



Published in final edited form as:

*Am J Transplant.* 2014 August ; 14(8): 1853–1861. doi:10.1111/ajt.12822.

## Mortality and Cardiovascular Disease among Older Live Kidney Donors

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### Abstract

Over the past two decades, live kidney donation by older individuals (> 55 years) has become more common. Given strong associations of older age with cardiovascular disease, nephrectomy could make older donors vulnerable to death and cardiovascular events. We performed a cohort study among older live kidney donors who were matched to healthy older individuals in the Health and Retirement Study. The primary outcome was mortality ascertained through national death registries. Secondary outcomes ascertained among pairs with Medicare coverage included death or cardiovascular disease ascertained through Medicare claims data. During the period from 1996 – 2006, there were 5717 older donors in the United States. We matched 3368 donors 1:1 to older healthy non-donors. Among donors and matched pairs, the mean age was 59 years; 41% were male and 7% were black race. In median follow-up of 7.8 years, mortality was not different between donors and matched pairs ( $p=0.21$ ). Among donors with Medicare, the combined outcome of death/CVD ( $p=0.70$ ) was also not different between donors and non-donors. In

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#### DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*. The funding sources were neither involved in the design, conduct nor analysis of the study.

#### Supporting Information

Additional Supporting Information may be found in the online version of this article.

summary, carefully selected older kidney donors do not face a higher risk of death or CVD. These findings should be provided to older individuals considering live kidney donation.

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## INTRODUCTION

The lower glomerular filtration rate (GFR) associated with aging has raised concerns about the safety of living kidney donation by older adults. Further, given the strong associations between both older age and chronic kidney disease with cardiovascular disease (CVD), older live kidney donors could have an augmented risk of CVD attributable to nephrectomy. Despite these concerns, older individuals (> 55 years of age) represent a rapidly growing segment of live kidney donors and two consecutive surveys of transplant center policies suggest that centers are increasingly willing to accept older kidney donors.(1, 2)

Epidemiological and physiological studies have demonstrated loss of kidney function associated with older age, although this loss varies widely among individuals.(3-6) The National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of stage 3 – 4 chronic kidney disease increased from 0.7% in the 20 – 39 year age group to 37.8% among individuals >70 years in the general population.(7) Directly measured hemodynamics and clearance reveal that healthy older individuals have lower renal plasma flow, increased vascular resistance, and higher filtration fraction compared to their younger counterparts.(8) Pathological examination of kidneys from older patients shows nephrosclerosis, loss of glomeruli, and loss of renal mass.(9-11)

For older donors, diminished filtration function at baseline might impair the ability of the remnant kidney to perform adaptive hyperfiltration and promote progressive kidney disease or comorbidities such as CVD. On the other hand, given that older donors have fewer expected years of survival compared to younger donors, older donors will experience a briefer period with a single kidney, which might reduce the opportunity for adverse consequences of nephrectomy.(12)

Prior epidemiological studies have been limited by small numbers of older live kidney donors, single-center populations, short-term follow-up, or a lack of CVD outcomes. In a single-center study of older live kidney donors in the Netherlands, older age was associated with lower GFR both pre-donation and post-donation, with lower eGFR and lesser augmentation of GFR in response to dopamine.(5) In three related studies using United States (US) registry data, older kidney donors had similar rates of mortality but higher rates of end-stage renal disease (ESRD) compared to healthy non-donors identified through NHANES. However, the health of the non-donor comparators was determined during an earlier period when the donors underwent nephrectomy, creating the possibility of a less-healthy comparison group.(13-15) Canadian studies of CVD outcomes among live kidney donors had a small percentage of older donors.(16,17) Therefore, the primary aim of this study was to compare rates of death and CVD in a large cohort of older live kidney donors to contemporary, healthy matched non-donors.

## METHODS

### Design

We conducted this matched cohort study after receiving approval from the University of Pennsylvania Institutional Review Board. Using risk set matching,(18,19) individuals who underwent donor nephrectomy between 1996 and 2006 and were 55 years at the time of donation were matched to similar individuals selected from the Health and Retirement Study (HRS).

### Data Sources

This study used registry data on live kidney donors from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS). The OPTN collects demographic and limited clinical data on all live kidney donors in the US at donation. The donor dataset was linked to Medicare Part A, Part B, and outpatient records.

