Outcomes of Living Kidney Donation: A Systematic Review for a Clinical Practice Guideline by the Kidney Diseases Improving Global Outcomes (KDIGO)

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FINAL EVIDENCE REPORT

Introduction

Living kidney donation has become essential in increasing the donor pool as kidney transplant waiting lists continue to grow and organ shortage increases.(Ahmadi et al., 2014; Lafranca et al., 2013; C. H. Wilson, Sanni, Rix, & Soomro, 2011) The use of living kidney donors varies widely around the world. Among countries with active kidney transplant programs, the proportion of kidney transplants from living donors varies from less than 5 percent in countries such as Finland, Poland, Ireland, Spain, and Hungary to more than 70 percent in countries such as South Korea, Japan, Turkey, Saudi Arabia, Iran, Jordan,(Horvat, Shariff, Garg, & Donor Nephrectomy Outcomes Research, 2009) and Mexico.(Carreno, 2014) Living kidney donation represents between one-third and one half of all kidney transplants in the United Kingdom, United States and Australia.(Tong, Chapman, Wong, de Bruijn, & Craig, 2011)

In most cases, transplantation with kidneys from living donors leads to better outcomes for transplant recipients compared to kidneys from deceased donors. Far less is understood about how donation affects the long-term health of donors.

Assessment of potential long term harms has primarily been studied by comparing donor data to data available on samples of non-donors collected for other purposes (i.e. NHANES).(Tong et al., 2011) These types of comparisons are subject to confounding from known and unknown factors and do not account for lifelong outcomes. These comparisons have been used to demonstrate the low risk associated with living kidney donation. While the comparisons are not ideal to draw this conclusion, they do suggest a low prevalence of major negative outcomes correlated with donation in the overall donor population. Far less is known about specific subgroups of living kidney donors, especially subgroups defined by sex and race.

Our need for improved understanding of long-term donor outcomes becomes more urgent as living kidney donation increases and eligibility criteria expand to accept kidneys from individuals with higher risk for negative health outcomes compared to traditional donors. These expanded donor criteria include accepting kidneys from older individuals and those with isolated medical abnormalities (overweight and obese, hypertension, reduced kidney function, etc.).(Iordanous et al., 2009)

Guidelines are beginning to address the acceptance of kidneys from expanded criteria donors and the long-term care of donors. However, there is a great deal of variation among guidelines on how and if these issues are addressed. A recent systematic review of existing guidelines addressing living kidney donation concluded: “Multiple major guidelines for living kidney donation have been published, resulting in unnecessary duplicative efforts. Most do not meet standard processes for development, and important recommendations about thresholds for exclusion based on comorbidities are contradictory. There is an urgent need for international collaboration and coordination to ensure, where possible, that guidelines for living donation are consistent, evidence based, and comprehensive to promote best outcomes for a precious resource.”(Tong et al., 2011)

In an effort to address these shortcomings, the Kidney Diseases Improving Global Outcomes (KDIGO) assembled a Work Group to develop comprehensive guidelines addressing the evaluation and care of living kidney donors (LKD). We conducted this systematic review to synthesize and assess the currently available evidence on the topic.

Methods

Formulating Questions of Interest and Ranking of Outcomes

The KDIGO Work Group developed a scoping document to describe topics to be covered by the LKD guideline. To inform the Work Group's initial work, we searched for and identified relevant clinical practice guidelines. We extracted data relevant to the identified guideline topics and provided a summary table describing which guidelines addressed which topics. This document was distributed to the Work Group in 2013. Certain topics within the scoping document were considered relevant to the systematic review and we developed research questions to address these. The Population, Intervention, Comparator, Outcome, study Design, and Duration of follow-up (PICODDs) evolved throughout the course of the review according to the needs of the Work Group and Evidence Review Team (ERT) scope and feasibility. Outcomes were selected and ranked by assessing patient-centeredness. This report reflects the final Key Questions and PICODDs criteria (Table 1) relevant for the systematic review:

Key Question 1: What is the incidence of peri/post nephrectomy outcomes among living kidney donors undergoing different types of nephrectomy?

Key Question 2: Does the incidence of peri/post nephrectomy outcomes vary by demographic subgroup (age, race, sex)?

Key Question 3: Does the incidence of peri/post nephrectomy outcomes vary by donor status with respect to isolated medical abnormalities (IMAs) (i.e., BMI status, hypertensive, glucose intolerant)?

Key Question 4: What is the incidence of long-term health outcomes for living kidney donors compared to healthy non-donors?

Key Question 5: Does the incidence of long-term living kidney donor outcomes vary by demographic subgroup (age, race, sex)?

Key Question 6: Does the incidence of long-term living kidney donor outcomes vary by donor status with respect to IMAs (i.e., hypertensive, glucose intolerant)?

Key Question 7: What is the incidence of maternal and fetal outcomes among female living kidney donors who become pregnant after donation compared to healthy non-donors?

Table 1. PICODD Criteria

Living Kidney Donor Outcomes		
	Peri/Post-Operative	**Long-term**
Population	Living kidney donors	Living kidney donors Living kidney donation – demographic subgroups (age, sex, race) Living kidney donation – specific IMAs Donors related to recipient/family history of kidney disease Donors with post-donation pregnancy
Intervention	Nephrectomy performed post 1994 Nephrectomy in IMA donor	Living kidney donation
Comparator	Nephrectomy with different type of surgery; Nephrectomy in donors without IMA	Healthy non-donors[a] (i.e. Non-donor with medical characteristics suggesting they meet LKD criteria)) Living kidney donors – demographic subgroups (age, sex, race) Healthy non-donors[a] – demographic subgroups (age, sex, race) Living kidney donors – without specific IMAs Healthy non-donors[a] – specific IMAs Donors with unrelated recipient & no family history of kidney disease Donors with pre-donation pregnancy Non-donors with pregnancy
Outcomes	**Critical:** all-cause mortality **High Importance:** CVD event **Moderate Importance:** peri/post-operative complications; time to return to work **Intermediate Outcomes:** blood loss; length of hospital stay	**Critical:** all-cause mortality; CV mortality; ESRD; fetal death **High Importance:**, psychosocial outcomes, major pregnancy complications **Moderate Importance:** fragility fractures, GI bleeding, kidney stones, minor pregnancy complications **Intermediate Outcomes:** renal function, proteinuria, hypertension
Study Design	Data from systematic reviews was extracted. Full-text screening also identified trials and observational studies.	Systematic Reviews, Randomized Controlled Trials, and Observational Studies Full-text screening identified studies with total sample sizes (donor and comparator combined over 50; Data were extracted from studies with total sample sizes over 100.
Duration of Follow-up	Systematic reviews with outcomes measured at 0 to 90 days post-nephrectomy were extracted. Full-text screening identified studies with outcomes measured up to one year.	Full-text screening identified studies with outcomes measured one year or more post-donation; Data was extracted from studies with a mean duration of 5 years or more post donation.

a – Healthy non-donor comparison groups must have matched or controlled for demographic and health characteristics to be considered 'healthy non-donor' comparisons.

Literature Searches and Article Selection

We searched Ovid Medline, Ovid Embase, and the Cochrane Library to identify previous systematic reviews, randomized controlled trials, and observational studies published and indexed in bibliographic databases through September of 2014. Our search strategy included relevant medical subject headings and natural language terms for the concept of living kidney donation (Appendix A). These terms were combined with filters to select RCTs, systematic reviews and observational studies. Bibliographic database searches were supplemented with backward and forward citation searches of highly relevant systematic reviews.

Two independent investigators reviewed titles and abstracts of search results published after 2003 to identify systematic reviews, trials and observational studies relevant to the topic. We relied on citation searching of relevant systematic reviews to identify relevant studies published prior to 2004. Citations deemed eligible by either investigator underwent full text screening. Two investigators independently screened full text to determine if PICODDs criteria were met. Discrepancies were resolved by a third investigator. We documented the inclusion and exclusion status of citations undergoing full-text screening. We often revisited the screening process as the Work Group identified new outcomes or subgroups not included in the original PICODDs. Screening criteria were liberal. We did not extract data from all eligible studies. In an effort to capture the highest quality and most relevant and meaningful data as efficiently as possible, we extracted data only from previous systematic reviews for peri/post-operative outcomes (KQ 1-3) and from systematic reviews and select observational studies for long-term outcomes (KQ 4-7). We extracted long-term outcomes data from observational studies with sample sizes over 100 and mean follow-up time of at least 5 years. Studies reporting long term outcomes had to have an adequate comparison group. For studies comparing living kidney donors to non-donors, we required that the non-donor comparison group have health characteristics suggesting eligibility for kidney donation. Studies comparing living kidney donors to the general population were not eligible.

Data Extraction

We extracted data from relevant comparisons in recent systematic reviews to replace the *de novo* extraction process for all peri/post nephrectomy outcomes. We extracted relevant narrative information from systematic reviews that did not provide meta-analyses. We extracted pooled results from previous meta-analyses. We extracted data from observational studies for long term outcomes.

One investigator extracted relevant study, population demographic, and outcomes data from studies eligible for extraction. In several cases, many comparisons were made within the same published study. In these cases, we extracted relevant comparisons but did not extract ineligible comparisons. Data fields extracted included author, year of publication, setting, donor and comparison inclusion and exclusion criteria, donor and comparison characteristics, follow-up duration, descriptions, and results of outcomes. Relevant data were extracted into tables for descriptive analysis.

Assessment of Previous Systematic Review Quality and Individual Study Risk of Bias

We assessed the quality of eligible systematic reviews using modified AMSTAR criteria.(White et al., 2009) We assessed risk of bias for observational studies using an instrument developed using the Research Triangle Institute Item Bank for assessing risk of bias and confounding in observational studies of interventions or exposures. (Viswananthan, Berkman, Dryden, & Hartling, 2013) Overall summary risk of bias is based upon the collective risk of bias inherent in each domain and confidence that results are believable given study limitations. We used overall summary risk of bias assessments when grading evidence quality as described below.

Evidence Profiles

A structured approach (GRADE) was used to grade the quality of the overall evidence (Table 2). ("Methods for Guideline Development," 2011) Evidence profiles were used to facilitate this process. The GRADE approach is prescriptive in how evidence quality is assessed. The study design suggests the initial quality of evidence; high for randomized controlled trials and low for observational studies. Evidence quality is then lowered by one level if the studies in the evidence base for a particular comparison have serious risk of bias and by two levels with very serious risk of bias. Evidence quality is also lowered when results across studies are inconsistent or very inconsistent, if the relationship between the intervention and the outcome is indirect or if the outcome does not directly influence patient well-being. Additionally, evidence quality is downgrade when estimates are imprecise and publication bias is likely. Evidence quality improves with a large effect size. A large effect size includes a relative risk confidence interval lower limit of at least 2; a very large effect size includes a relative risk confidence interval lower limit of 5. Evidence quality is also increased when an effect is demonstrated after all plausible confounding has been addressed.

Table 2. Evidence Quality Assessment Criteria

<table>
<tr><th>Study Design</th><th>Quality of Evidence</th><th>Lower if</th><th>Higher if</th></tr>
<tr><td>Randomized trial⟶</td><td>High</td><td rowspan="4">Risk of Bias
-1 Serious
-2 Very serious

Inconsistency
-1 Serious
-2 Very serious

Indirectness
-1 Serious
-2 Very serious

Imprecision
-1 Serious
-2 Very serious

Publication bias
-1 Likely</td><td rowspan="4">Large effect
+1 Large
+2 Very Large

All plausible confounding

+1 would reduce a demonstrated effect or

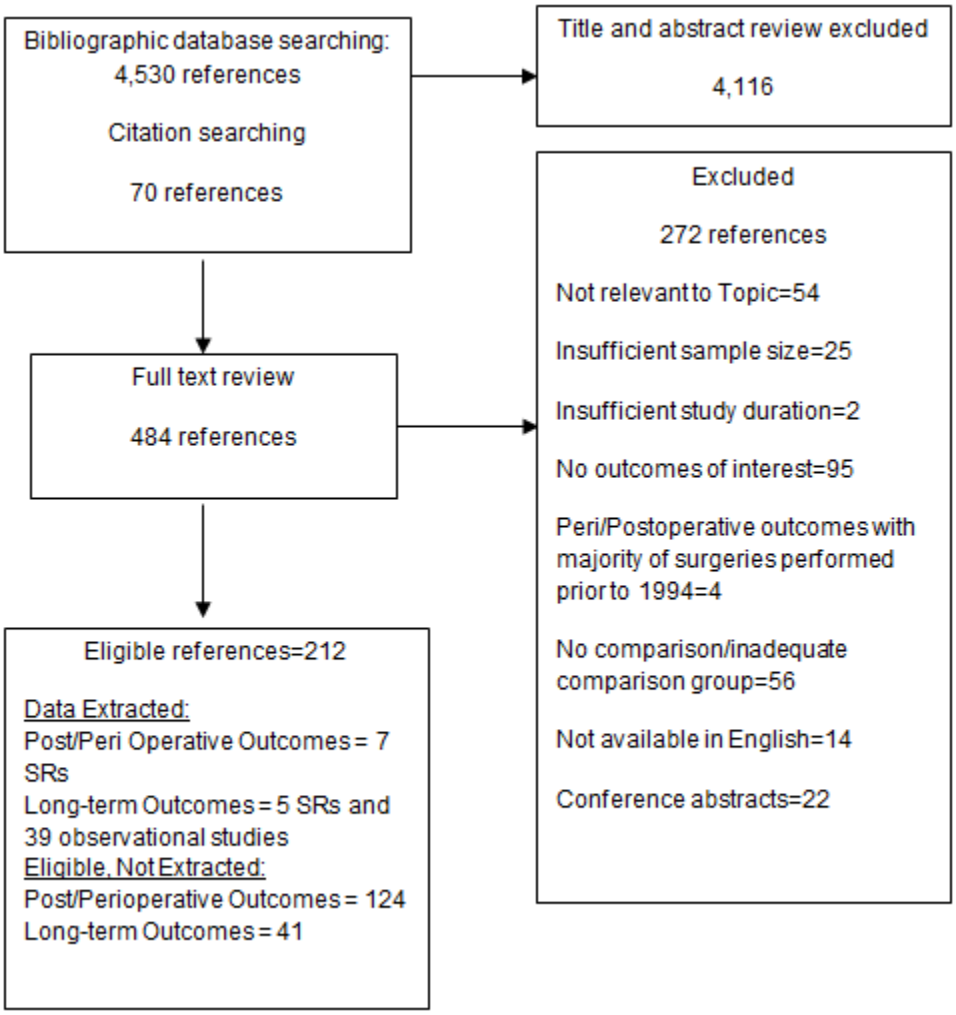
+1 would suggest a spurious effect when results show no effect</td></tr>
<tr><td></td><td>Moderate</td></tr>
<tr><td>Observational study⟶</td><td>Low</td></tr>
<tr><td></td><td>Very Low</td></tr>
</table>

Results

Search Results

Our search identified 4,530 citations, of which 417 required full text review after title and abstract screening. We identified an additional 70 references via supplemental citation searching for a total of 484 references undergoing full text review (Figure 1). Studies excluded after full text review are listed in Appendix B along with exclusion reasons.

Figure 2. Literature flow diagram



We extracted study characteristics; conducted systematic review quality assessments and risk-of-bias assessments; and extracted relevant outcomes into evidence tables for all studies eligible for extraction (Appendix C for peri/post-operative studies; Appendix D for long-term outcomes studies).

We grouped results by Key Question:

- Key Question 1: Peri/Post Nephrectomy Outcomes: surgical approach
- Key Question 2: Peri/Post Nephrectomy Outcomes: demographic subgroups
- Key Question 3: Peri/Post Nephrectomy Outcomes: isolated medical abnormalities
- Key Question 4: Long-term Living Kidney Donor Outcomes: comparison to healthy non-donors
- Key Question 5: Long-term Living Kidney Donor Outcomes: demographic subgroups (i.e., comparison to healthy non-donors from the same demographic subgroup or donors of different demographic subgroups)
- Key Question 6: Long-term Living Kidney Donor Outcomes: isolated medical abnormalities (i.e., comparison to non-donors with similar medical status or donors without IMA)
- Key Question 7: Long-term Living Kidney Donor Outcomes: pregnancy-related

1 - Key Question 1: Peri/Post-Nephrectomy Outcomes: Surgical Approach

Four recently published systematic reviews addressed peri and post-nephrectomy outcomes by surgical technique. (C. H. Wilson et al., 2011; Yuan et al., 2013) (Liu, Wazir, Wang, & Wang, 2014) (Fonouni et al., 2014) C1. Three reviews compared open versus laparoscopic nephrectomy.(Fonouni et al., 2014; C. H. Wilson et al., 2011; Yuan et al., 2013) Wilson et al. was assessed as high quality, Yuan et al. as moderate to high, and Fonouni et al. as low to moderate quality. Wilson et al. searched the literature through May 2010 and identified six RCTs analyzing 596 live kidney donors randomized to laparoscopic versus open nephrectomy.(C. H. Wilson et al., 2011) Yuan, et al. searched the literature through October of 2011 and identified 14 randomized controlled trials and 16 prospective controlled trials enrolling a total of 2,243 donors.(Yuan et al., 2013) All RCTs included in Wilson et al. were also included in Yuan et al.(Yuan et al., 2013) Fonouni et al. report results from previous systematic reviews and RCTs searching PubMed through 2013 and included 11 reviews including the reviews by Wilson and Yuan and 4 RCTs (3 of which were included in Wilson et al. and Yuan et al.).

One recent high quality systematic review compared right versus left laparoscopic donor nephrectomy.(Liu et al., 2014) The literature search through July 2013 identified 29 studies (one randomized controlled trial and 28 comparative studies) and analyzed 32,426 live kidney donors.

