Living kidney donation increases the risk of hypertension - findings from the Swiss prospective follow-up of living-kidney donors

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Living kidney donation increases the risk of hypertension - findings from the Swiss prospective follow-up of living-kidney donors

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Abstract

Objectives: To assess the role of nephrectomy as a risk factor for the development of hypertension and microalbuminuria.

Design prospective, long-term, follow-up study

Setting Swiss Organ Living-Donor Health Registry (SOL-DHR).

Participants All living kidney donors in Switzerland between 1993 and 2009

Interventions: Data on health status and renal function before, one year and biennially after donation were collected

Primary and Secondary Outcome Measures Comparison of 1 and 5 year occurrences of hypertension among normotensive donors with estimates from the Framingham Hypertension Risk Score. Multivariate random intercept models were used to investigate changes of albumin excretion after donation correcting for repeated measurements and co-factors such as age, male gender and body mass index.

Results: A total of 1,214 donors contributed 3,918 data entries with a completed biennial follow-up rate of 74% during a 10-year period. Mean (standard deviation, SD) follow-up of donors was 31.6 months (34.4). Median age at donation was 50.5 years (interquartile range, 42.2 to 58.8); 806 donors (66.4%) were female. Donation increased the risk of hypertension after 1 year by 3.64 (95% confidence interval (CI) 3.52 to 3.76; p<0.001) and returned to similar risks between the first and fifth year in the subgroup of donors remaining normotensive 1 year after donation.

Microalbuminuria before donation was dependent on donor age but not on the presence of hypertension. After nephrectomy, hypertension became the main driver for changes in albumin excretion (OR 1.19; 95%CI 0.13 to 2.25; p=0.03) and donor age had no effect.
Conclusion: Nephrectomy propagates hypertension and increases susceptibility for the development of hypertension-induced microalbuminuria.
Article Summary

Strength:

- Prospective design, the large donor group, a high follow-up rate and complete data sets
- Adequate control group
- Excellent follow-up rate

Limitations

- Missing information on donors’ smoking habits and the family history of hypertension.
- Use of anti-hypertensive medication as a part of the hypertension definition may lead to an overstated number of hypertensive.
Introduction

Knowledge of the health consequences of living kidney donation, such as the risk of developing hypertension, may have important implication for the long-term medical follow-up of donors. So far it is uncertain, whether nephrectomy alone is an independent risk factor for the development of hypertension and albuminuria. The occurrence of hypertension and albuminuria after kidney donation has been reported for decades, but as living organ donations continue to increase worldwide the health risk of donation are viewed more positively. A meta-analysis of 48 studies reporting the outcome of 5,145 donors showed a very minor and clinically non-relevant increased risk among kidney donors for the development of hypertension or proteinuria over long-term follow-up as compared to age-matched controls. However, the quality of the individual studies were limited by the retrospective study design, extensive loss to follow-up, small sample size resulting in underpowered statistical analyses, and the common use of a normal population as control group while donors are usually a positive selection and therefore healthier than the normal age-matched population.

Only recently, a new multivariate score based on the Framingham data to calculate hypertension risks has become available that allows tackling the problem of inappropriate comparisons. The new score allows making groups comparable for gender, age, systolic and diastolic blood pressure, smoking habits and family history of hypertension. To date, no study, including those summarized in the recent meta-analysis, applied the risk equation in the analysis. Therefore, the aim of this prospective, long-term, follow-up study was to assess the role of nephrectomy as an independent risk factor for the development of hypertension and microalbuminuria in living kidney donors when compared to estimates from the multivariable
Hypertension Risk Score of the Framingham Cohort including all relevant risk parameters of hypertension for potential donors without nephrectomy.

Methods

The ethics committee of Basle, Switzerland approved this study. Informed consent was obtained from all participants. The protocol used by the Swiss Organ Living-Donor Health Registry (SOL-DHR) to collect the data has been described in detail elsewhere. Briefly, all living kidney donors in Switzerland were enrolled before donation and followed one year after nephrectomy and biennially thereafter since 1993. Donors’ general practitioners provided medical follow-up data, which were collected by a central registry. So far there are sequential data for up to 17 years after donation; the current analysis was restricted to a 10-year follow-up period due to the scarcity of data beyond this time period. This resulted in the exclusion of 185 database entries.

Hypertension was defined as blood pressure values above 140 mmHg systolic and/or 90 mmHg diastolic or use of any blood pressure lowering drug. Blood pressure data were reported as a mean of three individual measurements at each time point taken before and one year after donation and thereafter biennially during life-long follow-up examinations requested by the Swiss transplant law. All new diagnoses of hypertension had to be verified by 24-hour ambulatory blood pressure recording using threshold values 135/85 mmHg or higher. Blood pressure values in the normal range were only accepted as “normal” if a list of drugs taken the same day was reported to SOL-DHR to exclude an antihypertensive treatment. Only follow-up exams with complete data sets were analyzed.

Urine albumin and urine creatinine were measured in a spot urine sample. A single central laboratory (Viollier AG, Basel Switzerland) performed all chemical analysis in
blood and urine. Microalbuminuria was defined as a ratio of mg albumin to mmol creatinine of 3.3 or more according to international guidelines. For statistical analysis, interval scaled variates were summarized with means and standard deviations (SD) or medians and interquartile ranges (IQR), where appropriate. Dichotomous variates were described as ratios and percentages. To assess the effect of donation on the occurrence of elevated blood pressure requiring medication, we fitted the Hypertension Risk Score of the Framingham Cohort for 1 year and 4 year risk of hypertension to our data as follows: For the first year analysis we fitted the data to the distribution prior to donation after excluding all cases of hypertension (n=271). For the subsequent four-year analysis, we focused on all donors remaining normotensive 1 year after donation. Since data on smoking habits and family history of hypertension were not available in our data set we imputed these data under the assumption of a smoking prevalence of 25 percent using the most recent epidemiologic data of the tobacco monitoring study in Switzerland and took the strength of association from the Hypertension Risk Score. We assumed positive family history (both parents) for hypertension of 25 percent using data of the Swiss survey on salt intake and again took the strength of association from the Hypertension Risk Score. We found no Swiss data on the correlation between the two parameters and therefore assumed no correlation between smoking habits and positive family history of hypertension. We performed sensitivity analyses assuming 20 and 30 percent prevalence. The estimated probabilities from the Framingham equations were compared to the probabilities estimated from two multivariate logistic regression models using the occurrence of hypertension 1 or 5 years after donation as the dependent variate and the available parameters of the Framingham equation (age, female gender, systolic and diastolic blood pressure, body mass index (BMI), smoking habits, family history
of hypertension, and an interaction term of age and diastolic blood pressure) prior to donation (for the 1 year assessment) and at 12 month after donation (for the 4 year assessment).

To examine the parameters associated with microalbuminuria prior to donation; a multivariate regression model was fitted using the following parameters as dependent variates (hypertension, donor age, male gender, and BMI). To examine the occurrence of microalbuminuria in the follow-up, a multivariate random intercept model with hypertension as an independent variate and accounting for co-variates (donor age, male gender, and body mass index (BMI)) and corrected for repeated measures per donor was fitted. This was done using the subject as a random factor.

All analyses were performed using the Stata 11.2 statistics software package (StataCorp LP, College Station, TX, USA).

Results

In the period from April 1993 to December 2009, all 1,214 living kidney donors in Switzerland were enrolled in the SOL-DHR database providing 3,918 complete data sets with blood pressure measurements, microalbuminuria results, and a list of drugs taken the day of blood pressure measurement. Figure 1 reports the number of donor follow-up exams at each time point. During the 10-year follow-up period, 22 donors died from non-renal causes resulting in 61 missed follow-up examinations. A total of 2,704 complete data sets out of 3,632 possible follow-up exams were returned and analyzed by SOL-DHR, resulting in an average follow-up rate of 74% over all time points.

At the time of donation, median donor age was 50.4 years (IQR 42.1 – 58.7). Eight hundred and six donors (66.4%) were female and 408 (33.6%) were male. Median BMI of all donors was 24.9 (IQR 22.7 – 27.7). A total of 923 donors (76.0%) had
normal blood pressure and 95.2% did not have microalbuminuria (ratio ≥3.3; median albumin-excretion ratio 0.7; IQR 0.4-1.3).

At the time of donation, 271 donors (22.3%) were diagnosed with hypertension (information on hypertension was missing in 20 patients). In 89 patients (32.6%) the diagnosis of hypertension was made on the basis of blood pressure measurement. All other patients were classified on the basis of use of blood pressure lowering medications. Mean systole was 140.7 (Range: 100 to 205) and mean diastole was 84.5 (Range: 60 to 113). Table 1 reports a comparison with normotensive donors in terms of albumin excretion rate, gender, age, and BMI.

Occurrence of Hypertension

Among initially normotensive donors, 398 (43.1%) developed hypertension in the observation period and provided 1302 data entries. Using the Framingham Risk calculator, the predicted risk for developing hypertension one year after donation was increased by 3.64 (95% confidence interval (CI) 3.52 to 3.76; p<0.001). The estimated mean 1-risk of hypertension from the Framingham risk equation was 3.5%. The observed incidence of hypertension after 1 year among responders was 18.7% (151/807). In the subset of the donor cohort that remained normotensive 1 year after donation and had non-missing values for hypertension status 5 years after donation (n=451) the risk was only modestly increased (1.19 95%CI 1.10 to 1.29; <0.001).

