Perspective on recent studies examining risk of ESRD and Death in Donors

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Conflict of Interest Disclosure

• I earn a living by doing kidney transplants
“Everything we see is a perspective, not the truth.”

- Marcus Aurelius
2 major challenges with determination of risks of living donation

- Rare Events
- Cannot determine causality from observational studies
Randomized Studies

- One of the key benefits of randomized experiments for estimating causal effects is that the treated and control groups are guaranteed to be only randomly different from one another on all background covariates, both observed and unobserved.
Observational Studies using Matching

- Rely on *ignorability*, which assumes that there are no unobserved differences between the treatment and control groups, conditional on the observed covariates.

- To satisfy the assumption of ignorable treatment assignment, it is important to include in the matching procedure all variables known to be related to both treatment assignment and the outcome.
Is the ignorability assumption violated when we compare living donors to controls from unrelated epidemiological studies?

Potentially........

Cannot match on relationship to recipient
Perioperative Mortality and Long-term Survival Following Live Kidney Donation

Dorry L. Segev, MD, PhD
Abimereki D. Muzaale, MD, MPH
Brian S. Caffo, PhD
Shruti H. Mehta, PhD
Andrew L. Singer, MD, PhD
Sarah E. Taranto
Maureen A. McBride, PhD
Robert A. Montgomery, MD, DPhil

Context: More than 6000 healthy US individuals every year undergo nephrectomy for the purposes of live donation; however, safety remains in question because longitudinal outcome studies have occurred at single centers with limited generalizability.

Objectives: To study national trends in live kidney donor selection and outcome, to estimate short-term operative risk in various strata of live donors, and to compare long-term death rates with a matched cohort of nondonors who are as similar to the donor cohort as possible and as free as possible from contraindications to live donation.

Design, Setting, and Participants: Live donors were drawn from a mandated national registry of 80,347 live kidney donors in the United States between April 1, 1994, and March 31, 2009. Median (interquartile range) follow-up was 6.3 (3.2-9.8) years. A matched cohort was drawn from 93,641 participants of the third National Health and (Reprinted) JAMA, March 10, 2010—Vol 303, No. 10
Risk of End-Stage Renal Disease Following Live Kidney Donation

Abimereki D. Muzaale, MD, MPH; Allan B. Massie, PhD; Mei-Cheng Wang, PhD; Robert A. Montgomery, MD, DPhil; Maureen A. McBride, PhD; Jennifer L. Wainright, PhD; Dorry L. Segev, MD, PhD

Strengths

• Captures every donor in U.S.

• Provide the best available information about the absolute risk of ESRD and Death in donors
Limitations
Relative Risk Estimates

• Donors were compared to a sub-set of participants in an unrelated epidemiology study (i.e. NHANES III n=9,364) without contraindications to donation
Perspectives Can Change Over Time
Same control group
Different Terminology

Segev 2010

Muzaale 2014
Original Investigation

Risk of End-Stage Renal Disease Following Live Kidney Donation

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<table>
<thead>
<tr>
<th>Number</th>
<th>Years</th>
<th>ESRD Outcome Source</th>
<th>Median Maximum Follow Up</th>
<th>Crude ESRD Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donors reported to OPTN</td>
<td>96,217</td>
<td>April 1, 1994 – Nov 30, 2011</td>
<td>CMS 2728 Activation to transplant Waiting List</td>
<td>7.6 years 15 years</td>
</tr>
<tr>
<td>Controls NHANES III Healthy sub-set</td>
<td>20,024, 9,364</td>
<td>1988 – 1994</td>
<td>CMS 2728</td>
<td>15 years</td>
</tr>
</tbody>
</table>
Incidence of ESRD in Donors Versus Controls

Cumulative incidence of end-stage renal disease

P<.001

30.8/10,000
Live donors

3.9/10,000
Nondonors

No. at risk
Live donors 96217 77587 58979 39231 21573 8781
Nondonors 96217 95930 95422 94734 94199 50124
<table>
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<td>99 cases</td>
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| **Controls NHANES III Healthy sub-set** | 20,024 | 1988 – 1994 |
| | CMS 2728 | 15 years |
| | 17 cases | 18.2 per 10,000 |