1a - Open versus Laparoscopic Nephrectomy

Three reviews present evidence in the comparison of open living donor nephrectomy versus laparoscopic donor nephrectomy (Appendix Table C3).(Fonouni et al., 2014; C. H. Wilson et al., 2011; Yuan et al., 2013) We assessed the quality of evidence on several outcomes including perioperative complications, operative time, blood loss, reoperation, length of hospital stay and time to return to work (Table 3).

Peri/post-Operative Complications

Four trials presented peri-/post-operative complications, variably defined. (Fonouni et al., 2014; C. H. Wilson et al., 2011; Young, Karpinski, et al., 2008; Yuan et al., 2013) Wilson et al. pooled data from six trials showing similar rates of complications with open versus laparoscopic nephrectomy (RR: 0.87; 95% CI: 0.47 to 1.59). (C. H. Wilson et al., 2011) The absolute risk for perioperative complications was 21% with open and 25% with laparoscopic. Results were

consistent in lower quality systematic reviews. Rates of peri-/post-operative complications are similar with laparoscopic and open nephrectomy (low quality evidence).

Operative Time

Operative time was measured in 26 studies of 2188 donors in a systematic review by Yuan et al.(Yuan et al., 2013) The open group had significantly shorter operative time than the laparoscopic group [weighted mean difference (WMD): 50.5 minutes; 95% CI: 32.7 to 68.4].(Yuan et al., 2013) There was substantial heterogeneity across studies (I^2=96%). Wilson et al. did not pool results, but showed that laparoscopic procedures took longer than open nephrectomy in five of six trials.(C. H. Wilson et al., 2011) Mean surgery times ranged from 101 to 164 minutes with open and 152 to 270 minutes with laparoscopic across six trials. Laparoscopic nephrectomy requires longer surgery time than open nephrectomy (low quality evidence).

Intraoperative blood Loss

Yuan et al. included 11 studies that reported blood loss in 917 donors.(Yuan et al., 2013) Meta-analysis showed significantly greater blood loss with open compared with standard laparoscopic nephrectomy (WMD: -99.64 mL; 95% CI: -165.90 to -33.37) or hand-assisted laparoscopic group (-112.84 mL 95% CI: -169.10 to -56).(Yuan et al., 2013) There was substantial heterogeneity across standard laparoscopic versus open trials (I^2=87%) but not across hand-assisted laparoscopic versus open (=27%). Wilson did not pool data, but four of the five included trials showed similar rates of blood loss. (C. H. Wilson et al., 2011) Mean blood loss varied widely among trials ranging from 1.5 to 240 mL with open and 1.8 to 200 mL with laparoscopic. It is unclear whether there are differences in the amount of blood loss with open versus laparoscopic nephrectomy (very low quality evidence).

Reoperation

Wilson et al. showed similar rates of reoperations with open nephrectomy and laparoscopic (RR: 0.57; 95% CI: 0.09 to 3.64). (C. H. Wilson et al., 2011) Rates of reoperation with either approach were low (0.7% with open and 2.2% with laparoscopic). Open and laparoscopic nephrectomy had similar rates of reoperation (moderate quality evidence).

Length of Hospital Stay

Hospital stay (in days) was reported in 18 of the studies (1851 donors) included in the Yuan et al. review.(Yuan et al., 2013) Meta-analysis showed significantly fewer hospital days with laparoscopic group than open group (WMD: -1.27; 95% CI: -1.72 to -.82).(Yuan et al., 2013) There was substantial heterogeneity among trials (I^2=93%). Wilson et al. reported data from five trials comparing open to laparoscopic nephrectomy and did not pool data. Three of five trials showed a statistically significantly shorter hospital stay with laparoscopic. Mean hospital stay was between 4 and 7 days with open and 2 and 6 days with laparoscopic. Length of hospital stay is longer with open nephrectomy than laparoscopic (low quality evidence).

Return to Work

Time to return to work (in days) was reported in one systematic review; data from nine studies including 1016 donors. Pooled results show significantly less time to return to work with laparoscopic than open (WMD: -16.35 days; 95% CI: -23.0 to -9.7). (Yuan et al., 2013) There was substantial heterogeneity among trials (I^2=78%). Mean time to return to work varied from 10 to 66 days with laparoscopic and 27 to 91 days with open. Return to work is sooner with laparoscopic than open nephrectomy (high quality evidence).

1b - Standard laparoscopic versus hand-assisted laparoscopic nephrectomy

Yuan et al. compared standard living donor laparoscopic nephrectomy and hand-assisted laparoscopic nephrectomy. (Yuan et al., 2013)

Peri/post-Operative Complications

There was no statistical difference in peri-/post-operative complications when comparing standard versus hand-assisted laparoscopic techniques (OR: 0.62; 95% CI:0.27 to1.39). (Yuan et al., 2013) Complication rates were below 15% with both techniques (7.5% with hand-assisted and 12% with standard). Complication rates are similar with hand-assisted and standard laparoscopic nephrectomy (low quality evidence).

Operative Time

There was no difference in operating time between standard and hand-assisted laparoscopic nephrectomy (WMD: -24.55 minutes; 95% CI:-50.81 to1.71). (Yuan et al., 2013) There was substantial heterogeneity among studies (I^2=92%). Mean operative times varied across studies and ranged from 121 to 269 minutes with hand-assisted and 180 to 311 minutes with standard. Standard and hand-assisted laparoscopic techniques have similar operating times (very low quality evidence).

Intraoperative blood Loss

There was no difference in blood loss between standard and hand-assisted nephrectomy (WMD: -20.65 mL; 95% CI: -43.88 to 2.57). (Yuan et al., 2013) There was little heterogeneity among studies (I^2=0.8%). Blood loss was similar with standard or hand-assisted laparoscopic nephrectomy (very low quality evidence).

Length of Hospital Stay

Six studies comprising 320 donors compared standard laparoscopic versus hand-assisted laparoscopic with respect to length of hospital stay. (Yuan et al., 2013) Donors undergoing standard laparoscopic nephrectomy had significantly shorter hospital stays than those undergoing hand-assisted laparoscopic nephrectomy (WMD: 0.33 days; 95% CI: 0.10–0.56). (Yuan et al., 2013) Mean length of stay ranged from 2 to 7 days with both techniques; statistical difference may not be clinically important. Standard laparoscopic has statistically significantly longer hospital length of stay, but the difference is not clinically meaningful (low quality evidence).

1c - Left versus right laparoscopic live donor nephrectomy

One systematic review comprising one trial and 28 observational studies including a total of 32,426 donors.(Liu et al., 2014) assessed the evidence comparing right- with left-laparoscopic live donor nephrectomy. Evidence profile for left versus right laparoscopic nephrectomy shows very low quality evidence for several outcomes (Table 5 and Appendix Table C5).

Peri/post-operative complications

There was no difference in the rate of complications with left or right laparoscopic nephrectomy (perioperative complications: OR: 1.31; 95% CI: 0.89 to 1.94; postoperative complications OR: 1.27; 95% CI: 0.86 to 1.88). (Liu et al., 2014) Data necessary to calculate absolute rates was not provided in the systematic review. Complication rates are similar with right- or left-nephrectomy (very low quality evidence).

Operative Time

Operation time (in minutes) in the 14 studies (2656 donors) reporting, was no different with left and right laparoscopic nephrectomy (WMD: 1.35 minutes; 95% CI: -11.73 to 14.44).

(Liu et al., 2014) Mean operative times for each included study was not provided. Left and right nephrectomy have similar operating times (very low quality evidence).

Intraoperative blood Loss

Liu et al. showed no difference in blood loss (in mL) between donors undergoing left or right nephrectomy in 15 studies reporting (3033 donors) (WMD: 4.36mL; 95% CI: -19.83 to 28.55).(Liu et al., 2014) Mean blood loss for each included study was not provided. Left and right living donor nephrectomy have similar blood loss (very low quality evidence).

Length of Hospital Stay

Mean length of hospital stay (in days) in 11 studies (1730 donors) was no different between those undergoing left and right nephrectomy (WMD: 0.05 days; 95% CI: -0.08 to .019). (Liu et al., 2014) Mean length of stay for each included study was not provided. Left and right living donor nephrectomy have similar lengths of hospital stay (very low quality evidence).

Table 3. Key Question 1 Evidence Profile 1a: Peri/Post Nephrectomy Outcomes - Open versus Laparoscopic Nephrectomy

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Peri/post-operative complications (RCTs and observational studies)	Moderate	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Complication rates are similar with open versus laparoscopic nephrectomy.	Low
Operative Time (RCTs and observational studies)	Moderate	No serious inconsistency	Serious indirectness	Serious imprecision	Undetected	Laparoscopic nephrectomy takes longer than open nephrectomy.	Low
Blood Loss (RCTs and observational studies)	Moderate	Serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Unclear if blood loss is different with open versus laparoscopic nephrectomy.	Very Low
Reoperation (RCTs and observational studies)	Low	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Rates are similar with laparoscopic versus open nephrectomy; some data indicates they may be slightly higher with laparoscopic.	Moderate
Length of Stay (RCTs and observational studies)	Moderate	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	length of stay is shorter for laparoscopic nephrectomy versus open	Low
Return to Work (RCTs and observational studies)	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Return to work is significantly sooner with laparoscopic nephrectomy versus open. Evidence upgraded for large effect size.	High

Table 4. Key Question 1 Evidence Profile 1b: Peri/Post Nephrectomy Outcomes - Standard Laparoscopic versus Hand-assisted Laparoscopic Nephrectomy

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Peri/post-operative complications (RCTs and observational studies)	Moderate	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Complication rates are similar with hand-assisted versus standard laparoscopic nephrectomy.	Low
Operative Time (RCTs and observational studies)	Moderate	Serious inconsistency	Serious indirectness	Serious imprecision	Undetected	Operating times are similar.	Very Low
Blood Loss (RCTs and observational studies)	Moderate	No serious inconsistency	Serious indirectness	Serious imprecision	Undetected	Blood loss is similar	Very Low
Length of Stay (RCTs and observational studies)	Moderate	Serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Standard laparoscopic nephrectomy has longer length of stay than hand-assisted, but difference is not clinically meaningful.	Low

Table 5. Key Question 1 Evidence Profile 1c: Peri/Post Nephrectomy Outcomes - Left versus right laparoscopic live donor nephrectomy

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Peri/post-operative complications (primarily observational studies)	Moderate to High	Unclear	No serious indirectness	Serious imprecision	Undetected	Complication rates are similar with left versus right nephrectomy.	Very Low
Operative Time (primarily observational studies)	Moderate to High	Unclear	Serious indirectness	No serious imprecision	Undetected	Operating times are similar.	Very Low
Blood Loss (primarily observational studies)	Moderate to High	Unclear	Serious indirectness	Serious imprecision	Undetected	Blood loss is similar.	Very Low
Length of Stay (primarily observational studies)	Moderate to High	Unclear	Serious indirectness	No serious imprecision	Undetected	Hospital length of stay is similar.	Very Low

2 - Key Question 2. Peri/post nephrectomy outcomes by demographic subgroups: age

One systematic review examined peri/postoperative outcomes by donor demographic groups.(Young, Karpinski, et al., 2008) We did not identify systematic reviews that analyzed peri/post-operative outcomes by race or sex.

2a – Older versus Younger Donors

We identified one systematic review that examined peri-/post-surgical outcomes by age.(Young, Storsley, et al., 2008) Young et al. included twenty-two articles comprising 987 donors (mean age: 66 years old; range: 60–85 at donation). Older donors were most commonly defined as ≥60 years. However, other definitions were used including: ≥61, ≥65 and ≥66 years. Young et al. pooled operating time, blood loss, and length of hospital stay by age group (Appendix C, table C6). The evidence profile for peri/post nephrectomy outcomes for older versus younger donors shows very low quality evidence for several outcomes (Table 6).

Operative Time

Operative time was reported by 3 studies comprising 339 donors. Most were retrospective observational studies. There was no significant difference in operative time (minutes) between older and younger donors (WMD: 11 minutes; 95% CI: -3.0 to 25).(Young, Storsley, et al., 2008) Mean operative time ranged from 134 to 238 minutes with older donors and 128 to 203 minutes with younger donors. Operative time is similar in older and younger donors (very low quality evidence).

Intraoperative blood Loss

Young et al. included two studies (146 donors) reporting blood loss (mL) by age. No statistical difference by age was found (WMD: 6.0 mL; 95% CI: -91.0 to 103.0).(Young, Storsley, et al., 2008) Reported mean blood loss was 157 and 192 mL for older donors and 112 and 248 in younger donors in the two included studies. Blood loss is similar in older and younger donors (very low quality evidence).

Length of Hospital Stay

Young et al. included three studies (339 donors) reporting length of hospital stay (in days) by age. In meta-analysis, no statistical difference by age was found (WMD: 0.0; 95% CI: -1.0 to 1.0).(Young, Storsley, et al., 2008) Mean length of stay ranged from 3 to 10 days with older donors and 3 to 11 days with younger donors. Hospital length of stay is similar in older and younger donors (very low quality evidence).

Table 6. Key Question 2 Evidence Profile 2a: Peri/Post Nephrectomy Outcomes – Older versus younger donors

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Operative Time (observational studies)	High	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Operating time is similar.	Very Low
Blood Loss (observational studies)	High	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Blood loss is similar.	Very Low
Length of Stay (observational studies)	High	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Hospital length of stay is similar.	Very Low

3 – Key Question 3: Peri and post-nephrectomy outcomes in living kidney donors with isolated medical abnormalities

We identified two systematic reviews that examined peri/post nephrectomy outcomes in donors with IMAs. Both analyzed peri/postoperative outcomes by overweight and obesity status. (Lafranca et al., 2013; Young, Storsley, et al., 2008) We did not identify systematic reviews that provided meta-analysis of peri/post-operative outcomes by other IMA groups.

3a - Overweight/Obese donors versus donors with normal BMI

Young et al. (Table C7) included 10 studies examining 484 living donors with a mean BMI of 34.5 kg/m^2 at donation (range: 32–39 kg/m^2). Eight studies used an obesity cut-point of 30 kg/m^2; the other studies used definitions of BMI ≥31 and 35 kg/m^2.(Young, Storsley, et al., 2008) Lafranca et al. included 14 studies and differentiated between obese and non-obese by defining the former group as those with a body mass index of >30kg/m^2.(Lafranca et al., 2013) Lafranca et al. performed additional analysis to gain better insight into differences within the high BMI group.(Lafranca et al., 2013) Three studies of the original analysis could be used as they described multiple cohorts. Kidney donors with a BMI of 30–34.9 kg/m^2 were compared with those with a BMI of 35 kg/m^2 and higher. These two systematic reviews comprised 16 unique studies. Studies were primarily retrospective observational studies. The evidence profile for peri/post nephrectomy outcomes for overweight/obese versus normal BMI donors shows very low quality evidence for several outcomes (Table 7).

Peri/post-operative Complications

Lafranca et al. pooled results from 7 studies analyzing perioperative complications by BMI status and showed no difference based upon BMI status (RR: 1.01; 95% CI: 0.75 to 1.36).(Lafranca et al., 2013) The complication rate was 7% in those with high BMI and 6% in those with low BMI. Complication rates are similar in obese and non-obese donors (very low quality evidence).

Operative Time

Lafranca et al. pooled data from 8 studies (n=1105) on operation duration of laparoscopic nephrectomy. The weighted mean difference was 16.9 minutes longer (95% CI: 9.06 to 24.76) for donors with high BMI.(Lafranca et al., 2013) Mean operating time ranged from 149 to 299 minutes in donors with high BMI and 131 to 298 in donors with low BMI. Young et al. pooled similar data and found similar results; however Lafranca et al. is more up to date. Operating time is longer in obese donors (very low quality evidence).

Blood Loss

Seven studies included in Lafranca et al. compared the estimated blood loss in milliliters during nephrectomy, in a total of 939 donors. Pooled results showed similar blood loss for both BMI categories (MD: 34.46; 95% CI: -6.73 to 75.66). (Lafranca et al., 2013) Mean blood loss ranged from 170 to 310 mL in high BMI donors to 113 to 278 mL in low BMI donors. Young et al. pooled similar data and found similar results; however Lafranca et al. is more up to date. Blood loss was similar in obese and non-obese donors (very low quality evidence).

Length of Hospital Stay

Hospital length of stay was similar across BMI categories (WMD:0.18; 95% CI: -0.02 to 0.39).(Lafranca et al., 2013) Length of stay ranged from 1.7 to 7.4 days with high BMI and 1.6 to 5.8 with low BMI. Young et al. pooled similar data and found similar results; however Lafranca et al. is more up to date. Length of stay is similar in obese and non-obese donors (very low quality evidence).

Table 7. Key Question 3 Evidence Profile: Peri/Post Nephrectomy Outcomes – Obese versus non-obese donors

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Peri/post-operative complications (7 observational studies)	High	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Complication rates are similar	Very Low
Operative Time (8 observational studies)	High	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Operating time is similar.	Very Low
Blood Loss (7 observational studies)	High	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Blood loss is similar.	Very Low
Length of Stay (observational studies)	High	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Hospital length of stay is similar.	Very Low

4 – Key Question 4: Long-term health outcomes

4a - Living Kidney Donors versus Healthy Non-donors (Table D5)

We identified two systematic reviews(Boudville, Ramesh Prasad, et al., 2006; A. X. Garg et al., 2006) and nine observational studies(Clemens et al., 2011; A. X. Garg, Meirambayeva, et al., 2012; A. X. Garg et al., 2008; Lam et al., 2012; Mjoen et al., 2014; Muzaale et al., 2014; Segev et al., 2010; Thomas et al., 2014; Thomas et al., 2013) that assessed long-term health outcomes after living kidney donation compared to healthy non-donors. Systematic reviews did not include only studies with comparison groups and comparison groups were not always 'healthy' comparisons. Studies reported mortality, cardiovascular events, ESRD, renal function, proteinuria, hypertension, psychosocial outcomes, GI bleeds, fragility fractures, and acute kidney injury requiring dialysis (Appendix D, Tables D5). Studies from which data were extracted reported mean or median lengths of follow-up ranging from 5.5 to 15 years. Several studies used the same group of donors so the number of unique donors analyzed across all outcomes is unclear. The evidence profile for peri/post nephrectomy outcomes for donors versus healthy non-donors shows very low to moderate quality evidence for several outcomes (Table 8).

