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Increased risk of ischemic 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 occurrence of ischemic 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 16084 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 donation.

Results. The mean (standard deviation) observation time was 11.3 (8.1) years for donors versus 16.4 (5.7) years for controls. Age at follow-up was 56.1 (12.4) years in donors vs 53.5 (11.1) years in controls and 44 % of donors were males vs 39.3 % in the controls.

At follow up 35 (3.5%) of the donors had been diagnosed with ischemic heart disease versus 267 (1.7%) of the controls. Adjusted odds ratio for ischemic 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 find an increased risk of ischemic heart disease compared to healthy controls. This information may be important in the follow-up and selection process of living kidney donors.

Keywords: cardiovascular disease, epidemiology, kidney donation
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 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.
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 and proteinuria after donation. Proteinuria, hypertension and reduced renal function are all risk factors for 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 increase of 40 % for cardiovascular mortality in donors compared to healthy controls (20). To further evaluate risk following kidney donation we now report the results from a national observational study of over 1000 living donors evaluating long-term risks for ischemic heart disease, cerebrovascular disease, diabetes and cancer after donation. For comparison a healthy control population was selected who fulfilled similar standard donation criteria and evaluated during similar time periods as the donors.

MATERIALS AND METHODS

Oslo University Hospital is the national transplant center 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 offered cost-free, life-
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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 from 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, SBP >140 mmHg or DBP >90 mmHg, use of antihypertensive medication or an estimated glomerular filtration rate <70 ml/min/1.73m$^2$ at 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 were from the time period 2008-2013 and represents 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 occurrence of any of the following diseases since donation: Ischemic heart disease, diabetes type 2, cerebrovascular disease,
hypothesis and any new diagnosis of cancer. The basis for each diagnosis was not further
specified on the registration form, and year when first given diagnosis was not recorded.
Systolic and diastolic blood pressures (office blood pressure), and height and weight were
measured. Donors answered questions regarding current medications, if using statins,
antidiabetic medication, blood pressure medication, acetylsalicylic acid, analgesics or
NSAIDs. 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 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, 1984-1986 (HUNT1), 1995-1997 (HUNT2) and 2006-2008 (HUNT3). The
HUNT 1, 2 and 3 surveys gathered data on comorbidity, blood pressure, and body mass index
on each occasion. HUNT2 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 filled in by the participants in the HUNT 1 and HUNT 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 occurrence of the following diseases:
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Myocardial infarction, diabetes, angina and stroke. In HUNT 2 participants were also asked about cancer.

Follow up of controls

Data from the HUNT3 study was used for follow-up and the data was 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” 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 ischemic heart disease, diabetes, cerebrovascular disease or any cancer.

We used data from participants in HUNT1 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 is 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 IBM Statistical Package for the Social Sciences (SPSS) version 23. 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
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groups. Consequently, we could not use survival statistics for analyzing time to event.

Logistic regression was therefore considered to be the appropriate method for the main analysis. Since the control group was included at two different time points, and the donors throughout the period, we used stratified logistic regression. The following disease outcomes were included: Ischemic heart disease, diabetes, cerebrovascular disease and cancer. We performed univariate analyses. Secondly, we repeated analyses adjusted for demographic variables age at follow-up, time since donation (time since participation in HUNT1 or HUNT2 for controls), and male gender. Finally, adjustments were made for gender, age at follow up, smoking at baseline, body mass index at baseline, systolic blood pressure 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 the main statistical analysis. As a sensitivity analysis we repeated the univariate analysis for ischemic 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 ischemic heart disease between the donor and control groups, respectively, we also calculated the multivariate odds ratio for ischemic 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 Chi-square test, Analysis of Variance (ANOVA) and T test. We considered eGFR at follow-up as a possible downstream mediator
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(23) in the association of kidney donation and ischemic 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.

