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Increased risk of ischaemic heart disease after kidney donation

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ABSTRACT

Background. Previous reports suggest increased risk of hypertension and cardiovascular mortality after kidney donation. In this study we investigate the occurrence of ischaemic heart disease and cerebrovascular disease, diabetes and cancer in live kidney donors compared with healthy controls eligible for donation.

Methods. Different diagnoses were assessed in 1029 kidney donors and 16 084 controls. The diagnoses at follow-up were self-reported for the controls and registered by a physician for the donors. Stratified logistic regression was used to estimate associations with various disease outcomes, adjusted for gender, age at follow-up, smoking at baseline, body mass index at baseline, systolic blood pressure at baseline and time since the donation.

Results. The mean observation time was 11.3 years [standard deviation (SD) 8.1] for donors versus 16.4 years (SD 5.7) for controls. The age at follow-up was 56.1 years (SD 12.4) in donors versus 53.5 years (SD 11.1) in controls and 44% of donors were males versus 39.3% in the controls. At follow-up, 35 (3.5%) of the donors had been diagnosed with ischaemic heart disease versus 267 (1.7%) of the controls. The adjusted odds ratio for ischaemic heart disease was 1.64 (confidence interval 1.10–2.43; $P = 0.01$) in donors compared with controls. There were no significant differences for the risks of cerebrovascular disease, diabetes or cancer.

Conclusions. During long-term follow-up of kidney donors, we found an increased risk of ischaemic heart disease compared with healthy controls. This information may be important in the follow-up and selection process of living kidney donors.

Keywords: cardiovascular disease, epidemiology, kidney donation

INTRODUCTION

Kidney transplantation from a live donor is the best available treatment for end-stage kidney disease [1].

Although live kidney donation is beneficial to the recipient, it may not be without risks for the individual who donates. A known consequence following a donor nephrectomy is an immediate reduction in glomerular filtration rate (GFR), followed by a slow compensatory increase before GFR slowly declines [2]. Previous meta-analyses and several studies [3–7] suggest that living donors have increased blood pressure (BP) and proteinuria after donation. Proteinuria, hypertension and reduced renal function are all risk factors for the development of cardiovascular disease [8–12].

Interpretation of earlier publications has been complicated by inappropriate control groups from the general population, small sample sizes and short follow-up [13–19].

We have previously shown a relative risk (RR) increase of 40% for cardiovascular mortality in donors compared with healthy controls [20]. To further evaluate risk following kidney donation we now report the results from a national observational study of >1000 living donors evaluating long-term risks for ischaemic heart disease, cerebrovascular disease, diabetes and cancer after donation. For comparison, a healthy control population was selected who fulfilled similar standard donation criteria and were evaluated during similar time periods as the donors.

MATERIALS AND METHODS

Oslo University Hospital is the national transplant centre performing all kidney transplantations and donor nephrectomies. All donors are evaluated and followed by a local nephrologist before and after nephrectomy. After nephrectomy they are

KEY LEARNING POINTS

What is already known about this subject?

- Previous reports suggest increased risk of hypertension and mortality after kidney donation.

What this study adds?

- Hypertension is a known risk factor for the development of cardiovascular disease, but it is unknown whether kidney donors are at increased risk of cardiovascular disease.
- Complete mapping of potential donor risk is important for the informed consent related to donor nephrectomy. This study shows that kidney donors may be at increased risk of disease long after donation.

What impact this may have on practice or policy?

- This information is important in the selection process of new donors as well as in the long-term follow-up of previous kidney donors.

offered cost-free, life-long medical follow-up and information on each donor is kept in the Norwegian Living Kidney Donor Registry.

Donor selection and baseline data

Donors were included for the time period 1972–2007 (time of donation) and baseline data were retrieved from the Norwegian Renal Registry and from hospital records. Only donors fulfilling current standard donation criteria were included in the study. The following were considered exclusion criteria: body mass index (BMI) $>30.0\,kg/m^2$ or $<17\,kg/m^2$, fasting plasma glucose >7 mmol/L, age >70 years, systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg, use of antihypertensive medication or an estimated GFR (eGFR) <70 mL/min/1.73 m^2 at the time of donation. Individuals with known comorbidities were also excluded and the final cohort consisted of 1029 donors.

Details of donor selection with exclusion criteria are presented in Figure 1.

Due to the long time span of the study, the donor population was divided into an early and a late cohort donating before or after 1990.

Donor follow-up

All live donors were called in for an interview and examination at 33 different local hospitals across Norway. The majority of these consultations was from the time period 2008–13 and represent cross-sectional data from the donor cohort. The standardized cross-sectional data were registered in the Norwegian Living Kidney Donor Registry.