Mortality

Three retrospective observational studies compared mortality among living kidney donors to healthy non-donors.(A. X. Garg, Meirambayeva, et al., 2012; Mjøen et al., 2013; Segev et al., 2010) One study(Mjoen et al., 2014) compared 1,901 donors to 32,621 healthy non-donor participants of the Nord-Trøndelag Health Study (The HUNT Study). The HUNT study population was drawn from a single county in Norway and enrolled participants without diabetes. Individuals were normotensive and not on blood pressure medications and had a BMI<30. Results revealed increased risk of death in donors (11.7% vs 7.4%, HR: 1.30; 95% CI: 1.11 to1.52) (Table D5). Donors were followed for an average of 15 years, while healthy non-donors were followed for 25 years confounding the results. (Mjoen et al., 2014) In contrast, two studies (one from the United States with a follow-up of up to 12 years and one from Canada with a median follow-up of 6.5 years) revealed lower risk of death in donors compared to healthy non-donors. (A. X. Garg, Meirambayeva, et al., 2012; Segev et al., 2010) The quality of evidence for the outcome was very low.

Cardiovascular Outcomes

Cardiovascular events were reported in two studies.(A. X. Garg, Meirambayeva, et al., 2012; Mjøen et al., 2013) One study revealed greater cardiovascular mortality in donors compared to healthy non-donors (3.6% vs 2.1%, HR: 1.40; 95% CI: 1.03 to1.91),(Mjoen et al., 2014) while another study reported no difference in composite death censored cardiovascular outcomes between donors and non-donors (1.3% vs 1.4%, RR: 0.91; 95% CI: 0.61 to1.35).(A. X. Garg, Meirambayeva, et al.) Quality of evidence for the outcomes was very low.

ESRD

Two studies compared the rate of ESRD in living kidney donors versus healthy non-donor controls.(Mjøen et al., 2013; Muzaale et al., 2014) Both studies showed high relative but low absolute risk increases. The study from Norway reported greater risk of ESRD in donors compared to healthy non-donors (0.5% vs 0.06%, HR: 11.38; 95% CI 4.37 to 29.63). (Muzaale et al., 2014) Similarly, the study from the US reported 15-year cumulative incidence rates of ESRD of 30.8 (95% CI: 24.3 to 38.5) per 10,000 patient-years of follow-up in kidney donors compared to 3.9 (95% CI: 0.8-8.9) per 10,000 in healthy non-donors. Quality of evidence for the outcome was moderate.

Acute Dialysis

One study reported similar rates of acute dialysis events, as defined by claims in an administrative database, in donors vs non-donors (6.5 versus 9.4/100,000 person-years of follow-up, RR: 0.58 (95% CI 0.08-4.47).(S. O. Lee) Quality of evidence for the outcome was moderate.

Renal outcomes

A systematic review of six studies (189 controls and 239 donors) with a follow-up of 6-13 years, reported 10 (95% CI: 15 to 6) ml/min/1.73m2 lower eGFR in donors compared to non-donors.(A. X. Garg et al.) Quality of evidence for the outcome was very low.

Proteinuria and Blood Pressure

One systematic review of three controlled studies (59 controls and 129 donors) with mean follow-up ranging between 7 and 15 years, reported proteinuria in donors to be 66 (95% CI: 2-108) mg/day greater than non-donors.(A. X. Garg et al.) Albuminuria was higher in donors in 2 of 4 studies that compared donors with non-donor controls with the greatest difference of 57 (95% CI 32, 78) mg/day.(A. X. Garg et al., 2006) In two studies (67 donors and 51 controls) with follow-up ranging between 2 and 13 years, risk of microalbuminuria was higher in donors compared to controls (20.9% vs 3.9%, RR: 3.9 (95% CI 1.2, 12.6).(A. X. Garg et al., 2006) Another systematic review of data from 6 studies with at least 5 years of follow-up after donation reported weighted mean for systolic blood pressure 6 (95% CI 1.6 to 10.5) mmHg ,and diastolic blood pressure 4 (95%CI 0.9-6.7) mmHg higher in donors compared to non-donors.(Boudville, Prasad, et al.) Quality of evidence for the outcomes was very low.

Psychosocial outcomes

One study reported psychosocial outcomes in donors and healthy non-donors: there was no difference in SF-36 components scores, 15D QOL scores, or feeling thermometer scores.(Clemens et al.) Quality of evidence for the outcomes was very low.

Other outcomes

We identified three studies that addressed other outcomes after living kidney donation. All studies were done in the same population in Ontario, Canada. Thomas et al. compared gastrointestinal bleeds in living donors compared to matched non-donors and found similar event rates in donors and non-donor (18.5 versus 14.9 /10,000 person years, (HR: 1.24; 95% CI: 0.87 to 1.81).(Thomas et al., 2013) One study looked at the risk for fragility fractures in living donors in comparison to matched non-donors and found similar event rate/10,000 person years in non-donors vs non-donors (18.7 versus 16.4) (HR: 0.88; 95% CI: 0.58 to1.32).(A. X. Garg, Pouget, et al., 2012) One study compared rates of kidney stones with need for surgical interventions (8.3 versus 9.7 per 10,000 person-years, RR: 0.85(95% CI 0.47-1.53) as well as hospitalizations for kidney stones (12.1 versus 16.1 per 10,000 person years, RR: 0.75(95% CI 0.45-1.24)) among kidney donors and healthy non-donors without prior history of kidney stones, respectively, and reported no difference. (Thomas et al., 2013) Quality of evidence for these outcomes was very low.

Table 8. Key Question 4 Evidence Profile: Long Term Living Kidney Donation Outcomes – Living Kidney Donors compared to Healthy Non-donors

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Mortality (retrospective observational studies)	Low-Moderate	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	One study shows higher death rate among donors; two show higher death rate among non-donors. Confounding is a major problem.	Very Low
CV Outcomes (retrospective observational studies)	Low-Moderate	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	One study shows a higher cardiovascular death rate among donors; the other study shows no statistical difference. Confounding is a major problem.	Very Low
ESRD (retrospective observational studies)	Low-Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Both studies show much higher rates of ESRD among donors over 15 years following donation. Evidence quality rated up for effect size.	Moderate
Renal Function (retrospective observational study and 1 SR which included 6 retrospective observational studies)	Moderate	Inconsistency	Serious indirectness	Serious imprecision	Undetected	One SR including 6 retrospective observational studies shows that mean GFR is lower in donors compared to non-donors after at 6 to 13 years follow-up.	Very Low
Hypertension (retrospective observational studies)		No serious inconsistency	Serious indirectness	Serious imprecision	Undetected	One SR including 6 retrospective observational studies shows that the risk of hypertension in donors compared to non-donors is inconsistent across studies after 2 to 13 years follow-up.	Very Low
Psychosocial (retrospective observational study)	High	Unknown	Unclear	Unclear	Undetected	One retrospective observational study with a high risk of bias shows no difference between living kidney donors and healthy non-donors on several psychosocial measures at a median follow-up of 5.5 years.	Very Low
Other: Fractures (retrospective observational study)	Moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	One retrospective observational study shows no difference in the rate of fractures after a median of 6.5 years follow-up.	Very Low
Other: GI Bleed (retrospective observational study)	Moderate	Unknown	No serious indirectness	No serious imprecision	Undetected	One retrospective observational study shows no difference in the rate of GI bleeding after a median of 6.5 years follow-up.	Very Low

Other: Kidney Stones (retrospective observational study)	Low-moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	One retrospective observational study shows no difference in the rate of GI bleeding after a median of 6.5 years follow-up.	Very Low

5 – Key Question 5: Long-term health outcomes in living kidney: demographic subgroups

5a –Older donors versus older healthy non-donors (Table D6)

We identified eight studies that compared outcomes in older donors compared to older healthy non-donors.(Berger et al., 2011; Clemens et al., 2011; A. X. Garg, Meirambayeva, et al., 2012; Mjoen et al., 2014; Reese et al., 2014; Segev et al., 2010; Thomas et al., 2014; Thomas et al., 2013) Mean (median) follow-up ranged from 5 to 15.1 years. Evidence profile for long term nephrectomy outcomes for donors versus healthy non-donors shows very low to moderate quality evidence for several outcomes (Table 9).

Mortality

Three studies from the OPTN registry,(Berger et al., 2011; Reese et al.; Segev et al., 2010) compared mortality between older donors and older healthy non-donors. Berger et al. reported survival at 5 and 10 years in donors over age 70 compared to matched non-donors from the NHANES III study.(Berger et al., 2011) At 10 years of follow-up, 73% of non-donors and 90% of donors were alive (HR for death: 0.37 (95% CI 0.21-0.65) for donors compared to non-donors).(Berger et al., 2011) Segev et al. compared donors to a matched cohort of NHANES III.(Segev et al., 2010) Both studies found mortality higher in older healthy non-donors than in older donors. The most recent study by Reese et al. reported similar risk of death for donors > 55 years old compared to non-donors > 55 years old from the Health and Retirement Study 4.9 versus 5.6 deaths per 1000 person-years, and lower risk of death in donors 60 years or older compared to non-donors 60 years or older (HR: 0.68; 95% CI: 0.49 to 0.95).(Reese et al.) The quality of evidence for the outcome was very low.

Cardiovascular Outcomes

Reese reported similar risk of death or cardiovascular event in older (> 55 and > 60) donors compared to non-donors with Medicare coverage.(Reese et al.) Garg et al reported no interaction between age and donation for the outcome of death censored cardiovascular events (p=0.48) and similar risk of cardiovascular events for donors and non-donors aged 55 and older (4.4% vs 6.4%, HR: 0.70 (95% CI: (0.3-1.4)).(A. X. Garg, Meirambayeva, et al., 2012) The quality of evidence for the outcome was low.

Psychosocial

One study reported psychosocial outcomes in donors 43 years old and older and healthy non-donors of the same age, there was no difference in SF-36 Mental component summary scores.(Clemens et al.) Quality of evidence for the outcome was very low.

Other Outcomes

Reese et al. reported similar rates of diabetes in donors and non-donors 55 years and older with Medicare (HR: 1.05; CI 95%: 0.83 to 1.32).(Reese et al.) Three studies addressed other outcomes after living kidney donation; all studies were done in the province of Ontario population.(A. X. Garg, Pouget, et al., 2012; Thomas et al.; Thomas et al., 2013) Thomas et al. compared gastrointestinal bleeds in living donors 40 years or older compared to matched non-donors of the same age and found similar event rates in donors and non-donors (23.4 versus 20.3 /10,000 person years, (HR: 1.19; 95% CI: 0.79 to 1.78)).(Thomas et al., 2013) One study looked at the risk for fragility fractures in living donors in comparison to matched non-donors 55 years and older and found similar event rate/10,000 person years in donors vs non-donors (43.2 versus 39.5) (HR: 1.14; 95% CI: 0.56 to 2.35).(A. X. Garg, Pouget, et al., 2012) One study compared rates of kidney stones with need for surgical interventions (9.4 versus 10.4 per 10,000 person-years) as well as hospitalizations for kidney stones (11.1 versus 17.0 per 10,000 person years) among kidney donors and healthy non-donors 40 years or older without prior

history of kidney stones, respectively, and reported no difference.(Thomas et al., 2013) Age did not influence the association between donation and GI bleeding (p for interaction 0.6) , fractures (p for interaction 0.5) , or kidney stones (p for interaction 0.8 .(A. X. Garg, Pouget, et al., 2012; Thomas et al., 2014; Thomas et al., 2013) Quality of evidence was rated as low or very low for all of the reported outcomes.

5b – Older Donors versus Younger Donors (Table D7)

Sixteen included studies analyzed donor outcomes by age at donation They reported the following long-term outcomes: mortality, cardiovascular events, ESRD, renal function, proteinuria, hypertension, GI bleeds, fragility fractures and psychosocial outcomes. Mean lengths of follow-up ranged from 5.5 to 31 years. Quality of evidence was rated low to very low for all of the outcomes (Table 10).

Mortality

Four studies reported long-term mortality outcomes stratified by pre-donation age. In the three studies comparing mortality in older donors to younger donors (55 years or older in one, 60 years or older in two) as would be expected older donors had greater all-cause mortality than younger donors over an average follow-up time 5.5 to 6.8 years.(Dols et al., 2011; A. X. Garg, Meirambayeva, et al., 2012; Segev et al., 2010) One small study reported no difference in frequency of deaths in donors who were younger than 18 years of age at donation compared to donors who were 18-30 years at donation over 30 year follow-up (5.1% versus 6.2%, p=0.990).(MacDonald et al.) The quality of evidence for the outcome was low.

Cardiovascular Outcomes

One study reported cardiovascular events by donor age.(A. X. Garg, Meirambayeva, et al., 2012) In donors aged 55 and older, the rate for cardiovascular events per 10,000 person years was 4.4, compared to 1.4 in their younger counterparts. Another study reported 9% greater risk of cardiovascular event for each year increase in donor age.(K. L. Lentine et al.) The quality of evidence for the outcome was low.

ESRD

End-Stage Renal Disease was reported in two studies. The first reported cumulative incidence rates of ESRD at 15 years in donors 18-39 years, 40-49 years, 50-59 years and 60 years and older. ESRD rates were 29.4, 17.4, 54.6 and 70.2 per 10,000 person-years respectively.(Muzaale et al., 2014) In one study, white donors who were younger than 35 years of age at the time of donation were more likely to be listed for kidney transplant compared to White donors who were 35 years or older at donation (0.2% vs 0.05%, RR:4.10(95% CI 2.35-7.16); African American donors who were younger than 35 years at the time of donation were also more likely to be listed for kidney transplant compared to African American donors who donated kidney at 35 years of age or later (0.6% vs 0.11%, RR: 7.68(95% CI 3.25-17.89).(Gibney, Parikh, & Garg) The quality of evidence for the outcome was very low.

Renal Function

Ten studies reported renal function by age. In the three that looked at those withGFR <60 mL/min, all found older donors at greater risk.(Dols et al., 2011; Ibrahim, Foley, et al., 2009; J. H. Lee et al., 2007) Age at donation was significantly associated with greater odds of CKD (defined as eGFR <60 ml/min/1.73m2) in three studies (Ibrahim, Foley, et al.; J. H. Lee et al.; K. L. Lentine et al.) and not associated in one study.(Tsai et al.) Greater donor age was correlated with lower GFR at follow-up in two studies in Swedish living donors.(Fehrman-Ekholm et al.)-(von Zur-Muhlen, Berglund, Yamamoto, & Wadstrom) Frequency of eGFR < 60 ml/min was greater among donors who were 60 years or older at the time of donation compared to donors who were younger than 60 years of age (80% vs 31%).(Dols et al.) Older age at donation was

associated with increased risk of CKD diagnoses as determined by administrative billing claims over an average 7.7 yrs followup (4% increase per year).(K. L. Lentine et al., 2010) Mean eGFR was 71ml/min among donors older than 60 at the time of donation compared to 78.5ml/min in younger donors after 6.7 years of follow-up.(Gracida, Espinoza, Cedillo, & Cancino) One study did not find any difference in eGFR, frequency of eGFR <60 ml/min, as well as eGFR < 45 ml/min among donors who donated before they turned 18 compared to donors who donated between the ages of 18 and 30.(MacDonald et al.) The one study that looked at serum creatinine found no difference at follow-up for those 21-35 and 36-50, but found a difference in those 51-69 (mean creatinine of 1.0 versus 0.8 mg/dL).(El-Agroudy et al., 2007) The quality of evidence for the outcome was very low.

Proteinuria

Three studies reported proteinuria by age at donation. In one, risk of proteinuria at 5 and 10 years was similar between older and younger donors.(Dols et al., 2011) In another study mean proteinuria (mg/24h) was also similar.(El-Agroudy et al., 2007) In a study that compared adolescent to adult donors, odds of proteinuria (defined as >1+ on a random dipstick) were not significantly different between adolescent and adult donors at about 30 years of follow-up.(MacDonald et al.) The quality of evidence for the outcome was very low.

Hypertension

Hypertension was reported in six included studies, defined by either blood pressure or treatment by medication. Dols et al. reported risk of HTN in older donors (>60 years old) comparable to that in younger donors (10% versus 6%, p=0.56).(Dols et al., 2011) In one study older age at follow-up was associated with 5 mmHg higher systolic blood pressure.(Fehrman-Ekholm et al.) Two studies reported that older age at donation was associated with greater risk of drug treated hypertension.(Ibrahim, Foley, et al.; K. L. Lentine et al.) El-Agroudy et al. looked at hypertension medications in donors ages 21-35, 36-50 and 51-69 and reported a greater number of older donors using one or two medication than younger donors at 10.7 years of follow-up (12.6%, 32.5% and 31.8%).(El-Agroudy et al., 2007) Donors who were younger than 18 years of age at donation were more likely to have drug treated hypertension compared to donors who were 18-30 years of age at donation (RR: 1.05; 95% CI: 1.03 to 1.06) at a slightly longer follow-up for donors who were < 18 at donation (31.8 vs 29.2 years).(MacDonald et al.) The quality of evidence for the outcome was very low.

Psychosocial Outcomes

Gross et al found that 10 year increase in age at donation was associated with decreased risk of Mental health HRQOL impairment (scoring > 5 points below average) at follow-up (OR (95% CI) 0.74(0.65-0.85).(Gross et al., 2013) Two studies reported similar SF-36 Mental Component Summary scores in donors of different age at donation.(Clemens et al., 2011) (Johnson et al., 1999) One study found that older age at donation was associated with increased likelihood of post-donation depression diagnoses.(K. L. Lentine et al., 2012) Mjoen et al. found that older age at donation was associated with decreased risk of doubt toward donation.(Mjoen et al., 2011) The quality of evidence for the outcome was very low.