The HRS is an NIH-funded longitudinal cohort study that, since the year 1992, has enrolled a nationally representative sample of >25,000 adults >50 years of age in the US. Through comprehensive interviews, the HRS collects information about physical and mental functioning, comorbidities, and quality of life.(20,21) The HRS conducts national probability sampling of US households, with oversampling of blacks and Hispanics. Participants are re-contacted at regular intervals (currently every two years).(22) The HRS linked interview data with Medicare claims for participants who provided consent to linkage.

### Study Population

The index date refers to the cohort entry date when follow-up began. Each kidney donor's index date was the date of nephrectomy. Each HRS comparator was assigned an index date corresponding to an interview date. Each donor was matched 1:1 to a non-donor without relevant comorbidities (described below) at an index date close in time to the donor's index date.

Kidney donors are carefully selected through an extensive medical evaluation. Multiple consensus guidelines describe diabetes, cancer, coronary artery disease, dementia, poor functional status, chronic serious infections, or major psychiatric or neurological conditions as contraindications to live kidney donation.(23,24) During the study period, some centers accepted donors with obesity.(1,2) A minority of centers accepted donors with hypertension controlled with a single anti-hypertensive medication (<1% of this cohort).(2,25,26) Because the selection process for kidney donors creates a much healthier group than unselected members of the general population, we used restriction and matching to create a healthy comparator group from the HRS cohort.(13,17) We excluded HRS participants who, by the time of their index date, reported hypertension, diabetes, cancer (except skin), CVD (defined as "heart condition", "angina", "congestive heart failure", "heart surgery", or "stroke"), pulmonary disease (defined as "lung condition"), major psychological or neurological illnesses (defined as "emotional/psychiatric problems"), body mass index (BMI) 40 or who did not self-rate their health as "good," "very good," or "excellent."

## Outcomes

The primary outcome was death. Donor deaths were ascertained through center reports and linkage to the Social Security Death Master File. HRS participant deaths were ascertained through linkage to the National Death Index and contacts with participants' surrogates.

For kidney donors and HRS participants with insurance coverage from the Centers for Medicare and Medicaid Service, we obtained claims data through 12/31/2008. A secondary composite outcome was death or, among pairs with Medicare coverage, CVD. Medicare claims used to define CVD comprised codes for ischemic cardiac disease, congestive heart failure, stroke and peripheral vascular disease.(27) These CVD codes are listed in Table S1A. In a post-hoc analysis, we examined the risk of diabetes defined by Medicare claims. (28) These claims are listed in Table S1B.

Live donors may be more likely to seek general medical care than members of the general population, creating the possibility for surveillance bias when comparing health outcomes using medical claims data. To evaluate this possibility using Medicare claims, we compared the rate of primary care visits for donors and matched comparators (Medicare codes for primary care are listed in Table S1C). We also compared the risk of diagnoses for thyroid disease, osteoarthritis, and skin cancer, none of which is plausibly related to kidney donation or is a main focus of the donor medical evaluation.(24) The supplementary material provides the Medicare claims used to define study outcomes and further information about study methods.

## Statistical Analysis

Analyses were performed using SAS (SAS Institute, North Carolina, US) and R (R Foundation for Statistical Computing, Vienna, Austria). Matches were completed prior to the assessment of any outcome. We performed risk-set matches using R MIPMatch (29-31) with fine balance and a distance defined through the Mahalanobis distance function.(18, 32) We matched exactly on race (black/non-black) and sex. Using zip codes, we categorized participants' neighborhoods into four groups based on the percentage of residents living in poverty.(33) Donors and comparators were matched on neighborhood poverty using fine balance.(34-38) Because BMI was not consistently reported to the OPTN until 2001, we did not match on BMI category (<25; 25 & <30; 30 & <35; 35 kg/m<sup>2</sup>) until after the year 2000. A very small percentage (n=15, or <1%) of older donors were categorized as having hypertension. Therefore, we did not match on hypertension, but instead matched donors to non-hypertensive participants in the HRS. We assessed how closely we achieved balance between donors and healthy comparators using the Wilcoxon ranksum test for each continuous covariate and Fisher's exact test for binary covariates. We used Cox's proportional hazards model for paired times to estimate hazard ratios with 95% confidence intervals for mortality and secondary study outcomes.(39) We used the Prentice-Wilcoxon statistic to test the hypothesis of no difference in study outcomes between donors and non-donors and reported p-values using this method.(40, 41)

For analyses of mortality, pairs were followed until one died or end of follow-up (12/31/2008). For analyses of the secondary outcome of death or CVD, we measured deaths

among pairs until both members entered Medicare, after which we measured deaths or CV events. We censored both members of pairs at age 66 years if either member did not enroll in Medicare. Pairs were also censored when either member left Medicare or enrolled in a health maintenance organization.