Each donor was evaluated by a physician who registered the occurrence of any of the following diseases since donation: ischaemic heart disease, type 2 diabetes, cerebrovascular disease, hypertension and any new diagnosis of cancer. The basis for each diagnosis was not further specified on the registration form and the year when first given the diagnosis was not recorded.

SBP, DBP (office BP), height and weight were measured. Donors answered questions regarding current medications, if using statins, antidiabetic medication, BP medication, acetylsalicylic acid, analgesics or non-steroidal anti-inflammatory drugs. If a donor used antidiabetic or antihypertensive medication, the name of each drug was noted. Relevant laboratory tests were also performed and collected.

Selection of controls and baseline data

Controls were included from the Nord-Trøndelag Health Study (HUNT) population surveys. The HUNT Study is a large longitudinal health study from Nord-Trøndelag, a county in the middle of Norway. More information can be found at www.ntnu.edu/hunt. HUNT 1, 2 and 3 were performed in three different decades, 1984–86 (HUNT 1), 1995–97 (HUNT 2) and 2006–08 (HUNT 3). The HUNT 1, 2 and 3 surveys gathered data on comorbidity, BP and BMI on each occasion. HUNT 2 and 3 also included blood tests.

We selected controls among those who participated in either HUNT 1 or 2 and also participated in the HUNT 3 study that provided follow-up data for all the controls.

All controls were selected to be equally healthy as the donors were at the time of donation, based on available baseline data as shown in Figure 1. Baseline data were retrieved from questionnaires completed by the participants in the HUNT 1 and 2 population surveys and from clinical measurements.

HUNT 1 served as controls for the early donor cohort and HUNT 2 participants for the late donor cohort. In HUNT 1, participants registered the occurrence of the following diseases: myocardial infarction (MI), diabetes, angina and stroke. In HUNT 2, participants were also asked about cancer.

Follow-up of controls

Data from the HUNT 3 study were used for follow-up and the data were registered during the same time period as the donor follow-up. All diagnoses were self-reported. The participants had a choice between 'angina' and 'myocardial infarction'

