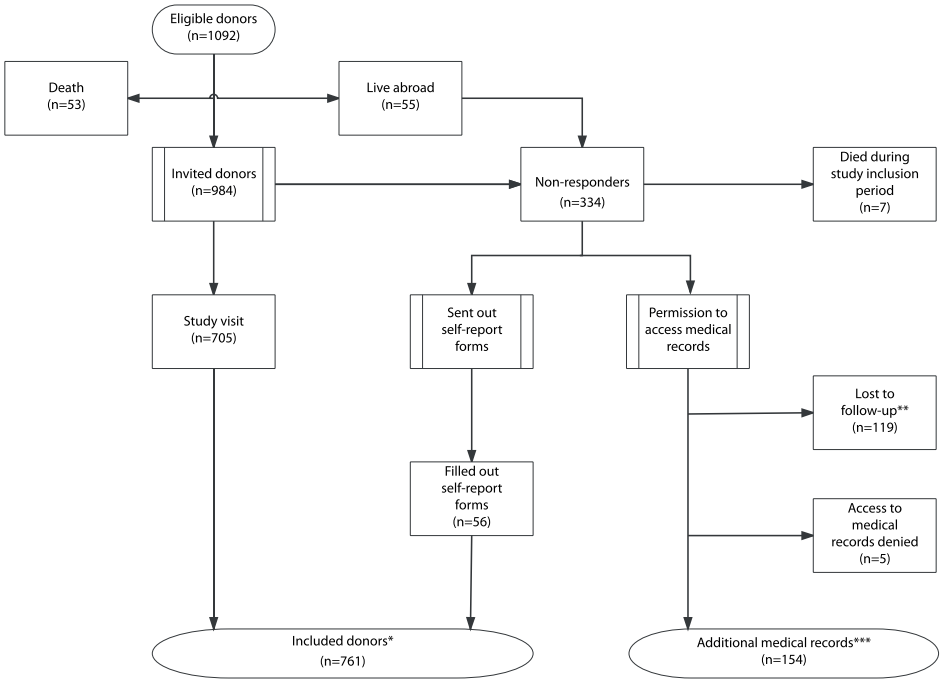
Our approach to data-analysis was as follows. Baseline characteristics were compared using the Kruskal-Wallis test for continuous variables and the Fisher's exact test for dichotomous variables.

All analyses were performed for each of the completed data sets and the results from the analysis of each imputed data combined using Rubin's formulas.[36] The analyses of continuous outcomes were based on linear regression and the analyses of dichotomous outcomes on logistic regression. For each regression analysis we tested for differences between donors and non-donors while also correcting for the covariates age, gender, start year (date of donation or enrollment in population-based study), education level, pre-existing hypertension, baseline serum creatinine, and baseline eGFR, as well as weight, height, alcohol use, and smoking status at follow-up. To evaluate potential effect modification, interactions were tested by age, gender, and follow-up duration in the final multivariate model of kidney function. The results have not been corrected for multiple testing.

PRELIMINARY RESULTS

Characteristics of the study participants

Between 1981 and 2011, a total of 1092 live kidney donations were performed at our center and all donors were eligible for inclusion. A total of 761 donors were matched with non-donors, including 705 who visited the outpatient clinic (Figure 1). The donors comprised 429 living-related (54.1%) and 332 living-unrelated (45.9%) live kidney donations. The median follow-up time for donors was 8.0 (5.1-11.9) years. Non-donors from the Rotterdam Study and SHIP were included; a total of 11,251 individuals participated in these population-based cohort studies. After restriction, 9270 non-donors were eligible for 2:1 matching, resulting in 1522 non-donors being included in the study, 54.1% from the Rotterdam Study and 45.9% from SHIP. The median follow-up time for non-donors was 7.0 (5.4-10.9) years. Age, baseline systolic blood pressure, ethnicity, and education were significantly different between donors and non-donors (Table 1), but differences were relatively small.



* 1 donor passed away during the inclusion period and 8 donors passed away after the inclusion period
** 46 donors live abroad and 3 donors passed away
*** including 15 donors who passed away prior(7), during(6), and after(2) inclusion period

Figure 1. Flowchart of inclusion in the live kidney donor process

Table 1. Baseline characteristics of included live kidney donors at the time of donation and matched non-donors at the time of enrolment in population based cohort studies

Characteristics	Donors (n=761)	Nondonors (n=1522)	P-value
	median (IQR)/N (%)	median (IQR)/N (%)	
age (years)	51.9 (42.8-60.1)	51.0 (37.8-57.9)	*p<0.001*
gender (male)	318 (41.8)	636 (41.8)	p=1.000
ethnicity (white)	681 (89.5)	1434 (94.2)	*p=0.001*
BMI (kg/m^2)	25.9 (23.4-28.4)	25.5 (22.9-28.2)	p=0.176
systolic blood pressure (mmHg)	130.0 (120.0-140.0)	125.5 (114.0-142.0)	*p=0.010*
diastolic blood pressure (mmHg)	79.0 (70.0-85.0)	77.0 (70.0-85.0)	p=0.964
eGFR (ml/min/1.73m^2)	92.6 (79.8-103.8)	90.0 (78.9-102.3)	p=0.160
serum glucose (mmol/l)	4.9 (4.3-5.4)	5.0 (4.7-5.4)	p=0.778
pre-existing hypertension*	299 (39.3)	592 (38.9)	p=0.891
pre-existing cardiovascular disease	13 (1.7)	28 (1.8)	p=0.956
smoking	400 (52.6)	867 (57.0)	p=0.051
alcohol use			p=0.560
never/rare	340 (44.7)	703 (46.2)	
≤7 glasses/week	294 (38.6)	553 (36.3)	
>7 glasses/week	127 (16.7)	266 (17.5)	
education degree			*p=0.011*
primary	86 (11.3)	159 (10.4)	
secondary	418 (54.9)	782 (51.4)	
tertiary	257 (33.8)	581 (38.2)	

* defined as use of antihypertensive medication, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg

Study outcomes

In the donor population, baseline eGFR was 92.6 ml/min/1.73 m^2 (IQR 79.8-103.8 ml/min/1.73 m^2), one-year eGFR was 59.0 ml/min/1.73 m^2 (IQR 50.5-68.6 ml/min/1.73 m^2), and median eGFR at follow-up after 8 years 59.9 ml/min/1.73 m^2 (IQR 51.4-70.7 ml/min/1.73 m^2) (Figure 2). The creatinine level for donors was 77.0 µmol/l (IQR 68.0-87.0 µmol/l) at baseline, 106.0 µmol/l (IQR 93.0-121.0 µmol/l) at one-year and 100.0 µmol/l (IQR 87.5-114.0) µmol/l at 8-year follow-up. The primary outcomes for renal function were all significantly inferior for donors compared to non-donors; serum creatinine was significantly higher (+26.03 µmol/l (95% CI 24.17; 27.89)) and the eGFR significantly lower (-27.23 ml/min/1.73 m^2 (95% CI -28.61; -25.85)). The eGFR declined 31.70 percent (95% CI 29.94; 33.46) more among donors than non-donors (all p<0.001, Table 2). Sixteen donors (2.4%) and 10 non-donors (1.2%) developed microalbuminuria (p=0.093). These donors had a median eGFR of 57.9 ml/min/1.73 m^2 (IQR 47.7-68.2 ml/min/1.73 m^2) and median creatinine of 99.5 µmol/l (IQR 86.1-112.9 µmol/l) at follow-up. Two donors (0.3%) devel-