For analyses of the rates of having Medicare claims for diabetes, hypothyroidism, osteoarthritis, and non-melanoma skin cancer, we censored both members of pairs at death, at age 66 years if either member did not enroll in Medicare, or if either member left Medicare or enrolled in a health maintenance organization.

To compare differences in the rate of primary care visits between donor and non-donor pairs who were enrolled in Medicare for at least a year, we used Wilcoxon's signed rank test and its associated Hodges-Lehmann estimators.<sup>(42)</sup> All p-values were two-sided. Any p-value 0.05 was considered significant.

### Secondary analyses

We repeated analyses of death and death/CVD in a pre-specified subgroup defined by median age at index date ( $< 60$  years). For analyses of CVD, we also implemented an alternative, validated set of Medicare codes to ascertain the outcome of CVD (27). This expanded list of Medicare codes included transient ischemic attack, venous thrombosis, and atrial fibrillation, in addition to codes encompassing the four cardiac complications addressed by our primary approach (coronary artery disease, congestive heart failure, stroke, peripheral vascular disease).

Additional information about study methods is provided in Supplementary Methods.

## RESULTS

During the study period, 5717 individuals were  $\geq 55$  years of age at the time of donor nephrectomy. We excluded 560 donors (9.8%) due to missing zip codes and 5 due to implausible BMI in a live donor ( $>40$  kg/m<sup>2</sup>). The final number of older donors considered for the match was 5152.

There were 25,309 individuals in the HRS cohort. We excluded 17,339 (69%) individuals due to comorbidities, 499 (2%) with low self-rated health status, and 152 (0.6%) with missing zip codes or implausible BMIs. There were 7319 non-donor candidates considered for the match.

The final match comprised 3368 donors (65% of the total) and 3368 healthy non-donor HRS participants. Figure 1 shows the process for assembling the matched cohort.

Table 1 shows characteristics of donors and non-donors. After matching, the mean age was 59 years, 41% were male, and 7% were African-American. For each pair, the median days between the donation date and the interview date was 162 (IQR:  $-4$  days, 358 days).

Figure 2 shows survival after the index date for matched pairs. In median follow-up of 7.84 years (IQR 5.11, 10.16), there were 115 deaths among donors and 152 deaths among non-

donors. The mortality rate was not different between donors versus non-donors (4.9 vs.5.6 deaths per 1000 person years,  $p=0.21$ ). The hazard ratio associated with kidney donation was 0.90 (95% CI 0.71, 1.15).

Sixty percent of donors and 44% of non-donors had any Medicare coverage. A total of 1312 pairs in the primary cohort had simultaneous Medicare coverage and were eligible to have CVD events ascertained. In an analysis of time to death or CVD, the rate of this combined outcome was not significantly different between donors and matched non-donors ( $p=0.70$ ). The hazard ratio associated with kidney donation was 1.02 (95% CI 0.87, 1.20). These results are shown in Figure 3.

The rate of primary care visits was slightly higher among donors than among non-donors (median 1.76 versus 1.43 per year,  $p=0.001$ ). As shown in Table 2, kidney donors did not have an increased risk of diabetes ( $p=0.80$ ), hypothyroidism ( $p=0.16$ ) or osteoarthritis ( $p=0.67$ ). Donors did have a greater hazard for having the outcome of non-melanoma skin cancers alone than non-donors (HR 1.53; CI 1.14, 2.05;  $p=0.006$ ).

Among the subset of pairs  $\geq 60$  years, donors had a slightly lower mortality risk ( $p=0.03$ ); the hazard ratio for death associated with kidney donation was 0.68 (95% CI 0.49, 0.95). Kidney donors and non-donors had a similar risk of the combined outcome of death or CVD ( $p=0.72$ ).

A secondary analysis of the outcome of death and CVD using an alternative set of Medicare claims revealed no difference in risk between donors  $\geq 55$  years and matched comparators ( $p=0.72$ ); these results are not shown.

Additional information about pairs with Medicare data is provided in Table S2.