Two hundred and one patients provided data up to 10 years after donation. Occurrence of hypertension is shown in Figure 2. 106 remained normotensive. In the subgroup of donors remaining normotensive five years after donation, the cumulative incidence of developing hypertension in the subsequent 5 years was 29/123 (23.6%). Results remained essentially unchanged in sensitivity analyses. Table 2 shows mean systolic and diastolic blood pressure values and ranges of hypertensive and
normotensive groups during follow-up. All hypertensive patients remained hypertensive during the observation period.

Occurrence of microalbuminuria

In all donors, the albumin excretion ratio increased from 1.2 ± 2.7 to 1.9 ± 10.7 mg albumin/mmol creatinine and the occurrence of microalbuminuria increased from 4.8% to 10.4% (Figure 3). Twenty out of 57 donors with microalbuminuria were hypertensive (35.1 percent). Ten years after nephrectomy the rate of microalbuminuria (>3.3 mg albumin/mmol creatinine) was significantly higher in the group of 271 initially hypertensive donors as compared to normotensive donors (16.6% vs. 6.0%, p=0.03) (See Figure 4). Before donation, albumin excretion was dependent upon donor age but not on the presence of hypertension (Table 1). However, after nephrectomy, multivariate random intercept models corrected for repeated measures per donor showed that the effect of age was lost and hypertension became the main driver for increased albumin excretion (OR 1.19; 95%CI 0.13 to 2.25; p=0.03).

Discussion

Our results show that kidney donation triplicates the short term risk among donors of developing hypertension and that after nephrectomy hypertension becomes the main risk factor for microalbuminuria.

In earlier studies, hypertension after living kidney donation was reported in 17-33% of donors 11-16. However, living kidney donation was not regarded as a risk factor for hypertension as the incidence of hypertension was similar to the age-matched general population 17-25. All these studies were limited by their retrospective design, small donor cohorts, high rate of donors lost to follow-up, and use of the general
population as a control group. In addition, the classification of living kidney donors as being normotensive or hypertensive is not as easy as primarily expected. Normal blood pressure values do not allow a donor to be classified as being normotensive when no information is available on the use of antihypertensive drugs the day of blood pressure measurement. On the other hand, hypertensive blood pressure readings without confirmation by 24-hour blood pressure recording may reflect white coat hypertension. In our study all new diagnoses of hypertension had to be verified by 24-hour ambulatory blood pressure recording. Blood pressure values in the normal range were only accepted as “normal” if a list of drugs taken the same day was reported to SOL-DHR. Only follow-up exams with complete data sets were analyzed. In 2006, Boudville and colleagues concluded in their meta-analysis that there was on average a 5 mm Hg increase in blood pressure post nephrectomy but that they were unable to evaluate for any differences in risk of hypertension because of heterogeneity in the data and weaknesses in the underlying studies. Strengths of the present study are the prospective design, the large donor group, a high follow-up rate and complete data sets allowing a robust classification of hypertensive outcomes. In contrast to the follow up of organ recipients, follow up of donors is cumbersome as donors frequently live far from the transplant centers and regard themselves as healthy without the need for regular medical check-ups. Therefore, donors are usually not prepared to travel long distances or cover the expenses for their follow-up exams. The key factor for the high follow-up rate in this prospectively designed long-term follow-up study was the Swiss transplant law requiring a central donor registry and coverage of medical expenses for donors’ biennial follow-up examination by the kidney recipients’ compulsory health insurance. At regular intervals, SOL-DHR provided donors with a questionnaire and medical follow-up form to be filled out by the donor’s preferred local family physician with all
medical expenses covered by the recipients’ health insurance. Donors not returning their follow-up forms were contacted by SOL-DHR using kidney recipients’ information to obtain donor contact details; if abroad, donors were contacted through the worldwide network of Swiss embassies. Hence, we regard the rate of 74% complete follow-up exams as the very best that can be achieved under ideal circumstances. The 2,704 completed follow-up data sets allow for robust statistical analyses.

Missing information on donors’ smoking habits and the family history of hypertension is a weakness of this study. We tried to deal with it by imputing the missing data. In the case of smoking we based our assumptions on the most recent epidemiologic data on smoking available in Switzerland. In view of the fact that donors represent a healthy subgroup of the general public we believe that this is a conservative assumption and think that the comparison is justifiable. Using lower rates for smoking would have increased the excess of risk among kidney donors. For positive family history we assumed that 25 percent had both parents with hypertension. This assumption was based on a recently performed nationwide survey in Switzerland on salt intake. Again, it can be argued that this is a conservative assumption given the overrepresentation of healthy subjects in our cohort resulting in a potential underestimation of the risk of developing hypertension after donation. Finally, we had no data on the correlation between the two parameters and thus decided to assume no correlation. We cannot fully rule-out that our definition of hypertension, taking use of anti-hypertensive medication as a part of the definition, led to an overstated number of hypertensive, because some normotensive patients might have received ACE inhibitors or AT1 receptor antagonists against microalbuminuria or beta-blockers against anxiety. Finally, even if a follow-up rate of 76 percent is very high, we cannot fully exclude selection bias.
An important problem of all earlier studies, including our own previous report, was use of the age-matched general population as a control group to assess the risk among living kidney donors for developing hypertension. Only recently, with the availability of the Framingham hypertension risk equation applied in this study, the problem could be addressed more adequately. Hypertension is a common disease in the general population, while kidney donors are a preselected healthier subgroup. Hence, even a tripling of the risk of hypertension, as shown in the present study, remained unnoticed when the subgroup of healthy donors was compared to the general population. Ideally, donors after nephrectomy should be compared to a population of accepted donors not possible to donate due to recipient reasons or refusing nephrectomy but still being followed long-term to accurately reflect the specific risk profile of donors, including a high proportion of females (66%) or normal BMI. Under the assumption that the model is correct, the Framingham risk equation allowed making the control population similar for all relevant risk factors of hypertension. Due to the large group of donors with complete follow-up data sets collected prospectively by SOL-DHR during 17 years it was possible to compensate for differences in the risk profile allowing a robust analyses of nephrectomy as an independent risk factor for hypertension.

By applying an appropriate multivariate statistical analysis and comparing the evolution of hypertension after nephrectomy to the risks from the Framingham equation, there is now clear evidence that unilateral nephrectomy does significantly enhance the short-term occurrence of hypertension after donation. Unilateral nephrectomy deprives the group of healthy donors from their initial health advantage and puts them at a threefold higher risk for developing hypertension. Those subjects remaining with normal blood pressure one year after donation return to a risk similar to that of the healthy Framingham population.
The second goal of this study was to assess the role of nephrectomy as an independent risk factor for microalbuminuria. Previous studies on small donor groups reported an increase in microalbuminuria, which was believed to be due to hyperfiltration of the remaining glomeruli after nephrectomy. Indeed, in the present donor cohort glomerular filtration rate (GFR) as estimated by the MDRD formula showed, despite removing half of the kidney mass, not the theoretically expected fall to 50% of its initial value but instead a reduction to approximately 70%, indicating hyperfiltration of the remaining glomeruli. Over the 10-year follow-up period with 2,704 serum creatinine measurements after nephrectomy, GFR remained stable with no sign of normal physiological loss of GFR due to aging or hyperfiltration. In addition, we could now identify hypertension as an important driver for the development of microalbuminuria after nephrectomy.

Another relevant finding was obtained by analyzing the risk factors for microalbuminuria in donors before and after nephrectomy. Before nephrectomy, variability in albumin excretion was related to donor age but not the presence of hypertension. However, after unilateral nephrectomy hypertension became the dominant factor for albumin excretion, whereas donor age had no effect. Having a single kidney seems to sensitize the remaining glomeruli to hypertensive damage expressed by elevated albumin excretion. This finding may be explained by the fact that hyperfiltration after unilateral nephrectomy is achieved at the level of single glomeruli by a higher capillary flow rate resulting in higher filtration rate. The higher flow rate is mediated by a change in the glomerular hemodynamic involving reduced vascular resistance in the vas afferens. In individuals with hypertension, the reduced pre-glomerular vascular resistance in nephrectomized donors will transmit systemic hypertension more easily to the glomerular capillary loops as compared to the pre-nephrectomy state. Hence, glomerular capillary pressure in hypertensive donors after
nephrectomy is probably higher than before nephrectomy; this might explain why hypertension after nephrectomy becomes an important factor for the development of microalbuminuria that may eventually lead to glomerular nephroclerosis.

In summary, kidney donation increases the risk among donors for developing hypertension and sensitizes the remaining kidney to hypertensive glomerular damage as expressed by increased albumin excretion. Whether such increased risk of developing hypertension and/or microalbuminuria translates to renal dysfunction, other morbidities or mortality post donation remains to be seen.

However, both risks must be addressed by offering donors life-long follow-up, providing continued monitoring of blood pressure and urinary albumin excretion. As hypertension becomes the main risk factor for microalbuminuria, adequate therapy with nephroprotective antihypertensive drugs (angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists) should be initiated as soon as kidney donors are diagnosed with hypertension. Transplant centers have to be aware of their responsibility to organize long-term follow-up schemes for living kidney donors to guarantee their optimal medical long-term management. Follow-up should be coordinated by the transplant center or a central registry but performed by the family physician in the donor's neighborhood to ensure life-long medical support.
Acknowledgments

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Authors’ contributions

GTT conceive the study and was the main responsible for the study design and study management.