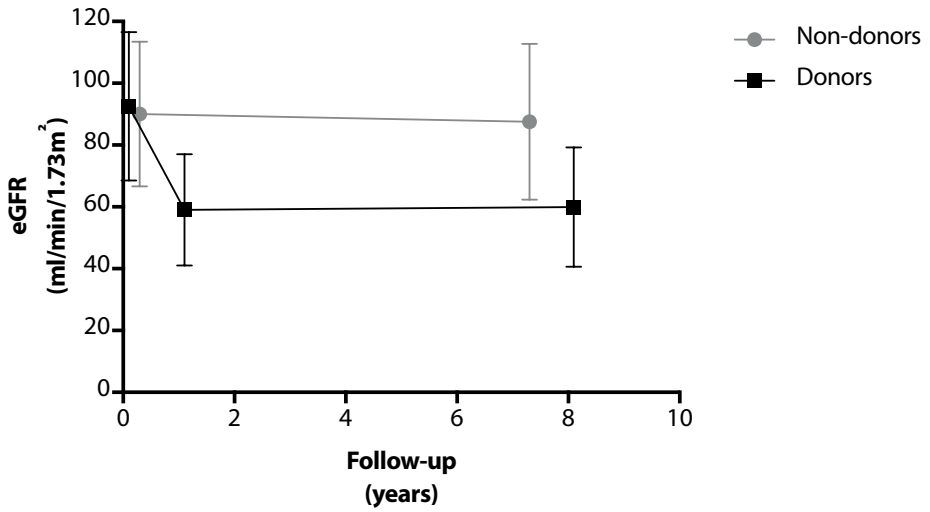


Figure 2. eGFR levels overtime

oped ESRD: one female donor, 60 years of age and 28 years after donating her kidney to her son and one male donor, 46 years of age and 12 years after donation to his sister. In the first patient the renal failure was caused by the use of diuretics to treat ascites due to alcoholic liver cirrhosis. Being on dialysis this patient passed away at the age of 66 due to progression of her liver disease. The second patient developed hypertensive nephropathy, proteinuria, and subsequent renal failure, caused by nephrosclerosis as demonstrated by renal biopsy. This donor had withdrawn himself from annual visits to the outpatient clinic for several years before renal failure was diagnosed. He received a kidney transplant from his son and his current eGFR at follow-up was 76.3 ml/min/1.73 m^2 with a creatinine level of 99.0 µmol/l.

Secondary outcomes showed no significant differencesbetween donors and non-donors for BMI (0.02, (95%CI -0.04; 0.07), incidence of diabetes (OR 1.14, 95%CI 0.71; 1.84), cardiovascular events (OR 1.06, 95%CI 0.64; 1.74), and cardiovascular mortality (OR 0.13, 95%CI 0.01; 1.24). A significantly lower risk of developing new-onset hypertension (OR 0.45, 95% CI 0.33; 0.62) and overall mortality (OR 0.13, 95% CI 0.06; 0.27) was found among donors. Nine donors (1.2%) passed away after visiting one of the study hospitals prior to their death, one of whom died of a cardiovascular event. Of the entire 1981-2011 donor population (n=1092), 80 donors passed away: 38 of a malignant disease and 15 of a cardiovascular event.

The health-related quality of life score was significantly higher among donors with 0.06 higher score for EQ-5D (95% CI 0.05; 0.08 on a scale of -0.59 to 1.00. The SF-12 physical

Table 2. Long-term outcomes of live kidney donors compared with matched non-donors after an overall median follow-up of 7.3 years

Outcome	Effect estimate*	95% CI	P-value
Primary outcomes			
Serum creatinine (µmol/l)	26.03	24.17; 27.89	*p<0.001*
eGFR (ml/min/1.73m^2)	-27.23	-28.61; -25.85	*p<0.001*
eGFR decline (%)	-31.70	-33.46; -29.94	*p<0.001*
Secondary outcomes			
BMI (kg/m^2)	0.02	-0.04; 0.07	p=0.583
New-onset diabetes	1.14	0.71; 1.84	p=0.585
New-onset hypertension**	0.45	0.33; 0.62	*p<0.001*
Cardiovascular event	1.06	0.64; 1.74	p=0.823
Cardiovascular mortality	0.13	0.01; 1.24	p=0.077
Overall mortality	0.13	0.06; 0.27	*p<0.001*
SF-12 physical component score	-1.36	-2.38; -0.33	*p=0.010*
SF-12 mental component score	-4.61	-5.75; -3.47	*p<0.001*
EQ-5D	0.06	0.05; 0.08	*p<0.001*

*β for continuous outcome, odds ratio for dichotomous outcome

** Study participants with pre-existent hypertension are excluded from analysis. Defined as use of antihypertensive medication, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg

Model adjusted for: age, gender, start year (date of donation or enrolment in population-based study), education degree level, pre-existing hypertension, baseline serum creatinine, baseline eGFR, and weight, height, alcohol use, and smoking status at follow-up.

and mental component score were both significantly lower among donors: -1.36 (95% CI -2.38; -0.33) and -4.61 (95% CI -5.75; -3.47), respectively, on a scale of 0-100.

DISCUSSION

In this European study of live kidney donors and matched non-donors from the general population, we demonstrated a reduction in renal function in the first year after donation, thereafter stabilizing at least until the moment of measurement after 8 years of follow-up; no effect of reduced renal function was found on the secondary health-related outcomes.

Notably, the eGFR and creatinine levels among donors were decreased at follow-up as compared to the general population (Table 2). This change in renal function may be attributed to the donation procedure, since the eGFR declined in the first year after donation and remained stable thereafter. Compared to previous studies[19] a main strength of our study lies in the quantification of renal function with repeated serum measurements

and additional urine analyses over time. In a study by Ibrahim et al. the outcome for eGFR and creatinine among donors were similar to our findings. The decline in eGFR among donors in our study was also similar to that reported in previous studies.[6,37] However, the microalbuminuria percentage in the study by Ibrahim et al. was found to be higher as compared to our findings.[8] In our study only 16 donors (2.4%) had microalbuminuria with a median eGFR of almost 60 ml/min/1.73 m^2, indicating that none of the donors were currently at risk for ESRD. The two donors that did develop ESRD did so because of reasons unrelated to the donation.

A strength of our study is that we collected, in addition to national registry data as used in other studies,[15,16] individual donor and non-donor level data on medical conditions, physical examinations, laboratory tests with quantification of renal function, medication use, all manually verified by medical records and with minimal missing data (<8%). Furthermore, as compared to previous studies the current study design was optimized for donor and non-donor comparison by matching on more baseline health characteristics, including renal function and comorbidity, adjusting for current lifestyle factors including alcohol use and smoking, and performing propensity score matching suitable for observational data which balances both groups on a large number of covariates without losing a large number of observations[4,8-10,15,16,18,19,38]. All donors and non-donors had access to similar health care services.

Our study has certain limitations. First, data on the use of antihypertensive medication were not available from our data sources. Second, blood pressure was measured once for donors and average of 2-3 measurements for non-donors. Third, for SHIP participants, percutaneous coronary intervention and coronary artery bypass surgery were not included as cardiovascular events. In addition, EQ-5D scores were only available in the Rotterdam Study and SF-12 scores were only available in the SHIP. Finally, the eGFR is only an estimation of the renal function. A GFR from a 24-h urine sample would be more accurate. However, the eGFR CKD-EPI formula[32] is a common clinically and internationally used equation. Furthermore, eGFR is common in population level studies due to logistic difficulties in 24-h urine collection.

Several studies on live kidney donation have used a similar comparison design with matched non-donors and reported similar outcomes in overall mortality and cardiovascular events.[4,8,10] However, others have reported contradicting results [15,38]. These contradictories can be explained by differences in the methodological design, questioning the comparability of donors and non-donors and the reliability of the results.[19] Live kidney donors are healthy individuals and submitting them to a surgical procedure stretches the Hippocratic oath taken by physicians. Therefore, prior to donation, a well-considered

decision has to be made regarding the surgical suitability and the risk estimation for donation. By extensively screening donors the healthiest individuals are selected, which may impede the comparability with non-donors from the general population. Comparing donors to the general background population can underestimate risks additional to donation.[9] Matching donors to selective non-donors with similar baseline health status can overcome this impediment. It is important that comprehensive data becomes available for this process to strive for an equal health status between donors and non-donors, allowing proper analysis of the donation procedure on risk factors. As compared to recent literature we have added these factors to our study design by matching and adjusting for multiple health characteristics. Thus, this study strives to be representative donors and non-donors in Western populations. The next step would be to predict the attributable risk for individual donors prior to donation.[17] This approach would help to identify those donors that may be at risk for reduction of renal function,[39] either related to future co-morbidity or medication affecting renal function.

In conclusion, live donors have reduced renal function compared to non-donors, occurring in the first year after donation and stabilizing thereafter for at least 8 years with equal outcome for morbidity or mortality as compared to non-donors. No differences were found in the risk on hypertension or cardiovascular disease and mortality. However, the substantial decline in renal function may be further compromised when unforeseen circumstances affect renal function later in life. With the knowledge of this risk, albeit small, donors should be well-informed before donation and be offered lifelong follow-up thereafter. By monitoring the remnant renal function, donors at risk may be identified in early stage and adequate treatment may be offered. We consider this approach a prerequisite to legitimize a living kidney donor program.