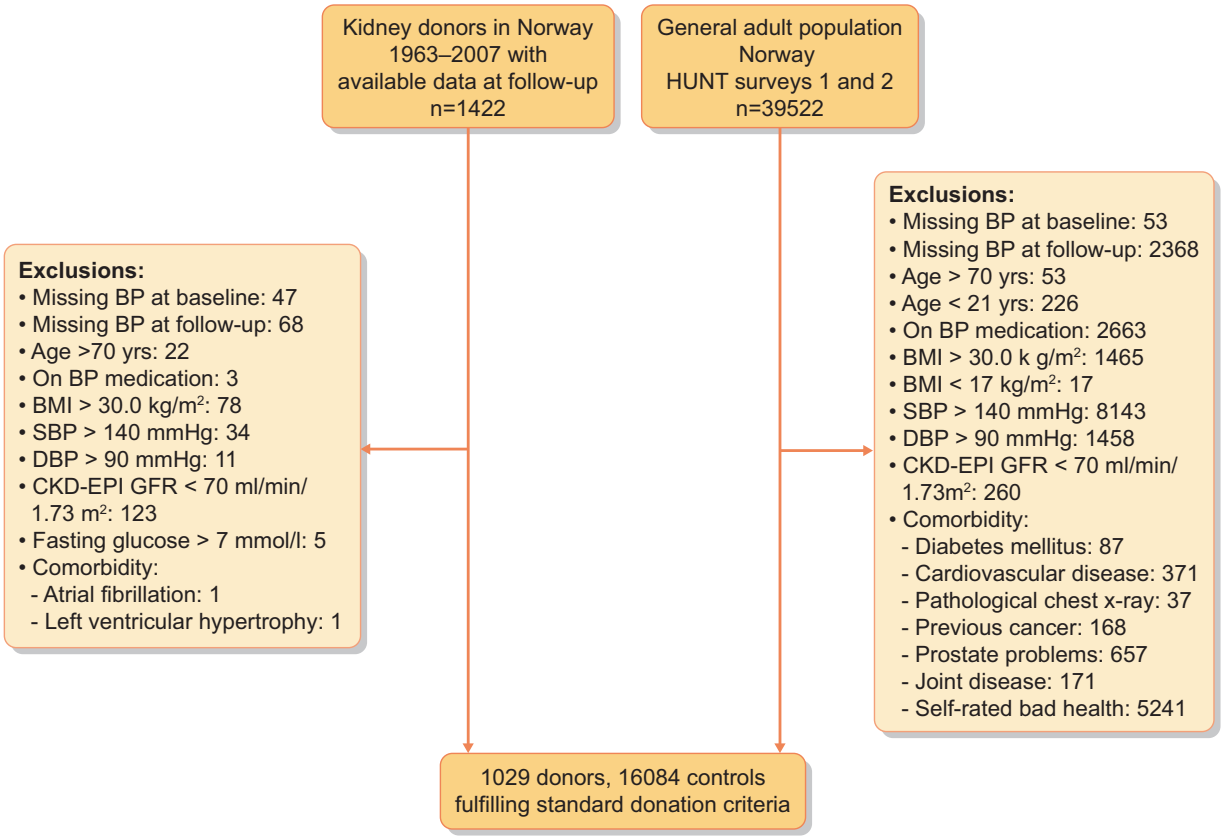

FIGURE 1: Baseline selection criteria. Of 1952 donors who were alive at the time of the study, follow-up data on 1422 (nephrectomized between 1963 and 2007) were available. A total of 1029 of these donors fulfilled standard donation criteria at the time of donation (1972–2007) and were included in the final analysis.

when reporting previous cardiovascular disease status on the questionnaire. Cerebrovascular disease was stated as 'stroke/cerebral hemorrhage' on the questionnaire and diabetes and cancer simply as 'diabetes' and 'cancer'.

The following outcomes in donors and controls were compared at this time: occurrence of ischaemic heart disease, diabetes, cerebrovascular disease or any cancer.

We used data from participants in HUNT 1 as controls for the early donor cohort transplanted before 1990 and data from HUNT 2 as controls for the late donor cohort, as they were conducted during relatively similar time periods. The donor and control stratification are presented in Figure 2. Details of the study design have previously been described [3].

As baseline evaluations of donors and controls did not take place at exactly the same time, we adjusted for time since donation/evaluation.

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 23 (IBM, Armonk, NY, USA). The outcomes were solely based on reported diagnoses obtained from cross-sectional data. The time when first receiving the diagnosis was not known in either group. Consequently we could not use survival statistics for analysing time to event. Logistic regression was therefore considered to be the appropriate method for the main analysis. Since the control group was

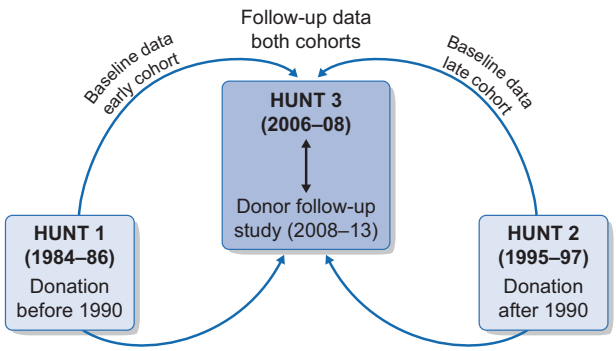

FIGURE 2: Stratification model.

included at two different time points and the donors throughout the period, we used stratified logistic regression. The following disease outcomes were included: ischaemic heart disease, diabetes, cerebrovascular disease and cancer. We performed univariate analyses. Second, we repeated analyses adjusted for demographic variables including the age at follow-up, time since donation (time since participation in HUNT 1 or 2 for controls) and male gender. Finally, adjustments were made for gender, age at follow-up, smoking at baseline, BMI at baseline, SBP at baseline and time since donation. Due to missing

baseline data for smoking and BMI among donors, analyses were repeated using multiple imputation [21]. This was considered as the main statistical analysis. As a sensitivity analysis, we repeated the univariate analysis for ischaemic heart disease after calculating a propensity score [22] using the other covariates in a logistic regression with kidney donation as the dependent variable. As an additional analysis, we adjusted for eGFR at follow-up in the multivariate analysis after multiple imputation to see if this affected our estimate.

To assess possible heterogeneity for the association between eGFR at follow-up and ischaemic heart disease between the donor and control groups, respectively, we also calculated the multivariate odds ratio (OR) for ischaemic heart disease separately within the two groups, including eGFR at follow-up as a covariate.

Lastly we evaluated the degree of correlation between eGFR at follow-up and kidney donation.

Univariate analyses were performed with SPSS using the chi-squared test, analysis of variance and *t*-test. We considered eGFR at follow-up as a possible downstream mediator [23] in the association of kidney donation and ischaemic heart disease. Consequently we did not include eGFR in the multivariate statistical model, as this could have diluted possible associations between kidney donation and the outcome variables.

Ethical Approval

The Regional Committees for Medical and Health Research Ethics approved this study prior to data collection (approval 2009/1588).

RESULTS

A total of 1029 donors and 16 084 controls fulfilled current standard donation criteria and were included in the study. The mean age of the donors was 44.8 years at the time of donation (Table 1) versus 37.1 years in the controls ($P < 0.001$). Forty-four per cent of the donors were male versus 39.3% of the controls ($P = 0.003$). Baseline BMI was 24.5 in donors versus 23.9 in controls ($P < 0.001$) and 33.5% of donors were smokers at the time of donation versus 28% of controls ($P < 0.001$). The mean SBP at baseline was 122.3 mmHg in donors versus 121.9 mmHg in the control group ($P = 0.19$). The eGFR was significantly different between donors and controls at baseline and follow-up ($P < 0.001$). The mean follow-up time was 11.3 years for donors and 16.4 years for the control group (Table 2).