CN, DT and JS were involved in data collection and management

LMB and GTT designed the analysis plan and LMB performed the statistical analyses.

GTT, JS and LMB drafted the manuscript

All authors provided important intellectual input and approved the final version of the manuscript.

GTT deceased. The submission is post-hum with Dr. Thiel as the first author, thereby acknowledging his contribution. He acknowledged the final version of this paper.

Conflict of interest

The authors confirm that they have no conflict of interest.

Data sharing statement

No additional data available
References


Figure Legends

Figure 1: Rate of living kidney donors with complete data sets at each follow-up time point.

Figure 2: Number of donors at risk of hypertension among 201 providing 10 years of follow-up.

Figure 3: Rates of hypertension in living kidney donors over a 10-year follow-up period and microalbuminuria (>3.3 mg albumin/mmol creatinine) in the entire donor group) stratified for hypertensives (red bars) and normotensives (blue bars).

Figure 4: Percentage of living kidney donors with microalbuminuria (>3.3 mg albumin/mmol creatinine) over a 10-year follow-up period and) stratified for hypertensives (red bars) and normotensives (blue bars).
Figure 1

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Figure 2
Figure 3
Figure 4
Table 1. Comparison of albumin excretion rate, age, gender, and body mass index (BMI) between donors with and without hypertension before donation

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Table 2. Mean systolic and diastolic blood pressure and ranges of hypertensive and normotensive groups during follow-up

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

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<td>1</td>
<td>(a)</td>
<td>Indicate the study's design with a commonly used term in the title or the abstract</td>
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<tr>
<td></td>
<td>(b)</td>
<td>Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>p.2, 3</td>
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| Introduction | 2 | Explain the scientific background and rationale for the investigation being reported | p.5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | p.6 |

| Methods | 4 | Present key elements of study design early in the paper | p.6, 7 |
| Study design | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | p.6 |
| Setting | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | p.6 |
| Participants | (b) For matched studies, give matching criteria and number of exposed and unexposed | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | p.6, 7, 8 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | p.7 |

| Bias | 9 | Describe any efforts to address potential sources of bias | p.7 |
| Study size | 10 | Explain how the study size was arrived at | p.6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | p.8 |

| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | p.7, 8 |
| (b) Describe any methods used to examine subgroups and interactions | p.7, 8 |
| (c) Explain how missing data were addressed | p.7, 8 |
| (d) If applicable, explain how loss to follow-up was addressed | |
| (e) Describe any sensitivity analyses | |

| Results | 13* | (a) Report numbers of individuals at each stage of study—e.g numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | p.8 |
| Participants | (b) Give reasons for non-participation at each stage | p.8 |
| (c) Consider use of a flow diagram | |

| Descriptive data | 14* | (a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders | p.8 |
| (b) Indicate number of participants with missing data for each variable of interest | p.26, 27 |
| (c) Summarise follow-up time (e.g. average and total amount) | p.9 |

| Outcome data | 15* | Report numbers of outcome events or summary measures over time | p.26, 27 |

<p>| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included | p.3, 10 |
| (b) Report category boundaries when continuous variables were categorized | p.9, 10 |
| (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |</p>
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<th>Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses</th>
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<tr>
<td>Key results</td>
<td>Summarise key results with reference to study objectives</td>
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<td>Limitations</td>
<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias</td>
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<tr>
<td>Interpretation</td>
<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</td>
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<tr>
<td>Generalisability</td>
<td>Discuss the generalisability (external validity) of the study results</td>
</tr>
<tr>
<td>Other information</td>
<td>Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based</td>
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</table>

*Give information separately for exposed and unexposed groups.

# Living kidney donation increases the risk of hypertension - findings from the Swiss prospective follow-up of living-kidney donors

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Living kidney donation increases the risk of hypertension - findings from the Swiss prospective follow-up of living-kidney donors

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Abstract

Objectives: To assess the role of nephrectomy as a risk factor for the development of hypertension and microalbuminuria.

Design: prospective, long-term, follow-up study

Setting: Swiss Organ Living-Donor Health Registry (SOL-DHR).

Participants: All living kidney donors in Switzerland between 1993 and 2009

Interventions: Data on health status and renal function before, one year and biennially after donation were collected

Primary and Secondary Outcome Measures: Comparison of 1 and 5 year occurrences of hypertension among normotensive donors with 1 and 5 year estimates from the Framingham Hypertension Risk Score. Multivariate random intercept models were used to investigate changes of albumin excretion after donation correcting for repeated measurements and co-factors such as age, male gender and body mass index.

Results: A total of 1,214 donors contributed 3,918 data entries with a completed biennial follow-up rate of 74% during a 10-year period. Mean (standard deviation, SD) follow-up of donors was 31.6 months (34.4). Median age at donation was 50.5 years (interquartile range, 42.2 to 58.8); 806 donors (66.4%) were female. Donation increased the risk of hypertension after 1 year by 3.64 (95% confidence interval (CI) 3.52 to 3.76; p<0.001) and returned to similar risks between the first and fifth year in the subgroup of donors remaining normotensive 1 year after donation.

Microalbuminuria before donation was dependent on donor age but not on the presence of hypertension. After nephrectomy, hypertension became the main driver for changes in albumin excretion (odds ratio 1.19; 95% CI 0.13 to 2.25; p=0.03) and donor age had no effect.
Conclusion: Nephrectomy propagates hypertension and increases susceptibility for the development of hypertension-induced microalbuminuria.
Article Summary

Strength:

- The prospective design, the large donor group, and the complete data sets are main assets of this study.
- The study compared the effects with an adequate control group accounting for the lower cardiovascular risk of the donor group.
- The study had an excellent overall follow-up rate of 74 percent.

Limitations

- Missing information on donors’ smoking habits and the family history of hypertension required assumptions and sensitivity analyses.
- The use of anti-hypertensive medication as a part of the hypertension definition may lead to an overstated number of hypertensive.
Introduction

Knowledge of the health consequences of living kidney donation, such as the risk of developing hypertension, may have important implication for the long-term medical follow-up of donors. So far it is uncertain, whether nephrectomy alone is an independent risk factor for the development of hypertension and albuminuria. The occurrence of hypertension and albuminuria after kidney donation has been reported for decades, but as living organ donations continue to increase worldwide the health risk of donation are viewed more positively. A meta-analysis of 48 studies reporting the outcome of 5,145 donors showed a very minor and clinically non-relevant increased risk among kidney donors for the development of hypertension or proteinuria over long-term follow-up as compared to age-matched controls. However, the quality of the individual studies were limited by the retrospective study design, extensive loss to follow-up, small sample size resulting in underpowered statistical analyses, and the common use of a normal population as control group while donors are usually a positive selection and therefore healthier than the normal age-matched population.

Only recently, a new multivariate score based on the Framingham data to calculate hypertension risks has become available that allows tackling the problem of inappropriate comparisons. The new score allows making groups comparable for gender, age, systolic and diastolic blood pressure, smoking habits and family history of hypertension. To date, no study, including those summarized in the recent meta-analysis, applied the risk equation in the analysis. Therefore, the aim of this prospective, long-term, follow-up study was to assess the role of nephrectomy as an independent risk factor for the development of hypertension and microalbuminuria in living kidney donors when compared to estimates from the multivariable
Hypertension Risk Score of the Framingham Cohort including all relevant risk parameters of hypertension for potential donors without nephrectomy.

Methods

The ethics committee of Basle, Switzerland approved this study. A written informed consent was obtained from all participants. The protocol used by the Swiss Organ Living-Donor Health Registry (SOL-DHR) to collect the data has been described in detail elsewhere. Briefly, all living kidney donors in Switzerland were enrolled before donation and followed one year after nephrectomy and biennially thereafter since 1993. Donors’ general practitioners provided medical follow-up data, which were collected by a central registry. So far there are sequential data for up to 17 years after donation; the current analysis was restricted to a 10-year follow-up period due to the scarcity of data beyond this time period. This resulted in the exclusion of 185 database entries.

Hypertension was defined as blood pressure values above 140 mmHg systolic and/or 90 mmHg diastolic or use of any blood pressure lowering drug. Blood pressure data were reported as a mean of three individual measurements at each time point taken before and one year after donation and thereafter biennially during life-long follow-up examinations requested by the Swiss transplant law. All new diagnoses of hypertension had to be verified by 24-hour ambulatory blood pressure recording using threshold values 135/85 mmHg or higher. Blood pressure values in the normal range were only accepted as “normal” if a list of drugs taken the same day was reported to SOL-DHR to exclude an antihypertensive treatment. Only follow-up exams with complete data sets were analyzed.

Urine albumin and urine creatinine were measured in a spot urine sample. A single central laboratory (Viollier AG, Basel Switzerland) performed all chemical analysis in
blood and urine. Microalbuminuria was defined as a ratio of mg albumin to mmol
creatinine of 3.3 or more according to international guidelines 8.