## DISCUSSION

In this matched cohort study, older kidney donors had similar mortality to healthy participants in the HRS. Similarly, the combined outcome of death and CVD was similar between groups. Donors also did not have an elevated risk of diabetes, a risk factor for CVD and renal disease, compared to matched non-donors. These results should be provided to older individuals considering live kidney donation. This information should be presented in the broader context of other risks attributable to donor nephrectomy, such as peri-operative complications, ESRD and quality of life.(15, 43, 44)

The ever-increasing waiting list for a deceased donor kidney has led transplant centers to focus resources on increasing the volume of live kidney donation. In this context, the number and proportion of older live kidney donors has also increased substantially. In the US in the year 2002, 407 donors (8% of all donors) were  $\geq 55$  years, whereas in 2009, 726 donors (14%) were in this age group.(45) However, the limited empirical data about health outcomes for older live kidney donors makes it difficult for clinicians to evaluate and counsel older individuals considering kidney donation.

The similar rates of death and CVD outcomes between older donors and matched healthy comparators may provide some reassurance to older individuals considering donation and the transplant professionals caring for them. The finding that older donors enjoy similar longevity to healthy older individuals generally confirms the results of prior studies in which donor outcomes were compared to outcomes among demographically and/or comorbidity matched members of the general population.(13, 14, 46, 47) Our finding that CVD rates were not different between donors and matched pairs extends prior results by Garg et al. showing no increased risk of CVD in a population of Canadian donors that comprised a small number of older individuals.(17) The similar rates of CVD and diabetes among older donors and matched healthy individuals from our study can also be considered in the context of the RELIVE cohort. RELIVE investigators examined live donors at three large transplant centers and reported that, prior to nephrectomy, older donors were more likely than younger donors to have obesity, hypertension, and abnormal glucose tolerance.(48) These findings raised the concern that older donors may be at elevated risk from CVD after donation. However, this observation was not based on the comparison of older donors to healthy non-donors. In our study, we conducted such a comparison by assembling a group of healthy matched older individuals from the HRS by excluding HRS participants with hypertension or diabetes and matching on BMI. Our results suggests that transplant centers are usually able to select older donors who are not at higher risk of developing CVD or diabetes than healthy members of the general population, despite a possible greater willingness by some centers to accept the presence of metabolic abnormalities among these older individuals.

Our study results should also be evaluated in the context of a higher risk of ESRD associated with donor nephrectomy that has been reported in two important studies by Muzaale et al. and Mjoen et al.(15,49) Muzaale et al. matched live donors in the US to healthy NHANES participants.(15) Notably, while live kidney donors experienced a greater relative risk of ESRD compared to non-donors, the cumulative incidence of this outcome for donors over a 15-year observation period was <1%. Among the 4,039 donors 60 years of age, only 7 developed the ESRD outcome. In the general public, renal disease is a very strong risk factor for death and CVD events.(50) A potential explanation for our findings of no increased death or CVD rates among older donors and these prior findings of a higher rate of ESRD is that the current evidence suggests that only a small proportion of donors progress to advanced renal disease. Additionally, kidney donors undergo extensive medical screening that typically includes abdominal imaging using CT scan, tests of renal and liver function, electrocardiogram, screening for blood-borne infections including hepatitis and HIV, and psychosocial counseling.(51) Thus, most kidney donors may enjoy longevity and low rates of CVD because of careful selection through the donor medical evaluation, which may offset the negative health effects of progressive loss of renal function in a small number of donors.

Our study must be viewed in the context of its limitations and compared to other studies of donor outcomes. First, the OPTN/UNOS does not report on the presence of all relevant comorbidities among donors.(52) Reviews and consensus guidelines indicate that a potential donor would not have been accepted if a major comorbidity such as hepatitis C or diabetes were present.(23, 24) Second, for the HRS, comorbidities used to exclude participants as matches were ascertained through interviews rather than physical examination or serological

testing. The HRS does not record certain important conditions such as HIV or hepatitis C infection that might lead to chronic kidney disease. However, HIV and hepatitis C infection are rare in the general population. The HRS dataset does not allow serological assessment of renal disease. The HRS only directly asked participants about the presence of diabetic kidney disease during the first two years of the study period. We did restrict our healthy comparison group to HRS participants without diabetes and hypertension; chronic kidney disease in the absence of these conditions is uncommon.(53, 54) Despite this restriction, it is possible that some HRS participants had mild or undiagnosed CKD.