Different Outcome Assessment
Limitation

Differential ascertainment of ESRD in donors/non-donors

- CMS 2728 form instituted in 1995
  - ESRD cases in non-donor controls not captured 1988-94
  - Explains why ESRD event rate in controls is initially flat
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<tr>
<td></td>
<td>9,364</td>
<td></td>
<td></td>
<td></td>
<td>10 X Fewer actual controls</td>
</tr>
</tbody>
</table>
Matching

• When matching with replacement, because the matched controls are no longer independent—some are in the matched sample more than once and this needs to be accounted for in the outcome analysis, for example by using frequency weights.

• When matching with replacement it is also possible that the treatment effect estimate will be based on just a small number of controls; the number of times each control is matched should be monitored.
No events in Simulated Cohort of White non-donor controls
Large simultaneous increases in event rates suggest these are the same “individual” counted multiple times.
Although NHANES III is a large, representative, and commonly studied population of potential comparison patients, this cohort was one-eighth the size of the live donor cohort after appropriate exclusions. As a result, in generating a matched cohort based on these patients, we had to sample with replacement (some patients were used more than once in the matched cohort). Although this accounted for confounding by making the matched cohort similar in demographics to the live donor cohort, the oversampling caused an artificially larger sample size for the purposes of standard error estimates.
Long-term risks for kidney donors

Geir Mjøen¹, Stein Hallan²,³, Anders Hartmann¹, Aksel Foss¹, Karsten Midtvedt¹, Ole Øyen¹, Anna Reisæter¹, Per Pfeffer¹, Trond Jenssen¹, Torbjørn Leivestad⁴, Pål- Dag Line¹, Magnus Øvrehus², Daq Olav Dale¹, Hege Pihlstrøm¹, Ingar Holme⁵, Friedo W. Dekker⁶ and Hallvard Holdaas¹

Kidney International 2014 86: 162-7
Hazard Ratio All Cause Mortality
1.31 (1.11 – 1.52)
Quantifying Risk of Kidney Donation: The Truth Is Not Out There (Yet)

Table 1 | Baseline characteristics of kidney donors and controls

<table>
<thead>
<tr>
<th></th>
<th>1901</th>
<th>32,601</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kidney donors</td>
<td>Controls</td>
</tr>
<tr>
<td>Age, years</td>
<td>46.0 ± 11.5</td>
<td>37.6 ± 11.7</td>
</tr>
<tr>
<td></td>
<td>n = 1901</td>
<td>n = 32,621</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>41.0</td>
<td>46.9</td>
</tr>
<tr>
<td></td>
<td>n = 1901</td>
<td>n = 32,621</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>41.5</td>
<td>39.5</td>
</tr>
<tr>
<td></td>
<td>n = 1375</td>
<td>n = 25,993</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>123.3 ± 10.0</td>
<td>121.4 ± 10.4</td>
</tr>
<tr>
<td></td>
<td>n = 1768</td>
<td>n = 31,398</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>77.4 ± 7.2</td>
<td>77.2 ± 7.9</td>
</tr>
<tr>
<td></td>
<td>n = 1768</td>
<td>n = 31,394</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2 ± 2.8</td>
<td>23.5 ± 2.6</td>
</tr>
<tr>
<td></td>
<td>n = 1558</td>
<td>n = 31,421</td>
</tr>
</tbody>
</table>
Controls were matched for age using a matching algorithm.
Limitations - Mjoen
Control group

• Significant differences between donors and controls
  – Age: Donors 46.0 ± 11.5 versus 37.6 ± 11.7
  – Era: Donors 1963-2007 versus 1985-87 controls

• The above limitations reduce confidence in the author’s finding of an attributable mortality risk
What should be the focus of future data collection strategies?

- Stop trying to determine RR
Relative Risks Can Be Misleading

36% RR reduction

36% RR reduction
What should be the focus of future data collection strategies?

• Stop trying to determine RR

• Determination of long-term absolute risks

• Not just sentinel events of death/ESRD

• Identification of opportunities to intervene and prevent ESRD and premature death