Approval

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

RESULTS

One thousand and twenty-nine donors and 16084 controls fulfilled current standard donation criteria and were included in the study. Mean age in the donors was 44.8 years at time of donation (table 1) vs 37.1 years in the controls (P<0.001). Forty four per cent of the donors were male vs 39.3 % of the controls (P=0.003). Baseline BMI was 24.5 in donors versus 23.9 in controls (P<0.001), 33.5 % donors were smokers at time of donation versus 28 % controls (P<0.001). Mean systolic blood pressure at baseline was 122.3 mmHg in donors versus 121.9 mmHg in the control group (P=0.19). eGFR was significantly different between donors and controls at baseline and follow up (P<0.001). Mean time of follow up of donors was 11.3 years for the donors and 16.4 years in the control group (table 2).

At the time of follow up, 35 (3.5 %) donors were diagnosed with ischemic heart disease versus 267 (1.7 %) in the control group. Prevalence of all disease outcomes are shown in table 2.
Table 3 and appendix tables 1-3 show the odds ratios for different disease outcomes in kidney donors compared to healthy controls. Baseline systolic blood pressure was inversely related to risk of ischemic heart disease, but this refers to systolic blood pressure increase within the normal range. In the main analyses after multiple imputation, odds ratio was significant for ischemic heart disease at 1.64 (confidence interval (CI) 1.10-2.43, \(P=0.01\)) in donors compared with healthy controls. Odds ratio for cerebrovascular disease was 1.06 (CI 0.65-1.72, \(P=0.82\)), for cancer 0.76 (CI 0.54-1.07, \(P=0.11\)), and for diabetes 1.27 (CI 0.85-1.91, \(P=0.24\)).

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

Odds ratio for ischemic heart disease was significant (\(P=0.005\)) after adjusting for demographic variables (age at follow-up, time since donation/time since participation in HUNT1 or HUNT2, and male gender). However, after adjusting for eGFR at follow-up, the odds ratio for ischemic heart disease was no longer significant. Estimated GFR at follow up was a significant risk factor for ischemic heart disease when performing a multivariate analysis including only the control group, but not significant when including only kidney donors in the analysis (appendix table 4).

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

**DISCUSSION**

In the present study we found a significantly increased risk for ischemic heart disease after kidney donation when compared to healthy controls, with a mean follow-up of more than a decade. The risk for developing cancer, diabetes or cerebrovascular disease was not significantly increased following kidney donation.
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These data are further substantiate a 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 ischemic heart disease after kidney donation. However, most studies have short follow-up time after donation, with few cases of ischemic heart disease resulting in lack of statistical power (24, 25). Garg et al followed 2028 donors with median age of 43 at donation for median 6.5 years (24). Fourteen donors were registered with myocardial infarction (MI) during follow-up. They found the risk of first cardiovascular event (including stroke and MI) to be lower in donors than controls after follow-up. It is however not likely that kidney donation reduces cardiovascular risk. These results may instead reflect the fact the control group may not have been healthy enough to serve as controls for kidney donors. In a large study with data on 2696 living donors Rizvi et al performed sub-analysis selecting data from potential donors (evaluated and accepted but whom did not proceed for nonmedical reason) as control group for real LD (25). They found 90 non-donor siblings whom 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 were diagnosed with ischemic heart disease. Reese et al combined the outcome of death/cardiovascular disease and found no difference between 3368 older donors (age >55 at time of donation) and age-matched controls after median follow-up of 7.8 years (26). 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 followed donors and healthy controls prospectively and found elevated parathyroid hormone and uric acid,
increase in left ventricular mass and increased risk of developing detectable troponin T after short term follow-up (27). In a recent publication, Kasiske et al found that uric acid, PTH and homocysteine remain elevated in donors after nine years when compared to controls (29). In a cohort study Altmann et al studied change in left ventricular mass from baseline to 12 months after donation, based on MRI 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 (28). These three studies indicate that reduced glomerular filtration rate from donor nephrectomy has physical consequences that may be measurable also in the short term.

We did not find an increased risk of cerebrovascular disease among donors. Stroke after donation has previously been analyzed in a number of controlled studies. In a large American study from 2009 a sub-group analysis was performed in 110 participants with > 20 years of follow-up. There was no significant increase in prevalence of cerebrovascular disease or transient ischemic attack between donors and controls (55 donors/55 controls) (14). Garg et al analyzed 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 (30).