Third, ascertainment of outcomes using Medicare data is limited by the fact that <50% of pairs had Medicare insurance coverage and Medicare provides minimal information about individuals before age 65 years. A lower percentage of HRS participants had Medicare claims compared to donors; a likely reason is that in the HRS study, participants had to provide consent for Medicare linkage, whereas no such consent process was required to link donor registry data to Medicare claims. This low percentage of cohort pairs that had simultaneous Medicare coverage may limit generalizability. On the other hand, we assembled a large cohort of older donors, including >1300 pairs with Medicare coverage. Our conservative approach of censoring both members of a pair when either member was not enrolled in Medicare should minimize the potential for bias. At any time when a Medicare claim might record CVD or any other study outcome, both members of the pair were in Medicare and capable of having a similar event recorded.

Finally, due to the potential for more frequent contacts with the health system after nephrectomy, it is possible that a comparison of medical conditions ascertained through claims data between donors and healthy comparators might be susceptible to surveillance bias.(16) Our results provided limited evidence of this bias. While kidney donors had a higher rate of primary care visits and claims for non-melanoma skin cancer than non-donors, non-significant differences were evident in the risk of hypothyroidism, osteoarthritis and diabetes. It is possible that the elevated risk of non-melanoma skin cancer among donors was due to skin examinations in the peri-operative period.

By comparison to other important studies of live kidney donor outcomes, this study had a number of advantages. Our study design matched donors to HRS participants on index dates when these non-donors had evidence of good health. By contrast, other cohort studies, including those by Muzaale et al. and Mjoen et al, have compared donors to non-donors whose health was not evaluated at the same time as the donor.(13-15, 46) The HRS provided a large, national sample of community-dwelling, healthy older adults using a validated sampling methodology. The HRS includes extensive questions about diverse elements of health. Unlike most other studies of donor outcomes, this study adjusted for the psychosocial characteristics of donors by excluding HRS participants with a history of psychiatric disorders and by matching on neighborhood poverty.(13, 46, 49) Psychiatric disorders and poverty are important predictors of longevity; these attributes would also plausibly be evaluated during the donor nephrectomy work-up.(24, 55)

In summary, this study provides valuable new data about outcomes that can be used in decision-making for older individuals considering live kidney donation. In the context of



careful medical evaluation and selection, older donors should expect similar medium-term survival and risk of CVD compared to healthy members of the general population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

The data reported here have been supplied by the United Network for Organ Sharing (UNOS) as the contractor for the Organ Procurement and Transplantation Network (OPTN). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation by the OPTN or the US Government.

Dr. Reese had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr. Reese's work was supported by NIH grant K23-DK078688-01 and the American Society of Transplantation. Dr. Feldman was supported by NIH grant K24-DK02651. Dr. Rosenbaum was supported by NSF grant 1260782.

## Abbreviations

<b>OPTN</b>	Organ Procurement and Transplantation Network
<b>SRTR</b>	Scientific Registry of Transplant Recipients
<b>NHANES</b>	The National Health and Nutrition Examination Survey
<b>GFR</b>	Glomerular filtration rate
<b>eGFR</b>	estimated Glomerular filtration rate
<b>BMI</b>	Body mass index
<b>HRS</b>	Health and Retirement Study
<b>CMS</b>	Center for Medicare and Medicaid Services
<b>UNOS</b>	United Network for Organ Sharing
<b>US</b>	United States
<b>HIV</b>	Human immunodeficiency virus
<b>ESRD</b>	End Stage Renal Disease
<b>CVD</b>	Cardiovascular Disease