Diabetes

Donors who were younger than 18 years of age at donation had risk of drug treated diabetes similar to that of donors who were 18-30 years of age at donation (RR: 0.61; 95% CI: 0.15 to 2.60).(MacDonald et al.) One study reported that older age at donation was associated with a 5% higher risk of drug-treated diabetes over an average 7.7 yrs of follow-up.(K. L. Lentine et al., 2010) The quality of evidence for the outcome was low.

Other Outcomes

One study looked at the risk for GI bleeds in living donors by age at donation and found a two-fold greater event rate/10,000 person years in donors older than 40 years of age compared to those younger than 40 (23.4 versus 11.9), the difference was not significant.(Thomas et al., 2013) One study looked at the risk for fragility fractures in living donors by age at donation and found a greater than three times higher event rate/10,000 person years in donors aged 55 and older compared to those younger than 55 (43.2 versus 12.7 – RR: 2.85; 95% CI: 1.24-6.55).(A. X. Garg, Pouget, et al., 2012) One study compared risk of surgical interventions for kidney stones and kidney stones with hospital encounters in donors 40 years or older at the time of donation versus donors younger than 40 years of age and did not find any difference.(Thomas et al.) The quality of evidence for the outcomes was low to very low.

5c – Male and Female Donors vs Male and Female Healthy Non-Donors (Table D8)

Seven studies compared outcomes between male kidney donors / female kidney donors with male / female healthy non-donors respectively. Follow-up ranged from 5 to 25 years. Two studies evaluated mortality, one study cardiovascular outcomes, one study ESRD, one study depression, and one study each, all from the same donor cohort, evaluated GI bleeding, kidney stones and fragility fractures. Quality of evidenced low to very low for all of the outcomes (Table 11).

Mortality

One study reported relative risk of death for male donors and non-donors compared to female donors and non-donors. Males (including donors and non-donors) had a greater risk of death (AHR: 1.52; 95% CI: 1.41 to1.65) compared to female donors and non-donors .(Mjoen et al.) One study compared mortality of donors and healthy non-donors stratified by sex. Mortality of healthy non-donors was higher than that of donors in males and females.(Segev et al.) The quality of evidence for the outcome was very low.

ESRD

One study reported relative risk of ESRD for male donors and non-donors compared to female donors and non-donors. Male donors and non-donors had similar risk of ESRD compared to female donors and non-donors (AHR: 0.90; 95% CI: 0.43 to 1.88).(Mjoen et al.) The quality of evidence for the outcome was very low.

Psychosocial Outcomes

Rates of diagnoses of depression were lower in male donors compared to non-donors (3.1 versus 4.7 per 100 person years), as well as female donors compared to non-donors (6.6 versus 9.2 per 100 person years).(K. L. Lentine et al.) The quality of evidence for the outcome was very low.

Other Outcomes

Three studies addressed other outcomes after living kidney donation; all studies were done in the province of Ontario population.(A. X. Garg, Pouget, et al., 2012; Thomas et al.; Thomas et al., 2013) Thomas et al. compared gastrointestinal bleeds in male and female living donors to matched non-donor controls of the same sex and found similar event rates in donors and non-donors (event rates were 15.7 vs 17.9 /10,000 person years for male donors and non-donors respectively, and 20.1 vs 12.9/10,000 person years for female donors and non-donors respectively, p for interaction 0.2).(Thomas et al., 2013) One study looking at the risk for fragility fractures in male and female living donors in comparison to matched non-donors found similar event rates in donors vs non-donors (12.9 vs 13.1/10,000 person years for male donors vs non-donors, and 18.8 vs 22.4/10,000 person years for female donors vs non-donors, p for interaction 0.7).(A. X. Garg, Pouget, et al., 2012) One study compared rates of kidney stones with need for surgical interventions (9.1 versus 13.7/ 10,000 person-years for male donors and non-donors and 7.7 vs 7.0 /10,000 person years for female donors and non-donors, p for interaction 0.4) as well as hospitalizations for kidney stones (9.1 versus 14.2/ 10,000 person-years for male donors and non-donors and 7.7 vs 7.0 /10,000 person years for female donors and non-donors, p for interaction 0.03).(Thomas et al., 2013) Quality of evidence was low or very low for all of the reported outcomes.

5d –Male Donors versus Female Donors (Table D9)

Seventeen studies analyzed donor outcomes by sex. The studies reported mean / median lengths of follow-up ranging from 5.4 to 12.2 years. Quality of evidenced was low to very low for all of the outcomes (Table 12).

Mortality

Two studies reported mortality. One small study reported two deaths, one among male and one among female donors (2.2% versus 1.7% respectively). In another study, male donors were 70% more likely to die during the 12 year follow-up compared to female donors (2.7% vs 1.9%).(Segev et al.) The quality of evidence for the outcome was very low.

Cardiovascular Events

In one study, male donors were more likely to have cardiovascular events compared to female donors (AHR: 2.11; 95% CI: 1.43 to 3.10).(K. L. Lentine et al.) In the Ontario study, female donors were less likely to have a death censored cardiovascular event compared to male donors, but the association was not statistically significant (2.4% vs 3.3%, HR (95% CI) : 0.57(0.26-1.23)).(A. X. Garg, Meirambayeva, et al., 2012)The quality of evidence for the outcome was low.

ESRD

Six studies analyzing data from 3 data sources, (Cherikh et al., 2011; Gibney et al., 2008; Muzaale et al., 2014) all analyzing OPTN data but with different inclusion criteria, reported ESRD events by donor gender. One study reported 1 case of ESRD among male donors (2.2%) and one among female donors (1.7%).(Tsai et al.) In one study, male donors had greater risk of ESRD compared to female donors (RR: 2.24; 95% CI: 1.30 to 3.86).(Cherikh et al.) In a study by Muzaale et al., women had a 15 year cumulative incidence of ESRD of 21.1 (14.9 to 29.9) per 10,000 person years compared to 44.1 (32.9 to 59.1) in men.(Muzaale et al.) In another study, men had greater risk of ESRD but it was not statistically significant.(Wafa 2011) One study reported greater risk of being waitlisted for a kidney transplant among male donors compared to female donors (0.18% versus 0.04%, RR: 4.83; 95% CI: 2.54 to 9.18). This was true among White and African American donors.(Gibney et al.) The quality of evidence for the outcome was low.

Renal Function

Six studies reported renal function by gender. Two studies reported no significant increase in risk of post-donation eGFR <60 ml/min by MDRD in women compared to men.(J. H. Lee et al.; Tsai et al.) One study reported greater odds of iohexol GFR < 60 ml/min/1.73m2 in women compared with men (OR: 3.11; 95% CI:1.11 to 8.67),(Ibrahim, Foley, et al.) One study reported greater risk of claims for CKD in male donors compared to female donors (AHR: 1.64; 95% CI: 1.16 to 2.34).(K. L. Lentine et al.) One study reported similar GFR in male (81.6) and female (79.4) donors at 10 year of follow-up, p-value was not provided,(Karakayali, Moray, Demirag, Yildirim, & Bilgin, 1998) while another study reported higher MDRD eGFR in males (69$\pm$13 ml/min/1.73m2) than females (65$\pm$12 ml/min/m2), p<0.01.(von Zur-Muhlen et al.) The quality of evidence for the outcome was very low.

Proteinuria

Two studies reported proteinuria by gender.(Ibrahim, Foley, et al., 2009; Tsai et al., 2013) In one study incidence of proteinuria (defined as > 150 mg/day of protein or >1+ dipstick proteinuria on UA) was similar between female and male donors (RR: 1.87; 95% CI: 0.63-5.50).(Tsai et al., 2013) In the second study, albuminuria was less common in women (OR: 0.31, 95% CI: 0.12-0.79).(Ibrahim, Foley, et al.) The quality of evidence for the outcome was very low.

Hypertension

Three studies reported HTN by gender.(El-Agroudy et al.; K. L. Lentine et al., 2010; Tsai et al., 2013) In one study incidence of HTN was not different between male and female donors at 5.5 years.(Tsai et al.) In another study HTN (>140/90 mmHg) was more common among

female donors (24.7 versus 17.8%, p=0.03).(El-Agroudy et al., 2007) A third study revealed a greater risk of drug-treated HTN among male donors (AHR: 1.21; 95% CI: 1.03 to 1.43).(K. L. Lentine et al.) The quality of evidence for the outcome was very low.

Psychosocial Outcomes

Three studies reported psychosocial outcomes by donor gender.(Johnson et al.; K. L. Lentine et al.; Mjoen et al.) One study reported that women were more likely to find the experience of donation stressful,(Johnson et al.) though the finding was not significant. Another study reported that male donors were not more likely to have doubt toward donation.(Mjoen et al.) A study by Lentine et al. revealed a lower rate of depression diagnoses among male (3.1 per 100 person-years) compared to female (6.6 per 100 person-years) donors.(K. L. Lentine et al.) The quality of evidence for the outcome was very low.

Diabetes

One study reported diabetes diagnosis by gender.(K. L. Lentine et al.) There was no significant difference in risk of diabetes by claims diagnosis or drug-treated diabetes between male and female donors.(K. L. Lentine et al.) The quality of evidence for the outcome was very low.

Other Outcomes

One study looked at the risk for GI bleeding in living donors by sex and found a small increase in GI bleeding/10,000 person years in male donors compared to female donors (20.1 versus 15.7, not significantly different (RR: 0.78; 95% CI: 0.39 to 1.55)).(Thomas et al., 2014) One study looked at the risk for fragility fractures in living donors by sex and found small and non-significant absolute differences in fracture risk in male donors compared to female donors (12.9 versus 18.8 per 10,000 person years) (RR: 0.71; 95% CI: 0.31 to 1.63).(A. X. Garg, Pouget, et al., 2012) The quality of evidence for the outcome was very low.

5e - African American / Hispanic donors vs African American / Hispanic Healthy Non-donors (Table D10)

Three studies compared outcomes of African American and/ or Hispanic LKDs to African American and Hispanic healthy non-donors. Follow-up ranged from 6.3 to 7.6 years (Table D10). Quality of evidence was rated moderate for ESRD and low to very low for all other outcomes. (Table 13).

Mortality

One study compared mortality between AA donors and AA healthy non-donors, and white donors with white healthy non-donors. Non-donor mortality was slightly higher than donor mortality for both races.(Segev et al.) The quality of evidence for the outcome was very low.

ESRD

One study compared absolute risk of ESRD in donors and healthy non-donors by race and ethnicity. There was a large and significant increase in relative risk of ESRD for African American, Hispanic, and white donors (compared to non-donors). The 15-year increase in absolute risk was small (< 0.5%). African American donors had the greatest absolute increase in the 15 year incidence of ESRD compared to controls (absolute risk increase 50.8 per 10,000 person years for AA donors (74.7 per 10,000 (95% CI, 47.8-105.8) in AA donors vs 23.9 per 10,000 (95% CI, 1.6-62.4) in AA non-donors) , 29.5 per 10,000 person years for Hispanic donors (32.6 per 10,000 (95% CI, 17.9-59.1) in Hispanic donors vs 6.7 per 10,000 person years (95% CI, 0-15.5) in Hispanic non-donors), and 22 per 10,000 person years for white donors (22.7 per 10,000 (95% CI, 15.6-30.1) in white donors vs 0.0 per 10,000 person years (95% CI, 0.0-0.0) in white non-donors).(Muzaale et al.) The quality of evidence for the outcome was moderate for all three racial groups (upgraded for effect size).

Renal function

One study compared eGFR in African American donors compared to African American non-donors. The average serum creatinine was 1.2 +0.3 mg/dL and the average eGFR 77 +19 mL/min/1.73 m^2 in donors and 0.9 +0.2 mg/dL and 109 +17 mL/min/1.73 m^2, in non-donors, respectively at an average follow-up of 6.8 years. The number (proportion) of donors with an eGFR < 60 and < 45 mL/min/1.73 m^2 was 16 (15.5%) and 6 (6%), respectively, in donors while none of the non-donors had an eGFR<60 mL/min/1.73 m^2.(Doshi, Goggins, Li, & Garg) The quality of evidence for the outcome was low.

Proteinuria

One study compared risk of proteinuria (microalbuminuria) among African American donors and African American healthy non-donors. After an average of 6.8 years from donation, African American donors had greater mean urinary albumin than non-donors, 15 microgram/mg vs 7 microgram/mg, but the difference was not statistically significant. Incidence of micro-albuminuria did not differ between African American donors and non-donors (5.8% vs 3.8% [RR: 1.52; 95% CI: 0.55 to 4.16]).(Doshi et al.) The quality of evidence for the outcome was very low.

Hypertension

One study compared risk of hypertension defined as BP> 140/90 mmHg or use of blood pressure medications among African American donors and African American healthy non-donors. After a mean follow-up of 6.8 years, African American donors had greater risk of hypertension compared to African American non-donors (40.8%vs 17.9%, absolute difference of 22.9%, [RR: 2.3; 95% CI: 1.6 to 3.4]).(Doshi et al.) The quality of evidence for the outcome was very low.

Diabetes

One study compared risk of diabetes among African American donors and African American healthy non-donors. After a mean follow-up of 6.8 years, African American donors had a frequency of diabetes similar to that of African American non-donors (1.9% vs 1.7%, absolute risk difference of 0.2%, [RR: 1.14; 95% CI: 0.21 to 6.13]).(Doshi et al.) The quality of evidence for the outcome was very low.

5f - African American / Hispanic donors versus White donors (Table D11)

Eight studies reported living donor outcomes by donor race or ethnicity.(Cherikh et al.; Gibney, King, Maluf, Garg, & Parikh; Gross et al.; K. L. Lentine et al.; K. L. Lentine et al.; Muzaale et al.; Segev et al.; Storsley et al.) Follow-up ranged from 6 to 17 years. (Table 14) Quality of evidenced was low to very low for all of the outcomes.

Mortality

Two studies reported on donor mortality by race.(Segev et al.; Storsley et al.) Compared to White donors, African American donors had 30 percent greater risk of death after a mean follow-up of 6.3 years (12 year mortality 2.8% vs 1.7%, HR: 1.3; 95% CI: 1.0 to 1.6).(Segev et al.) Hispanic donors had 40 percent lower mortality compared to White donors (HR: 0.6; 95% CI: 0.4 to 0.9).(Segev et al.) Aboriginal donors' risk of death was similar to White donors (RR: 1.33; 95% CI: 0.40 to 4.44).(Storsley et al.) The quality of evidence for the outcomes was very low for African American and Aboriginal donors and low for Hispanic donor comparisons.

Cardiovascular Events

One study reported cardiovascular event risk (from administrative claims data) by race; African American (RR: 1.15; 95% CI: 0.63 to 2.11) and Hispanic (RR: 0.91; 95% CI: 0.37 to 2.26) donors had similar risk to White donors (Table D11).(K. L. Lentine et al.) The quality of evidence for the outcome was very low.

ESRD

Five studies reported ESRD events by race.(Cherikh et al.; Gibney et al.; K. L. Lentine et al.; Muzaale et al.; Storsley et al.) One study only reported an ESRD case in anAboriginal donor and none in White donors.(Storsley et al.) African American but not Hispanic donors had higher rate of placement on the transplant waiting list compared to White donors.(Gibney et al.) Two other studies reported greater risk of ESRD in African American donors compared to White donors.(Cherikh et al.; K. L. Lentine et al.) Cumulative incidence of ESRD at 15 years per 10,000 person years (95% CI) was 74.5 (47.8 to 105.8) in African American donors, 32.6 (17.9-59.1) in Hispanic donors, and 22.7 (15.6-30.1) in White donors.(Muzaale et al.) The quality of evidence for the outcome was moderate for African American donors and low for Hispanic donor comparisons.

Renal Function

Three donor pool studies evaluated renal function in kidney donors by race and insurance status at a median follow-up of 7-14 years. In one study of Medicare-insured donors, African American race and Hispanic ethnicity were associated with a higher risk of post-donation CKD diagnoses compared to White donors.(K. L. Lentine et al., 2010) Another report by the same group revealed greater risk of claims for CKD diagnoses in African American and Hispanic donors with private insurance compared to White donors with private insurance.(K. Lentine et al., 2014) In this study Hispanic ethnicity was not associated with increased risk of CKD diagnosis among Medicare insured donors.(K. L. Lentine et al.) In another study, Aboriginal donors had higher eGFR compared to White donors after 14 years of follow-up (adjusted difference 5.9 ml/min).(Storsley et al.) The quality of evidence for the outcome was very low.

Proteinuria

Two studies reported proteinuria by race or ethnicity. Both Medicare insured and privately insured African American donors had a higher risk and Hispanic donors had a similar risk of proteinuria diagnosis compared to similarly insured White donors.(K. L. Lentine et al.) Aboriginal donors have greater proteinuria compared to White donors (21% vs 4% with > 0.3 gm per 24 hours, RR for (95% CI) 5.89 (1.27 to 27.41)).(Storsley et al.) The quality of evidence for the outcome was very low.

Hypertension

Three studies with two unique cohorts reported hypertension risk by race.(K. L. Lentine et al.; K. L. Lentine et al.; Storsley et al.) Two studies used the same cohort twice.(K. L. Lentine et al.; K. L. Lentine et al.) African American donors had a greater risk of drug treated hypertension and hypertension diagnoses compared to White donors in both privately and Medicare insured cohorts.(K. L. Lentine et al.; K. L. Lentine et al.) Privately insured Hispanic donors had a greater risk of hypertension compared to privately insured White donors (HR: 1.36; 95% CI: 1.04 to 1.78), while Medicare insured Hispanic donors had a risk of hypertension similar to that of Medicare insured White donors (HR: 1.11; 95% CI: 0.95 to 1.46).(K. L. Lentine et al.) Aboriginal donors had greater frequency of hypertension compared to White donors at 10 and 20 years post-donation.(Storsley et al.) The quality of evidence for the outcome was very low.

