

# BMJ Open Kidney function, cardiovascular outcomes and survival of living kidney donors with hypertension: a systematic review protocol

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## ABSTRACT

**Introduction** Hypertension has been considered a contraindication for living kidney donation in the past. Since transplantation from living kidney donors remains the best modality for kidney failure, there is now an increased acceptance of living kidney donors with hypertension. However, the safety of this practice for the cardiovascular and kidney health of the donor is unclear. We will conduct a systematic review to summarise and synthesise the existing literature on this topic.

**Methods and analysis** A systematic review of prospective randomised and non-randomised and retrospective studies will be conducted. MEDLINE, EMBASE, Cochrane CENTRAL and EBM reviews published from January 1946 to December 2021 will be reviewed. Primary outcome will be the difference in the survival, major adverse cardiovascular events, estimated glomerular filtration rate of 45 mL/min or less and development of end-stage kidney failure, between living kidney donors with and without hypertension. Study screening, selection, and data extraction will be performed by two independent reviewers. Studies must fulfil all eligibility criteria for inclusion into the systematic review and meta-analysis. The Risk of Bias in Non-Randomised studies tool will be used to assess bias.

**Ethics and dissemination** No ethical approval is required for this systematic review. The results of this review will be disseminated in a peer-reviewed, open-access journal to ensure access to all stakeholders in kidney transplantation and to inform clinical guidelines on the evaluation and follow-up care of living kidney donor candidates.

**PROSPERO registration number** CRD42022300119.

## INTRODUCTION

Living donor kidney transplantation offers patients living with end-stage kidney disease (ESKD) better quality of life and survival than deceased donor kidney transplantation or dialysis.<sup>1</sup> Five-year Canadian survival rates on dialysis, with a deceased donor kidney transplant, and with a living donor kidney transplant are 41%, 82% and 90%, respectively.<sup>2</sup> Over 40 000 people in Canada have ESKD, of whom only 43% have a functioning transplant.<sup>2</sup> The

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This systematic review will provide the highest level of evidence related to the safety of the increasing practice of accepting individuals with hypertension to be living kidney donors.
- ⇒ There is a potential for inconsistent quality in the reporting of hypertension and outcomes.
- ⇒ Certain subgroups at higher risk of adverse outcomes, such as black people, may be under-reported.
- ⇒ The scarcity of long-term follow-up in the living kidney donor literature may be the main limitation of the study.

number of living donor kidney transplants has stagnated at 12–13 per million population, while the number of patients living with kidney failure has increased by 35% in the past 10 years in Canada.<sup>2</sup> The consequence of stagnant living donor kidney transplant rates is severe. Approximately, 3000 people are on a waitlist for a kidney transplant and up to 100 people die waiting for a kidney every year in Canada.<sup>2</sup>

On the other hand, living kidney donation is not without potential complications. The risk of death 90 days after nephrectomy for kidney donation is 3.1 per 10 000.<sup>3</sup> The risk of developing ESKD is small, less than 1%, but may be higher in certain populations.<sup>3</sup> Additionally, there is a small increase in the incidence of hypertension after kidney donation in donors with previously normal blood pressure.<sup>4</sup> Although, living kidney donors undergo rigorous assessment to ensure their perioperative and long-term safety<sup>5 6</sup> there is increased acceptance of living kidney donors with hypertension in the last decade.<sup>7 8</sup> This is controversial because hypertension is an independent predictor of cardiovascular disease and mortality in the general population and is a leading contributor to ESKD. Despite these concerns, the Kidney Disease

Improving Global Outcomes international living kidney donor guideline states that donor candidates with hypertension and no target organ damage, may be accepted as donors, based on a few studies which have short-term follow-up.<sup>9</sup>

To examine these important outcomes after donation and transplantation, we will systematically review, appraise and synthesise all studies that evaluated cardiovascular disease, kidney function and mortality of living kidney donors with hypertension. Our primary objective is to determine how living kidney donation from a donor with hypertension impacts kidney function, major adverse cardiovascular events (MACEs) and survival for the donor.

## METHODS AND ANALYSIS

The protocol has been registered in the PROSPERO register for systematic reviews.<sup>10</sup> The methods for this systematic review and meta-analyses are based on the previously published study by Rodriguez *et al.*<sup>11</sup> The preferred reporting items for systematic reviews described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines will be followed and a checklist file for these recommendations will be provided (online supplemental appendix 1).<sup>12</sup>

### Population and eligibility criteria

We will include adults who are over 18 years of age who underwent unilateral nephrectomy for living kidney donation with and without known hypertension. Approved donors who underwent unilateral nephrectomy other than for living kidney donation and children and adolescents with solitary kidney after unilateral nephrectomy will be excluded. Pregnant living kidney donors will be excluded.

### Intervention

The main interventions are as follows: (1) open or laparoscopic unilateral nephrectomy for living kidney donation and (2) kidney transplantation from a living donor.