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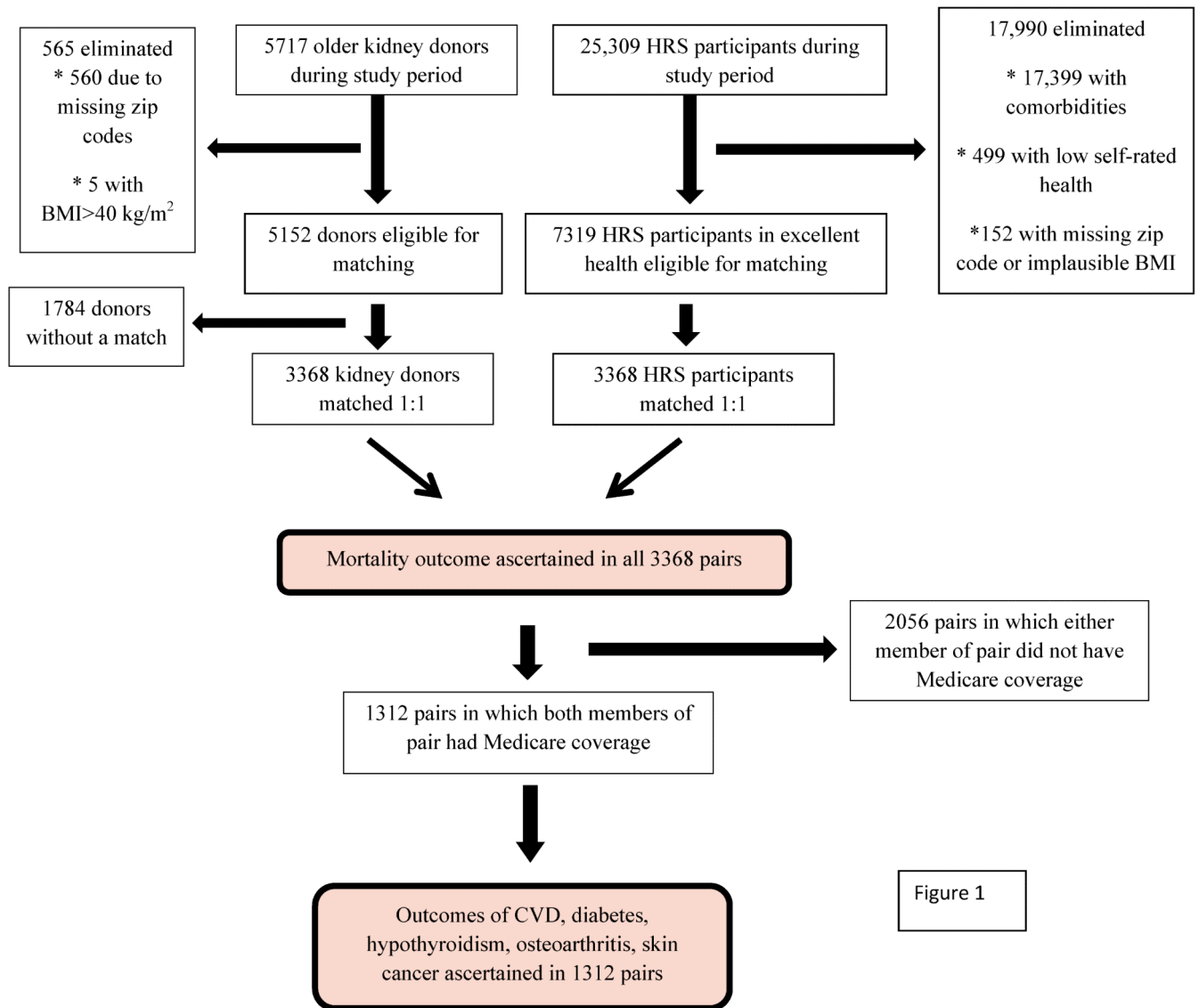