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SUPPLEMENTAL METHODS

Restriction, multiple imputation, and matching

A total of 11,251 participants from the SHIP (n=4308) and the Rotterdam Study (n=6943) were eligible as non-donors. After restricting participants (total n=1981; SHIP n= 816, Rotterdam Study n=1165) with pre-existing diabetes, an (e)GFR < 60 ml/min/1.73 m^2, and BMI > 40 kg/m^2, a total of 9270 participants were identified (SHIP n= 3492, Rotterdam Study n= 5778).

Due to missing baseline data on BMI (5.9%), ethnicity (2.7%), eGFR (7.8%), systolic (5.5%) and diastolic (5.5%) blood pressure, pre-existing hypertension (4.6%), pre-existing cardiovascular events (0.2%), serum glucose level (7.5%), current smoking (0.5%), alcohol use (3.5%), and education level (2.6%), multiple imputations based on the method of chained equations[28] was performed for 1092 donors, 3492 participants from SHIP, and 5778 participants from the Rotterdam Study.

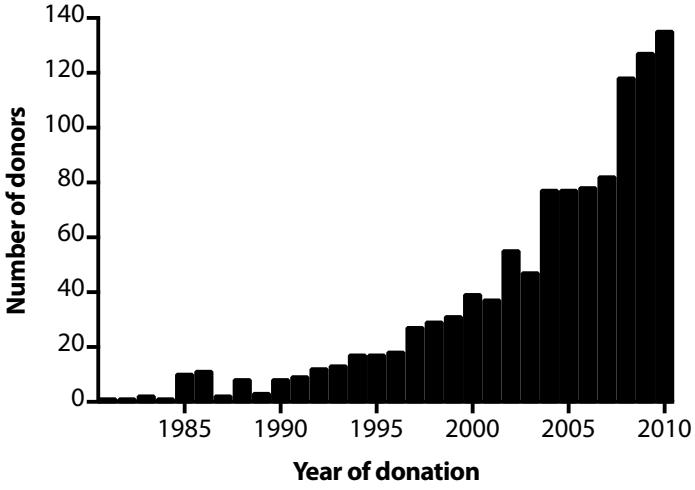
All 761 donors included in the study were matched based on propensity scores to two non-donors from among the 9270 participants with replacement. Matching covariates were age, gender, year of donation/enrollment in the population-based cohort study, BMI, ethnicity, eGFR, systolic and diastolic blood pressure, pre-existing hypertension, pre-existing cardiovascular events, serum glucose level, current smoking, alcohol use, and education level. Matching was performed using the optimal matching algorithm implemented in the R package as optmatch.[30] This algorithm finds the best match based on all variables together. On average (over the 20 multiple imputed data sets), 103 non-donors were used more than once to match with a donor.

Supplemental Table S1. STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item no.	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract.
		(*b*) Provide an informative and balanced summary of what was done and what was found.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported.
Objectives	3	State specific objectives, including any pre-specified hypotheses.
Methods		
Study design	4	Present key elements of study design early in the paper.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.
Participants	6	(*a*) Give the eligibility criteria and the sources and methods of selecting participants. Describe follow-up methods.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria if applicable.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of the methods of assessment (measurement). Describe the comparability of assessment methods if there is more than one group.
Bias	9	Describe any efforts to address potential sources of bias.
Study size	10	Explain how the study size was arrived at.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding.
		(*b*) Describe any methods used to examine subgroups and interactions.
		(*c*) Explain how missing data were addressed.
		(*d*) If applicable, explain how loss to follow-up was addressed.
		(*e*) Describe any sensitivity analyses.
Results		
Participants	13*	(a) Report number of individuals at each stage of the study: e.g., potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed.
		(b) Give reasons for non-participation at each stage.
		(c) Consider use of a flow diagram.

Supplemental Table S1. STROBE Statement—Checklist of items that should be included in reports of cohort studies (continued)

	Item no.	Recommendation
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposure and potential confounders.
		(b) Indicate the number of participants with missing data for each variable of interest.
		(c) Summarize follow-up time (e.g., average and total amount).
Outcome data	15*	Report number of outcome events or summary measures over time.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Clearly indicate which confounders were adjusted for and why they were included.
		(*b*) Report category boundaries when continuous variables were categorized.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.
Other analyses	17	Report other analyses done: e.g., analyses of subgroups and interactions, and sensitivity analyses.
Discussion		
Key results	18	Summarize key results with reference to study objectives.
Limitations	19	Discuss study limitations taking into account sources of potential bias or imprecision. Discuss both the direction and magnitude of any potential bias.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.
Generalizability	21	Discuss the generalizability (external validity) of the study results.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.



Supplemental Figure S1. Number of donations per year (1981-2010)


LOVE

Chapter 7

General discussion, recommendations, and future perspectives

Live kidney donation has become a wide accepted and implemented renal replacement therapy with the best prognosis and patient and graft survival as compared to dialysis. Nowadays, it is no longer indispensable in the treatment for patients with end-stage renal disease. However, the donation program is dependent on healthy individuals who are willing to undergo major surgery to improve the well-being of another individual. Therefore, the living donation program can only be legitimized when minimal discomfort during the procedure and maximum lifelong safety after donation can be guaranteed. In the past decades surgical techniques have been optimized and minimal invasive procedures have become the standard of care, leading to minimized discomfort and faster recovery compared to open procedures. Prior to donation potential donors are exhaustively screened to evaluate their medical suitability according to the Amsterdam forum donor eligibility acceptance criteria, established in 2004. These criteria evaluate potential donors with low risk for kidney-related morbidity or end-stage renal disease. However, due to the higher demand of organ donors, these criteria have been extended gradually and older donors and donors with minor comorbidities have become accepted for donation in the past decade. To date, short-term studies show excellent results regarding kidney function, mortality and morbidity but it should be noted that these studies do not include significant numbers of donors with extended eligibility acceptance criteria. In addition, focus on risk factors following live kidney donation has shifted from short-term to long-term evaluation, and from analysis of single center or national donor cohort studies to studies comparing donors with selected matched non-donors. Currently, knowledge is gathered to evaluate the lifelong health implications after living kidney donation.

EXISTING LITERATURE

Live kidney donation has started in the 1960s and has been implemented worldwide. Previous long-term studies demonstrated excellent results in favour of the donor, but recently discussion started on the long-term safety as studies were published suggesting unfavourable outcomes following donation compared with a cohort of matched non-donors (Chapter 2). These studies comprised large donor sample sizes compared with a matched cohort of non-donors from the general population. The baseline data for donors were derived from prospective national donor registries and for non-donors from population-based cohort studies or national health registries. The absolute risks for donors were demonstrated to be very low, while the adjusted risk analysis showed an increased risk additional to donation. Several explanations for these increased risks additional to donation have been suggested, most of them based on methodological design of studies; leading to bias and overestimation of risk. Donors are a medically

screened selection of the general population and thus inherently healthier. Therefore, donors should be matched to non-donors based on similar baseline conditions. Furthermore, the selection of donors and the comparison cohort of matched non-donors should maintain similar criteria. In recent studies, stricter exclusion criteria for non-donors led to a healthier non-donor cohort. In addition, after donation donors might be more aware of their health, being monitored on a regular base, and medical conditions could therefore be registered earlier in these donors than in non-donors. This might lead to a higher number of donors with a new event in their medical history as compared with non-donors and bias study outcome. As the absolute risks on morbidity after kidney donation are low, it's a challenge to define proper statistical analyses when trying to correct for confounding. Indeed, study design as such might lead to overadjusting for confounders and less reliable results. On the other hand, strong points of recent studies are the large sample sizes and longer follow-up. Future studies have to take the limitations and strong points in mind when trying to answer the question on long-term safety of living kidney donation. When consulting potential donors the results of these studies should be taken in consideration with their limitations in mind.

LONG-TERM FOLLOW-UP EVALUATION

Living kidney donors are selected according to the Amsterdam forum donor eligibility acceptance criteria and probably will have a lower risk for cardiovascular disease, kidney-related morbidity or end-stage renal disease during follow-up. However, life style may influence and dominate outcome and donors may have a disadvantage as renal reserve to compensate for loss of kidney function is reduced due to donation. As the development of cardiovascular disease or chronic kidney disease takes years, short-term follow-up studies might underreport these consequences. Therefore, long-term studies are necessary to define the safety boundaries of live kidney donation.