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 stroke during follow-up (24). When compared to non-donor controls 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 ischemic 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 ischemic 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 ischemic heart disease also within the group of kidney donors. However, the lack of such a finding could be due to 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 ischemic 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 reduced GFR itself, or due to associated cardiovascular risk factors. In a large, community-based population, Go et al studied the multivariable association between eGFR and risk of cardiovascular events (31). The adjusted hazard ratio increased inversely with eGFR, showing an independent association between reduced eGFR and risk of cardiovascular events. Mafham et al conducted a meta-
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analysis on the relationship of reduced GFR and cardiovascular events (stroke, myocardial infarction or other major vascular event) (32). In the studies of people without prior vascular events, each 30% lower level of 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 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 increased risk of hypertension and cardiovascular mortality after donor nephrectomy also support this relationship (3, 4, 20). After controlling for confounders that also represents potential cardiovascular risk factors (baseline BMI, smoking, and systolic blood pressure), kidney donation was a significant risk factor for ischemic heart disease.

Van Biesen studied an otherwise healthy population with mild chronic renal impairment looking at risk of cardiovascular morbidity and mortality (33). Adjusting for traditional cardiovascular risk factors they found an impact of chronic kidney disease on cardiovascular risk starting already at GFR <90 ml/min, which is equivalent to usual GFR levels of donors after nephrectomy. Increasing incidence of cardiovascular disease with declining GFR suggests a link between cardiovascular risk and early uremic 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 be used to estimate susceptibility of developing kidney dysfunction in the
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Donor. By using this information one can introduce a renoprotective strategy. In CKD patients, novel antihyperglycemic agents are shown to slow disease progression in those with diabetes (35). Preliminary results from the DAPA-CKD study (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 partially be due to the selection of the control population. The outcome of kidney donors should ideally be compared to that of controls selected from the same population as donors and having 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, health status of the controls should preferably be evaluated at the same time as the donor. Including controls that are healthy at the time of study but not at the time of donation (time of donation could for example be a decade before the time of 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, 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 amount of events to allow for the detection of statistically significant group differences.

Diabetes was not significantly more prevalent in donors compared to 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 prevalence of diabetes after several years observation (14, 26, 37).

We did not find higher risk of cancer among donors compared to controls. This result is in agreement with previous findings (41,14). Compared to controls Lentine et al found a significantly less frequent non-skin cancer rate in donors 9 years after donation (41). 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 time since donation and stratified groups according to time period of donation, this could still introduce bias. Diagnoses were based on self-report among the controls which may result in underreporting and recall bias. Year of given diagnoses is unknown in both donor 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 analyze this data set. Also, controls reside in one particular part of the country whereas donors come from all of Norway. Geographic prevalence of disease in these groups may be different and affect the results. Last, the donor population consists of Caucasians and results might not extrapolate to other ethnicities.

Our study also has some strengths. 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 ischemic heart disease in live kidney donors when compared to 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 lack of statistical power for these outcomes, and more studies are needed to evaluate this. The increased risk for ischemic heart disease is an alarming finding and we urge others to perform similar studies.

ACKNOWLEDGEMENTS
The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

FUNDING
Anders Haugen is supported by a PhD scholarship sponsored by the South-Eastern Norway Regional Health Authority. This project is also supported by The Norwegian Union for Kidney Patients and Transplant Recipients (LNT) and Oslo University Hospital Fund Foundation (OUS Fondsstiftelsen).

CONFLICT OF INTEREST STATEMENT
K.I.B. has received honorariums to the university from the following in the past two years (consulting fees or paid advisory boards): MSD Europe, Aztra Zenica, Boehringer Ingelheim, Novo Nordisk Pharma, Lilly, Sanofi-Aventis, Roche. Travel Support from Aztra Zenica, MSD. Grant support from industry: Astra Zenica, Boehringer Ingelheim, MSD, Novo Nordisk Pharma, Lilly, Sanofi-Aventis, Roche.
D.O.D, S.H., A.R., H.H., G.M., H.P., A.J.H., A.H., K.M., N.E.L. have no conflicts of interest to disclose.
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The results presented in this paper have not been published previously in whole or part, except in abstract format.