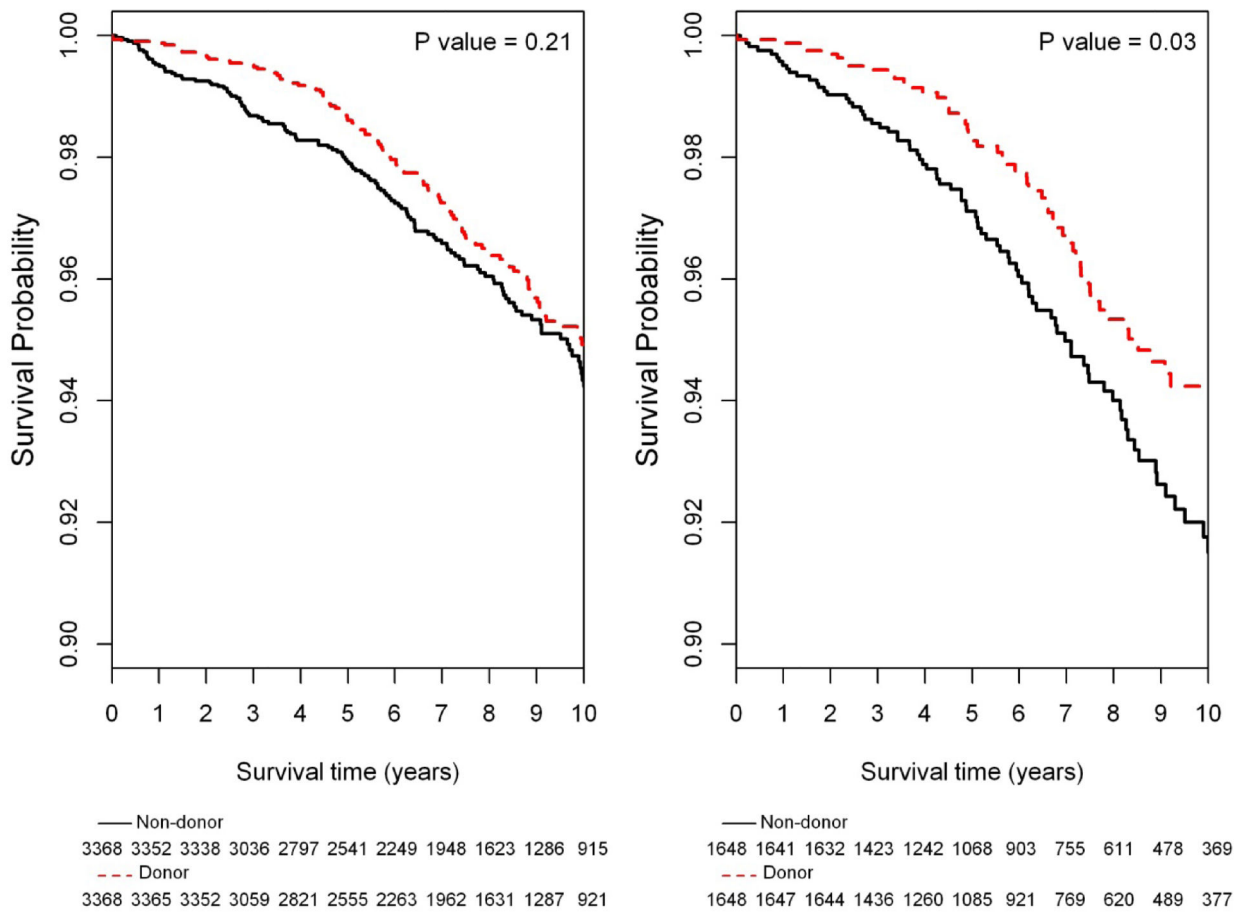
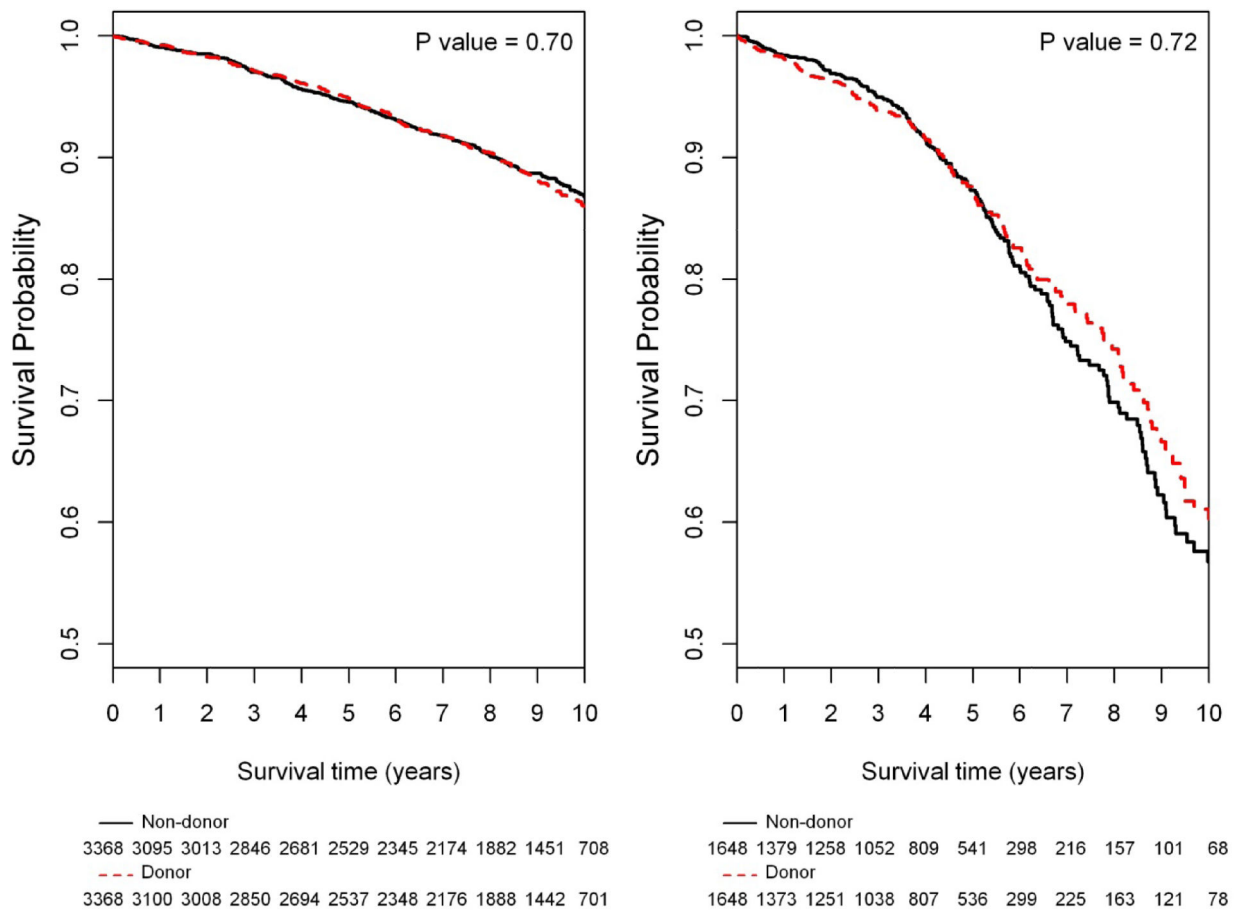