For statistical analysis, interval scaled variates were summarized with means and
standard deviations (SD) or medians and interquartile ranges (IQR), where
appropriate. Dichotomous variates were described as ratios and percentages. To
assess the effect of donation on the occurrence of elevated blood pressure requiring
medication, we fitted the Hypertension Risk Score of the Framingham Cohort 6 for 1
year and 4 year risk of hypertension to our data as follows: For the first year analysis
we fitted the data to the distribution prior to donation after excluding all cases of
hypertension (n=271). For the subsequent four-year analysis, we focused on all
donors remaining normotensive 1 year after donation. Since data on smoking habits
and family history of hypertension were not available in our data set we created two
random variates under the assumption of a smoking prevalence of 25 percent using
the most recent epidemiologic data of the tobacco monitoring study in Switzerland 9
and took the strength of association from the Hypertension Risk Score. We assumed
positive family history (both parents) for hypertension of 25 percent using data of the
Swiss survey on salt intake 10 and again took the strength of association from the
Hypertension Risk Score. We found no Swiss data on the correlation between the
two parameters and therefore assumed no correlation between smoking habits and
positive family history of hypertension. We performed sensitivity analyses by
repeating the random process 100 times and by assuming 20 and 30 percent
prevalence.

The estimated probabilities from the Framingham equations were compared to the
probabilities estimated from two multivariate logistic regression models using the
occurrence of hypertension 1 or 5 years after donation as the dependent variate and
the available parameters of the Framingham equation (age, female gender, systolic
and diastolic blood pressure, body mass index (BMI), smoking habits, family history of hypertension, and an interaction term of age and diastolic blood pressure) prior to donation (for the 1 year assessment) and at 12 month after donation (for the 4 year assessment).

To examine the parameters associated with microalbuminuria prior to donation; a multivariate logistic regression model was fitted using the following parameters as dependent variates (hypertension, donor age, male gender, and BMI). To examine the occurrence of microalbuminuria in the follow-up, a multivariate random intercept model with hypertension as an independent variate and accounting for co-variates (donor age, male gender, and body mass index (BMI)) and corrected for repeated measures per donor was fitted. This was done using the subject as a random factor. All analyses were performed using the Stata 11.2 statistics software package (StataCorp LP, College Station, TX, USA).

Results
In the period from April 1993 to December 2009, all 1,214 living kidney donors in Switzerland were enrolled in the SOL-DHR database providing 3,918 complete data sets with blood pressure measurements, microalbuminuria results, and a list of drugs taken the day of blood pressure measurement. Figure 1 reports the number of donor follow-up exams at each time point. Fifty-nine percent of donors were related (28 percent parents, 26 percent siblings, 5 percent otherwise), 33 percent were living partners and 8 percent of donors were unrelated to the kidney recipient. During the 10-year follow-up period, 22 donors died from non-renal causes resulting in 61 missed follow-up examinations. A total of 2,704 complete data sets out of 3,632 possible follow-up exams were returned and analyzed by SOL-DHR, resulting in an average follow-up rate of 74% over all time points. We checked whether those with
hypertension at the one year follow-up were more likely to show up at the five year follow-up and found no significant difference (p= 0.641).

At the time of donation, median donor age was 50.4 years (IQR 42.1 – 58.7). Eight hundred and six donors (66.4%) were female and 408 (33.6%) were male. Median BMI of all donors was 24.9 (IQR 22.7 – 27.7). A total of 923 donors (76.0%) had normal blood pressure and 95.2% did not have microalbuminuria (ratio ≥3.3; median albumin-excretion ratio 0.7; IQR 0.4-1.3).

At the time of donation, 271 donors (22.3%) were diagnosed with hypertension (information on hypertension was missing in 20 patients). In 89 patients (32.6%) the diagnosis of hypertension was made on the basis of blood pressure measurement. All other patients were classified on the basis of use of blood pressure lowering medications. Mean systole was 140.7 (Range: 100 to 205) and mean diastole was 84.5 (Range: 60 to 113). Table 1 reports a comparison with normotensive donors in terms of albumin excretion rate, gender, age, and BMI.

Occurrence of Hypertension
Among initially normotensive donors, 398 (43.1%) developed hypertension in the observation period and provided 1302 data entries. Using the Framingham Risk calculator, the predicted risk for developing hypertension one year after donation was increased by 3.64 (95% confidence interval (CI) 3.52 to 3.76; p<0.001). The estimated mean 1-risk of hypertension from the Framingham risk equation was 3.5%.

The observed incidence of hypertension after 1 year among responders was 18.7% (151/807). In the subset of the donor cohort that remained normotensive 1 year after donation and had non-missing values for hypertension status 5 years after donation (n=451) the risk was only modestly increased (1.19 95%CI 1.10 to 1.29; <0.001).

Two hundred and one patients provided data up to 10 years after donation Occurrence of hypertension is shown in Figure 2. 106 remained normotensive. In the
subgroup of donors remaining normotensive five years after donation, the cumulative incidence of developing hypertension in the subsequent 5 years was 29/123 (23.6%). Results remained essentially unchanged in sensitivity analyses. Table 2 shows mean systolic and diastolic blood pressure values and ranges of hypertensive and normotensive groups during follow-up. All hypertensive patients remained hypertensive during the observation period. The mean systolic (6.2 mmHg (95% CI: 4.1 mmHg to 8.4 mmHg); p<0.001) and diastolic (5.0 mmHg (3.4 mmHg to 6.6 mmHg); p<0.001) blood pressure values of normotensive donors pre-donation, who developed hypertension at 1-year follow-up were slightly albeit significantly higher than the pre-donation values of those patients how were normotensive at the 1-year follow-up, when correcting for differences in age, male gender and BMI.

Occurrence of microalbuminuria

In all donors, the albumin excretion ratio increased from 1.2 ± 2.7 to 1.9 ± 10.7 mg albumin/mmol creatinine and the occurrence of microalbuminuria increased from 4.8% to 10.4% (Figure 3). Twenty out of 57 donors with microalbuminuria were hypertensive (35.1 percent). Ten years after nephrectomy the rate of microalbuminuria (≥3.3 mg albumin/mmol creatinine) was significantly higher in the group of 271 initially hypertensive donors as compared to normotensive donors (16.6% vs. 6.0%, p=0.03) (See Figure 4). Before donation, albumin excretion was dependent upon donor age but not on the presence of hypertension (Table 1). However, after nephrectomy, multivariate random intercept models corrected for repeated measures per donor showed that the effect of age was lost and hypertension became the main driver for increased albumin excretion (OR 1.19; 95%CI 0.13 to 2.25; p=0.03).
Discussion

Our results show that kidney donation triplicates the short term risk among donors of developing hypertension and that after nephrectomy hypertension becomes the main risk factor for microalbuminuria.

In earlier studies, hypertension after living kidney donation was reported in 17-33% of donors. However, living kidney donation was not regarded as a risk factor for hypertension as the incidence of hypertension was similar to the age-matched general population. All these studies were limited by their retrospective design, small donor cohorts, high rate of donors lost to follow-up, and use of the general population as a control group. Also, in a prospective study on 51 consenting donors that derived from a pool of 129 eligible, Ramesh Prasad and colleagues showed that the pre-donation 24-hour ambulatory blood pressure dipping profile (nocturnal blood pressure dipping) of normotensive living kidney donors was not correlated with renal function and cardiovascular risk status at the one-year follow-up after donation.

The classification of living kidney donors as being normotensive or hypertensive is not as easy as primarily expected. Normal blood pressure values do not allow a donor to be classified as being normotensive when no information is available on the use of antihypertensive drugs the day of blood pressure measurement. On the other hand, hypertensive blood pressure readings without confirmation by 24-hour blood pressure recording may reflect white coat hypertension. In our study all new diagnoses of hypertension had to be verified by 24-hour ambulatory blood pressure recording. Blood pressure values in the normal range were only accepted as “normal” if a list of drugs taken the same day was reported to SOL-DHR. Only follow-up exams with complete data sets were analyzed. In 2006, Boudville and colleagues concluded in their meta-analysis that there was on average a 5 mm Hg increase in blood
pressure post nephrectomy but that they were unable to evaluate for any differences in risk of hypertension because of heterogeneity in the data and weaknesses in the underlying studies. ³

Strengths of the present study are the prospective design, the large donor group, a high follow-up rate and complete data sets allowing a robust classification of hypertensive outcomes. In contrast to the follow up of organ recipients, follow up of donors is cumbersome as donors frequently live far from the transplant centers and regard themselves as healthy without the need for regular medical check-ups. Therefore, donors are usually not prepared to travel long distances or cover the expenses for their follow-up exams. The key factor for the high follow-up rate in this prospectively designed long-term follow-up study was the Swiss transplant law requiring a central donor registry and coverage of medical expenses for donors’ biennial follow-up examination by the kidney recipients’ compulsory health insurance. At regular intervals, SOL-DHR provided donors with a questionnaire and medical follow-up form to be filled out by the donor’s preferred local family physician with all medical expenses covered by the recipients’ health insurance. Donors not returning their follow-up forms were contacted by SOL-DHR using kidney recipients’ information to obtain donor contact details; if abroad, donors were contacted through the worldwide network of Swiss embassies. Hence, we regard the rate of 74% complete follow up exams as the very best that can be achieved under ideal circumstances. The 2,704 completed follow-up data sets allow for robust statistical analyses.