We have studied long-term outcomes ten and five years after donation in two prospective cohorts of 100 and 190 donors included between 2001-2004 and 2009-2011 respectively (Chapters 3 and 4), in randomized controlled trials comparing different surgical techniques. In the first study ten years after donation next to kidney function additional analyses were performed on (new-onset) hypertension, quality of life and survival. In the second study more donors with extended eligibility acceptance criteria were included, proteinuria and microalbuminuria were measured, kidney function decline registered, and kidney function compared to a selection of non-donors derived from the general population. In addition, longitudinal analyses were added on kidney function and quality of life to evaluate the effect of extended eligibility acceptance criteria, such as higher

age, higher BMI and the prevalence or incidence of hypertension, and to evaluate if donors were at risk for a progressive decline in kidney function.

Both studies demonstrated that kidney function initially declined after donation as might be expected, restored somewhat in the months thereafter and stabilized at a level identical to the one-year follow up measurement. Thereafter, the kidney function remained stable up to over ten years. The overall eGFR decline was 14% after ten years in the first cohort and 34% after five years in the second cohort. The additional comparison in the second study demonstrated that donors had a kidney function within the lower range of matched age-categories of a population-based reference group. Furthermore, there was no different outcome in eGFR or eGFR decline in donors with extended eligibility criteria. In addition, the second study demonstrated that no proteinuria or microalbuminuria was observed in any of the donors, not even in donors with an eGFR <60 ml/min/1.73 m^2. Donors with an eGFR <60 ml/min/1.73m^2 were significantly older at the time of donation and had a lower pre-donation kidney function than donors with an eGFR ≥60 ml/min/1.73m^2. In addition, the second study demonstrated that their eGFR decline was higher. Also, in longitudinal analyses of this study age and gender were associated with a decline in eGFR, whereas male gender was associated with a progressive decline in kidney function. None of the donors developed end-stage renal disease or required renal replacement therapy.

Donors who developed hypertension were significantly older at time of donation, with a higher BMI, and lower eGFR before donation when compared to donors who did not develop hypertension. Furthermore, the second study demonstrated that there were more donors with an eGFR <60 ml/min/1.73m^2 with new-onset hypertension compared to non-hypertensive donors. In addition, the second study found that donors with a pre-existent or new-onset hypertension did not have a progressive decline in kidney function. The kidney function of pre-existent hypertensive donors was not significantly different compared to non-hypertensive donors, while that of new-onset hypertensive donors was. However, the decline in kidney function of all these donors was not significantly different.

The quality of life scores of both studies were better or similar compared to general population scores, except for the mental component score in the second study. This was likely related to other life events than the donation. All quality of life scores significantly decreased at follow-up, as might be expected from data derived from the general population. The overall decrease in all measures overtime is a phenomenon that has also been observed in the general population. In longitudinal analyses age and gender were

associated with a decline in quality of life, which are known factors. Donors who have passed away during follow-up died due to non-donation related causes.

To increase the sample size of our studies and evaluate risk additional to donation by comparing donors to non-donors, we designed a comparitive follow-up study with individual level donor data matched with non-donors from two population-based prospective cohort studies to cover the whole age range of our donors (Chapter 6). We have incorporated the limitations of previous studies by selecting the entire donor cohort from 1981-2010 to evaluate outcomes on the long-term, selecting more and similar covariates for matching, and adjusting for more follow-up covariates during the analysis to enhance the comparability of donors to non-donors. This study comprised 761 included donors and 1522 non-donors from the general population for analysis. Our study demonstrated that live donors have reduced renal function compared to non-donors, occurring in the first year after donation and stabilizing thereafter for at least 8 years with equal outcome for morbidity or mortality as compared to non-donors. No differences were found in the risk on hypertension or cardiovascular disease and mortality.

CONCLUSION AND FUTURE PERSPECTIVES

In this thesis we have evaluated the long-term impact of living donation by reviewing the recent literature and analysing the current donor eligibility criteria. We have pointed out the limitations of recent studies on long-term outcome after live kidney donation that could have led to a potential overestimation of risk additional to donation. Key problems remain such as that donors are a pre-screened healthy selection of the general population, making it difficult to find an equal healthy unscreened comparison group. Studies should select the entire donor cohort to evaluate long-term outcomes, maintain similar selection criteria for donors and non-donors, match on baseline covariates to enhance comparability, and adjust for follow-up covariates to correct for lifestyle factors. We have evaluated the current donor eligibility acceptance criteria of our own center by performing a comparative follow-up cohort study in which donors were compared to matched non-donors and aforementioned adjustments have been implemented in the study design. The results demonstrated that one year after donation live kidney donors have a reduced renal function, remaining stable without any kidney-related morbidity or mortality to at least eight years of follow-up. However, the substantial decline in renal function may be further compromised when unforeseen circumstances affect renal function later in life. With the knowledge of this risk, albeit small, donors should be well-informed before donation and be offered lifelong follow-up thereafter. By monitoring the remnant renal function, donors

at risk may be identified in early stage and adequate treatment may be offered. We consider this approach a prerequisite to legitimize a living kidney donor program.

Future studies are indicated to consult potential donors on their specific additional risk for a progressive loss of renal function after kidney donation. Ideally, the next step would be to predict the attributable risk for future donors prior to donation by uncovering risk estimates for long-term outcomes and how these risks would change if an individual becomes a live kidney donor. It is of utmost importance to further evaluate the possible attributable risk for donors prior to donation to maintain lifelong donor safety.


LOVE

Chapter 8

Summary in English and Dutch

SUMMARY

Chapter 1 provides a general introduction with an overview of the development of live kidney donation over the years. The increasing incidence of end-stage renal disease (ESRD) and the persistent organ shortage warranted the need for new developments in renal replacement therapy in the late 1980s and 1990s. Studies demonstrated that renal transplantation offers the best prognosis and long-term benefit for patients with ESRD compared to other renal replacement therapies. The gap between deceased organ demand and supply increased the number of live kidney donations. Significant benefits for recipients from live kidney donor transplantation as compared to deceased organ transplantation were demonstrated in several studies: superior organ quality, increased graft survival and the possibility of pre-emptive transplantation. Furthermore, the surgical technique improved and it was demonstrated in several studies that live donor nephrectomy is a safe surgical procedure with a very low mortality rate. It must be noted that donors do have to meet the live kidney donor acceptance criteria to reduce risk additional to donation. Medical suitability of the donor is assessed by using criteria defined by the Amsterdam Forum, a group of experts that developed an international standard of care on live donor evaluation in 2004. Despite the excellent results and increasing numbers of live kidney donor transplantations, a shortage in donor kidneys still remained. Against this background a gradually extension of the donor acceptance criteria can be observed in recent years; donors with comorbidities such as cardiovascular disease, obesity and higher age are no longer denied for donation. Until now, short-term follow-up studies show excellent results regarding kidney function, morbidity, and mortality. In this thesis, data from the Erasmus MC program for living kidney donation, one of the largest programs in this area in Europe with a clear pioneering role, are analysed. Focus is directed on evaluation of live kidney donor safety and short-as well as long-term results are meticulously evaluated.

Chapter 2 presents a methodological review of the design and analysis of three larger studies suggesting a detrimental effect of live kidney donation at long-term follow-up. Interestingly, these studies were published by centers that did not observe any negative effects from live kidney donation in their donor population as described in earlier reports. Therefore, we analysed their data and compared reports to uncover contradictory outcomes. The three recent studies reported unfavourable long-term outcomes for live kidney donors following donation compared to non-donors, including an increased risk for cardiovascular and overall mortality, increased risk for ESRD, and increased risk for gestational hypertension and preeclampsia. Previous publications from these same research groups did not demonstrated unfavourable outcomes detrimental to live kidney donors. Moreover, they reported a lower risk of long-term cardiovascular and

overall mortality and lower risk of cardiovascular events. Our detailed review of the methodology revealed key differences with respect to selection criteria for donors and non-donors, data quality, follow-up, and statistical analysis. Recently published papers still face bias. In all studies, the comparison group of non-donors was healthier than donors due to more extensive exclusion criteria for non-donors. Selecting a healthier comparison group overestimates the risk additional to donation. Furthermore, donors could be more aware of their health than non-donors, leading to differential misclassification because all medical conditions could have been registered earlier, thus leading to more registered outcomes among donors and an overestimated risk additional to donation. Different matching strategies and statistical analyses were used in the more recent studies compared to the previous studies. In addition, the follow-up was longer in the recent studies. Strong points of the more recent papers as compared to initial analyses in the previous studies were the extended follow-up time, large sample sizes and better analysis, hence increasing the reliability to estimate potential risks for living kidney donors on the long-term. Even if risks are elevated among live kidney donors compared to non-donors, the absolute risks for donors following donation are very low and should therefore not discourage potential donors.