At the time of follow-up, 35 (3.5%) donors were diagnosed with ischaemic heart disease versus 267 (1.7%) in the control group. The prevalence of all disease outcomes is shown in Table 2.

Table 3 and Appendix Tables A1–A3 show the ORs for different disease outcomes in kidney donors compared with healthy controls. Baseline SBP was inversely related to the risk of ischaemic heart disease, but this refers to an SBP increase within the normal range. In the main analyses after multiple imputation, the OR was significant for ischaemic heart disease {1.64 [confidence interval (CI) 1.10–2.43]; $P = 0.01$} in donors compared with healthy controls. The OR for cerebrovascular disease was 1.06 (CI 0.65–1.72; $P = 0.82$), 0.76 (CI 0.54–1.07; $P = 0.11$) for cancer and 1.27 (CI 0.85–1.91; $P = 0.24$) for diabetes.

The univariate analysis for ischaemic heart disease was repeated, adjusting for the propensity score. This did not change the result.

OR for ischaemic heart disease was significant ($P = 0.005$) after adjusting for demographic variables (age at follow-up, time since donation, time since participation in HUNT 1 or 2 and male gender). However, after adjusting for eGFR at follow-up, the OR for ischaemic heart disease was no longer significant. The eGFR at follow-up was a significant risk factor for ischaemic heart disease when performing a multivariate analysis including only the control group, but was not significant when including only kidney donors in the analysis (Appendix Table A4).

There was a significant correlation between donor status and eGFR at follow-up.

Table 1. Baseline characteristics of kidney donors and controls

	Kidney donors		Controls	
Variables	*n*	Values	*n*	Values
eGFR (CKD-EPI), mean (SD)	1027	92 (13.5)	8703	108.8 (13.4)[a]
SBP (mmHg), mean (SD)	1029	122.3 (9.8)	16 084	121.9 (10.2)
DBP (mmHg), mean (SD)	1029	76.8 (7.3)	16 084	74.8 (8)
Age (years), mean (SD)	1029	44.8 (10.8)	16 084	37.1 (10.1)
BMI (kg/m^2), mean (SD)	971	24.5 (2.8)	16 055	23.9 (2.6)
Current smoking, *n* (%)	862	345 (33.5)	14 864	4498 (28)
Gender (male), *n* (%)	1029	453 (44)	16 084	6323 (39.3)

[a]CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SD, standard deviation.
HUNT 2 participants.

Table 2. Follow-up data in kidney donors and controls

	Kidney donors		Controls	
Variables	*n*	Values	*n*	Values
Time since donation (years), mean (SD)	1029	11.3 (8.1)	16 084	16.4 (5.7)[a]
eGFR (CKD-EPI), mean (SD)	1029	71 (14.5)	15 974	97.9 (14.2)
Age (years), mean (SD)	1029	56.1 (12.4)	16 084	53.5 (11.1)
Cancer, *n* (%)	993	37 (3.7)	16 082	710 (4.4)
Diabetes, *n* (%)	1029	29 (2.8)	16 084	313 (1.9)
Cerebrovascular disease, *n* (%)	986	18 (1.8)	16 083	225 (1.4)
Ischaemic heart disease, *n* (%)	988	35 (3.5)	16 083	267 (1.7)
Urine albumin:creatinine ratio (mg/mmol), mean (SD)	517	5.2 (22.2)	1365	2.8 (4.2)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SD, standard deviation.
[a]Time since last examination.

Table 3. Risk factors for ischaemic heart disease

	Unadjusted OR (95% CI), P-value	Adjusted OR (95% CI), P-value[a]	Adjusted OR (95% CI), P-value[b]	Adjusted OR (95% CI),[c] P-value; adjusted OR (95% CI),[d] P-value
Time since donation	1.17 (1.10–1.24), <0.001	1.07 (1.01–1.13), 0.018	1.09 (1.01–1.17), 0.02	1.08 (1.02–1.15), 0.01; 1.05 (1.04–1.07), <0.001
Male gender	3.69 (2.87–4.74), <0.001	3.64 (2.8–4.7), <0.001	3.34 (2.50–4.45), <0.001	3.43 (2.66–4.43), <0.001; 1.95 (1.64–2.33), <0.001
Smoking status at baseline	2.14 (1.68–2.74), <0.001		2.57 (2.01–3.29), <0.001	2.43 (1.91–3.09), <0.001; 1.87 (1.57–2.22), <0.001
BMI at baseline	1.19 (1.13–1.24), <0.001		1.10 (1.05–1.16), <0.001	1.10 (1.05–1.15), <0.001; 1.06 (1.03–1.10), <0.001
Age at follow-up	1.08 (1.07–1.09), <0.001	1.08 (1.07–1.09), <0.001	1.07 (1.06–1.09), <0.001	1.08 (1.07–1.09), <0.001; 1.06 (1.05–1.07), <0.001
SBP at baseline	1.05 (1.03–1.06), <0.001		1.01 (1.00–1.03), 0.06	0.99 (0.98–0.99), <0.001; 1.01 (1.00–1.02), 0.10
Kidney donation	3.10 (2.17–4.43), <0.001	1.75 (1.18–2.60), 0.005	2.07 (1.33–3.22), 0.001	1.64 (1.10–2.43), 0.01; 0.91 (0.66–1.26), 0.59
eGFR (CKD-EPI) at follow-up	–	–	–	0.99 (0.98–0.1.00), <0.001