Missing information on donors’ smoking habits and the family history of hypertension is a weakness of this study. We tried to deal with it by imputing the missing data. In the case of smoking we based our assumptions on the most recent epidemiologic data on smoking available in Switzerland ⁹. In view of the fact that donors represent a
healthy subgroup of the general public we believe that this is a conservative assumption and think that the comparison is justifiable. Using lower rates for smoking would have increased the excess of risk among kidney donors. For positive family history we assumed that 25 percent had both parents with hypertension. This assumption was based on a recently performed nationwide survey in Switzerland on salt intake. Again, it can be argued that this is a conservative assumption given the overrepresentation of healthy subjects in our cohort resulting in a potential underestimation of the risk of developing hypertension after donation. Finally, we had no data on the correlation between the two parameters and thus decided to assume no correlation. We cannot fully rule-out that our definition of hypertension, taking use of anti-hypertensive medication as a part of the definition, led to an overstated number of hypertensive, because some normotensive patients might have received ACE inhibitors or AT1 receptor antagonists against microalbuminuria or beta-blockers against anxiety. Finally, even if a follow-up rate of 76 percent is very high, we cannot fully exclude selection bias.

An important problem of all earlier studies, including our own previous report, was use of the age-matched general population as a control group to assess the risk among living kidney donors for developing hypertension. Only recently, with the availability of the Framingham hypertension risk equation applied in this study, the problem could be addressed more adequately. Hypertension is a common disease in the general population, while kidney donors are a preselected healthier subgroup. Hence, even a tripling of the risk of hypertension, as shown in the present study, remained unnoticed when the subgroup of healthy donors was compared to the general population. Ideally, donors after nephrectomy should be compared to a population of accepted donors not possible to donate due to recipient reasons or refusing nephrectomy but still being followed long-term to accurately reflect the
specific risk profile of donors, including a high proportion of females (66%) or normal BMI. Under the assumption that the model is correct, the Framingham risk equation allowed making the control population similar for all relevant risk factors of hypertension. On the other hand, the Framingham risk score was not specifically validated for Switzerland, and also does not take into account that many donors are first degree relatives to someone with a kidney disease or possibly cardiovascular problems. However, due to the large group of donors with complete follow-up data sets collected prospectively by SOL-DHR during 17 years it was possible to compensate for differences in the risk profile allowing a robust analyses of nephrectomy as an independent risk factor for hypertension.

By applying an appropriate multivariate statistical analysis and comparing the evolution of hypertension after nephrectomy to the risks from the Framingham equation, there is now clear evidence that unilateral nephrectomy does significantly enhance the short-term occurrence of hypertension after donation. Unilateral nephrectomy deprives the group of healthy donors from their initial health advantage and puts them at a threefold higher risk for developing hypertension. Those subjects remaining with normal blood pressure one year after donation return to a risk similar to that of the healthy Framingham population.

The second goal of this study was to assess the role of nephrectomy as an independent risk factor for microalbuminuria. Previous studies on small donor groups reported an increase in microalbuminuria, which was believed to be due to hyperfiltration of the remaining glomeruli after nephrectomy. Indeed, in the present donor cohort glomerular filtration rate (GFR) as estimated by the MDRD formula showed, despite removing half of the kidney mass, not the theoretically expected fall to 50% of its initial value but instead a reduction to approximately 70%, indicating hyperfiltration of the remaining glomeruli. Over the 10-year follow-up period...
with 2,704 serum creatinine measurements after nephrectomy, GFR remained stable with no sign of normal physiological loss of GFR due to aging or hyperfiltration. In addition, we could now identify hypertension as an important driver for the development of microalbuminuria after nephrectomy.

Another relevant finding was obtained by analyzing the risk factors for microalbuminuria in donors before and after nephrectomy. Before nephrectomy, variability in albumin excretion was related to donor age but not the presence of hypertension. However, after unilateral nephrectomy hypertension became the dominant factor for albumin excretion, whereas donor age had no effect. The possible underlying mechanisms explaining this phenomenon remain unclear and warrant additional (patho-)physiologic investigations.

In summary, kidney donation increases the risk among donors for developing hypertension and sensitizes the remaining kidney to hypertensive glomerular damage as expressed by increased albumin excretion. Whether such increased risk of developing hypertension and/or microalbuminuria translates into renal dysfunction, other morbidities, or mortality post donation remains to be seen. However, both risks must be addressed by offering donors life-long follow-up, providing continued monitoring of blood pressure and urinary albumin excretion. As hypertension becomes the main risk factor for microalbuminuria, adequate therapy with nephroprotective antihypertensive drugs (angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists) should be initiated as soon as kidney donors are diagnosed with hypertension. Transplant centers have to be aware of their responsibility to organize long-term follow-up schemes for living kidney donors to guarantee their optimal medical long-term management. Follow-up should be coordinated by the transplant center or a central registry but performed by the family physician in the donor’s neighborhood to ensure life-long medical support.
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Main Sponsors:
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Authors’ contributions

GTT conceived the study and was the main responsible for the study design and study management.

CN, DT and JS were involved in data collection and management

LMB and GTT designed the analysis plan and LMB performed the statistical analyses.

GTT, JS and LMB drafted the manuscript

All authors provided important intellectual input and approved the final version of the manuscript.

GTT deceased. The submission is post-hum with Dr. Thiel as the first author, thereby acknowledging his contribution. He acknowledged the final version of this paper.

Conflict of interest

The authors confirm that they have no conflict of interest.

Data sharing statement

No additional data available
References


Figure Legends

Figure 1: Rate of living kidney donors with complete data sets at each follow-up time point.

Figure 2: Number of donors at risk of hypertension among 201 providing 10 years of follow-up.

Figure 3: Rates of hypertension in living kidney donors over a 10-year follow-up period and microalbuminuria (>3.3 mg albumin/mmol creatinine) in the entire donor group) stratified for hypertensives (red bars) and normotensives (blue bars).

Figure 4: Percentage of living kidney donors with microalbuminuria (>3.3 mg albumin/mmol creatinine over a 10-year follow-up period and) stratified for hypertensives (red bars) and normotensives (blue bars).
Table 1. Comparison of albumin excretion rate, age, gender, and body mass index (BMI) between donors with and without hypertension before donation

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<th>Normotensive donors (n = 943)</th>
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<td>Albumin excretion ratio</td>
<td>1.29 (SD 1.55)</td>
<td>1.22 (SD 3.02)</td>
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<td>Age</td>
<td>58.1 (SD 9.0)</td>
<td>48.2 (SD 11.1)</td>
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<td>Male gender</td>
<td>40.2%</td>
<td>31.9%</td>
<td>0.01</td>
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<tr>
<td>BMI</td>
<td>26.6 (SD 3.5)</td>
<td>24.8 (SD 3.6)</td>
<td>&lt;0.001</td>
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Table 2. Mean systolic and diastolic blood pressure and ranges of hypertensive and normotensive groups during follow-up. Number of hypertensive subjects on ACE inhibitor or AT1 receptor antagonist treatment (italics)

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<td></td>
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<td>mean systole</td>
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<td>mean diastole</td>
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Figure 1: Rate of living kidney donors with complete data sets at each follow-up time point.
199x130mm (300 x 300 DPI)
Figure 2: Number of donors at risk of hypertension among 201 providing 10 years of follow-up

199x153mm (300 x 300 DPI)
Figure 3: Rates of hypertension in living kidney donors over a 10-year follow-up period and microalbuminuria (>3.3 mg albumin/mmol creatinine) in the entire donor group) stratified for hypertensives (red bars) and normotensives (blue bars).

<table>
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<th>Years after donation</th>
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<th>% Hypertensives (red bars)</th>
<th>% Normotensives (blue bars)</th>
<th>% Albumin excretion ≥ 3.3 mg Albumin/ mmol Crea.</th>
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<td>47.0</td>
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199x150mm (300 x 300 DPI)
Figure 4: Percentage of living kidney donors with microalbuminuria (>3.3 mg albumin/mmol creatinine over a 10-year follow-up period and) stratified for hypertensives (red bars) and normotensives (blue bars).

299x198mm (300 x 300 DPI)
STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

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</tbody>
</table>
Other analyses 17 Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results 18 Summarise key results with reference to study objectives

Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

Generalisability 21 Discuss the generalisability (external validity) of the study results

Other information

Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Investigating kidney donation as a risk factor for hypertension and microalbuminuria: findings from the Swiss prospective follow-up of living-kidney donors.

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SOL_DHR_Hypertension_final_BMJopen_r3_final_CLEAN_wo_fig_revised.doc
Investigating kidney donation as a risk factor for hypertension and microalbuminuria: findings from the Swiss prospective follow-up of living-kidney donors.

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Manuscript statistics:
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References: 38
Tables and Figures: 5
Abstract

Objectives: To assess the role of nephrectomy as a risk factor for the development of hypertension and microalbuminuria.

Design: prospective, long-term, follow-up study

Setting: Swiss Organ Living-Donor Health Registry (SOL-DHR).

Participants: All living kidney donors in Switzerland between 1993 and 2009

Interventions: Data on health status and renal function before, one year and biennially after donation were collected

Primary and Secondary Outcome Measures: Comparison of 1 and 5 year occurrences of hypertension among normotensive donors with 1 and 5 year estimates from the Framingham Hypertension Risk Score. Multivariate random intercept models were used to investigate changes of albumin excretion after donation correcting for repeated measurements and co-factors such as age, male gender and body mass index.