In 1981, the first live donor kidney transplantation was performed at the Erasmus MC, University Medical Center, Rotterdam, the Netherlands. Until now, over 1500 procedures have taken place. During this period surgical techniques were improved and evaluated by randomized controlled trials, which were conducted between 2001-2004, 2008-2010, and 2011-2012. The availability of these large prospective databases gives us the unique opportunity to study the long-term outcome. **Chapter 3** presents the ten-year follow-up of 100 donors included in a previous conducted randomized controlled trial (2001-2004) at the Erasmus MC comparing mini-incision open and laparoscopic donor nephrectomy. The follow-up period was between November 2011 and February 2014. Ninety-one percent of the initial donor cohort was alive at 10-year follow-up. The donor response rate with regard to the quality of life forms was 80%. One donor lives abroad and was lost to follow-up. Therefore, annual data on kidney function and blood pressure was available for 90% of the donors. Median follow-up of the donor population was 10 years. After an initial decline in eGFR in the first year after donation, the kidney function remained stable over the rest of the follow-up years, resulting in a median eGFR loss of 14%. Donors with a ten-year eGFR <60 ml/min/1.73m^2 had a significantly lower baseline eGFR and were significantly older at the moment of donation. No donors were found at risk for ESRD. Donors with pre-existing hypertension had a well-regulated blood pressure and a median eGFR of 69.0 ml/min/1.73m^2 at follow-up. Twenty-three donors developed new-onset hypertension 10 years after donation, which was adequately treated with medication. These donors had a significantly lower median eGFR at follow-up than

donors without hypertension. Donors with new-onset hypertension were significantly older at the time of donation than donors who did not developed hypertension. Most of the ten-year follow-up quality of life and fatigue scores were significantly decreased compared to predonation scores. However, all follow-up data on quality of life and fatigue scores was either better or similar as compared to the general population scores. Nine donors died during follow-up of unrelated causes to donation.

Chapter 4 presents the five-year follow-up of 190 donors included in a previous conducted randomized controlled trial (2008-2010) at the Erasmus MC comparing left-sided laparoscopic and hand-assisted donor nephrectomy. During this period extended donor acceptance criteria were already implemented in our center, giving us the unique opportunity to evaluate the safety of donors with extended acceptance criteria. Thirty-two percent of the donors (n=61) had (multiple) extended eligibility criteria: pre-existent hypertension (n=30), age >70 years (n=10), and BMI >30 kg/m^2 (n=26). The follow-up measurements were between November 2015 and January 2016. Five donors were lost to follow-up, leaving clinical data available for >90% of the donors. The mean follow-up was 5.1 years. After an initial decline post-donation, the renal function was stable in living kidney donors at five-year follow-up; mean eGFR of 60.2 ml/min/1.73m^2, with a mean serum creatinine level of 105.1 µmol/ml, resulting in a mean decline in eGFR of 33.7%. Furthermore, no different outcome in eGFR (p=0.479) or eGFR decline (p=0.159) was found in donors with extended eligibility criteria (n=61) as compared with donors without these criteria. At five-year follow-up none of the donors had proteinuria or microalbuminuria. The five-year follow-up mean eGFR of male and female donors stratified in age categories were significantly different to that of the general population. Ninety-three donors had an eGFR <60 ml/min/1.73m^2 at five-year follow-up without proteinuria or microalbuminuria. These donors were significantly older at the time of donation and had a significantly lower eGFR pre-donation than donors with a current eGFR of ≥60 ml/min/1.73m^2. In addition, their eGFR decline was significantly higher at five-year follow-up. No donors were found at risk for ESRD or renal replacement therapy. In longitudinal analysis, eGFR and creatinine were significantly affected by male gender and declined with ageing. Thirty donors had pre-existent hypertension with a mean eGFR of 57.6 ml/min/1.73m^2 at five-year follow-up with a corresponding mean serum creatinine level of 103 µmol/ml. Their mean eGFR and serum creatinine level was not significantly different than non-hypertensive donors. These donors had well-regulated hypertension at follow-up. Twenty-nine donors developed new-onset hypertension, which was mostly treated with medication. There was no significant change in mean eGFR and serum creatinine level at one-year versus five-year after donation in donors who developed new-onset hypertension. The five-year mean eGFR was 54.2 ml/min/1.73m^2 with a corresponding mean serum creatinine level of 119 µmol/ml. However, their five-year

mean eGFR and serum creatinine level were significantly different compared to non-hypertensive donors, while the eGFR decline was not significantly different. New-onset hypertensive donors were significantly older at the time of donation, with a significantly higher BMI and a significantly lower eGFR before donation than non-hypertensive donors. Furthermore, there were more new-onset hypertension donors with an eGFR <60 ml/min/1.73m^2 than non-hypertensive donors. Longitudinal analysis demonstrated no significant effect of new-onset hypertension on eGFR. All follow-up data from donors on quality of life scores were higher as compared to data from the general Dutch population, except for the mental component score. Eight donors died during follow-up due to causes unrelated to donation.

Live kidney donation is possible due to the capacity of the remnant kidney to compensatory increase in size post-donation. It represents renal adaptation and is associated with renal function. During live kidney donor screening a CT or MRI is performed to assess the size of both kidneys. The correlation between kidney size on these imaging modalities and ultrasonography is unknown. As ultrasonography is the preferred imaging modality for follow up after donation, being less time-consuming for health care professionals, and less harmful and expensive for patients, we compared the results of this imaging technique with CT findings in **chapter 5**. Fifty consecutive donors, with a pre-donation CT-scan, were approached preoperatively for an additional ultrasound examination by two ultrasonographists (US-1; US-2). The ultrasound kidney volume measurements were compared to the pre-donation CT kidney volume measurement. The ultrasound measurements were considered accurate when the mean differences between both ultrasonographists for similar measurements were <5 mm. Ultrasound volumes were calculated with the ellipsoid equation (length x width x thickness x π/6) and an adjusted equation (correction factor 0.674 instead of π/6), and CT volumes with the voxel count method. The latter is considered the gold standard. One hundred kidneys were measured. The mean differences between US-1 and US-2 for similar measurements of length, width and thickness were <5 mm and were therefore deemed accurate. Ultrasound measurements for kidney volume were comparable with the pre-donation CT measurements, especially when the adjusted ultrasound volume equation was used. Based on these results a personalised correction factor can be calculated.

Chapter 6 presents the preliminary results of a study comparing donors of the Erasmus MC donor population from 1981 through 2010 and non-donors from population-based cohort studies of the Rotterdam Study and Study of Health in Pomerania (SHIP). Between 1981 and 2011 a total of 1092 live kidney donations were performed at our center and all donors were eligible for inclusion in the analysis; 761 donors were included of whom 705 visited the outpatient clinic. Non-donors were included from the Rotterdam

Study and SHIP, resulting in 1522 included non-donors; 54.1% from the Rotterdam Study and 45.9% from SHIP. Age, baseline systolic blood pressure, ethnicity, and education were significantly different between donors and non-donors, but differences were relatively small. The eGFR for the entire studied donor population was a median of 59.9 ml/min/1.73m^2 at follow-up with a median creatinine of 100 µmol/l. The primary outcomes for renal function were all significantly inferior for donors compared to non-donors; serum creatinine was significantly higher (+26.03 µmol/l (95% CI 24.17; 27.89)) and the eGFR significantly lower (-27.23 ml/min/1.73 m2 (95% CI -28.61; -25.85)). The eGFR declined 31.70 percent (95% CI 29.94; 33.46) more among donors than non-donors (all p<0.001). Sixteen donors (2.4%) and 10 non-donors (1.2%) developed microalbuminuria (p=0.09). Two of the included donors (0.3%) developed ESRD. The secondary outcomes demonstrated that there is no difference in BMI, new-onset diabetes, and cardiovascular mortality between donors and non-donors. A significantly lower risk of developing new-onset hypertension (OR 0.45, 95% CI 0.33; 0.62) and overall mortality (OR 0.13, 95% CI 0.06; 0.27) was found among donors. Nine included donors (1.2%) passed away after visiting one of the study hospitals prior to their death of non-donation related causes. The health-related quality of life score was significantly higher among donors with 0.06 higher score for EQ-5D (95% CI 0.05; 0.08 on a scale of -0.59 to 1.00) The SF-12 physical and mental component score were both significantly lower among donors: -1.36 (95% CI -2.38; -0.33) and -4.61 (95% CI -5.75; -3.47), respectively, on a scale of 0-100. One year after donation live donors have a reduced renal function, remaining stable without any kidney-related morbidity or mortality to at least eight years of follow-up. However, the decline in renal function may be further compromised when unforeseen conditions would develop that additionally affect renal function. Having knowledge of this risk, albeit small, donors should be well-informed by the medical team and offered lifelong follow-up to monitor the remnant renal function.