### Outcomes

The primary outcome is the difference in survival, MACEs (composite of total death, myocardial infarction, stroke, hospitalisation for heart failure, need for coronary or peripheral arterial revascularisation), the development of estimated glomerular filtration rate (eGFR) 45 mL/min or less, and the development of ESKD between living kidney donors with and without hypertension.

### Study design

Our systematic review will include all prospective randomised controlled trials and non-randomised (cohort, case-control, case series and before-and-after studies) and retrospective studies that are reported in English, provided that 10 or more participants are included in the primary analysis. Single-arm studies of outcomes of hypertensive living kidney donors and

studies comparing living kidney donors with hypertension to donors without hypertension or to the general population and comparable non-donors will be included.

### Search strategy

Our search strategy will be conducted using MEDLINE, EMBASE, Cochrane CENTRAL databases and EBM reviews published from January 1946 to December 2021. A health information specialist will create a comprehensive search strategy with the research team. Our proposed search strategy is outlined in online supplemental appendix 2. Manual abstract review will be conducted according to predefined screening criteria (table 1). The final data extraction and analysis will be restricted to articles reported in English. Duplicate citations will be removed, and search strategies will be kept up to the time of the end of this review.

### Study screening, exclusions and selection

Study screening, exclusions and selection in the screening phase will include all retrospective and prospective randomised and non-randomised studies reporting outcomes of both hypertensive and normotensive donors. A process of study selection will be followed using the inclusion and exclusion criteria set out in table 1. We will exclude the following studies: studies reporting individuals age less than 18 years), narrative reviews, mathematical modelling reports, duplicates, substudies of previously published trials, abstracts and conference proceedings without full publication. All stages of review will be independently performed by two individuals, with a third reviewer (AB) available for consensus in cases of discrepancies. All citations will first be screened by title and abstract, then full-text review will be performed prior to data extraction of the final included studies. In cases of missing information, we will attempt to contact study authors to obtain it. Reviewers will not be blinded to the abstracts, full texts or their corresponding study authors and institutions.

### Data extraction (selection and coding)

A data extraction form will be prepared and optimised using a subset of 45 randomly selected studies prior to full extraction by two independent reviewers (ME and SA). When multiple publications arise from one study, relevant data will be extracted into a single form. Data extraction will include: (1) study characteristics, design and methods: title, authors, journal/source/year, language of publication, country, type of study design, study period, publication status, total number of donors and non-donors, inclusion and exclusion criteria, and points of measurement; (2) sample characteristics: age, sex, race, age at time of nephrectomy, age at time of assessment, duration of follow-up and type of blood pressure measurement and (3) outcomes: serum creatinine levels, eGFR, systolic blood pressure, diastolic blood pressure, cardiovascular events, development of ESKD. We will document if the diagnosis of hypertension is reported based on numerical

**Table 1** List of inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Participants	Approved donors (age 18 years and greater) who underwent unilateral nephrectomy as selected candidates who met criteria for living kidney donation with or without hypertension	Participants who underwent unilateral nephrectomy other than for kidney donation Children and adolescents with solitary kidney after unilateral nephrectomy Pregnant living kidney donors of living donor kidneys will be excluded. Studies that do not report that consent was obtained will be excluded. Studies that do not report having obtained ethics approval will be excluded. Studies that report on executed prisoners or any other marginalised population will be excluded.
Intervention	Approved donors (age 18 years and older) who underwent nephrectomy who met criteria for kidney donation with hypertension	
Comparator	Approved donors (age 18 years and older) who underwent nephrectomy who met criteria for kidney donation without hypertension Comparable non-donors and general population with hypertension	None
Outcome	Donor Outcomes: Survival, major adverse cardiovascular events, eGFR 45 mL/min or less, development of end-stage kidney disease	None
Study Design	Prospective studies (cohort, case–control, case series, before-and-after studies, randomised controlled trials) and retrospective studies to be included in the primary analysis Articles reported in English	Paediatric and non-human studies Narrative reviews Mathematical modelling reports Duplicates Substudies of previously published trials Abstracts, conference proceedings

eGFR, estimated glomerular filtration rate.

values, by patient report and/or using blood pressure lowering medications. We will report the number and type of blood pressure lowering medications used.

### Risk assessment of bias

The risk of bias for non-randomised studies will be assessed using the Risk of Bias in Non-Randomised studies (ROBINS-I) tool.<sup>13</sup> The Cochrane risk of bias tool will be used for any randomised controlled trials.<sup>14</sup> The ROBINS-I tool comprises seven domains for the assessment of bias: participant selection (adult living kidney donors), confounding, classification of the intervention (ie, hypertension in living kidney donors), deviation from the intended intervention, missing data, outcome measurement and selection of the reported results. Each domain is judged as either low, moderate, serious or critical risk of bias or no information available and each study will be evaluated by two independent reviewers. A final overall assessment of study bias for each study domain will be determined after discussion among reviewers and a corresponding table outlining all seven domains for each study will be constructed. Any conflicts or disagreements will be resolved with a third reviewer (AB).