Results: A total of 1,214 donors contributed 3,918 data entries with a completed biennial follow-up rate of 74% during a 10-year period. Mean (standard deviation, SD) follow-up of donors was 31.6 months (34.4). Median age at donation was 50.5 years (interquartile range, 42.2 to 58.8); 806 donors (66.4%) were female. Donation increased the risk of hypertension after 1 year by 3.64 (95% confidence interval (CI) 3.52 to 3.76; p<0.001). Those subjects remaining normotensive one year after donation return to a risk similar to that of the healthy Framingham population. Microalbuminuria before donation was dependent on donor age but not on the presence of hypertension. After nephrectomy, hypertension became the main driver for changes in albumin excretion (odds ratio 1.19; 95%CI 0.13 to 2.25; p=0.03) and donor age had no effect.
Conclusion: Nephrectomy propagates hypertension and increases susceptibility for the development of hypertension-induced microalbuminuria.
Article Summary

Strength:

- The prospective design, the large donor group, and the complete data sets are main assets of this study.
- The study compared the effects with an adequate control group accounting for the lower cardiovascular risk of the donor group.
- The study had an excellent overall follow-up rate of 74 percent.

Limitations

- Missing information on donors’ smoking habits and the family history of hypertension required assumptions and sensitivity analyses.
- The use of anti-hypertensive medication as a part of the hypertension definition may lead to an overstated number of hypertensives.
Introduction

Knowledge of the health consequences of living kidney donation, such as the risk of developing hypertension, may have important implication for the long-term medical follow-up of donors. So far it is uncertain, whether nephrectomy alone is an independent risk factor for the development of hypertension and albuminuria. The occurrence of hypertension and albuminuria after kidney donation has been reported for decades, but as living organ donations continue to increase worldwide the health risk of donation are viewed more positively. A meta-analysis of 48 studies reporting the outcome of 5,145 donors showed a very minor and clinically non-relevant increased risk among kidney donors for the development of hypertension or proteinuria over long-term follow-up as compared to age-matched controls. However, the quality of the individual studies were limited by the retrospective study design, extensive loss to follow-up, small sample size resulting in underpowered statistical analyses, and the common use of a normal population as control group while donors are usually a positive selection and therefore healthier than the normal age-matched population.

Only recently, a new multivariate score based on the Framingham data to calculate hypertension risks has become available that allows tackling the problem of inappropriate comparisons. The new score allows making groups comparable for gender, age, systolic and diastolic blood pressure, smoking habits and family history of hypertension. To date, no study, including those summarized in the recent meta-analysis, applied the risk equation in the analysis. Therefore, the aim of this prospective, long-term, follow-up study was to assess the role of nephrectomy as an independent risk factor for the development of hypertension and microalbuminuria in living kidney donors when compared to estimates from the multivariable
Hypertension Risk Score of the Framingham Cohort including all relevant risk
parameters of hypertension for potential donors without nephrectomy.

**Methods**

The ethics committee of Basle, Switzerland approved this study. A written informed
consent was obtained from all participants. The protocol used by the Swiss Organ
Living-Donor Health Registry (SOL-DHR) to collect the data has been described in
detail elsewhere \(^7\). Briefly, all living kidney donors in Switzerland were enrolled before
donation and followed one year after nephrectomy and biennially thereafter since
1993. Donors’ general practitioners provided medical follow-up data, which were
collected by a central registry. So far there are sequential data for up to 17 years
after donation; the current analysis was restricted to a 10-year follow-up period due
to the scarcity of data beyond this time period. This resulted in the exclusion of 185
database entries.

Hypertension was defined as blood pressure values above 140 mmHg systolic and/or
90 mmHg diastolic or use of any blood pressure lowering drug. Blood pressure data
were reported as a mean of three individual measurements at each time point taken
before and one year after donation and thereafter biennially during life-long follow-up
examinations requested by the Swiss transplant law. All new diagnoses of
hypertension had to be verified by 24-hour ambulatory blood pressure recording
using threshold values 135/85 mmHg or higher. Blood pressure values in the normal
range were only accepted as “normal” if a list of drugs taken the same day was
reported to SOL-DHR to exclude an antihypertensive treatment. Only follow-up
exams with complete data sets were analysed.

Urine albumin and urine creatinine were measured in a spot urine sample. A single
central laboratory (Viollier AG, Basel Switzerland) performed all chemical analysis in
blood and urine. Microalbuminuria was defined as a ratio of mg albumin to mmol creatinine of 3.3 or more according to international guidelines. For statistical analysis, interval scaled variates were summarized with means and standard deviations (SD) or medians and interquartile ranges (IQR), where appropriate. Dichotomous variates were described as ratios and percentages. To assess the effect of donation on the occurrence of elevated blood pressure requiring medication, we fitted the Hypertension Risk Score of the Framingham Cohort for 1 year and 4 year risk of hypertension to our data as follows: For the first year analysis we fitted the data to the distribution prior to donation after excluding all cases of hypertension (n=271). For the subsequent four year analysis, we focused on all donors remaining normotensive 1 year after donation. Since data on smoking habits and family history of hypertension were not available in our data set we created two random variates under the assumption of a smoking prevalence of 25 percent using the most recent epidemiologic data of the tobacco monitoring study in Switzerland and took the strength of association from the Hypertension Risk Score. We assumed positive family history (both parents) for hypertension of 25 percent using data of the Swiss survey on salt intake and again took the strength of association from the Hypertension Risk Score. We found no Swiss data on the correlation between the two parameters and therefore assumed no correlation between smoking habits and positive family history of hypertension. We performed sensitivity analyses by repeating the analyses 100 times with each newly drawn random samples of the two parameters “smoking habits” and “family history of hypertension” and when assuming 20 and 30 percent prevalence rather than 25 percent.

The estimated probabilities from the Framingham equations were compared to the probabilities estimated from two multivariate logistic regression models using the occurrence of hypertension 1 or 5 years after donation as the dependent variate and
the available parameters of the Framingham equation (age, female gender, systolic and diastolic blood pressure, body mass index (BMI), smoking habits, family history of hypertension, and an interaction term of age and diastolic blood pressure) prior to donation (for the 1 year assessment) and at 12 month after donation (for the 4 year assessment).

To examine the parameters associated with microalbuminuria prior to donation; a multivariate logistic regression model was fitted using the following parameters as dependent variates (hypertension, donor age, male gender, and BMI). To examine the occurrence of microalbuminuria in the follow-up, a multivariate random intercept model with hypertension as an independent variate and accounting for co-variates (donor age, male gender, and body mass index (BMI)) and corrected for repeated measures per donor was fitted. This was done using the subject as a random factor. All analyses were performed using the Stata 11.2 statistics software package (StataCorp LP, College Station, TX, USA).

Results

In the period from April 1993 to December 2009, all 1,214 living kidney donors in Switzerland were enrolled in the SOL-DHR database providing 3,918 complete data sets with blood pressure measurements, microalbuminuria results, and a list of drugs taken the day of blood pressure measurement. Figure 1 reports the number of donor follow-up exams at each time point. Fifty-nine percent of donors were related (28 percent parents, 26 percent siblings, 5 percent otherwise), 33 percent were living partners and 8 percent of donors were unrelated to the kidney recipient. During the 10-year follow-up period, 22 donors died from non-renal causes resulting in 61 missed follow-up examinations. A total of 2,704 complete data sets out of 3,632 possible follow-up exams were returned and analysed by SOL-DHR, resulting in an
average follow-up rate of 74% over all time points. We checked whether those with hypertension at the one year follow-up were more likely to show up at the five year follow-up and found no significant difference (p= 0.641).

At the time of donation, median donor age was 50.4 years (IQR 42.1 – 58.7). Eight hundred and six donors (66.4%) were female and 408 (33.6%) were male. Median BMI of all donors was 24.9 (IQR 22.7 – 27.7). A total of 923 donors (76.0%) had normal blood pressure and 95.2% did not have microalbuminuria (ratio ≥3.3; median albumin-excretion ratio 0.7; IQR 0.4-1.3).

At the time of donation, 271 donors (22.3%) were diagnosed with hypertension (information on hypertension was missing in 20 patients). In 89 patients (32.6%) the diagnosis of hypertension was made on the basis of blood pressure measurement. All other patients were classified on the basis of use of blood pressure lowering medications. Mean systole was 140.7 (Range: 100 to 205) and mean diastole was 84.5 (Range: 60 to 113). Table 1 reports a comparison with normotensive donors in terms of albumin excretion rate, gender, age, and BMI.

Occurrence of Hypertension

Among initially normotensive donors, 398 (43.1%) developed hypertension in the observation period and provided 1302 data entries. Using the Framingham Risk calculator, the predicted risk for developing hypertension one year after donation was increased by 3.64 (95% confidence interval (CI) 3.52 to 3.76; p<0.001). The estimated mean 1-risk of hypertension from the Framingham risk equation was 3.5%.

The observed incidence of hypertension after 1 year among responders was 18.7% (151/807). In the subset of the donor cohort that remained normotensive 1 year after donation and had non-missing values for hypertension status 5 years after donation (n=451) the risk was only modestly increased (1.19 95%CI 1.10 to 1.29; <0.001).

Two hundred and one patients provided data up to 10 years after donation.
Occurrence of hypertension is shown in Figure 2. 106 remained normotensive. In the subgroup of donors remaining normotensive five years after donation, the cumulative incidence of developing hypertension in the subsequent 5 years was 29/123 (23.6%). Results remained essentially unchanged in sensitivity analyses. Table 2 shows mean systolic and diastolic blood pressure values and ranges of hypertensive and normotensive groups during follow-up. All hypertensive patients remained hypertensive during the observation period. The mean systolic (6.2 mmHg (95% CI: 4.1 mmHg to 8.4 mmHg); p<0.001) and diastolic (5.0 mmHg (3.4 mmHg to 6.6 mmHg); p<0.001) blood pressure values of normotensive donors pre-donation, who developed hypertension at 1-year follow-up were slightly albeit significantly higher than the pre-donation values of those patients how were normotensive at the 1-year follow-up, when correcting for differences in age, male gender and BMI.