SAMENVATTING

Hoofdstuk 1 geeft een overzicht van de ontwikkeling en opkomst van levende nierdonatie. De stijgende incidentie van eindstadium nierfalen en het aanhoudende tekort aan organen leidde tot nieuwe ontwikkelingen in nierfunctievervangende therapie in de jaren '90. Uit studies bleek dat niertransplantatie de beste prognose biedt met langdurig voordeel voor patiënten met eindstadium nierfalen in vergelijking met andere nierfunctievervangende therapie. De kloof tussen vraag naar en aanbod van organen heeft geleid tot een stijging van het aantal levende nierdonaties in meerdere landen. De voordelen van levende nierdonatie ten opzichte van postmortale nierdonatie voor de ontvanger werden in meerdere studies aangetoond en betreffen een betere orgaankwaliteit, een verhoogde overleving van het transplantaat en de mogelijkheid om preemptief te transplanteren. Bovendien werden de chirurgische technieken steeds beter en studies toonden aan dat het uitnemen van een nier bij een levende donor een veilige chirurgischeprocedure is met een zeer laag mortaliteitsrisico. Deze uitkomsten zijn echter gebaseerd op data uit een periode waarin werd uitgegaan van goed gedefinieerde en veilige criteria waaraan een donor moest voldoen om risico's van de ingreep voor de donor zo klein mogelijk te maken. Deze criteria werden in 2004 opgesteld in een internationale consensusbijeenkomst georganiseerd in Amsterdam. Ondanks de goede resultaten en verdere groei van levende nierdonatie bleef er een tekort aan donornieren bestaan. Op basis van enerzijds de goede uitkomsten en anderzijds het persisterende tekort aan donornieren werden in de loop der jaren de acceptatiecriteria voor donoren geleidelijk verruimd: een minimale comorbiditeit, zoals bijv. hart- en vaatziekten, obesitas en een hogere leeftijd, werd niet meer beschouwd als absolute contra-indicatie. Tot op heden tonen studies met een korte termijn follow-up van nierdonoren uitstekende resultaten voor nierfunctie, morbiditeit en mortaliteit. In dit proefschrift wordt in dit kader de data van het Erasmus MC programma voor nierdonatie bij leven geanalyseerd, één van de grootste programma's op dit gebied in Europa met een duidelijke pioniersfunctie. Zowel korte als lange termijn resultaten zullen worden gepresenteerd met nadruk op veiligheid voor de donor.

Hoofdstuk 2 geeft de resultaten weer van een methodologische review naar de opzet en analyses van studies van drie gerenommeerde onderzoeksgroepen op het gebied van levende nierdonatie. Deze review is opgezet om een verklaring te vinden voor de tegenstrijdige resultaten van recente en eerdere studies van dezelfde onderzoeksgroepen. De meest recente studies tonen ongunstige resultaten voor donoren ten opzichte van niet-donoren. Volgens deze studies hebben donoren een verhoogd risico op (cardiovasculaire) mortaliteit, eindstadium nierfalen en zwangerschapshypertensie en pre-eclampsie. In de drie eerdere studies van deze onderzoeksgroepen was er echter

geen sprake van ongunstige resultaten voor donoren. Deze studies lieten juist zien dat donoren een lager risico hebben op (cardiovasculaire) mortaliteit en cardiovasculaire incidenten ten opzichte van niet-donoren. Onze gedetailleerde beschrijving van de methodologie van de zes studies laat belangrijke verschillen zien in de selectiecriteria van donoren en niet-donoren, kwaliteit van de data, follow-up duur en statistische analyses, die de tegenstrijdige resultaten kunnen verklaren. In de recente studies is nog steeds sprake van bias. In alle studies was de vergelijkingsgroep van niet-donoren gezonder dan de donoren door de uitgebreidere niet-donor exclusiecriteria. Hierdoor worden risico's die toe te schrijven zijn aan donatie overschat. Daarnaast kan het zo zijn dat donoren zich meer bewust zijn van hun gezondheid dan niet-donoren. Dit leidt tot differentiële misclassificatie, omdat aandoeningen eerder geregistreerd worden. Hierdoor zijn er meer geregistreerde uitkomstmaten onder donoren, waardoor het risico van donatie overschat wordt. Sterke punten van de recentere studies waren de langere follow-up duur, de grotere aantallen donoren en de verbeterde statistische analyses. Hierdoor zijn de uitkomsten van de recentere studies betrouwbaarder. Ondanks dat studies een verhoogd risico onder donoren laten zien in vergelijking met niet-donoren, moet benadrukt worden dat de absolute risico's zeer laag zijn en een toekomstige donor niet mogen ontmoedigen.

In 1981 is in het Erasmus MC de eerste nierdonatie bij leven uitgevoerd. Sindsdien zijn er meer dan 1500 procedures uitgevoerd. Gedurende deze periode zijn er tussen 2001-2004, 2008-2010 en 2011-2012 drie gerandomiseerde onderzoeken uitgevoerd om de chirurgische techniek te verbeteren. Deze drie grote prospectieve databases bieden de unieke kans om langetermijnuitkomsten te onderzoeken. In **hoofdstuk 3** worden de resultaten gepresenteerd van een 10-jaars follow-up studie onder 100 donoren, die tussen 2001-2004 in het Erasmus MC hebben deelgenomen aan een gerandomiseerd onderzoek naar mini-open versus laparoscopische donor nefrectomie. De follow-up periode eindigde tussen november 2011 en februari 2014, afhankelijk van het moment van donatie. Na 10 jaar is 91% van het initiële donor cohort nog in leven. Tachtig procent van deze donoren heeft de toegestuurde vragenlijsten over de kwaliteit van leven ingevuld. Van één donor waren geen follow-up gegevens beschikbaar. Hierdoor was er klinische data over de nierfunctie en bloeddruk beschikbaar van 90% van het initiële donor cohort. De gemiddelde follow-up was 10 jaar. De nierfunctie is in de loop van de afgelopen 10 jaar stabiel gebleven na een initiële daling van de eGFR binnen het eerste jaar na de donatie. Dit resulteert in een eGFR verlies van 14% na 10 jaar. Donoren met een 10-jaars eGFR <60 ml/min/1.73m^2 hadden een significant lagere baseline eGFR en waren significant ouder bij de follow-up. Geen van de donoren heeft een risico gehad op eindstadium nierfalen. Donoren met een pre-existente hypertensie bleken een goed gereguleerde bloeddruk te hebben met een mediane eGFR van 69,0 ml/min/1,73m^2 bij

follow-up. Drieëntwintig donoren hebben 10 jaar na donatie hypertensie ontwikkeld, die adequaat medicamenteus behandeld werd. Deze donoren hebben een significant lagere mediane eGFR bij follow-up dan donoren zonder hypertensie. Donoren die hypertensie hebben ontwikkeld, waren significant ouder op het moment van donatie in vergelijking met de donoren die geen hypertensie ontwikkelden. De meeste 10-jaars scores voor kwaliteit van leven en vermoeidheid zijn significant gedaald ten opzichte van de scores ten tijde van donatie. Echter, al deze follow-up scores voor kwaliteit van leven en vermoeidheid zijn beter of vergelijkbaar met die van de algemene bevolking. Negen donoren zijn gedurende de follow-up overleden aan niet-donatie gerelateerde oorzaken.