Figure 1

**Figure 1.**  
Flow diagram



**Figure 2.** Mortality among Kidney Donors 55 years (*left panel*) and Donors 60 years (*right panel*) versus Matched Healthy Older Individuals using the Kaplan-Meier Method\*



**Figure 3.** Mortality and Cardiovascular Outcomes among Kidney Donors 55 years (*left panel*) and Donors 60 years (*right panel*) versus Matched Healthy Older Individuals using the Kaplan-Meier Method\*\*

**Table 1**

Subject Characteristics of Older Kidney Donors and Non-Donors, Before and After Matching\*

	All donors (n=5152)	Matched Donors (n=3368)	Matched Healthy Non-donors (n=3368)	All Non-Donors (n=7319)	P-value**
Age (years)	59.1	59.0	59.0	64.2	0.3423
Male (%)	38	41	41	43	1
Black race (%)	6	7	7	10	1
Neighborhood poverty 12.3%	73	71	71	65	1
Neighborhood poverty 12.4-19.9% (%)	18	19	19	21	1
Neighborhood poverty 20-39.9% (%)	9	10	10	13	1
Neighborhood poverty 40% (%)	<1	<1	<1	<1	1
BMI Missing*** (%)	15	3	3	4	1
BMI 15-25 (%)	32	38	38	42	1
BMI 25-30 (%)	37	42	42	38	1
BMI 30-35 (%)	14	14	14	13	1
BMI 35-40 (%)	2	3	3	3	1

\* For each kidney donor, the index date was the date of nephrectomy. On that date, each donor was matched to a demographically similar, healthy non-donor from the HRS; the index date for this non-donor was the date of an interview close in time to the donor's date of donation.

\*\* For comparison of matched donors to non-donors

\*\*\* Matches were made on BMI category only after the year 2000 due to a high percentage of missing data on BMI in the donor registry dataset before that year.



**Table 2**

Hazard for Diabetes and other Medical Conditions among Kidney Donors  $\geq$  55 years versus Matched Healthy Non-Donors\*

Diagnosis	Hazard Ratio	95% CI (lower)	95% CI (upper)	P-value
Diabetes	1.05	0.83	1.32	0.80
Hypothyroidism	1.08	0.88	1.33	0.16
Osteoarthritis	1.10	0.92	1.30	0.67
Non-melanoma skin cancer	1.53	1.14	2.05	0.006

\* Death censored analyses among pairs with Medicare coverage