AUTHORS’ CONTRIBUTIONS

A. Haugen: drafted paper, collected data, participated in the statistical analyses, participated in planning of research design. Responsible for the overall content as guarantor.

S. Hallan, N. Langberg, D. O. Dahle, H. Pihlstrøm, K. Birkeland, A. Reisæter, K. Midtvedt, A. Hartmann, H. Holdaas: Participated in writing of the manuscript, approved final version of paper. G Mjøen: Participated in the statistical analyses and in the writing of the manuscript, planning of research design and approved final version of paper.

DATA AVAILABILITY STATEMENT

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

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Risks of kidney donation

Table 1. Baseline characteristics of kidney donors and controls

| Variable               | Kidney donors |                  | Controls   |                  |
|------------------------|---------------|------------------|------------|------------------|
|                        | n             | Means (SD)       | n          | Means (SD)       |
|                        |               | Frequencies (%)  |            | Frequencies (%)  |
| eGFR CKD-EPI           | 1027          | 92 (13.5)        | 8703       | 108.8 (13.4)*    |
| Systolic BP, mmHg      | 1029          | 122.3 (9.8)      | 16084      | 121.9 (10.2)     |
| Diastolic BP, mmHg     | 1029          | 76.8 (7.3)       | 16084      | 74.8 (8)         |
| Age, years             | 1029          | 44.8 (10.8)      | 16084      | 37.1 (10.1)      |
| BMI, kg/m²             | 971           | 24.5 (2.8)       | 16055      | 23.9 (2.6)       |
| Current smoking        | 862           | 345 (33.5)       | 14864      | 4498 (28)        |
| Male gender            | 1029          | 453 (44)         | 16084      | 6323 (39.3)      |

*HUNT 2 participants

BP, blood pressure

BMI, body mass index

eGFR, estimated glomerular filtration rate
Table 2. Follow-up data in kidney donors and controls

| Variable                      | Kidney donors | Controls |
|-------------------------------|---------------|----------|
|                               | n             | Means (SD) | Frequencies (%) | n          | Means (SD) | Frequencies (%) |
| Time since donation, yrs      | 1029          | 11.3 (8.1) |                  | 16084      | 16.4 (5.7)*|                  |
| eGFR CKD-EPI                  | 1029          | 71 (14.5)  |                  | 15974      | 97.9 (14.2)|                  |
| Age, yrs                      | 1029          | 56.1 (12.4)|                  | 16084      | 53.5 (11.1)|                  |
| Cancer                        | 993           | 37 (3.7)   |                  | 16082      | 710 (4.4)  |                  |
| Diabetes                      | 1029          | 29 (2.8)   |                  | 16084      | 313 (1.9)  |                  |
| Cerebrovascular disease       | 986           | 18 (1.8)   |                  | 16083      | 225 (1.4)  |                  |
| Ischemic heart disease        | 988           | 35 (3.5)   |                  | 16083      | 267 (1.7)  |                  |
| Urine albumin creatinine ratio, mg/mmol | 517   | 5.2 (22.2)|                  | 1365       | 2.8 (4.2)  |                  |

*Time since last examination

Yrs, Years
eGFR, estimated glomerular filtration rate
## Risks of kidney donation

Table 3. Risk factors for ischemic heart disease, odds ratio (OR) and 95% confidence interval (CI)