In **hoofdstuk 4** worden de resultaten gepresenteerd van een 5-jaars follow-up studie onder 190 donoren, die tussen 2009-2011 in het Erasmus MC hebben deelgenomen aan een gerandomiseerd onderzoek naar linkszijdige hand-geassisteerde versus laparoscopische donor nefrectomie. Dit cohort is bijzonder omdat in deze periode verruiming van acceptatiecriteria voor nierdonoren in ons centrum al was geïntroduceerd. Dit biedt ons de mogelijkheid om ook de veiligheid van deze groep donoren te evalueren. Tweeëndertig procent van de donoren (n=61) behoorde tot deze groep. De follow-up periode was tussen november 2015 en januari 2016. Follow up gegevens waren niet beschikbaar voor vijf donoren. Hierdoor was er klinische data beschikbaar van meer dan 90% van het initiële donor cohort. De gemiddelde follow-up duur was 5,1 jaar. Vijf jaar na donatie is de nierfunctie stabiel gebleven, overigens na een initiële daling van de nierfunctie direct na donatie. De 5-jaars eGFR is 60,2 ml/min/1,73 m^2 met een gemiddeld serum creatinine van 105,1 µmol/ml. Dit resulteert in een eGFR daling van 33,7% na 5 jaar. Tevens was er geen verschil in eGFR (p=0.479) en eGFR daling (p=0.159) tussen donoren met verruimde acceptatiecriteria en de andere donoren. Bij geen van de donoren was er sprake van proteïnurie of microalbuminurie. Na stratificatie van de 5-jaars eGFR van mannen en vrouwen in leeftijdscategorieën, blijkt dat de gemiddelden van deze waarde significant verschillen van de eGFR waarden van de algemene bevolking. Drieënnegentig donoren hebben een eGFR <60 ml/min/1.73m^2 vijf jaar na donatie zonder dat er sprake is van proteïnurie of microalbuminurie. Deze donoren waren beduidend ouder op het moment van donatie en hadden een significant lagere eGFR pre-donatie dan donoren met een huidig eGFR van ≥60 ml/min/1,73m^2. Bovendien is de eGFR daling van deze donoren significant hoger na vijf jaar follow-up, overigens zonder dat er een risico is op nierfalen. Uit de longitudinale analyse blijkt dat de eGFR en creatinine significant beïnvloed worden door het mannelijk geslacht en respectievelijk dalen en stijgen met de stijging van de leeftijd. Dertig donoren met pre-existente hypertensie hadden na vijf jaar een gemiddelde eGFR van 57,6 ml/min/1,73m^2 met een serum creatinine van 103 µmol/ml. De eGFR en het serum creatinine waren niet significant verschillend ten

opzichte van donoren zonder hypertensie. De bloeddruk van deze donoren was middels medicatie goed gereguleerd bij follow-up. Negenentwintig donoren hebben in de loop van 5 jaar hypertensie ontwikkeld, bij de meesten medicamenteus behandeld. Er was geen significant verschil tussen de 1-jaars en 5-jaars eGFR of het serum creatinine van deze donoren bij een 5-jaars eGFR van 54.2 ml/min/1,73m^2 en een serum creatinine van 119 µmol/ml. Deze waarden zijn wel significant verschillend ten opzichte van de 5-jaars eGFR en het serum creatinine van donoren zonder hypertensie. De eGFR daling tussen deze twee groepen is niet significant verschillend. Donoren die hypertensie hebben ontwikkeld waren significant ouder ten tijde van donatie met een significant hogere BMI en een significant lagere eGFR dan donoren zonder hypertensie na 5 jaar. Daarnaast waren er meer donoren met een eGFR <60 ml/min/1,73m^2 in de groep donoren die hypertensie had ontwikkeld dan in de groep donoren die geen hypertensie had ontwikkeld. Uit de longitudinale analyse blijkt dat er geen effect is van nieuw ontstane hypertensie op de eGFR. Alle 5-jaars kwaliteit van leven scores waren hoger in vergelijking met die van de algemene Nederlandse bevolking, met uitzondering van de mentale component score. Acht donoren zijn gedurende de follow-up overleden aan niet-donatie gerelateerde oorzaken.

Levende nierdonatie is mogelijk, doordat na donatie de overgebleven nier compensatoir toeneemt in grootte. Dit is een uiting van adaptatie om te compenseren voor het verlies van nierfunctie. Voor donatie wordt de grootte van de nieren bepaald met een CT-scan of MRI. Het verschil tussen de grootte van de nier gemeten met voorgaand genoemde modaliteiten van afbeeldend onderzoek en echografische bepaling van het niervolume zijn onbekend. Echografie is echter de eerste keuze voor beeldvormend onderzoek in de follow-up van nierdonoren. Er zijn duidelijke voordelen om echografisch onderzoek te gebruiken voor follow-up van nierdonoren: de techniek is niet invasief, het onderzoek duurt korter, is patientvriendelijker en brengt minder kosten met zich mee. In **hoofdstuk 5** hebben we uitgezocht of echografisch niervolumemetingen gebruikt kunnen worden om de mate van adaptatie en, indirect, de stabilisatie van de nierfunctie na donatie te vervolgen. Vijftig opeenvolgende donoren met een predonatie CT-scan werden een dag voor de donor nefrectomie benaderd voor een extra echografie onderzoek door twee ervaren echografisten (US-1 en US-2). De echografie niervolumes werden vergeleken met de pre-donatie CT niervolumes. De echografie metingen werden accuraat bevonden als het gemiddelde verschil tussen US-1 en US-2 voor dezelfde metingen minder dan 5 mm zou zijn. Echografi31,70 niervolumes werden berekend middels de ellips formule (lengte x breedte x dikte x π/6) en een aangepaste formule (correctiefactor 0,674 in plaats van π/6). De CT volumes werden berekend middels de voxel count methode wat wordt gezien als de gouden standaard. In totaal zijn er 100 nieren door de twee echografisten afzonderlijk gemeten. De gemiddelde verschillen tussen US-1 en US-2 in lengte, breedte

en dikte metingen is <5 mm en daardoor is aangenomen dat dit accurate metingen zijn. Indien de aangepaste niervolume formule wordt gebruikt, komen de echografische niervolume metingen overeen met de pre-donatie CT niervolume metingen. Tevens kan op basis van deze resultaten een persoonlijke correctiefactor berekend worden.

Hoofdstuk 6 geeft de eerste resultaten weer van een studie waarin donoren van het Erasmus MC uit de periode 1981 tot en met 2010 worden vergeleken met niet-donoren uit prospectieve cohort studies van de Rotterdam Studie en Study of Health in Pomerania (SHIP). In deze periode zijn 1092 levende nierdonaties uitgevoerd in ons centrum, welke allen in aanmerking kwamen voor inclusie in deze studie. In totaal zijn 761 donoren geïncludeerd. De gemiddelde follow-up tijd voor donoren was 8,0 (5,1-11,9) jaar. De populatie niet-donoren bedroeg 1522 deelnemers, 54,1% van de Rotterdamse Studie en 45,9% van SHIP. De gemiddelde follow-up tijd voor niet-donoren was 7,0 (5,4-10,9) jaar. Leeftijd, systolische bloeddruk, opleidingsniveau en etniciteit toonden een significant verschil tussen donoren en niet-donoren, maar deze verschillen waren relatief klein. De gemiddelde eGFR voor de geïncludeerde donorpopulatie was 59.9 ml/min/1,73m^2 bij follow-up met een gemiddeld creatinine van 100 µmol/l. De primaire uitkomstmaten voor de nierfunctie waren allen significant verschillend voor donoren en niet-donoren (p <0,001). Het serumcreatinine was significant hoger met +26,03 µmol/l voor donoren en de eGFR was significant lager met -27,23 ml/min/1,73m^2. De eGFR daling was 31,70% lager voor donoren. Zestien donoren (2,4%) en tien niet-donoren (1,2%) ontwikkelden microalbuminurie (p=0,09). Twee van de geïncludeerde donoren (0,3%) ontwikkelden eindstadium nierfalen. De secundaire uitkomstmaten tonen dat er geen verschil is in BMI, ontwikkelen van diabetes en cardiovasculaire events en sterfte tussen donoren en niet-donoren. Tevens hebben donoren een significant lager risico op het ontwikkelen van hypertensie (OR 0,45, 95% CI 0,33; 0,62) en sterfte (OR 0,13, 95% CI 0,06; 0,27). Negen donoren (1,2%) overleden na inclusie aan niet-donatie gerelateerde oorzaken. De gezondheid gerelateerde kwaliteit van leven scores waren lager, maar de verschillen waren relatief klein. In deze studie hebben we aangetoond dat donoren een verminderde nierfunctie hebben in vergelijking met personen uit de algemene populatie zonder een verhoogd effect op morbiditeit en mortaliteit in de geanalyseerde tijdsperiode. Deze studie toont aan dat een jaar na donatie levende donoren een verminderde nierfunctie hebben welke daarna stabiel blijft, zonder nier gerelateerde morbiditeit of mortaliteit gedurende de geanalyseerde periode. Echter, de afname van nierfunctie zou verder kunnen worden aangetast door onvoorziene medische omstandigheden die een additioneel effect hebben op de nierfunctie. Met dit risico in het achterhoofd, hoe klein ook, dienen donoren goed geïnformeerd te worden door het medisch team. Daarnaast is het verantwoord om donoren een levenslange follow-up van de overgebleven nierfunctie aan te bieden om deze te kunnen monitoren.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Appendices