Psychosocial outcomes

One study with a mean follow up of 17 years reported psychosocial functioning by race.(Gross et al.) Whites reported higher level of social functioning than African Americans (p=0.0007). White donors were more likely to report good health than African Americans (p=0.0034) and other races (p=0.0004). One study found that non-Hispanic white donors had twice the likelihood of depression diagnoses based on billing claims as non-white or Hispanic donors.(K. L. Lentine et al., 2012) The quality of evidence for the outcome was very low.

Diabetes

Three publications reporting analysis of two databases of donors reported diabetes risk by race or ethnicity.(K. L. Lentine et al.; K. L. Lentine et al.; Storsley et al.) Two studies used the same cohort twice.(K. L. Lentine et al.; K. L. Lentine et al.) African American and Hispanic donors had greater risk of diabetes diagnosis and medication treated diabetes in both Medicare and privately insured cohorts.(K. L. Lentine et al.; Thomas et al., 2014) Also, Aboriginal donors had greater frequency of diabetes compared to White donors (19% vs 2%, p=0.05) at 14 years of follow-up.(Storsley et al.) The quality of evidence for the outcome was very low.

Table 9. Key Question 5 Evidence Profile: Long Term Living Kidney Donation Outcomes – Older donors versus Older Healthy Non-donor Controls

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Mortality (4 retrospective observational studies)	Low to moderate	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Inconsistent results across studies. Known and unknown confounders likely explain higher mortality rates in healthy non-donor controls, corroborated by inconsistency based upon comparison group across studies.	Very Low
CV Outcomes(retrospective observational studies)	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Older donors had similar risk of cardiovascular event older nondonors during 5 to 7 year follow-up.	Low
Psychosocial (1 retro/prospective observational study)	High	Unknown	Serious indirectness	Serious imprecision	Undetected	One study shows similar mental component of SF-36 summary scores in older donors and older non-donors at median follow-up of 5.5 years after living kidney donation.	Very Low
Other: Fractures (1 retrospective observational study)	Moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	One study shows similar rates of fragility fractures in older donors and older non-donors over a median of 7 years follow-up. Confounding is a major problem.	Very Low
Other: GI Bleed (1 retrospective observational study)	Low-Moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	One study shows similar rates of GI bleeds in older donors and older non-donors over a median of 7 years follow-up. Confounding is a major problem.	Very Low
Other: Diabetes (retrospective observational study)	Moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	Older donors are more likely than younger donors to develop diabetes over a median of 8 years follow-up.	Low

Table 10. Key Question 5 Evidence Profile: Long Term Living Kidney Donation Outcomes – Older versus Younger Donors

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Mortality (4 retrospective observational studies)	Low-moderate	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Older donors are more likely to die than younger donors during 5 to 7 year follow-up.	Low
CV Outcomes (retrospective observational studies)	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Older donors are more likely to have a cardiovascular event than younger donors during 5 to 7 year follow-up.	Low
ESRD (2 retrospective observational studies)	Moderate	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Older donors (>60) have a higher cumulative incidence of ESRD at 15 years post-donation than younger donors.	Very Low
Renal Function (10 retrospective observational studies)	Moderate	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Older donors are more likely to develop CKD than younger donors during 5 to 7 year follow-up.	Very Low
Proteinuria (3 retrospective observational studies)	Moderate-high	No serious inconsistency	Serious indirectness	Serious imprecision	Undetected	Older donors have similar rates of proteinuria as younger donors during 5 to 7 year follow-up.	Very Low
Hypertension (6 retrospective observational studies)	Moderate-high	No serious inconsistency	Serious indirectness	Serious imprecision	Undetected	Evidence is inconsistent in the rates of hypertension between older and younger donors at mean follow up between 5 and 14 years.	Very Low
Psychosocial (1 retrospective observational study)	Moderate-high	Serious inconsistency	Serious indirectness	Unclear	Undetected	Older donors were less likely to feel doubt about living kidney donation at follow-up.	Very Low
Other: Fractures (retrospective observational study)	Moderate	Unknown	No serious indirectness	No serious imprecision	Undetected	Older donors are more likely than younger donors to have stress fractures over a median of 7 years follow-up.	Low
Other: GI Bleed (retrospective observational study)	Low-moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	There is no difference in the rate of GI bleeds between older donors and younger donors over a median of 7 years follow-up.	Very Low
Other: Diabetes (retrospective observational study)	Moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	Older donors are more likely than younger donors to develop diabetes over a median of 8 years follow-up.	Low

Table 11. Key Question 5 Evidence Profile: Long Term Living Kidney Donation Outcomes – Donor versus healthy non-donors by gender

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of effect**	**Quality of Evidence**
Mortality (1 retrospective observational study)	High	Unknown	No serious indirectness	No serious imprecision	Undetected	Healthy non-donors showed greater death rates than same sex donor controls in one study; However, little confidence in this result due to known and unknown confounders associated with administrative controls.	Very Low
ESRD (1 retrospective observational studies)							
Psychosocial (1 retrospective observational study)	High	Unknown	No serious indirectness	Unclear	Undetected	Depression is lower among female donors compared to female non-donors; and male donors compared to male non-donors.	Very Low

Table 12. Key Question 5 Evidence Profile: Long Term Living Kidney Donation Outcomes – Male versus Female Donors

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Mortality (2 retrospective observational studies)	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Male donors have higher mortality rates than female donors over mean or median follow-up times between 5 and 6 years.	Low
CV Outcomes (1 retrospective observational study)	Moderate	Unknown	No serious indirectness	No serious imprecision	Undetected	Male donors have higher rates of cardiovascular events than female donors over median follow-up of 7 years.	Low
ESRD (5 retrospective observational studies)	Moderate	Unknown	No serious indirectness	No serious imprecision	Undetected	Male donors have higher rates of ESRD than female donors over mean or median follow-up over 5 years.	Low
Renal Function (6 retrospective observational studies)	Moderate	No serious inconsistency	Serious indirectness	Serious imprecision	Undetected	Inconsistent evidence on donor sex and rates of CKD over median or mean follow-up times over 5 years.	Very Low
Proteinuria (2 retrospective observational studies)	Moderate	No serious inconsistency	Serious indirectness	Serious imprecision	Undetected	Unclear whether there is a difference in proteinuria over median or mean follow-up times over 5 years.	Very Low
Hypertension (3 retrospective observational studies)		No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Similar rates of hypertension in male donors and female donors over median or mean follow-up times over 5 years.	Very Low
Psychosocial (3 retrospective observational studies)	High	Unknown	No serious indirectness	Unclear	Undetected	Female donors report the living kidney donation process more stressful and were more likely to become depressed than male donors. Male and female donors experienced similar levels of doubt post-donation.	Very Low
Other: Fractures (1 retrospective observational study)	Moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	Similar rates of fragility fractures over median follow-up of 7 years.	Very Low
Other: GI Bleed (1 retrospective observational study)	Low-moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	Similar rates of GI bleeds over median follow-up of 7 years.	Very Low
Other: Diabetes (1 retrospective observationalstudy)	Moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	Similar rates of diabetes over median follow-up of 8 years.	Very Low

Table 13. Key Question 5 Evidence Profile: Long Term Living Kidney Donation Outcomes –Donors versus Non-Donor Racial Subgroups

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Mortality (1 retrospective observational study)	High	Unknown	No serious indirectness	unclear	Undetected	One study showed mortality rates higher for healthy White and African American non-donors than White and African American donors, respectively. Known and unknown confounders likely explain observed differences.	Very Low
ESRD (1 retrospective observational study)	High	Unknown	No serious indirectness	No serious imprecision	Undetected	One study showed ESRD rates much higher for African American donors than healthy African American non-donors. Evidence quality upgraded for effect size.	Moderate
	High	Unknown	No serious indirectness	No serious imprecision	Undetected	One study showed ESRD rates much higher for Hispanic donors than healthy Hispanic non-donors. Evidence quality upgraded for effect size.	Moderate
	High	Unknown	No serious indirectness	No serious imprecision	Undetected	One study showed ESRD rates much higher for White donors than healthy White non-donors. Evidence quality upgraded for effect size.	Moderate
Renal Function (1 retrospective observational study)	Low to moderate	Unknown	Serious indirectness	No serious imprecision	Undetected	One retrospective observational study shows that African American donors have a higher rate of CKD than healthy African American non-donors. Evidence quality upgraded for effect size.	Low
Proteinuria (1 retrospective observational study)	Low to moderate	Unknown	Serious indirectness	No serious imprecision	Undetected	One study shows that the rate of microalbuminuria in African American living kidney donors is no different from that of healthy African American non-donors in a mean follow-up time over 6 years.	Very Low
Hypertension (1 retrospective observational study)	Low to moderate	Unknown	Serious indirectness	No serious imprecision	Undetected	One study shows that the rate of hypertension in African American living kidney donors is higher (RR= 2.3; 95% CI=1.6 to 3.3) than that of healthy African American non-donors in a mean follow-up time of over 6 years.	Very Low
Other: Diabetes (1 retrospective observational study)	Low to moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	One study shows that the rate of diabetes in African American living kidney donors is no different from that of healthy African American non-donors in a mean follow-up time of over 6 years.	Very Low

Table 14. Key Question 5 Evidence Profile: Long Term Living Kidney Donation Outcomes – Comparison between Donor Racial Subgroups

Quality Assessment						Summary of Findings	
Outcome (Number of Studiesand Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Mortality (2 retrospective observational studies)	Low-moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	One retrospective observational study found that the odds of mortality over a follow-up period up to 12 years (mean 6 years) were similar for African American donors and White donors.	Very Low
	Low-moderate	Unknown	No serious indirectness	No serious imprecision	Undetected	One retrospective observational study found that the odds of mortality over a follow-up period up to 12 years (mean 6 years) were lower for Hispanic donors compared to white donors.	Low
	High	Unknown	No serious indirectness	Serious imprecision	Undetected	One retrospective observational study shows that rates of mortality are similar for aboriginal donors and White donors over a mean follow-up of 14 years.	Very Low
CV Outcomes (1 retrospective observational study)	High	Unknown	No serious indirectness	Serious imprecision	Undetected	One retrospective observational study shows that the rate of cardiovascular disease is similar among Whites, Hispanics, and African Americans over a median follow-up of 7.7 years.	Very Low
ESRD (several publications of same data)	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Analyses of OPTN data show that black donors develop ESRD at least twice the rate of White donors. Evidence quality upgraded for effect size.	Moderate
	Moderate	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Analyses of OPTN data show that the rate of ESRD in Hispanic donors is not statistically different than that of White donors.	Low
Renal Function (2 retrospective observational studies)	Moderate	Unknown	Serious indirectness	No serious imprecision	Undetected	One retrospective observational study shows that African American donors have a higher rate of CKD than White donors over a median follow-up of 7.7 years.	Very Low
	Moderate	Unknown	Serious indirectness	Serious imprecision	Undetected	One retrospective observational study shows that privately-insured Hispanic donors have higher rates of CKD than privately-insured White donors over a median follow-up of 7.7 years.	Very Low

						The same retrospective observational study shows that Medicare-insured Hispanic donors have similar rates of CKD as Medicare-insured White donors over a median follow-up of 7.7 years.	
Proteinuria (2 retrospective observational study)	Moderate	Unknown	Serious indirectness	No serious imprecision	Undetected	One retrospective observational study shows that African American donors have a higher rate of proteinuria than White donors over a median follow-up of 7.7 years.	Very Low
	Moderate	Unknown	Serious indirectness	No serious imprecision	Undetected	One retrospective observational study shows that Hispanic donors have similar rates of proteinuria as White donors over a median follow-up of 7.7 years.	Very Low
Hypertension (3 publications of retrospective observational study of two unique donor cohorts)	Moderate	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Two retrospective observational studies analyzing similar data found that African American donors had higher rates of hypertension than White donors over a median follow-up of 7.7 years.	Very Low
	Moderate	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Analysis of UNOS data shows that African American donors had higher rates of hypertension than White donors.	Very Low
Psychosocial (1 retrospective observational study)	Moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	White donors had higher psychosocial outcomes than African American donors after donation.	Very Low
Other: Diabetes (2 retrospective observational studies)	Moderate	Unknown	No serious indirectness	No serious imprecision	Undetected	Two retrospective observational studies analyzing similar data found that African American and Hispanic donors had higher rates of diabetes than White donors over a median follow-up of 7.7 years.	Very Low

6 - Key Question 6 Long Term Outcomes of Donors with Isolated Medical Abnormalities

We found no studies that fit our inclusion criteria and compared outcomes of kidney donors with isolated medical abnormities to outcomes of otherwise healthy non-donors matched by the isolated medical abnormality. Following literature compares outcomes of donors with IMA to outcomes of donors without IMA.

6a - Obese Donors versus Non-Obese Donors (Table D12)

Five studies compared long-term outcomes among donors by pre-donation BMI status.(Gracida et al., 2003; Gross et al., 2013; Ibrahim, Foley, et al., 2009; Mjoen et al.) Follow-up ranged from 6.7 to 15.1 years (Table D12). The quality of evidence was rated as very low for all outcomes (Table 15).

Mortality

One study presented adjusted risk of death per 1 BMI unit increase in a combined cohort of kidney donors and healthy non-donors.(Mjoen et al., 2014) The study did not find a significant increase in risk of death associated with greater BMI (AHR: 1.01; 95% CI: 0.99 to 1.03 per BMI unit).(Mjoen et al.) The quality of evidence for the outcome was very low.

Cardiovascular mortality

One study presented adjusted risk of death from cardiovascular causes per unit BMI increase in a combined cohort of kidney donors and healthy non-donors.(Mjoen et al.) Higher BMI was associated with greater risk of cardiovascular mortality (AHR: 1.03; 95% CI: 1.01 to 1.07 per BMI unit).(Mjoen et al.) The quality of evidence for the outcome was very low.

ESRD

One study presented adjusted risk of ESRD per unit BMI increase in a combined cohort of kidney donors and healthy non-donors.(Mjoen et al.) The study did not find a significant increase in risk of ESRD associated with greater BMI (AHR: 1.13; 95% CI: 0.96 to 1.32 per BMI unit).(Mjoen et al.) The quality of evidence for the outcome was very low.

Renal function

Three studies analyzed the association of BMI and renal function.(Gracida et al., 2003; Ibrahim, Foley, et al., 2009) One study at high risk of bias reported follow-up eGFR of 83.9 ml/min in donors with BMI > 30 kg/m2 at baseline compared to eGFR of 78.5 ml/min in donors with normal BMI.(Gracida et al., 2003) One study revealed greater odds of iohexol GFR < 60 ml/min/1.73m2 at follow-up per unit increase in BMI at baseline (OR (95% CI): 1.12(1.02-1.23)) .(Ibrahim, Foley, et al.) Similarly, another study reported that higher BMI at donation was correlated with lower eGFR at follow-up.(von Zur-Muhlen et al.) The quality of evidence for the outcome was very low.

Hypertension

Two studies reported blood pressure or hypertension by BMI at donation. One study reported MAP of 91.2 in donors with BMI >30 compared to MAP of 88.2 in donors with BMI < 30 at donation.(Gracida et al.) One study reported increased odds of hypertension requiring medication at follow-up associated with greater BMI at donation (OR: 1.12; 95% CI: 1.04 to 1.21 per BMI unit).(Ibrahim, Foley, et al.) The quality of evidence for the outcome was very low.

Psychosocial Outcomes

One study revealed greater odds of physical component of HRQoL impairment (defined as Physical Component Score >1 SD below sex-by-age norms in donors with higher BMI.(Gross et al.) Donors with BMI >=35 were more likely to be impaired (OR: 4.32; 95% CI: 2.37 to 7.87)

than donors with normal BMI. The same was true with donors whose BMI was 30 – 34.9 (OR: 2.85; 95% CI: 2.37 to 7.87) and in donors with BMI 25 – 29.9 (OR: 1.84; 95% CI: 1.31 to 2.65).(Gross et al.) The quality of evidence for the outcome was very low.

6b - Donors with Lower Renal Function versus Donors with Higher Renal Function(Table D13)

Three included studies from three countries analyzed donor outcomes by pre-donation GFR.(J. H. Lee et al.; Tsai et al.; von Zur-Muhlen et al.) The studies reported mean lengths of follow-up of 5.4 to 11 years. The quality of evidence was very low.

Renal function

Three studies reported kidney function at follow-up by baseline kidney function.(J. H. Lee et al.; Tsai et al.; von Zur-Muhlen et al.) One study reported no significant association between baseline measured creatinine clearance and odds of MDRD estimated GFR < 60 ml/min/1.73m2: (OR: 1.00; 95% CI: 0.98 to 1.03) per unit change in the measured creatinine clearance.(J. H. Lee et al.) Another study revealed an association between greater eGFR at baseline (per 1 ml/min/1.73m2) and lower risk of developing chronic kidney disease defined as eGFR < 60 ml/min/1.73m^2 (OR: 0.95; 95% CI: 0.92 to 0.99).(Tsai et al.) The third study reported a significant correlation between lower eGFR at baseline and lower eGFR at follow-up.(von Zur-Muhlen et al.) Quality of evidence was very low.

Proteinuria

One study reported lack of correlation between lower measured GFR at donation and urine albumin-creatinine ratio at follow-up.(von Zur-Muhlen et al., 2014) Quality of evidence was very low.

Hypertension

One study reported that lower measured GFR at donation was correlated to higher mean arterial blood pressure at follow-up.(von Zur-Muhlen et al.) The quality of evidence for the outcome was very low.