|                  | Unadjusted | Adjusted¹ | Adjusted² | Adjusted³ | Adjusted⁴ |
|------------------|------------|-----------|-----------|-----------|-----------|
| Time since       | 1.17 (1.10-1.24, P<0.001) | 1.07 (1.01-1.13, P=0.018) | 1.09 (1.01-1.17, P=0.02) | 1.08 (1.02-1.15, P=0.01) | 1.05 (1.04-1.07, P=0.001) |
| donation         |            |           |           |           |           |
| Male gender      | 3.69 (2.87-4.74, P<0.001) | 3.64 (2.8-4.7, P<0.001) | 3.34 (2.50-4.45, P<0.001) | 3.43 (2.66-4.43, P<0.001) | 1.95 (1.64-2.33, P<0.001) |
| Smoking status   | 2.14 (1.68-2.74, P<0.001) | 2.57 (2.01-3.29, P<0.001) | 2.43 (1.91-3.09, P<0.001) | 1.87 (1.57-2.22, P<0.001) |           |
| at baseline      |            |           |           |           |           |
| BMI at baseline  | 1.19 (1.13-1.24, P<0.001) | 1.10 (1.05-1.16, P<0.001) | 1.10 (1.05-1.15, P<0.001) | 1.06 (1.03-1.10, P<0.001) |           |
| Age at follow-up | 1.08 (1.07-1.09, P=0.001) | 1.08 (1.07-1.09, P=0.001) | 1.07 (1.06-1.09, P=0.001) | 1.08 (1.07-1.09, P=0.001) | 1.06 (1.05-1.07, P=0.001) |
| Systolic blood   | 1.05 (1.03-1.06, P<0.001) | 1.01 (1.00-1.03, P=0.001) | 0.99 (0.98-0.99, P=0.001) | 1.01 (1.00-1.02, P=0.001) |           |
| pressure at      |            |           |           |           |           |
| baseline         |            |           |           |           |           |
| Kidney donation  | 3.10 (2.17-4.43, P<0.001) | 1.75 (1.18-2.60, P=0.005) | 2.07 (1.33-3.22, P=0.001) | 1.64 (1.10-2.43, P=0.01) | 0.91 (0.66-1.26, P=0.59) |
| eGFR CKD-EPI     |            |           |           |           |           |
| at follow-up     |            |           |           |           |           |

¹ Adjusted for time since donation, male gender and age at follow-up

² Adjusted for time since donation, male gender, smoking status at baseline, BMI at baseline, age at follow up and systolic blood pressure at baseline

³ After multiple imputation

⁴ Adjusted for time since donation, male gender, smoking status at baseline, BMI at baseline, age at follow up, systolic blood pressure at baseline and eGFR CKD EPI at follow-up, after multiple imputation.

BMI, body mass index
Risks of kidney donation

FIGURE 1: Baseline selection criteria. Of 1952 donors who were alive at the time of study, follow-up data on 1422 (nephrectomized between 1963 and 2007) were available. 1029 of these donors fulfilled standard donation criteria at the time of donation (1972-2007) and were included in the final analysis.
FIGURE 2: Stratification model
Exclusions:
- Missing BP at baseline: 47
- Missing BP at follow-up: 68
- Age > 70 yrs: 22
- On BP medication: 3
- BMI > 30.0 kg/m²: 78
- SBP > 140 mmHg: 34
- DBP > 90 mmHg: 11
- CKD-EPI GFR < 70 ml/min/1.73 m²: 123
- Fasting glucose > 7 mmol/l: 5
- Comorbidity:
  - Atrial fibrillation: 1
  - Left ventricular hypertrophy: 1

Exclusions:
- Missing BP at baseline: 53
- Missing BP at follow-up: 2368
- Age > 70 yrs: 53
- Age < 21 yrs: 226
- On BP medication: 2663
- BMI ≥ 30.0 kg/m²: 1465
- BMI < 17 kg/m²: 17
- SBP > 140 mmHg: 8143
- DBP > 90 mmHg: 1458
- CKD-EPI GFR < 70 ml/min/1.73 m²: 260
- Comorbidity:
  - Diabetes mellitus: 87
  - Cardiovascular disease: 371
  - Pathological chest x-ray: 37
  - Previous cancer: 168
  - Prostate problems: 657
  - Joint disease: 171
  - Self-rated bad health: 5241

Kidney donors in Norway 1963–2007 with available data at follow-up
n=1422

General adult population Norway HUNT surveys 1 and 2
n=39522

1029 donors, 16084 controls fulfilling standard donation criteria
HUNT 1 (1984–86)
Donation before 1990

HUNT 2 (1995–97)
Donation after 1990

HUNT 3 (2006–08)
Donor follow-up study (2008–13)

Follow-up data both cohorts

Baseline data early cohort

Baseline data late cohort