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List of publications

PhD Portfolio

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A

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LIST OF PUBLICATIONS

This thesis

Impact after live kidney donation study: a long-term comparative follow-up study
Janki S, Dehghan A, van de Wetering J, Steyerberg EW, Klop KWJ, Kimenai HJAN, Rizopoulos D, Hoorn EJ, Stracke S, Weimar W, Völzke H, Hofman A, IJzermans JNM
Manuscript in preparation

Follow-up after living kidney donation: validation of ultrasonographic kidney volume measurements to monitor compensatory kidney adaptation
Janki S, Kimenai HJAN, Looman CW, Dijkshoorn ML, Dwarkasing RS, IJzermans JNM
Exp Clin Transpl. 2016 Nov 7 *Accepted for publication*

Five-year follow-up after live donor nephrectomy – Analysis of a prospective cohort within the era of extended donor acceptance criteria
Janki S, Dols LFC, Timman R, Mulder EEAP, Dooper PhMM, van de Wetering J, IJzermans JNM
Transpl Int 2016 Oct 7 *In Press*

Live kidney donation: are concerns about long-term safety justified? - A methodological review
Janki S, Steyerberg EW, Hofman A, IJzermans JNM
Eur J Epidemiol. 2016 Jun 28 *In Press*

Long-term follow-up after live kidney donation (LOVE) study: a longitudinal comparison study protocol
Janki S, Klop KWJ, Kimenai HJAN, van de Wetering J, Weimar W, Massey EK, Dehghan A, Rizopoulos D, Völzke H, Hofman A, IJzermans JNM
BMC Nephrol. 2016 Feb 1;17(1):14

More than a decade after live donor nephrectomy - a prospective cohort study.
Janki S, Klop KWJ, Dooper PhMM, Weimar W, IJzermans JNM, Kok NF
Transpl Int. 2015 Nov;28(11):1268-75

Surgical aspects of live kidney donation - An updated review
Janki S, Dor FJMF, IJzermans JNM
Front Biosci (Elite Ed). 2015 Jan 1;7:346-65

Others

Left ventricular echocardiographic measurements and decline in kidney function: the Rotterdam Study
Janki S, Sedaghat S, IJzermans JNM, Hofman A, Franco OH, Hoorn EJ, Felix JF, Dehghan A
Submitted

Ergonomics in the operating room
Janki S, Mulder EEAP, IJzermans JNM, Tran TCK
Surg Endosc. 2016 Oct 17 *in Press*

First case report of chylous ascites after robot-assisted donor nephrectomy: overview of occurrence and management of this rare complication
Janki S, Terkivatan T, Kimenai HJAN, IJzermans JNM, Tran TCK
J Surg Case Rep. 2016 Jul 5;2016(7)

Robotic surgery fast and successfully implemented in a high volume laparoscopic center on living kidney donation
Janki S, Klop KWJ, Hagen SM, Terkivatan T, Betjes MGH, Tran TCK, IJzermans JNM
Int J Med Robot. 2016 Mar 14 *in Press*

Renal vascular management during live donor nephrectomy
Janki S, Verver D, Klop KWJ, Friedman AL, Peters TG, Ratner LE, IJzermans JNM, Dor FJMF
Am J Transplant. 2015 Jun;15(6):1701-7

Levende nierdonatie niet louter via sleutelgaten
IJzermans JNM, Janki S
Je nier of je leven! Den Haag: Stichting Biowetenschappen en Maatschappij; 2014. p. 42-3

PHD PORTFOLIO

Name PhD student: Shiromani Janki
PhD period: 2012-2016
Erasmus MC Department: Surgery
Promotors: Jan N.M. IJzermans & A. Hofman
Research School: Molecular Medicine
Supervisor: Jan N.M. IJzermans

1. PHD TRAINING

	Year	Workload (ECTS)
General courses		
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2012	1.5
- Systematic literature retrieval	2013	0.5
- Basiscursus in SPSS	2013	0.8
- Centrum voor Patientgebonden Onderzoek	2013	1.0
Specific courses (e.g. Research school, Medical Training)		
- Hesperis Course	2013	1.0
- Evidence in Transplantation Course - Systematic review and meta-analysis	2013	0.5
Seminars and workshops		
- Erasmus MC Transplant Seminar Series	2013-2016	1.0
- European Transplant Fellow Workshop	2014	2.0
Oral and poster presentations		
- European Society of Organ Transplantation Congress	2013, 2015	3.0
- European Association for Endoscopic Surgery Congress	2013, 2016	2.0
- Nederlandse Vereniging voor Endoscopische Chirurgie Jaarcongres	2014	1.0
- World Transplant Congress	2014	2.0
- European Society for Surgical Research Congress	2014	1.0
- Wetenschapsdag Heelkunde, Erasmus MC	2014-2015	2.0
- Nederlandse Transplantatie Vereniging Congres	2014-2015	2.0
- American Transplant Congress	2015-2016	2.0
- International Congress of The Transplantation Society	2016	1.0
(Inter)national conferences		
- Chirurgendagen	2013-2016	4.0
- Najaarsvergadering	2014	1.0
- Nederlandse Vereniging voor Endoscopische Chirurgie Jaarcongres	2015	1.0
- Nederlandse Transplantatie Vereniging Congres	2016	1.0

2. TEACHING

	Year	Workload (ECTS)
Lecturing		
- Proefstuderen 5/6 VWO scholieren	2013	0.5
- Live Donor Nephrectomy Course	2013-2016	2.0
- 3e Regionale nascholing afdeling Nefrologie, Erasmus MC	2016	0.5
Supervising practicals and excursions, Tutoring		
- Examination of Basic Life Support of medical students	2013-2016	1.0
Supervising Master's theses		
- D. Verver	2014	2.0
- E.E.A.P. Mulder	2015	2.0

CURRICULUM VITAE

Shiromani Janki werd op 25 januari 1986 geboren te 's-Gravenhage, alwaar zij opgroeide. Na het behalen van haar VWO-diploma aan het Segbroek College te 's-Gravenhage in 2004, startte zij met de opleiding Geneeskunde aan de Erasmus Universiteit Rotterdam. De laatste fase van haar opleiding heeft zij voltooid op de afdeling Heelkunde van het Reinier de Graaf Gasthuis in Delft, waarna zij 3 maanden doorbracht in Australië voor een keuze-coschap op de afdeling Spoedeisende Hulp van het Alfred Hospital in Melbourne. In februari 2012 behaalde zij haar artsenbul en een maand later begon zij als arts-assistent niet in opleiding op de afdeling Heelkunde van het Erasmus MC in Rotterdam. In november 2012 begon zij als arts-onderzoeker aan een promotie-traject op de afdeling Heelkunde van het Erasmus MC onder begeleiding van prof.dr. J.N.M. IJzermans (Heelkunde) en prof.dr. A. Hofman (Epidemiologie). De onderzoeken naar langetermijngevolgen na nierdonatie hebben geleid tot de totstandkoming van dit proefschrift. Tijdens haar promotie-traject heeft zij de Master of Health Sciences opleiding afgerond met als specialisatie Clinical Epidemiology aan het Netherlands Institute for Health Sciences - Erasmus MC. Na afronding van haar promotie-traject in juli 2016 is zij weer teruggekeerd naar de kliniek als arts-assistent niet in opleiding.