6c - Donors with Impaired Fasting Glucose versus Donors with Normal Glucose Tolerance (Table D14)

Two studies included 110 donors with impaired glucose metabolism and 775 donors with normal glucose metabolism and followed them for 7-10 years. The quality of evidence was low to very low for all outcomes. (54,55)

Mortality

One study reported mortality: 3 of 65 (4.6%) donors with glucose intolerance and 14 of 330 (4.1%) donors with normal glucose tolerance died during an average follow-up of 7.3 years (RR: 1.09; 95% CI: 0.32 to 3.68).(Okamoto et al.) Quality of evidence was very low.

ESRD

The same study as noted above for mortality reported no cases of ESRD among 65 donors with impaired glucose tolerance and 2 cases of ESRD among 330 donors with normal glucose tolerance.(Okamoto et al.) Quality of evidence was very low.

Renal function

Two studies reported kidney function at follow-up by glucose tolerance or fasting glucose impairment at baseline.(Chandran, Masharani, Webber, & Wojciechowski; Okamoto et al.) One study reported similar MDRD eGFRs at mean follow-up of 10.2 years: donors with impaired fasting glucose at baseline had a mean eGFR of 70.7(16.1) ml/min/1.73m^2 versus donors with

normal fasting glucose who had a mean eGFR of 67.3(16.6) ml/min/1.73 m^2.(Chandran et al.) Another study reported self-reported renal dysfunction in 7.7% of donors with glucose intolerance at baseline and 6.7% of donors with normal glucose tolerance at 7.3 years of follow-up.(Okamoto et al., 2010) Quality of evidence was very low.

Proteinuria

One study reported similar albumin/creatinine ratios after 7.3 years of follow-up in donors with and without impaired fasting glucose at baseline (9.8 [23.6] mg/g versus 5.9 [11.0] mg/g, p=0.29).(Chandran et al.) Quality of evidence was very low.

Hypertension

Two studies did not find a difference in incidence of hypertension during the follow-up period between donors with impaired fasting glucose or glucose intolerance and donors with normal glucose metabolism.(Chandran et al.; Okamoto et al.) In one study, 35.6% of donors with impaired fasting glucose and 22.2% of donors with normal fasting glucose developed hypertension after 10.2 years of follow-up. (Chandran et al., 2014) In the second study, 29.2% of glucose intolerant donors and 22.1% of donors with normal glucose metabolism developed blood pressure > 140/90 after 7.3 years of follow-up (RR (95% CI): 1.32(0.86-2.03)). (Okamoto et al., 2010) In the same study, 13.8% of donors with glucose intolerance and 11.2% of donors without glucose intolerance developed drug treated hypertension (RR(95%CI): 1.23(0.63-2.43)). (Okamoto et al., 2010) Quality of evidence was very low.

Diabetes

Two studies reported greater frequency of diabetes at follow-up between donors with impaired fasting glucose, diabetes, or glucose intolerance and donors with normal glucose metabolism at baseline.(Chandran et al.; Okamoto et al.) In one study, 15.6% of donors with impaired fasting glucose and 2.2% of donors with normal fasting glucose developed diabetes after 10.2 years. (Chandran et al., 2014) In the other study, 21.4% of donors with glucose intolerance and 2.4% of donors with normal glucose tolerance developed diabetes by self-report, and 26.2 and 0% required medications for diabetes respectively after a mean follow-up of 7.3 years. (Okamoto et al., 2010) Quality of evidence was very low.

6d - Donors with Metabolic Syndrome versus donors without metabolic syndrome(Table D15)

One included study analyzed donor outcomes by pre-donation presence of metabolic syndrome. Metabolic syndrome was defined as meeting three or more of the criteria 1) waist circumference of >88 cm in women or >102 cm in men; 2) hypertriglyceridemia; 3) hyperlipidemia; 4) hyperglycemia; and 5) hypertension (>130/85). This study reported on renal function and proteinuria. The mean length of follow-up was 5 years and data on 140 participants were analyzed.(Cuevas-Ramos et al.) The quality of evidence was very low for all outcomes.

Renal Function

One study reported 5-year post-donation MDRD eGFR (mean (SD)) of 66.3(12.7) ml/min/1.73m2 in donors with and 71.8(16.2) ml/min/1.73m2 in donors without metabolic syndrome at baseline.(Cuevas-Ramos et al.) The quality of evidence was very low.

Proteinuria

One study reported 5-year post-donation 24-hour albuminuria (mean (SD)) of 0.5(0.6) mg/day in donors with and 0.2(0.5) mg/day in donors without metabolic syndrome at baseline.(Cuevas-Ramos et al.) The quality of evidence was very low.

6e - Hypertensive Donors versus Normotensive Donors (Table D16)

Three included studies analyzed donor outcomes by pre-donation hypertension status.(Gracida et al., 2003; J. H. Lee et al., 2007; Mjoen et al.) One study reported blood pressure as a risk factor for mortality, cardiovascular mortality, and ESRD in a combined cohort of donors and healthy non-donors.(Mjoen et al.) Two other studies defined hypertension as BP>140/90 easily controlled with one medication and reported renal function by hypertension status. However, evidence quality was assessed using only Lee et al. because Gracida et al. was assessed as having a high risk of bias and the comparison groups used in the two studies were not comparable. Quality of evidence was very low for all outcomes (Table 19).

Mortality

In one study, a 1 mmHg increase in SBP was not associated with significant increase in risk of death in a mixed cohort of donors and matched non-donors without hypertension (AHR: 1.00: 95% CI: 1.00 to 1.01).(Mjoen et al.) The quality of evidence was very low.

Cardiovascular Mortality

In one study, a 1 mmHg increase in SBP was associated with a small but significant increase in the risk of cardiovascular death in a mixed cohort of donors and matched non-donors (AHR: 1.01; 95% CI: 1.00 to 1.02).(Mjoen et al.) The quality of evidence was very low.

ESRD

In one study, 1 mmHg increase in SBP was associated with a small but significant increase in the risk of ESRD in a mixed cohort of donors and matched non-donors without hypertension (AHR: 1.01; 95% CI: 1.00 to 1.06).(Mjoen et al.) The quality of evidence was very low.

Renal Function

In one small study more donors with hypertension developed CKD as defined by eGFR < 60 ml/min/1.73m2 compared to donors without hypertension (67% vs 22%, RR: 2.97; 95% CI: 1.51 to 5.83) after 5.4 years of follow-up.(J. H. Lee et al.) One study reported similar eGFRs in donors with (78.1 ml/min/1.73m2) and without (78.5 ml/min/1.73m2) hypertension at donation at mean follow-up of 6.7 years.(Gracida et al.) The quality of evidence was very low.

6f - Donors with Proteinuria or Hematuria versus donors without

None of the included studies analyzed donor outcomes by pre-donation proteinuria or hematuria.

6g - Long Term Donor Outcomes by Relationship to the Recipient (Table D17)

Nine studies evaluated long term donor outcomes by relationship to the recipient. Follow-up ranged from 5 to 17 years. Quality of evidence was rated as moderate to very low for the outcomes (Table 20).

Mortality or Cardiovascular Outcome

Two studies reported cardiovascular outcomes in donors by relationship to the recipient. Both studies used the same cohort of Ontario donors.(A. X. Garg, Pouget, et al.; A. X. Garg et al.) One study reported outcomes of cardiovascular events and mortality by relationship to the recipient. Genetically related living donors had cardiovascular event rate of 1.2 percent while unrelated donors had event rate of 1.6 percent over 6.2 years of follow-up.(A. X. Garg et al.) In another study, event rate was similar between donors (1.6 per 1000 person years) and healthy non-donors (1.9 per 1000 person years) and the association was not modified by relationship to

the recipient (p for interaction 0.87).(A. X. Garg, Pouget, et al.) The quality of evidence for the outcome was very low.

ESRD

One study reported 15 year cumulative incidence of ESRD by relationship to the recipient, cumulative incidence was lower in unrelated donors compared to related donors15.1 (95% CI: 8.7 to 26.3) versus 34.1 (95% CI: 26.9 to 43.3) per 10,000).(Muzaale et al.) The quality of evidence for the outcome was moderate.

Renal function

One study did not find an association between relationship to the recipient and CKD (eGFR< 60ml/min/1.73m2).(J. H. Lee et al.) Among donors who were a first degree relative of the recipient, 18% had CKD versus 28% among donors who were not first degree relative of the recipient, after 7.4 years of follow-up.(J. H. Lee et al., 2007) The quality of evidence for the outcome was very low.

Hypertension

One study did not find an association between relationship to the recipient and hypertension (15.9% in related and 17.3% in unrelated, RR (95% CI): 1.0(0.7-1.3)).(A. X. Garg et al.) The quality of evidence for the outcome was very low.

Psychosocial Outcomes

Four studies reported psychosocial outcomes by relationship to the recipient.(Gross et al.; Johnson et al.; K. L. Lentine et al.; Mjoen et al.) Related donors had better psychosocial outcomes compared to unrelated donors.(Gross et al.; Johnson et al.; Mjoen et al.) Being a first degree relative of a recipient was associated with lower odds of physical HRQOL impairment.(Gross et al.) Relative other than first degree were 3.5 times more likely to regret donating compared to first degree relatives.(Johnson et al.) Being an unrelated donor was associated with greater risk of having doubts towards donation.(Mjoen et al.) Rates of depression diagnoses didn't differ between donors related to recipients, spouses or partners of recipients, and not biologically related or spouse donors (4.9%, 5.0%, and 5.9% respectively) in a privately insured US sample.(K. L. Lentine et al., 2012) The quality of evidence for the outcome was low.

6h - Donors with history of Kidney Stones

We identified no studies analyzing long-term donor outcomes by pre-donation kidney stones status.

Table 15. Key Question 6 Evidence Profile: Long Term Living Kidney Donation Outcomes – Obese Donors versus non-obese donors

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Mortality (1 retrospective observational study)	Moderate-high	Unknown	No serious indirectness	No serious imprecision	Undetected	One study did not find a significantly different risk of death per 1 BMI unit increase in a combined cohort of kidney donors and healthy non-donors.	Very Low
CV Outcomes (1 retrospective observational study)	Moderate-high	Unknown	No serious indirectness	Serious imprecision	Undetected	One study found a significant increase in risk of death from cardiovascular causes per unit BMI increase in a combined cohort of kidney donors and healthy non-donors.	Very Low
ESRD (1 retrospective observational study)	Moderate-high	Unknown	No serious indirectness	Serious Imprecision	Undetected	One study did not find a significantly different risk of ESRD per 1 BMI unit increase in a combined cohort of kidney donors and healthy non-donors.	Very Low
Renal Function (2 retrospective observational study)	Moderate	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	Two retrospective studies show that in living kidney donors, higher BMI is associated with a slightly greater risk of developing chronic kidney disease after donation.	Very Low
Hypertension (1 retrospective observational study)	Moderate	Unknown	Serious indirectness	No serious imprecision	Undetected	One retrospective study with a moderate risk of bias shows that in living kidney donors higher BMI is associated with a slightly greater risk of developing hypertension over a mean follow-up of 6.7 years.	Very Low
Psychosocial (1 retrospective observational study)	Moderate	Unknown	Serious indirectness	No serious imprecision	Undetected	One retrospective study with a moderate risk of bias shows that physical health-related quality of life (SF-36) does not vary across four categories of living kidney donor BMI status over a mean follow-up of 6.7 years.	Very Low

Table 16. Evidence Profile: Long Term Living Kidney Donation Outcomes – Donors with lower renal function versus donors with normal renal function

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Renal Function (3 retrospective observational studies)	Low	Unknown	Serious indirectness	No serious imprecision	Undetected	High risk of bias study not used in evidence quality assessment. One retrospective observational study with a moderate risk of bias shows that the mean time to CKD is shorter (3.55 years) among donors with pre-donation MDRD eGFR <90 compared to donors with pre-donation MDRD eGFR ≥90 (>7 years).	Very Low
Proteinuria (1 retrospective observational study)	High-Moderate	Unknown	Serious indirectness	Unclear	Undetected	Lower measured GFR at donation was not correlated to urine albumin creatinine ratio at follow-up. Relationship of pre-donation renal function to post-donation proteinuria unclear.	Very low
Hypertension (1 retrospective observational study)	High-Moderate	Unknown	Serious indirectness	Unclear	Undetected	Lower measured GFR at donation was correlated to Mean Arterial Pressure at follow-up. Relationship of pre-donation renal function to hypertension unclear.	Very Low

Table 17. Evidence Profile: Long Term Living Kidney Donation Outcomes – Donors with impaired glucose tolerance versus donors with normal glucose tolerance

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of effect**	**Quality of Evidence**
Mortality (1 retrospective observational study)	Moderate-high	Unknown	No serious indirectness	No serious imprecision	Undetected	One retrospective observational study with a high risk of bias shows similar rates of mortality in glucose intolerant donors and donors with normal glucose tolerance over a mean follow-up of 7.3 years.	Very Low
ESRD (1 retrospective observational study)	Moderate-high	Unknown	No serious indirectness	Serious Imprecision	Undetected	One retrospective observational study with a high risk of bias shows similar rates of ESRD in glucose intolerant donors and donors with normal glucose tolerance over a mean follow-up of 7.3 years.	Very Low
Renal function (2 observational studies)	High	Unknown	Serious indirectness	Serious Imprecision	Undetected	Two studies reported similar kidney function at follow-up by glucose tolerance or fasting glucose impairment at baseline	Very Low
Proteinuria (1 retrosepctive observational study)	High	Unknown	Serious indirectness	Serious Imprecision	Undetected	One study reported similar albumin/creatinine ratios in donors with and without impaired fasting glucose.	Very Low
Hypertension (1 retrospective observational study)	Moderate-high	Unknown	Serious indirectness	Serious Imprecision	Undetected	Two studies found similar frequencies. One retrospective observational study with a high risk of bias shows that the percent of donors with hypertension on medication was 13.8% in glucose intolerant donors and was 11.2% donors with normal glucose tolerance (mean follow-up of 7.3 years)	Very Low
Diabetes	High	Unknown	Serious indirectness	Serious Imprecision	Undetected	Two studies reported greater frequency of diabetes at follow-up between donors with impaired fasting glucose or glucose intolerance and donors with normal glucose metabolism at baseline	Very Low

Table 18. Evidence Profile: Long Term Living Kidney Donation Outcomes – Donors with metabolic syndrome versus donors without metabolic syndrome

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Renal Function (1 retrospective observational study)	Moderate-high		Very serious indirectness	Serious Imprecision	Undetected	One retrospective observational study shows similar mean MDRD eGFR in donors with metabolic syndrome and those without metabolic syndrome over a mean follow-up time of 5 years.	Very Low
Proteinuria (1 retrospective observational study)	Moderate-high	Unknown	Serious indirectness	Serious Imprecision	Undetected	One retrospective observational study shows similar mean albuminuria in donors with metabolic syndrome and those without metabolic syndrome over a mean follow-up time of 5 years.	Very Low

Table 19. Evidence Profile: Long Term Living Kidney Donation Outcomes – Hypertensive donors versus normotensive donors

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Mortality (1 retrospective observational study)	Moderate-high	Unknown	No serious indirectness	No serious imprecision	Undetected	In one study, a 1 mmHg increase in SBP was not associated with a significant increase in risk of death in a mixed cohort of donors and matched non-donors without hypertension.	Very Low
CV Outcomes (1 retrospective observational study)	Moderate-high	Unknown	No serious indirectness	Serious imprecision	Undetected	In one study, a 1 mmHg increase in SBP was associated with an increase in the risk of cardiovascular death in a mixed cohort of donors and matched non-donors without hypertension.	Very Low
ESRD (1 retrospective observational study)	Moderate-high	Unknown	No serious indirectness	Serious Imprecision	Undetected	In one study, a 1 mmHg increase in SBP was associated with an increase in the risk of ESRD in a mixed cohort of donors and matched non-donors without hypertension.	Very Low
Renal Function (1 retrospective observational study)	Moderate-high	Unknown	Serious indirectness	Serious Imprecision	Undetected	One retrospective observational study with a moderate-high risk of bias shows that CKD was more prevalent among donors with hypertension than donors without hypertension (OR=7.88, 95% CI: 1.14 to 54.45) after median follow-up of 5.4 years.	Very Low

Table 20. Evidence Profile: Long Term Living Kidney Donation Outcomes – Donor relationship to recipient

Quality Assessment						Summary of Findings	
Outcome (Number of Studies and Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of effect**	**Quality of Evidence**
Mortality (2 retrospective observational studies; same population)	Low - moderate	Unknown	No serious indirectness	Serious imprecision	Undetected	Similar rates of mortality in living kidney donors with biological relationship to recipient and living kidney donors with no biological relationship to the recipient over a median of 6 years..	Very Low
ESRD (1 retrospective observational study)	Low - moderate	Unknown	No serious indirectness	No serious imprecision	Undetected	Donors with a biological relationship to the recipient had a much higher rate of ESRD (34 per 10,000 (95% CI: 26.9 to 43.3) when compared to living kidney donors that were not 1st degree relatives (15 per 10,000 (95% CI: 8.7 to 26.3) over a median of 7.6 years. Evidence quality rated up for effect size.	Moderate
Renal Function (1 retrospective observational study)	Moderate	Unknown	Serious indirectness	Unclear	Undetected	Donors that were 1st degree relatives of the recipient had similar rate of CKD when compared to living kidney donors that were not 1st degree relatives over a median of 7.4 years.	Very Low
Hypertension (1 retrospective observational study)	Low - moderate	Unknown	Serious indirectness	No serious imprecision	Undetected	Similar rates of hypertension among living kidney donors with biological relationship to recipient and living kidney donors with no biological relationship to the recipient over a median of 6 years.	Very Low
Psychosocial: doubts about donation (1 retrospective observational studies)	Moderate	Unknown	No serious Indirectness	No serious imprecision	Undetected	Donors without a biological relationship to the recipient were more likely to have doubts about donation when compared to living kidney donors with a biological relationship to the donor (OR=2.2 (95% CI: 1.2 to 3.9) over a median of 12.6 years.	Low
Psychosocial: physical Health-related Quality of Life (1 retrospective observational studies)	Moderate-high	Unknown	No serious Indirectness	No serious imprecision	Undetected	Donors that were 1st degree relatives of the recipient were less likely to have a physical HRQoL impairment on the SF-36 when compared to living kidney donors that were not 1st degree relatives (OR=0.54 (95% CI: 0.36 to 0.80) over a median of 17 years.	Very Low

Key Question 7: Female Donors of Child-bearing Age (Table D18)

We identified two studies addressing pregnancy outcomes by pre-donation or post-donation timings.(Ibrahim, Akkina, et al.; Reisaeter, Roislien, Henriksen, Irgens, & Hartmann) Both studies compared post-donation pregnancy (n=596) outcomes to pre-donation pregnancy (n=3343) outcomes in 1428 living kidney donors. Outcomes in the Ibrahim et al. study were ascertained by questionnaires using historical recall of events during pregnancy.(Ibrahim, Akkina, et al.) Outcomes in the Reisaeter study were ascertained from a database. They reported the following outcomes: fetal loss, prematurity, gestational hypertension, gestational diabetes, preeclampsia, proteinuria and low fetal birth weight. Quality of evidence was very low for all of the outcomes.