Occurrence of microalbuminuria

In all donors, the albumin excretion ratio increased from 1.2 ± 2.7 to 1.9 ± 10.7 mg albumin/mmol creatinine and the occurrence of microalbuminuria increased from 4.8% to 10.4% (Figure 3). Twenty out of 57 donors with microalbuminuria were hypertensive (35.1 percent). Ten years after nephrectomy the rate of microalbuminuria (>3.3 mg albumin/mmol creatinine) was significantly higher in the group of 271 initially hypertensive donors as compared to normotensive donors (16.6% vs. 6.0%, p=0.03) (See Figure 4). Before donation, albumin excretion was dependent upon donor age but not on the presence of hypertension (Table 1). However, after nephrectomy, multivariate random intercept models corrected for repeated measures per donor showed that the effect of age was lost and hypertension became the main driver for increased albumin excretion (OR 1.19; 95%CI 0.13 to 2.25; p=0.03).
Discussion

Our results show that kidney donation triplicates the short term risk among donors of developing hypertension and that after nephrectomy hypertension becomes the main risk factor for microalbuminuria.

In earlier studies, hypertension after living kidney donation was reported in 17-33% of donors. However, in the past, living kidney donation was not regarded as a risk factor for hypertension as the incidence of hypertension was similar to the age-matched general population. These studies were limited by their retrospective design, small donor cohorts, high rate of donors lost to follow-up, and use of the general population as a control group. Also, a prospective study by Ramesh Prasad and colleagues on 51 consenting donors that derived from a pool of 129 eligible, showed that the pre-donation 24-hour ambulatory blood pressure dipping profile (nocturnal blood pressure dipping) of normotensive living kidney donors was not correlated with renal function and cardiovascular risk status at the one-year follow-up after donation. Only recently, publications taking an opposite view have become available. In 2014, Mjoen and colleagues published a paper estimating the all-cause and the cardiovascular mortality, and risk for end-stage renal disease in kidney donors. Compared to a selected population of non-donors who would have qualified for donation the showed an increased long-term risks for kidney failure and mortality in kidney donors. Very recently, results from the Chronic Renal Impairment in Birmingham (CRIB)–Donor study showed that the unilateral nephrectomy in healthy subjects lead to an increase in LV mass that correlated with the reduction in the glomerular filtration rate within one year. The classification of living kidney donors as being normotensive or hypertensive is not as easy as primarily expected. Normal blood pressure values do not allow a donor to be classified as being normotensive when no information is available on the
use of antihypertensive drugs the day of blood pressure measurement. On the other hand, hypertensive blood pressure readings without confirmation by 24-hour blood pressure recording may reflect white coat hypertension. In our study all new diagnoses of hypertension had to be verified by 24-hour ambulatory blood pressure recording. Blood pressure values in the normal range were only accepted as “normal” if a list of drugs taken the same day was reported to SOL-DHR. Only follow-up exams with complete data sets were analysed. In 2006, Boudville and colleagues concluded in their meta-analysis that there was on average a 5 mm Hg increase in blood pressure post nephrectomy but that they were unable to evaluate for any differences in risk of hypertension because of heterogeneity in the data and weaknesses in the underlying studies.

Strengths of the present study are the prospective design, the large donor group, a high follow-up rate and complete data sets allowing a robust classification of hypertensive outcomes. In contrast to the follow up of organ recipients, follow up of donors is cumbersome as donors frequently live far from the transplant centres and regard themselves as healthy without the need for regular medical check-ups. Therefore, donors are usually not prepared to travel long distances or cover the expenses for their follow-up exams. The key factor for the high follow-up rate in this prospectively designed long-term follow-up study was the Swiss transplant law requiring a central donor registry and coverage of medical expenses for donors’ biennial follow-up examination by the kidney recipients’ compulsory health insurance. At regular intervals, SOL-DHR provided donors with a questionnaire and medical follow-up form to be filled out by the donor’s preferred local family physician with all medical expenses covered by the recipients’ health insurance. Donors not returning their follow-up forms were contacted by SOL-DHR using kidney recipients’ information to obtain donor contact details; if abroad, donors were contacted through
the worldwide network of Swiss embassies. Hence, we regard the rate of 74% complete follow up exams as the very best that can be achieved under ideal circumstances. The 2,704 completed follow-up data sets allow for robust statistical analyses.

Missing information on donors’ smoking habits and the family history of hypertension is a weakness of this study. We tried to deal with it by imputing the missing data. In the case of smoking we based our assumptions on the most recent epidemiologic data on smoking available in Switzerland. In view of the fact that donors represent a healthy subgroup of the general public we believe that this is a conservative assumption and think that the comparison is justifiable. Using lower rates for smoking would have increased the excess of risk among kidney donors. For positive family history we assumed that 25 percent had both parents with hypertension. This assumption was based on a recently performed nationwide survey in Switzerland on salt intake. Again, it can be argued that this is a conservative assumption given the overrepresentation of healthy subjects in our cohort resulting in a potential underestimation of the risk of developing hypertension after donation. However, we cannot deny that the lack of data on two risk parameters that are used in the Framingham equation remains a problem. All we could do was to assess to what extend our assumptions affected the overall results. We were reassured that the results only varied minimally when repeating the analyses. Moreover, we cannot fully rule-out that our definition of hypertension, taking use of anti-hypertensive medication as a part of the definition, led to an overstated number of hypertensive, because some normotensive patients might have received ACE inhibitors or AT1 receptor antagonists against microalbuminuria or beta-blockers against anxiety. Finally, even if a follow-up rate of 76 percent is very high, we cannot fully exclude selection bias.
Hypertension is a common disease in the general population, while kidney donors are a preselected healthier subgroup. Hence, even a tripling of the risk of hypertension, as shown in the present study, remained unnoticed when the subgroup of healthy donors was compared to the general population. Ideally, donors after nephrectomy should be compared to a population of accepted donors not possible to donate due to recipient reasons or refusing nephrectomy but still being followed long-term to accurately reflect the specific risk profile of donors, including a high proportion of females (66%) or normal BMI. Under the assumption that the model is correct, the Framingham risk equation allowed making the control population similar for all relevant risk factors of hypertension. On the other hand, the Framingham risk score was not specifically validated for Switzerland, and also does not take into account that many donors are first degree relatives to someone with a kidney or possibly cardiovascular disease. However, due to the large group of donors with complete follow-up data sets collected prospectively by SOL-DHR during 17 years it was possible to compensate for differences in the risk profile allowing a robust analyses of nephrectomy as an independent risk factor for hypertension. Unilateral nephrectomy deprives the group of healthy donors from their initial health advantage and puts them at a threefold higher risk for developing hypertension. Those subjects remaining with normal blood pressure one year after donation return to a risk similar to that of the healthy Framingham population. The second goal of this study was to assess the role of nephrectomy as an independent risk factor for microalbuminuria. Previous studies on small donor groups reported an increase in microalbuminuria, which was believed to be due to hyperfiltration of the remaining glomeruli after nephrectomy. Indeed, in the present donor cohort glomerular filtration rate (GFR) as estimated by the MDRD formula showed, despite removing half of the kidney mass, not the theoretically
expected fall to 50% of its initial value but instead a reduction to approximately 70%, indicating hyperfiltration of the remaining glomeruli. Over the 10-year follow-up period with 2,704 serum creatinine measurements after nephrectomy, GFR remained stable with no sign of normal physiological loss of GFR due to aging or hyperfiltration. In addition we could now identify hypertension as an important driver for the development of microalbuminuria after nephrectomy.

Another relevant finding was obtained by analysing the risk factors for microalbuminuria in donors before and after nephrectomy. Before nephrectomy, variability in albumin excretion was related to donor age but not the presence of hypertension. However, after unilateral nephrectomy hypertension became the dominant factor for albumin excretion, whereas donor age had no effect. The possible underlying mechanisms explaining this phenomenon remain unclear and warrant additional (patho-) physiologic investigations.

In summary, kidney donation increases the risk among donors for developing hypertension and sensitizes the remaining kidney to hypertensive glomerular damage as expressed by increased albumin excretion. Whether such increased risk of developing hypertension and/or microalbuminuria translates in to renal dysfunction, other morbidities or mortality post donation remains to be seen. However, both risks must be addressed by offering donors life-long follow-up, providing continued monitoring of blood pressure and urinary albumin excretion. As hypertension becomes the main risk factor for microalbuminuria, adequate therapy with nephroprotective antihypertensive drugs (angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists) should be initiated as soon as kidney donors are diagnosed with hypertension. Transplant centres have to be aware of their responsibility to organize long-term follow-up schemes for living kidney donors to guarantee their optimal medical long-term management. Follow-up should be
coordinated by the transplant centre or a central registry but performed by the family
physician in the donor’s neighbourhood to ensure life-long medical support.
Acknowledgments

We are indebted to the medical/surgical team and the transplant coordinators of the Transplant Centres of Basel, Bern, Geneva, Lausanne, St. Gallen, and Zürich. We would like to thank Ruth Lützelschwab and Christina Wolf-Heidegger for secretarial help. We are grateful to Thomas Voegele (transplant coordinator) for his initial participation when SOL-DHR was initiated (1993) and Hanspeter Hort (graphic artist) for designing the SOL-DHR logo free of charge. We thank Guy Kollwelter and Heinz Herrmann (both from Astellas) for providing us with medals and individual diplomas for living donors.