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
[a]Adjusted for time since donation, male gender and age at follow-up.
[b]Adjusted for time since donation, male gender, smoking status at baseline, BMI at baseline, age at follow-up and SBP at baseline.
[c]After multiple imputation.
[d]Adjusted for time since donation, male gender, smoking status at baseline, BMI at baseline, age at follow-up, SBP at baseline and eGFR CKD-EPI at follow-up, after multiple imputation.

DISCUSSION

In this study we found a significantly increased risk for ischaemic heart disease after kidney donation when compared with healthy controls, with a mean follow-up of >10 years. The risk for developing cancer, diabetes or cerebrovascular disease was not significantly increased following kidney donation. These data further substantiate the finding of increased cardiovascular mortality found in a previous analysis of this donor cohort [20].

To the best of our knowledge, no previous study has described an increased risk of ischaemic heart disease after kidney donation. However, most studies have a short follow-up time after donation, with few cases of ischaemic heart disease, resulting in a lack of statistical power [24, 25]. Garg *et al.* [24] followed 2028 donors with a median age of 43 years at donation for a median of 6.5 years. Fourteen donors were registered with MI during follow-up. They found the risk of a first cardiovascular event (including stroke and MI) to be lower in donors than controls after follow-up. However, it is not likely that kidney donation reduces cardiovascular risk. These results may instead reflect the fact that the control group may not have been healthy enough to serve as controls for kidney donors. In a large study with data from 2696 living donors, Rizvi *et al.* [25] performed a subanalysis, selecting data from potential donors (evaluated and accepted but who did not proceed for non-medical reason) as a control group for real living donors. They found 90 non-donor siblings who could be paired with actual donors for age, sex and BMI. During a mean follow-up time of 5 years, only one person in each group was diagnosed with ischaemic heart disease. Reese *et al.* [26] combined the outcomes of death and cardiovascular disease and found no difference between 3368 older donors (age >55 years at the time of donation) and age-matched controls after a median follow-up of 7.8 years. The above-mentioned studies all suffer from few events, relatively short follow-up and uncertainty whether the control group was healthy enough.

There have been a few prospective studies addressing cardiovascular effects of kidney donation by describing the effect on surrogate markers [27–29]. Moody *et al.* [27] followed donors and healthy controls prospectively and found elevated parathyroid hormone and uric acid, an increase in left ventricular mass and increased risk of developing detectable troponin T after a short-term follow-up. In a recent publication, Kasiske *et al.* [29] found that uric acid, parathyroid hormone and homocysteine remain elevated in donors after 9 years when compared with controls. In a cohort study, Altmann *et al.* [28] studied the change in left ventricular mass from baseline to 12 months after donation, based on magnetic resonance imaging. The authors found a significant increase in ventricular mass in addition to an increase in heart rate and mildly impaired diastolic function after nephrectomy. These three studies indicate that reduced GFR from donor nephrectomy has physical consequences that may be measurable in the short term.

We did not find an increased risk of cerebrovascular disease among donors. Stroke after donation has previously been analysed in a number of controlled studies. In a large American study from 2009, a subgroup analysis was performed in 110 participants with >20 years of follow-up. There was no significant increase in the prevalence of cerebrovascular disease or transient ischaemic attack between donors and controls (55 donors, 55 controls) [14].

Garg *et al.* [30] analysed a cohort using health administrative data for donations and included 1278 donors (mean age at donation 41 years, follow-up time 6.2 years) and found no events of stroke in donors.

In a matched cohort study, 2028 donors (mean age at donation 43 years) were followed for a median of 6.5 years. Five donors were reported having a stroke during follow-up [24]. When compared with non-donor controls, the risk of stroke was not significantly increased in these two studies. These reports may be underpowered due to short observation time and few events. This was also evident in the previously mentioned study by Rizvi *et al.* [25], where only two donors experienced a cerebrovascular incident after donation. Although the observation time was longer in our study, the results are comparable, with no increase in the risk of cerebrovascular events.