### Strategy for data synthesis

Study characteristics will be summarised using means and SD or median and IQRs for continuous variables and numbers and percentages for categorical variables.

A narrative report of study characteristics will also be provided. We will identify potential sources of clinical heterogeneity according to differences in study design characteristics, methodological quality, characteristics at baseline between hypertensive donors and their controls, and duration of follow-up periods. If at least two studies report on the same outcome, a quantitative synthesis (ie, meta-analysis) will be attempted on those studies. Statistical heterogeneity will be characterised with the  $I^2$  and Cochran's  $Q$  statistics. We will primarily choose the random effects model according to the methodology of DerSimonian and Laird,<sup>15</sup> but a fixed-effects meta-analysis will also be modelled as part of our sensitivity analysis. We will calculate pooled effect estimates using either standardised or mean differences and their 95% CIs.

### Sensitivity analysis

Sensitivity analyses may be performed to evaluate the effects of study bias, and any confounding effects associated with differences in the reporting of adjusted or non-adjusted values of cardiovascular outcomes according to changes in blood pressure or classification of blood pressure as hypertension or normotension. We will assess differences between fixed and random effects models on the pooled effect estimates.

### Subgroup analysis

We will determine the effects of potential confounders by performing subgroup analyses based on age, duration of follow-up after kidney donation (short vs medium vs long term), type of comparator (recipient related vs non-recipient related), number and type of medications used for the control of blood pressure and sex, depending on the level of detailed information reported in each study. Intergroup differences will be analysed using the Cochran's Q statistics with  $p \leq 0.10$ .

### Confidence in cumulative evidence

To assess the certainty in the evidence and strength of recommendations on the effects of blood pressure in living kidney donors, reviewers will evaluate the quality of evidence for each outcome measure according to the Grading of Recommendations Assessment, Development and Evaluation recommendations.<sup>16</sup>

### Amendments

Protocol amendments will be summarised in a table, with date of amendment, description of changes and rationale provided.

### Patient and public involvement

Patients and the public were not involved in the design of the protocol.

## ETHICS AND DISSEMINATION

No ethical approval is required for this systematic review. The results of this review will be disseminated in a peer-reviewed, open-access journal to ensure access to all stakeholders in kidney transplantation and to inform clinical guidelines on the evaluation of living kidney donor candidates.

## DISCUSSION

Living kidney donation is an altruistic procedure with no medical benefit and it exposes the donor to health risks associated with nephrectomy and the effects of living with one remaining kidney. As the demand for living donor kidney transplantation grows to support the increasing number of patients living with ESKD, there is pressure to expand the acceptance criteria for living kidney donor candidates. In the general population, reduced kidney function may cause or worsen hypertension.<sup>17</sup> Nephrectomy for kidney donation may accelerate the risk of worsening kidney function to a greater extent with hyperfiltration in the remaining kidney in a donor due to hyperperfusion and hypertrophy.<sup>18</sup>

As donor candidates are increasingly accepted with hypertension, it is vital that donor survival and cardiovascular and kidney outcomes be examined to ensure donor long-term safety and health.<sup>7 8</sup> This is also necessary to inform the donor consent process, provide individualised cardiovascular risk assessment and ensure optimum follow-up.

Presently, the acceptance of donors with underlying hypertension varies across centres. If our review concludes that this practice is safe with little to no increase in safety signal to the donor, it will reaffirm the existing practice for some programmes and may encourage other transplant programmes who do not accept donors with hypertension to reconsider their practice. Conversely, a finding of a clear increased risk of any relevant adverse outcome would serve to inform existing transplant programmes of the need to consider this practice more carefully, and incorporate these findings into shared decision making. Lastly, it is possible that we may find inconclusive or mixed evidence, which would help in the design and conduct of future studies in this field.

In this proposed systematic review study, we have outlined the types of studies, participants, interventions and outcomes to be included, as well as the data sources, search strategy, data extraction methods and analytical methods of combining data. Potential limitations of our study include inconsistent quality in the reporting of hypertension and outcomes. Certain subgroups at higher risk of adverse outcomes, such as black people, may be under-reported. The scarcity of long-term follow-up in the living kidney donor literature may be the main limitation of the study. Our results will inform kidney transplant programmes and guide the follow-up care of living kidney donors.

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**Contributors** AB conceived, designed the study and created the analytical plan. AB and ME drafted the protocol; AB and RS designed the search strategy; ME, SA, SH, EGC, KDB, GK and RS will be involved in one or more of the following tasks: study screening and selection, data extraction, verification, quality appraisal, synthesis, analysis of the evidence and data interpretation. All authors have read, reviewed and approved the final version of the manuscript. AB is the guarantor. Data extraction and other materials will be made available upon request. ME is cofirst author.

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