Preeclampsia

Preeclampsia was reported in both studies.(Ibrahim, Akkina, et al.; Reisaeter et al.) Ibrahim et al. reported greater risk of preeclampsia with post-donation pregnancies (6.6%) compared to pre-donation pregnancies (0.9%), the difference was significant in the analysis that included post- and pre-donation pregnancies of donors with history of either pregnancy, but not significant in the analysis limited to donors with both pre- and post-donation pregnancies.(Ibrahim, Akkina, et al., 2009) Reisaeter et al. also reported greater frequency of preeclampsia in post-donation pregnancies (5.7%) compared to pre-donation (2.6%) pregnancies.(Reisaeter et al.) The quality of evidence was very low.

Fetal Loss

Fetal loss defined as stillbirth or fetal death was reported in both studies. Both studies compared frequency of stillbirths or fetal deaths between post-donation pregnancies and pre-donation pregnancies and found they were similar.(Ibrahim, Akkina, et al.; Reisaeter et al.) The quality of evidence was very low.

Miscarriage

Miscarriages were reported in one study.(Ibrahim, Akkina, et al.) In analysis that included donors with either pre or post-donation pregnancies, frequency of miscarriages was higher in post-donation pregnancies (13.2%) compared to pre-donation pregnancies (8.2%). The difference was not significant in analysis limited to women with both pre-and post-donation pregnancies.(Ibrahim, Akkina, et al.) The quality of evidence was very low.

Prematurity

Prematurity was reported in both studies.(Ibrahim, Akkina, et al.; Reisaeter et al.) Ibrahim et al. reported greater risk of prematurity with post-donation pregnancies compared to pre-donation pregnancies, the difference was significant in the analysis that included post- and pre-donation pregnancies of donors with history of either pregnancy (6% vs 3.7%, RR(95% CI):1.67(1.05-2.67)), but not significant in the analysis limited to donors with both pre- and post-donation pregnancies (8.7% vs 7.4%, RR(95% CI:1.18(0.59-2.34)).(Ibrahim, Akkina, et al.) Reisaeter et al. did not find a significant difference in prematurity defined as either < 22 weeks (1% vs0.3%) or < 37 weeks (9.8% vs 7.5%) between post and pre-donation pregnancies.(Reisaeter et al.) The quality of evidence was very low.

Gestational Hypertension

Gestational hypertension was reported in both studies.(Ibrahim, Akkina, et al.; Reisaeter et al.) Ibrahim et al. reported greater risk of gestational hypertension with post-donation pregnancies compared to pre-donation pregnancies, the difference was significant in the analysis that included post- and pre-donation pregnancies of donors with history of either pregnancy (6.9% vs 0.6% (RR(95% CI): 10.9(5.8-20.6))), but not significant in the analysis limited to donors with both pre- and post-donation pregnancies (3.5% vs 0.5%, RR (95% CI):

7.1(0.9-58.2)) .(Ibrahim, Akkina, et al.) Reisaeter et al. found a similar frequency of gestational hypertension in post and pre-donation pregnancies (2.8% vs 1.8%, RR (95% CI):1.59(0.45-5.62)).(Reisaeter et al.) The quality of evidence was very low.

Gestational Diabetes

Ibrahim et al. reported greater risk of gestational diabetes with post-donation pregnancies compared to pre-donation pregnancies, the difference was significant in the analysis that included post- and pre-donation pregnancies of donors with history of either pregnancy (93.8% vs 0.8%, RR (95% CI): 5.0(2.5-10.2)), but not significant in the analysis limited to donors with both pre- and post-donation pregnancies (0.6% vs 0.5%, RR (95% CI): 1.38(0.65-2.89)).(Ibrahim, Akkina, et al.) The quality of evidence was very low.

Proteinuria

Ibrahim et al. reported greater risk of proteinuria with post-donation pregnancies compared to pre-donation pregnancies, the difference was significant in the analysis that included post- and pre-donation pregnancies of donors with history of either pregnancy (4.1% vs 1.0%, RR (95% CI): 4.1(2.13-7.99)), but not significant in the analysis limited to donors with both pre- and post-donation pregnancies (4.6% vs 1.5%, RR (95% CI): 2.36(0.72-7.7)).(Ibrahim, Akkina, et al.) The quality of evidence was very low.

Low Fetal Birth Weight

One study found similar frequency of extremely low birth weight (< 500 gm) (0.9% vs 0.5%) and low birth weight (500-2500gm) (7.5% vs 5.5%, RR (95% CI): 1.38(0.65-2.89)) in post and pre-donation pregnancies.(Reisaeter et al.) The quality of evidence was very low.

Table 21. Key Question 7 Evidence Profile: Long Term Living Kidney Donation Outcomes – Post Donation Pregnancy-related Outcomes

Quality Assessment						Summary of Findings	
Outcome (Number of Studiesand Design)	**Study Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Description of Effect**	**Quality of Evidence**
Fetal Loss of Life (2 retrospective observational studies)	High	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Two high risk of bias retrospective observational studies found similar rates of fetal death in pre- and post-donation pregnancies.	Very Low
Prematurity (2 retrospective observational studies)	High	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Two high risk of bias retrospective observational studies found inconsistent results in terms of prematurity in pre- and post-donation pregnancies.	Very Low
	High	Unknown	No serious indirectness	Serious imprecision	Undetected	Donors with both a pre- and a post-donation pregnancy were more likely to deliver prematurely in the post-donation pregnancy (RR=14.1, 95% CI: 7.01 to 28.36).	Very Low
Gestational Hypertension (2 retrospective observational studies)	High	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Two high risk of bias retrospective observational studies found that the rate of gestational hypertension is higher in women during a post-donation pregnancy as compared to a pre-donation pregnancy.	Very Low
	High	Unknown	No serious indirectness	No serious imprecision	Undetected	Donors with both a pre- and a post-donation pregnancy were more likely to develop gestational hypertension in the post-donation pregnancy (RR=20.74, 95% CI: 10.97 to 39.20).	Very Low
Gestational Diabetes (1 retrospective observational study)	High	Unknown	No serious indirectness	Serious imprecision	Undetected	Donors with both a pre- and a post-donation pregnancy were more likely to develop gestational diabetes in the post-donation pregnancy (RR=5.02, 95% CI: 2.46 to 10.24). Donors with both a pre- and a post-donation pregnancy were more likely to develop gestational hypertension in the post-donation pregnancy (RR=20.74, 95% CI: 10.97 to 39.20).	Very Low
Preeclampsia (2 retrospective observational	High	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Two high risk of bias retrospective observational studies show inconsistent results regarding the rate of preeclampsia	Very Low

studies)						during post-donation pregnancy as compared to a pre-donation pregnancy.	
						Donors with both a pre- and a post-donation pregnancy were not more likely to develop preeclampsia during post-donation pregnancy as compared to a pre-donation pregnancy.	Very Low
Composite Outcome of Gestational Hypertension, Diabetes, or Preeclampsia (1 retrospective observational studies)	Moderate-High	Unknown	No serious indirectness	No serious imprecision	Undetected	Adjusted analysis shows significantly greater odds of composite outcome (hypertension, diabetes, and preeclampsia) in post-donation pregnancies compared to pre-donation pregnancies.	Very Low
Proteinuria (1 retrospective observational study)	High	Unknown	Serious indirectness	No serious imprecision	Undetected	Donors with both a pre- and a post-donation pregnancy had similar development of develop proteinuria similarly during post-donation pregnancy as compared to a pre-donation pregnancy.	Very Low
	High	Unknown	Serious indirectness	Serious imprecision	Undetected	Donors with both a pre- and a post-donation pregnancy had similar development of proteinuria during post-donation pregnancy as compared to a pre-donation pregnancy.	Very Low
Low Birth Weight (1 retrospective observational study)	High	Unknown	No serious indirectness	Serious imprecision	Undetected	Donors with both a pre- and a post-donation pregnancy had similar development of low birth-weight babies after post-donation pregnancy as compared to pre-donation pregnancy.	Very Low
	High	Unknown	No serious indirectness	Serious imprecision	Undetected	Donors with both a pre- and a post-donation pregnancy had similar development of low birth-weight babies after post-donation pregnancy as compared to pre-donation pregnancy.	Very low

Discussion

We conducted a systematic review of evidence related to peri-/post-operative and long term outcomes of living kidney donation and how donor characteristics modify these outcomes. Except for the association of donation with increased risk of ESRD (moderate grade), evidence quality for all other comparisons was low or very low due to limitations with the evidence base. Evidence quality was primarily low or very low when the studies in the evidence base were observational. Limitations such as retrospective designs, selection bias, and confounding were common among observational studies. Confounding or inadequate control of prognostic variables are likely to be the most serious flaws in observational studies. The screening that potential living kidney donors experience is much more comprehensive than the screening of records about individuals' health status collected for other purposes. Matching living kidney donors to records of individuals in these secondary databases on a few variables such as age, sex, race, and BMI status is likely insufficient. An appropriate comparison would involve matching based upon results of health screenings similar to what potential donors experience. However, this represents a less feasible and more expensive study.

Peri- and Post-Operative Outcomes of Living Kidney Donation

Results from previous systematic reviews assessing living kidney donors peri/post-operative outcomes by surgical approach provide evidence about three different comparisons: open versus laparoscopic nephrectomy, standard laparoscopic versus hand-assisted laparoscopic nephrectomy, and left versus right nephrectomy. We identified two systematic reviews that examined peri/post nephrectomy outcomes in donors with isolated medical abnormalities, namely older age and obesity.(Lafranca et al., 2013; Young, Storsley, et al., 2008)

Mixed quality evidence shows laparoscopic living donor nephrectomy results in longer operative times, more reoperations, shorter hospital stays and fewer days to return to work than open donor nephrectomy. Standard laparoscopic nephrectomy had shorter hospital stays than hand-assisted laparoscopic nephrectomy. Very low quality evidence shows similar results with left and right living donor nephrectomy on all outcomes. Apart from operative time, there appears to be no differences in peri and post-operative outcomes for older versus younger donors and donors with higher versus lower BMI.

Long Term Outcomes of Living Kidney Donation

Moderate quality evidence shows a correlation between living kidney donation and ESRD. Very low quality evidence shows a correlation between kidney donation and mortality, cardiovascular events, low kidney function, proteinuria, hypertension, and psychosocial outcomes. Very low quality evidence shows that age does not modify the associations. In living kidney donors, older age is a risk factor for all cause and CV mortality, ESRD, CKD, HTN, fractures. There is very low grade evidence that female donors have lower reported death rates, CV events, and ESRD events but higher prevalence of lower eGFR compared to male donors. It is unknown whether gender modifies outcomes of living kidney donation. African American race appears to be a risk factor for ESRD, hypertension, CKD, proteinuria, and diabetes. Aboriginal ethnicity appears to be a risk factor for diabetes, HTN, and proteinuria. Association of Hispanic ethnicity with poor outcomes is inconsistent. We found moderate grade evidence that African American, Hispanic and White donors appear to have greater absolute risk of ESRD compared to non-donors, with African American donors sustaining the greatest increase in absolute risk. We found very low grade evidence from small retrospective observational studies with non-uniform exposure, outcome definitions and ascertainment and high attrition rate that some

isolated medical abnormalities are associated with risk of worse kidney function, proteinuria, hypertension or diabetes but it remains unclear whether donation modifies association between isolated medical abnormalities and clinical outcomes. From evidence of very low grade from two studies with serious design limitations preeclampsia, gestational hypertension, and preterm delivery complicated post-donation pregnancies more frequently than pre-donation pregnancies. Interpretation of the evidence is limited by the retrospective observational nature of the studies, risk of bias introduced by unobserved differences between donors and controls, high attrition in some studies, small sample sizes to ascertain clinical outcomes, short duration follow-up to see rare events such as ESRD and non-uniform outcome definitions and ascertainment. As all evidence in the field is of an observational nature, no causality can be inferred. In addition, our report does not address the impact of these donor characteristics on recipient outcomes which are also an important component in donation decision making.

Outcomes of Living Kidney Donors Compared to Healthy Non-Donors

Living kidney donation is an intervention for which it may not be possible to conduct a randomized controlled trial to evaluate the short-term and long-term outcomes compared to not donating a kidney. Kidney donors are carefully selected for donation and are healthier than general population. In order to minimize bias, our review included only studies that compared long term outcomes in living kidney donors to outcomes of matched healthy controls. However, there is strong potential for findings to be biased by selection and/or residual confounding between donors and controls. Furthermore, some findings (such as increased mortality in older vs. younger donors or those with comorbidities) may be due to underlying demographics or comorbidities rather than kidney donation itself.

We included four studies that compared clinical outcomes such as mortality, cardiovascular events, and ESRD during long-term follow-up of on average 5 years to 15 years.(A. X. Garg, Meirambayeva, et al., 2012; Mjoen et al., 2014; Muzaale et al., 2014; Segev et al., 2010) The data were obtained from administrative donor registries of three countries: the United States, the Canadian province of Ontario, and Norway. Non-donor comparisons were obtained from an administrative database in one study(A. X. Garg, Meirambayeva, et al., 2012) and from population based cohorts in the other studies.(Mjoen et al., 2014; Muzaale et al., 2014; Segev et al., 2010) Two studies showed lower mortality in living kidney donors(A. X. Garg, Meirambayeva, et al., 2012; Segev et al., 2010) while another study(Mjoen et al., 2014) found higher all-cause mortality and cardiovascular mortality in kidney donors compared to controls. The discrepancy in the findings is puzzling. It is difficult to find biological plausibility of nephrectomy extending life span. It is likely that the lower mortality in donors can be explained by residual confounding. Mjoen et al. demonstrated greater mortality in living kidney donors compared with matched non-donor controls.(Mjoen et al., 2014) However, these results might have been confounded by several issues – donors were almost 10 years older than non-donors (mean age of 46.0 versus 37.6), time of cohort entry differed between donors and non-donors, and donors were followed for up to 43.9 years compared to non-donors who were followed for a maximum of 24.9 years allowing for more events to occur. These differences could have biased the study towards finding greater mortality among donors compared to non-donors. Alternatively, it is possible that mortality differences were due to lower kidney function and greater incidence of ESRD in donors compared to non-donors. Therefore, it is difficult to draw conclusions on long-term mortality due to living kidney donation.

Two studies compared ESRD in living kidney donors compared with healthy non-donor controls.(Mjøen et al., 2013; Muzaale et al., 2014) Both showed rates of ESRD almost 10 times higher among donors compared to non-donors, though absolute risk increases were small. For example, in Norway, incidence of ESRD in donors was 302 per million person years compared to the overall incidence of ESRD of 100 per million person-years.(Mjoen et al.) In the US study,

estimated lifetime risk of ESRD was 90 per 10,000 donors. Although higher than the rate of 14 per 10,000 in healthy non-donors it was still lower than the rate of 326 per 10,000 representatives of the general population(Muzaale et al., 2014) These estimates are limited by the relatively short follow-up duration making lifetime ESRD risk estimates imprecise. Additionally, neither data source had longitudinal measurements of kidney function among kidney donors and comparator population. Despite these limitations, the evidence raises concern about of the effect of kidney donation on ESRD risk, especially in those with very long life expectancy.

Two systematic reviews reported lower eGFR, slightly higher proteinuria, and greater incidence of hypertension among kidney donors compared with healthy non-donors(Boudville, Prasad, et al., 2006; A. X. Garg et al., 2006; A. X. Garg et al., 2008) Although quality of evidence for these outcomes is very low, it is possible that these early changes mediate the association between kidney donation and greater rate of ESRD in kidney donors. In addition, related donors have a family history of ESRD and therefore are inherently at increased risk. For example, in the Mjoen study all nine donors who developed ESRD were related to graft recipients and had immunologic causes of ESRD(Mjoen et al., 2014) However, family history of ESRD does not fully explain the increase in ESRD rates among kidney donors: in the Muzaale et al. study, donors with biological relationship to the recipient had only about twice the 15 year cumulative incidence of ESRD (34.1) compared to non-related donors (15.1 per 10,000).(Muzaale et al., 2014) As 15 year incidence of ESRD is 8 times higher in donors compared to healthy non-donors, some of the increased risk is likely attributable to donation itself rather than donor characteristics. However, because of study design limitations, we graded the evidence as moderate. Life time risk of ESRD associated with donation, especially for young donors remains unclear. Prospective cohort studies with contemporaneous recruitment of kidney donors and matched healthy non-donors with long term follow-up and longitudinal measurements of kidney function, urinary protein and blood pressure as well as ascertainment of clinical outcomes such as cardiovascular events, ESRD and death are needed to fill in the information gap. Meanwhile, current evidence provides important information for informed consent of potential donors. Evidence of greater risk of ESRD among kidney donors might impact criteria for donor selection, especially among young donors who have long projected life spans and are at risk for health event outcomes. Evidence of risk associated with kidney donation should also promote careful follow-up among kidney donors and promotion of good access to care for donors as well as healthy lifestyle choices in order to mitigate the risks associated with kidney donation.