In a separate analysis, the association between previous kidney donation and current ischaemic heart disease was no longer significant after including eGFR at follow-up as a covariate. This finding may be difficult to interpret in light of kidney donation, since removing a kidney inevitably causes a reduction in GFR, making it difficult to evaluate causality or the possible role of eGFR as a mediator. Consequently this finding does not necessarily show that eGFR is a mediator for the effect of donation on ischaemic heart disease. These are observational data and both these factors could be correlated without necessarily proving causality. We cannot exclude some degree of multicollinearity between eGFR at follow-up and kidney donor status. In line with this, we found a significant moderate correlation between kidney donation and eGFR at follow-up. The role of eGFR at follow-up would have been even more relevant in this study if we had found a significant association between eGFR and the outcome of ischaemic heart disease also within the group of kidney donors. However, the lack of such a finding could be due to a lack of statistical power based on the total number of events when performing a multivariate analysis within the group of kidney donors. On the other hand, the epidemiologic evidence suggesting an association between reduced GFR and cardiovascular disease is overwhelming, supporting the role of eGFR as a possible mediator for the effect of kidney donation on ischaemic heart disease.

In the general population, reduced GFR is associated with cardiovascular events and death [11, 31]. It is not clear whether this association is due to the decreased GFR itself or to associated cardiovascular risk factors. In a large, community-based population, Go *et al.* [31] studied the multivariable association between eGFR and the risk of cardiovascular events. The adjusted hazard ratio increased inversely with eGFR, showing an independent association between reduced eGFR and the risk of cardiovascular events. Mafham *et al.* [32] conducted a meta-analysis on the relationship between decreased GFR and cardiovascular events (stroke, MI or other major vascular events). In the studies of people without prior vascular events, each 30% decrease in GFR was associated with a 29% increase in the risk of a major vascular event [RR 1.29 (CI 1.28–1.30)]. Overall, the strength of the associations did not appear to be influenced by the participant's history of vascular disease.

Kidney donors are ideal for studying the relationship between reduced GFR and cardiovascular disease, since they do not have any other associated diseases. Consequently, when we observe this association in kidney donors, it strengthens the hypothesis of a causal relationship between reduced GFR and cardiovascular disease. Other studies finding an increased risk of hypertension and cardiovascular mortality after donor nephrectomy also support this relationship [3, 4, 20]. After controlling for confounders that also represent potential cardiovascular risk factors (baseline BMI, smoking and SBP), kidney donation was a significant risk factor for ischaemic heart disease.

Van Biesen *et al.* [33] studied an otherwise healthy population with mild chronic renal impairment, looking at the risk of cardiovascular morbidity and mortality. Adjusting for traditional cardiovascular risk factors, they found an impact of chronic kidney disease on cardiovascular risk starting at a GFR $<$90 mL/min, which is equivalent to usual GFR levels of donors after nephrectomy. The increasing incidence of cardiovascular disease with declining GFR suggests a link between cardiovascular risk and an early uraemic state. Such a mechanism may also be operative in kidney donors.

Higher-risk donors with low GFR can be identified by measuring renal function reserve with renal stress testing [34]. Original global filtration capacity of the donor kidneys can be measured and then used to estimate the susceptibility of developing kidney dysfunction in the donor. By using this information, one can introduce a renoprotective strategy. In CKD patients, novel antihyperglycaemic agents are shown to slow disease progression in those with diabetes [35]. Preliminary results from the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease [36] show similar findings in CKD patients without diabetes. This nephroprotective strategy may apply in kidney donors who have reduced GFR without established CKD.

The discrepancies between previous study findings and ours may be partially due to the selection of the control population. The outcome of kidney donors should ideally be compared with that of controls selected from the same population as donors and having a similar health status at the time of the donor nephrectomy. Donors are well screened prior to donation and are considered healthier than the background population. If the controls are less healthy than the donors at the time of the donors' nephrectomy, it may mask a potential risk increase in donors. In addition, the health status of the controls should be evaluated at the same time as the donor. Including controls that are healthy at the time of the study but not at the time of donation (e.g. the time of donation could be a decade before the time of the study) is also wrong, as these controls may be too healthy since they are evaluated and declared healthy at a later time point than the kidney donors.

Ideally, donors and controls should be followed prospectively from the time of donation, with the control group undergoing the same screening procedures as donors. Since donors are young and healthy at donation, a long observation time is needed to register a sufficient number of events to allow for the detection of statistically significant group differences.

Diabetes was not significantly more prevalent in donors compared with controls after long-term follow-up. Several retrospective studies have been conducted on diabetes after donation [14, 26, 37–40] and the ones using control populations have not detected a difference in the prevalence of diabetes after several years of observation [14, 26, 37].