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Authors’ contributions

GTT conceived the study and was the main responsible for the study design and study management.

CN, DT and JS were involved in data collection and management

LMB and GTT designed the analysis plan and LMB performed the statistical analyses.

GTT, JS and LMB drafted the manuscript

All authors provided important intellectual input and approved the final version of the manuscript.

GTT deceased. The submission is post-hum with Dr. Thiel as the first author, thereby acknowledging his contribution. He acknowledged the final version of this paper.

Conflict of interest

The authors confirm that they have no conflict of interest.

Data sharing statement

No additional data available
References


Figure Legends

Figure 1: Rate of living kidney donors with complete data sets at each follow-up time point.

Figure 2: Number of donors at risk of hypertension among 201 providing 10 years of follow-up

Figure 3: Rates of hypertension in living kidney donors over a 10-year follow-up period and microalbuminuria (>3.3 mg albumin/mmol creatinine) in the entire donor group) stratified for hypertensives (red bars) and normotensives (blue bars).

Figure 4: Percentage of living kidney donors with microalbuminuria (>3.3 mg albumin/mmol creatinine over a 10-year follow-up period and) stratified for hypertensives (red bars) and normotensives (blue bars).
Table 1. Comparison of albumin excretion rate, age, gender, and body mass index (BMI) between donors with and without hypertension before donation

<table>
<thead>
<tr>
<th>Donor characteristics before kidney donation</th>
<th>Hypertensive donors (n = 271)</th>
<th>Normotensive donors (n = 943)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin excretion ratio</td>
<td>1.29 (SD 1.55)</td>
<td>1.22 (SD 3.02)</td>
<td>0.72</td>
</tr>
<tr>
<td>Age</td>
<td>58.1 (SD 9.0)</td>
<td>48.2 (SD 11.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>40.2%</td>
<td>31.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>26.6 (SD 3.5)</td>
<td>24.8 (SD 3.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Table 2. Mean systolic and diastolic blood pressure and ranges of hypertensive and normotensive groups during follow-up. Number of hypertensive subjects on ACE inhibitor or AT1 receptor antagonist treatment (italics)

<table>
<thead>
<tr>
<th>Variable</th>
<th>normotensive</th>
<th>hypertensive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td># Mean Min Max</td>
<td># Mean Min Max</td>
<td>#</td>
</tr>
<tr>
<td>before donation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean systole</td>
<td>923 120.7 89 140</td>
<td>271 140.7 100 205</td>
<td></td>
</tr>
<tr>
<td>mean diastole</td>
<td>923 74.9 46 90</td>
<td>271 84.5 60 113</td>
<td>260</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean systole</td>
<td>555 121.0 86 140</td>
<td>252 140.9 88 220</td>
<td></td>
</tr>
<tr>
<td>mean diastole</td>
<td>555 77.1 50 90</td>
<td>252 87.3 60 116</td>
<td>229</td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean systole</td>
<td>408 122.3 90 140</td>
<td>198 142.9 109 187</td>
<td></td>
</tr>
<tr>
<td>mean diastole</td>
<td>408 78.4 59 90</td>
<td>198 86.4 60 110</td>
<td>194</td>
</tr>
<tr>
<td>5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean systole</td>
<td>272 121.9 85 140</td>
<td>179 141.0 100 190</td>
<td></td>
</tr>
<tr>
<td>mean diastole</td>
<td>272 78.0 56 90</td>
<td>179 85.3 60 115</td>
<td>161</td>
</tr>
<tr>
<td>7 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean systole</td>
<td>177 123.3 95 140</td>
<td>142 140.1 100 189</td>
<td></td>
</tr>
<tr>
<td>mean diastole</td>
<td>177 78.2 53 90</td>
<td>142 84.3 61 109</td>
<td>128</td>
</tr>
<tr>
<td>10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean systole</td>
<td>86 122.5 83 140</td>
<td>93 141.2 107 210</td>
<td></td>
</tr>
<tr>
<td>mean diastole</td>
<td>86 77.1 59 90</td>
<td>93 84.0 60 111</td>
<td>74</td>
</tr>
</tbody>
</table>
Figure 1: Rate of living kidney donors with complete data sets at each follow-up time point.

<table>
<thead>
<tr>
<th>Years after donation</th>
<th>#Donors</th>
<th>#Responders</th>
<th>% Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1214</td>
<td>1214</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>1116</td>
<td>918</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>933</td>
<td>703</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>720</td>
<td>510</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>630</td>
<td>373</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>306</td>
<td>201</td>
<td>65</td>
</tr>
</tbody>
</table>
Figure 2: Number of donors at risk of hypertension among 201 providing 10 years of follow-up

199x153mm (300 x 300 DPI)
Figure 3: Rates of hypertension in living kidney donors over a 10-year follow-up period and microalbuminuria (>3.3 mg albumin/mmol creatinine) in the entire donor group) stratified for hypertensives (red bars) and normotensives (blue bars).

<table>
<thead>
<tr>
<th>Years after donation</th>
<th>Donors</th>
<th>Hypertensives (red bars)</th>
<th>Normotensives (blue bars)</th>
<th>Albumin excretion ≥ 3.3 mg Albumin/ mmol Creat.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1214</td>
<td>22.3</td>
<td>77.7</td>
<td>4.8</td>
</tr>
<tr>
<td>1</td>
<td>918</td>
<td>27.5</td>
<td>72.5</td>
<td>6.5</td>
</tr>
<tr>
<td>3</td>
<td>703</td>
<td>28.3</td>
<td>71.7</td>
<td>7.9</td>
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<tr>
<td>5</td>
<td>510</td>
<td>35.1</td>
<td>64.9</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>373</td>
<td>38.3</td>
<td>81.7</td>
<td>8.7</td>
</tr>
<tr>
<td>10</td>
<td>201</td>
<td>53.9</td>
<td>47.0</td>
<td>10.4</td>
</tr>
</tbody>
</table>
Figure 4: Percentage of living kidney donors with microalbuminuria (>3.3 mg albumin/mmol creatinine over a 10-year follow-up period and) stratified for hypertensives (red bars) and normotensives (blue bars).

299x198mm (300 x 300 DPI)
<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1. (a) Indicate the study’s design with a commonly used term in the title or the abstract&lt;br&gt; (b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
</tr>
<tr>
<td>Introduction</td>
<td>2. Explain the scientific background and rationale for the investigation being reported</td>
</tr>
<tr>
<td>Objectives</td>
<td>3. State specific objectives, including any prespecified hypotheses</td>
</tr>
<tr>
<td>Methods</td>
<td>4. Present key elements of study design early in the paper&lt;br&gt; 5. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection&lt;br&gt; 6. (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up&lt;br&gt; (b) For matched studies, give matching criteria and number of exposed and unexposed&lt;br&gt; 7. Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable&lt;br&gt; 8. For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group&lt;br&gt; 9. Describe any efforts to address potential sources of bias&lt;br&gt; 10. Explain how the study size was arrived at&lt;br&gt; 11. Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why&lt;br&gt; 12. (a) Describe all statistical methods, including those used to control for confounding&lt;br&gt; (b) Describe any methods used to examine subgroups and interactions&lt;br&gt; (c) Explain how missing data were addressed&lt;br&gt; (d) If applicable, explain how loss to follow-up was addressed&lt;br&gt; (e) Describe any sensitivity analyses</td>
</tr>
<tr>
<td>Bias</td>
<td>13.</td>
</tr>
<tr>
<td>Study size</td>
<td>14.</td>
</tr>
<tr>
<td>Quantitative variables</td>
<td>15.</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>16.</td>
</tr>
<tr>
<td>Results</td>
<td>17. (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed&lt;br&gt; (b) Give reasons for non-participation at each stage&lt;br&gt; (c) Consider use of a flow diagram&lt;br&gt; 18.</td>
</tr>
<tr>
<td>Participants</td>
<td>19.</td>
</tr>
<tr>
<td>Descriptive data</td>
<td>20. (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders&lt;br&gt; (b) Indicate number of participants with missing data for each variable of interest&lt;br&gt; (c) Summarise follow-up time (eg, average and total amount)</td>
</tr>
<tr>
<td>Outcome data</td>
<td>21. Report numbers of outcome events or summary measures over time</td>
</tr>
<tr>
<td>Main results</td>
<td>22. (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included&lt;br&gt; (b) Report category boundaries when continuous variables were categorized&lt;br&gt; (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</td>
</tr>
</tbody>
</table>
**Discussion**

<table>
<thead>
<tr>
<th>Other analyses</th>
<th>Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key results</td>
<td>Summarise key results with reference to study objectives</td>
</tr>
<tr>
<td>Limitations</td>
<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias</td>
</tr>
<tr>
<td>Interpretation</td>
<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</td>
</tr>
<tr>
<td>Generalisability</td>
<td>Discuss the generalisability (external validity) of the study results</td>
</tr>
</tbody>
</table>

| Other information | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for exposed and unexposed groups.

Investigating kidney donation as a risk factor for hypertension and microalbuminuria: findings from the Swiss prospective follow-up of living kidney donors

Gilbert T Thiel, Christa Nolte, Dimitrios Tsinalis, Jürg Steiger and Lucas M Bachmann

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