Long Term Outcomes in Living Kidney Donors Within Demographic Subgroups (age, sex, race)

Age

Eight studies compared long-term outcomes in older donors and older healthy non-donors. In all three studies that compared mortality in older donors to older healthy non-donors,(Berger et al., 2011; Reese et al.; Segev et al., 2010) mortality was higher among older healthy non-donors than in older donors. This finding likely reflects residual selection bias, as older individuals who are approved for donation are likely healthier than their older non-donor counterparts selected from population cohort studies based on available data. Older age did not modify the association between donation and CV events,(A. X. Garg, Meirambayeva, et al., 2012) clinically significant nephrolithiasis,(Thomas et al., 2013) gastrointestinal bleeding,(Thomas et al., 2014) or fractures.(A. X. Garg, Meirambayeva, et al., 2012) Over a limited follow-up duration, greater donor age increased risk for death,(Dols et al., 2011; A. X. Garg, Meirambayeva, et al., 2012; Segev et al., 2010) cardiovascular events,(A. X. Garg, Meirambayeva, et al., 2012; K. L. Lentine et al., 2010) ESRD,(Mjoen et al., 2014; Muzaale et al.,

2014) lower kidney function(Dols et al., 2011; Ibrahim, Foley, et al., 2009; J. H. Lee et al., 2007) hypertension(Dols et al., 2011; Ibrahim, Foley, et al., 2009; K. L. Lentine et al., 2010) and diabetes.(K. L. Lentine et al., 2010) However, this is not surprising as age is significant risk factor for all these outcomes regardless of kidney donation status. Thus the greater outcomes noted in older versus younger donors may not be due to kidney donation per se. Psychosocial outcomes were similar to younger donors. Older donors were less likely to regret donating.(Mjoen et al., 2011) As few studies checked for interaction between age and donation for outcomes of interest, it remains unknown whether age modifies long term risks inherent in donation. Muzaale et al. reported greater 15 year cumulative incidence of ESRD in donors 60 years or older, 50-59 years and 18-39 years with the lowest cumulative incidence among donors who were 40 to 49 years of age at donation.(Muzaale et al., 2014) Greater cumulative incidence in very young donors is concerning. Life time risk of ESRD is higher for young donors compared to older donors.

A single center study evaluated long term outcomes among donors who donated their kidney before 18 years of age.(MacDonald et al., 2014) The study found that donating a kidney prior to the age of 18 did not increase the risk of hypertension, proteinuria, eGFR<60 ml/min/1.73m2 and diabetes over an average of 31 years of follow-up compared to donating between 18 and 30, though for those who developed these conditions time to diagnosis was similar between the age groups.(MacDonald et al., 2014)

In conclusion, older donors had similar to better outcomes compared to older healthy non-donors though these findings are likely due, at least in part, to selection biases between groups. Age is a risk factor for poor outcomes after donation, though it is unknown whether donation modifies the risk associated with age. Most available studies have limited follow-up making estimation of life time risk of uncommon events difficult. Life-time risk of long term harms associated with donation (e.g. ESRD) is greater in young donors with long life expectancy. However, because the life-time risk of ESRD is greater in those with long-life expectancy regardless of kidney donation status it is not clear whether donation alters that risk. Long cohort studies that include donors and matched non-donors of all age groups are needed to better delineate the risks.

Sex

Mortality of healthy non-donors was higher than that of donors in both sex strata.(Segev et al., 2010) Male sex was a risk factor for death(Mjoen et al., 2014; Segev et al., 2010) and cardiovascular events.(K. L. Lentine et al., 2010) Male donors had greater risk of ESRD compared to female donors in one study and a greater risk of being placed on a kidney transplant waiting list,(Gibney et al., 2008) but male sex was not a risk factor for ESRD in a mixed cohort of donors and healthy non-donors.(Mjoen et al., 2014) Association between sex and lower GFR and hypertension in kidney donors was inconsistent.(Ibrahim, Foley, et al., 2009; K. L. Lentine et al., 2010) Psychosocial outcomes were largely similar between genders (Johnson et al., 1999; Mjoen et al., 2011), though one study found that, among privately insured U.S. donors, women had twice the rate of post-donation depression diagnoses compared to men.(K. L. Lentine et al., 2012) For all of these outcomes it is not clear if kidney donation alters the risk association with an individual's sex.

Race

When compared with healthy African American non-donors, African American donors have slightly lower mortality(Segev et al., 2010) but greater rate of ESRD.(Muzaale et al., 2014) While the evidence for mortality is likely explained by residual confounding, evidence for ESRD is concerning. Although overall rate of ESRD is low, there is a significant increase in the rate of

ESRD in donors compared with healthy non-donors across all races, with African American donors acquiring the greatest risk (absolute risk increase 50.8 / 10,000 person years for African American donors, 29.5 for Hispanic donors, and 22 for White donors, compared to non-donors).(Muzaale et al., 2014) In addition, African American donors have higher risk of hypertension but not of albuminuria or diabetes compared with African American non-donors.(Doshi et al., 2013)

When compared to White donors, African American donors had a greater risk of death, hypertension, diabetes mellitus, chronic kidney disease, proteinuria..(Gibney et al., 2007; K. L. Lentine et al.; K. L. Lentine et al., 2010; Muzaale et al., 2014; Segev et al., 2010) However, White donors more commonly developed depression diagnoses compared with non-White donors.(K. L. Lentine et al., 2012) While African American donors incur the highest ESRD risk attributable to donation on top of already higher risk of ESRD associated with African American race, there is greater organ shortage in African American population with ESRD. Incident rate of ESRD in African Americans is more than 3 times that of Caucasians and African American patients have decreased access to transplantation, that manifests in lower rates of placement on the waiting list and longer waiting times while waitlisted.(K. L. Lentine & Segev, 2013) Despite the need for African American living kidney donors it is essential to select donor candidates who are less likely to incur harms of donation and to develop ESRD. Further research is needed to establish risks attributable to donation in African American donors compared to healthy African American non-donors and to determine how isolated medical abnormalities such as obesity, metabolic syndrome, glucose intolerance and mild hypertension modify the risk. Testing for apolipoprotein L1 (APOL1) alleles associated with poor renal prognosis might help risk stratification of African American living donors.

Aboriginal donors had higher eGFR, but had greater frequency of hypertension, diabetes, and proteinuria compared to White donors.(Storsley et al., 2010) Aboriginal peoples living in Canada are among the highest risk populations for diabetes and related complications.(Canadian Diabetes Association Clinical Practice Guidelines Expert, Booth, & Cheng, 2013) Whether donation modifies this risk is unclear.

Long Term Outcomes in Living Kidney Donors with Isolated Medical Abnormalities

We identified studies that provided long term follow-up of living kidney donors by kidney function at donation, presence of proteinuria, hematuria, history of nephrolithiasis, obesity, impaired glucose tolerance or fasting glucose, and presence of metabolic syndrome.

Body Mass Index

Our systematic review includes five studies that compared long-term outcomes of kidney donors by pre-donation BMI,(Gracida et al., 2003; Gross et al., 2013; Ibrahim, Foley, et al., 2009; Mjoen et al., 2014; von Zur-Muhlen et al., 2014) BMI was not associated with all-cause mortality or ESRD in a cohort of donors and matched healthy non-donors.(Mjoen et al., 2014) Higher BMI was associated with lower GFR at follow-up, greater risk of hypertension(Ibrahim, Foley, et al., 2009; von Zur-Muhlen et al., 2014) and greater odds of physical component of health related quality of life impairment.(Gross et al., 2013) The quality of evidence was very low for all outcomes. High BMI is generally considered a contraindication for donation: four existing guidelines considered BMI $\geq$ 35 a contraindication (ERBP, BTS, SEN ONT, AF). A study by Segev et al. revealed no difference in short term (3 months and 12 months) mortality after kidney transplantation by donors' BMI.(Segev et al., 2010) A systematic review that addressed a question of the relation between BMI and short-term outcomes of laparoscopic donor nephrectomy did not find any difference between high and low BMI for short term outcomes such as warm ischemia time, estimated blood loss, length of stay, perioperative complications,

or decrease in GFR, but did find longer operation duration, greater risk for conversion to open nephrectomy, and greater rise in serum creatinine in donors with higher BMI.(Lafranca et al., 2013) Only one study had follow-up that exceeded one year; this did not find any difference in serum creatinine between donors with BMI >30 compared to donors with lower BMI, but found greater risk of developing hypertension in obese donors over 11 years of follow-up.(Tavakol et al., 2009) Two other systematic reviews found greater incidence of hypertension among overweight and obese donors compared to non-obese donors.(Ahmadi et al., 2014; Young, Storsley, et al., 2008) Our systematic review confirms their finding that obesity is a risk factor for hypertension and cardiovascular disease in kidney donors. These findings are consistent with obesity as a risk factor in a non-donor population.(P. Wilson, D'Agostino, Sullivan, Parise, & Kannel, 2002) It remains unknown if donation modifies long term risk of obesity and how obesity interacts with other donor characteristics. From the current literature it is unclear if there is a threshold BMI above which donor prognosis worsens. Future large prospective cohort studies that compare donors from various BMI categories to healthy non-donors from the same BMI category are needed to determine whether overweight and obese donors can be safely accepted for live kidney donation.

Impaired glucose metabolism, diabetes or metabolic syndrome

We identified two studies that reported long term outcomes of donors with impaired glucose metabolism and one study that reported long term outcomes of donors with metabolic syndrome compared to donors without these abnormalities. Non-surprisingly, donors with impaired glucose metabolism were more likely to be diagnosed with diabetes during the follow-up compared with donors with normal glucose metabolism. Other outcomes did not differ between the groups. Donors with metabolic syndrome had lower eGFR and higher proteinuria that was small in magnitude and of uncertain clinical significance, compared to donors without metabolic syndrome. This evidence is of very low quality.

Baseline renal function

Three studies reported long term outcomes by baseline renal function with very low grade of evidence for all outcomes. These data are limited by variable definition of kidney function at baseline and follow-up, retrospective nature and high attrition. None reported clinical outcomes. Although, in one study donors with baseline eGFR > 90 ml/min took a longer time to develop CKD compared to donors with baseline eGFR< 90 ml/min (median time to CKD > 7 years compared to 3.55 years respectively),(Tsai et al., 2013) evidence was insufficient to recommend a kidney function threshold for kidney donation. In addition, it is unknown whether other donor characteristics such as age, race, or presence of other medical abnormalities should modify the threshold GFR. Further studies are needed to inform clinical practice.

Blood pressure

Only three studies reported long-term donor outcomes by baseline blood pressure. Quality of evidence was low to very low for all outcomes. Higher baseline blood pressure in a mixed cohort of donors and healthy non-donors was associated with cardiovascular mortality and ESRD(Mjoen et al., 2014) mirroring findings in the general population. Donors with baseline hypertension were more likely to develop CKD at follow-up.(J. H. Lee et al., 2007) Again, it is unknown whether donation modifies the risk associated with hypertension or how other donor characteristics interact with hypertension influencing the risk of donation.

Proteinuria, hematuria, nephrolithiasis

We found no studies with ≥100 participants with ≥ 5 years of follow-up that reported outcomes of living kidney donors by proteinuria, hematuria, or history of nephrolithiasis. Donors without a history of nephrolithiasis have a risk of nephrolithiasis comparable to that of matched non-donors.(Thomas et al., 2013) Male donors had lower rate of surgical procedures for nephrolithiasis compared to male non-donors over 8.4 years of follow-up.(Thomas et al., 2013)

Few studies of long term outcomes for donors with isolated medical abnormalities were available. Most were retrospective with incomplete follow-up and outcome ascertainment. Studies were too small to document clinical and patient centered health outcomes. Definitions of isolated medical abnormalities and outcomes differed between the studies.
Further research should determine life-time risk of ESRD and cardiovascular events associated with the isolated medical abnormalities of interest in the general population and how kidney donation alters the risk associated with medical abnormalities. Pooled data from the currently available well characterized population based cohorts with measurement of proteinuria, kidney function, blood pressure, lipid and glucose metabolism, etc. as well as careful ascertainment of renal and cardiovascular outcomes can be used to define life time risk in the general population. Well-designed prospective cohort studies that include both kidney donors and matched healthy non-donors with standardized definitions and measures of participant characteristics and outcomes are needed to establish risks attributable to kidney donation. Knowledge of these baseline risks and more importantly the risks attributable to kidney donation would greatly facilitate the donor selection process and informed consent.

Female Donors of Child-bearing Age – Pregnancy Outcomes

Our report includes two studies of pregnancy outcomes in kidney donors.(Ibrahim, Akkina, et al., 2009; Reisaeter et al., 2009) Both studies compared outcomes of post-donation pregnancies to outcomes of pre-donation pregnancies and found a greater rate of pre-eclampsia in post-donation pregnancies (6.6% in post- and 0.9% in pre-donation pregnancies in the Ibrahim et al study and 5.7% in post- compared to 2.6% in pre-donation pregnancies in the Reisaeter study).(Ibrahim, Akkina, et al., 2009; Reisaeter et al., 2009) In addition, Ibrahim but not Reisaeter reported greater rates of prematurity and gestational hypertension in post-donation pregnancies.(Ibrahim, Akkina, et al., 2009; Reisaeter et al., 2009) Both studies had design features limiting validity and generalizability. One was done in a single center in Norway and pregnancy outcomes were obtained from a centralized birth registry.(Reisaeter et al., 2009) Another study was done in Minnesota. Pregnancy outcomes were self-reported by women years after their pregnancies and had a substantial number of donors lost to follow-up.(Ibrahim, Akkina, et al., 2009) Neither study had matched healthy comparison groups. Neither study reported blood pressure values, kidney function or proteinuria during pregnancy. Bias due to recall in the Ibrahim study as well as bias due to ageing of women between pregnancies could have confounded the results.

After the conclusion of our literature search we became aware of an additional study that would have met eligibility criteria. Garg et al.(A. Garg et al., 2014) used an administrative provincial healthcare database from Ontario to match 85 kidney donors without prior history of pregnancy complications in 1:6 ratio with 510 healthy non-donors and followed them prospectively for a median of 10.9 years for the primary outcome of gestational hypertension or preeclampsia. Donors had 131 pregnancy and non-donors had 788 pregnancies during the follow-up. Overall donors and non-donors were matched well with respect to their known characteristics. Outcomes were obtained from diagnostic claims codes. Similarly to the above studies, they found that the combined outcome of gestational hypertension or preeclampsia was more common in donors compared to non-donors (11% vs 5%). There were no differences

between donor and non-donor pregnancies for outcomes of Cesarean section, preterm birth at < 37 weeks of gestation, or low birth weight.(A. Garg et al., 2014) Study limitations included that this was a retrospective cohort, used claims based outcome definitions, lacked biochemical parameter measures during pregnancy, controlled for a limited number of variables and thus had potential for unmeasured differences between donors and non-donors, was relatively small in sample size, was conducted in a predominately white population in a single province in Canada and may have had differential outcome ascertainment.(A. Garg et al., 2014) Despite these limitations, this study addressed some sources of bias that affected prior evidence. While supporting prior findings of greater rate of pre-eclampsia and gestational hypertension in kidney donors the overall grade of evidence for these outcomes would not change significantly with inclusion of this study to our report. Other maternal and fetal outcomes were similar in donors and matched non-donors, although the study was not powered to detect rare outcomes.

Limitations

We focused our inclusion criteria to studies with at least 100 participants, adequate controls, and follow-up of at least 5 years. In the absence of randomized controlled trials, the best available evidence comes from observational studies. Unfortunately, few prospective cohort studies have been conducted and the bulk of the evidence on this topic comes from retrospective studies. These studies rarely have sufficient data to adequately match donors to non-donor comparison groups or statistically control for all potential confounders. The risk that selection bias between donor and non-donors results in differences in outcomes observed is large. Thus the quality of evidence for each outcome was rated as low to very low. Outcomes are often varied in how they are reported and may not be validated, or do not allow pooling or have small absolute differences of unknown clinical importance. Psychosocial outcomes are defined by a variety of instruments, rarely validated and quite heterogeneous with few clinical differences. This significantly limits our confidence in study results. It is unclear whether the differences in long-term outcomes are due to donation or to inherent differences between the groups. Data for long term outcomes are particularly scarce for donors with isolated medical abnormalities. While clinicians, policy makers, patients and donors must act the strength and quality of data currently available limits accurate information. Further research in the area is needed to inform clinicians, policy makers, donors and recipients alike.

Future Research Needs

In theory, randomized trials could generate estimates of donor risk that are less prone to bias; however, randomized trials of donation are not ethically feasible. Large prospective cohort studies with contemporaneously identified kidney donors and matched healthy non-donors with careful cohort characterization, uniform variable definition and outcome ascertainment are needed. If included, donors with isolated medical abnormalities can be matched to non-donors with similar conditions and condition severity. In particular it would be helpful to know how healthy non-donors differ from healthy donors. Studies that conduct further “donor screening” of healthy non-donors may yield such information. Further research that determines lifetime risk associated with living kidney donation is necessary to fully understand the effect of living kidney donation on donors and their families. This is particularly important because much of the association of outcomes with demographics and comorbidities observed in donors is not unique and may not be due to donation (e.g. increase mortality, cardiovascular events etc. with age, hypertension, obesity etc.). In addition, the field would benefit from determining life-time risk of ESRD and cardiovascular events associated with the isolated medical abnormalities of interest in the general population and how this risk is modified by kidney donation. This information can be used to determine donor acceptance criteria, to provide informed consent of prospective living donors, and to structure long term donor follow-up and support programs.

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