We did not find a higher risk of cancer among donors compared with controls. This result is in agreement with previous findings [14, 41]. Compared with controls, Lentine *et al.* [41] found a significantly less frequent non-skin cancer rate in donors 9 years after donation. This finding probably reflects that controls were less healthy than the donors and not that kidney donation reduces cancer risk.

There are limitations to our study. Controls and donors were not included at exact matched time points. Even though we adjusted for the time since donation and stratified groups according to the time period of donation, this could still introduce bias. Diagnoses were based on self-reports among the controls, which may result in underreporting and recall bias.

The years of given diagnoses are unknown in both donors and controls. As these follow-up data on donors and controls are cross-sectional, the more preferable time-to-event methods are not applicable to analyse this data set. Also, controls reside in one particular part of the country, whereas donors come from all of Norway. The geographic prevalence of disease in these groups may be different and affect the results. Lastly, the donor population consists of Caucasians and results might not extrapolate to other ethnicities.

Our study has some strengths as well. Control persons with comorbidities were excluded from the analysis. This makes controls and donors more comparable. Second, both controls and donors were evaluated by a physical screening at baseline. Finally, we had a relatively long follow-up period, increasing the number of events among donors, making this the most adequately powered study to date.

In summary, our analysis showed an increased long-term risk of ischaemic heart disease in live kidney donors when compared with a healthy control group eligible to be donors. Although the result was no longer significant when including eGFR at follow-up as a covariate, this may be difficult to interpret in light of the inherent correlation between removing a kidney and reduced GFR. The risks for cerebrovascular disease, diabetes and cancer were not increased, but we cannot exclude that this was due to a lack of statistical power for these outcomes and more studies are needed to evaluate this. The increased risk for ischaemic heart disease is an alarming finding and we urge others to perform similar studies.

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AUTHORS' CONTRIBUTIONS

A.J.H. drafted the paper, collected data, participated in the statistical analyses, participated in planning the research design and is responsible for the overall content as guarantor. S.H., N.L., D.O.D., H.P., K.B., A.R., K.M., A.H. and H.H. participated in writing the manuscript and approved the final version of the paper. G.M. participated in the statistical analyses, writing the manuscript and planning the research design and approved the final version of the paper.

CONFLICT OF INTEREST STATEMENT

K.I.B. has received the following honoraria to the university in the past 2 years: consulting fees or paid advisory boards from MSD Europe, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Sanofi-Aventis and Roche; travel support from AstraZeneca and MSD; grant support from AstraZeneca, Boehringer Ingelheim, MSD, Novo Nordisk, Eli Lilly, Sanofi-Aventis and Roche. D.O.D, S.H., A.R., H.H., G.M., H.P., A.J.H., A.H., K.M. and N.E.L. have no conflicts of interest to disclose. The results presented in this article have not been published previously in whole or part, except in abstract format.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

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APPENDIX

Table A1. Risk factors for cerebrovascular disease

Risk factors	Unadjusted; P-value	Adjusted[a]; P-value	Adjusted[b]; P-value	Adjusted[c]; P-value
Time since donation	1.11 (1.02–1.20; 0.01)	1.04 (0.97–1.13; 0.27)	1.04 (0.95–1.13; 0.36)	1.05 (1.02–1.08; <0.001)
Male gender	1.26 (0.98–1.62; 0.07)	1.24 (0.96–1.60; 0.09)	1.08 (0.81–1.43; 0.61)	1.15 (0.88–1.50; 0.29)
Smoking status at baseline	1.05 (0.79–1.39; 0.74)	–	1.21 (0.91–1.61; 0.18)	1.18 (0.89–1.56; 0,24)
BMI at baseline	1.12 (1.06–1.17; <0.001)	–	1.06 (1.00–1.12; 0.05)	1.05 (0.99–1.10; 0.08)
Age at follow-up	1.08 (1.06–1.09; <0.001)	1.08 (1.06–1.09; <0.001)	1.07 (1.06–1.09; <0.001)	1.07 (1.06–1.09; <0.001)
SBP at baseline	1.03 (1.01–1.04; <0.001)	–	1.01 (0.99–1.02; 0.46)	1.01 (0.99–1.02; 0.34)
Kidney donation	1.77 (1.09–2.87; 0.02)	1.08 (0.65–1.79; 0.77)	1.37 (0.78–2.40; 0.26)	1.06 (0.65–1.72; 0.82)

[a]Adjusted for time since donation, male gender and age at follow-up.
[b]Adjusted for time since donation, male gender, smoking status at baseline, BMI at baseline, age at follow-up and SBP at baseline.
[c]After multiple imputation.

Table A2. Risk factors for diabetes, OR and 95% CI

	Unadjusted OR (95% CI), P-value	Adjusted[a] OR (95% CI), P-value	Adjusted[b] OR (95% CI), P-value	Adjusted[c] OR (95% CI), P-value
Time since donation	1.13 (1.05–1.20), <0.001	1.08 (1.01–1.14), 0.015	1.13 (1.05–1.21), 0.001	1.10 (1.04–1.17), 0.002
Male gender	1.39 (1.12–1.72), 0.002	1.38 (1.11–1.70), 0.003	1.00 (0.79–1.28), 0.96	1.03 (0.83–1.29), 0.76
Smoking status at baseline	1.40 (1.11–1.77), 0.004		1.61 (1.27–2.03), <0.001	1.57 (1.24–1.98), <0.001
BMI at baseline	1.33 (1.27–1.38), <0.001		1.32 (1.26–1.39), <0.001	1.30 (1.25–1.36), <0.001
Age at follow-up	1.04 (1.03–1.05), <0.001	1.04 (1.03–1.05), <0.001	1.03 (1.02–1.04), <0.001	1.03 (1.02–1.04), <0.001
SBP at baseline	1.03 (1.02–1.04), <0.001		1.01 (1.00–1.02), 0.17	1.01 (1.00–1.02), 0.10
Kidney donation	1.80 (1.22–2.64), 0.003	1.36 (0.91–2.04), 0.13	1.47 (0.93–2.31), 0.09	1.27 (0.85–1.91), 0.24

[a]Adjusted for time since donation, male gender and age at follow-up.
[b]Adjusted for time since donation, male gender, smoking status at baseline, BMI at baseline, age at follow-up and SBP at baseline.
[c]After multiple imputation.

Table A3. Risk factors for cancer

Risk factors	Unadjusted OR (95% CI), P-value	Adjusted[a] OR (95% CI), P-value	Adjusted[b] OR (95% CI), P-value	Adjusted[c] OR (95% CI), P-value
Time since donation	1.08 (1.03–1.13), 0.002	1.04 (0.99–1.09(, 0.10	1.04 (0.98–1.10), 0.24	1.04 (0.99–1.09), 0.12
Male gender	0.75 (0.64–0.87), <0.001	0.74 (0.64–0.86), <0.001	0.76 (0.64–0.90), 0.002	0.77 (0.66–0.90), 0.002
Smoking status at baseline	0.96 (0.82–1.13), 0.64	–	1.01 (0.86–1.19), 0.88	1.00 (0.85–1.18), 0.98
BMI at baseline	1.01 (0.98–1.04), 0.45	–	0.98 (0.95–1.01), 0.28	0.98 (0.95–1.01), 0.17
Age at follow-up	1.05 (1.05–1.06), <0.001	1.05 (1.05–1.06), <0.001	1.06 (1.05–1.07), <0.001	1.06 (1.05–1.06), <0.001
SBP at baseline	1.00 (0.99–1.01), 0.51		0.99 (0.99–1.00), 0.20	1.00 (0.99–1.00), 0.34
Kidney donation	1.07 (0.76–1.49), 0.70	0.75 (0.54–1.06), 0.11	0.79 (0.53–1.19), 0.25	0.76 (0.54–1.07), 0.11

[a]Adjusted for time since donation, male gender and age at follow-up.
[b]Adjusted for time since donation, male gender, smoking status at baseline, BMI at baseline, age at follow-up and SBP at baseline.
[c]After multiple imputation.

Table A4. Risk factors for ischaemic heart disease within donors and controls

Risk factors	Controls, OR[a] (95% CI), P-value	Donors (including baseline eGFR), OR[a] (95% CI), P-value	Donors (including follow-up eGFR), OR[a] (95% CI), P-value
Time since donation	1.20 (1.02–1.40), 0.02	1.07 (1.0–1.15), 0.06	1.06 (0.99–1.14), 0.07
Male gender	3.12 (2.36–4.12), <0.001	4.7 (2.10–10.5), <0.001	4.47 (2.03–9.86), <0.001
Smoking status at baseline	2.66 (2.06–3.45), <0.001	1.90 (0.85–4.24), 0.11	1.90 (0.84–4.28), 0.12
BMI at baseline	1.08 (1.03–1.14), 0.002	1.04 (0.91–1.19), 0.56	1.04 (0.91–1.19), 0.56
Age at follow-up	1.06 (1.05–1.08), <0.001	1.05 (1.01–1.09), 0.009	1.05 (1.01–1.10), 0.01
SBP at baseline	1.02 (1.00–1.03), 0.006	0.97 (0.94–1.01), 0.18	0.97 (0.94–1.01), 0.18
eGFR (CKD-EPI) at follow-up	0.98 (0.97–0.99), 0.004	–	0.99 (0.97–1.02), 0.75
eGFR (CKD-EPI) at baseline	–	0.99 (0.96–1.02), 0.6	–

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
[a]After multiple imputation.