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

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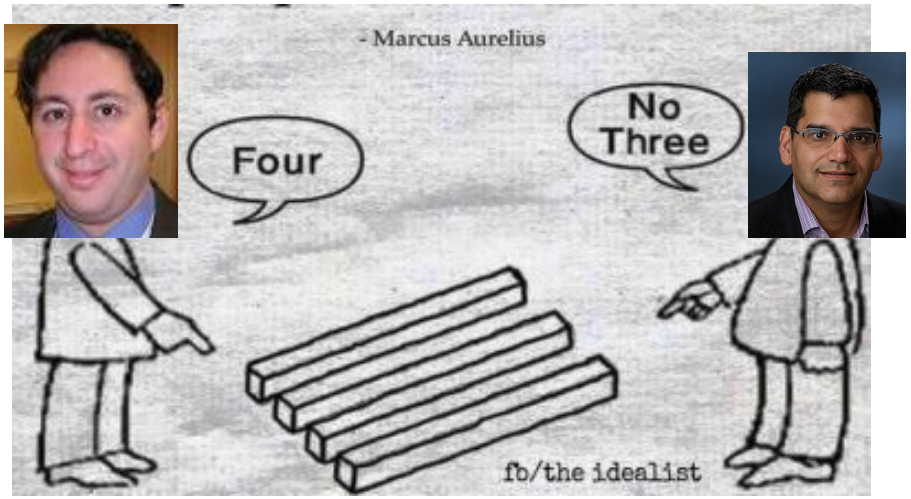
Conflict of Interest Disclosure

- 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

ORIGINAL CONTRIBUTION

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 9364 participants of the third National Health and

Research

Original Investigation

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

JAMA. 2014;311(6):579-586. doi:10.1001/jama.2013.285141

Strengths

- Captures every donor in U.S.
- Provide the best available information about the absolute risk of ESRD and Death in donors

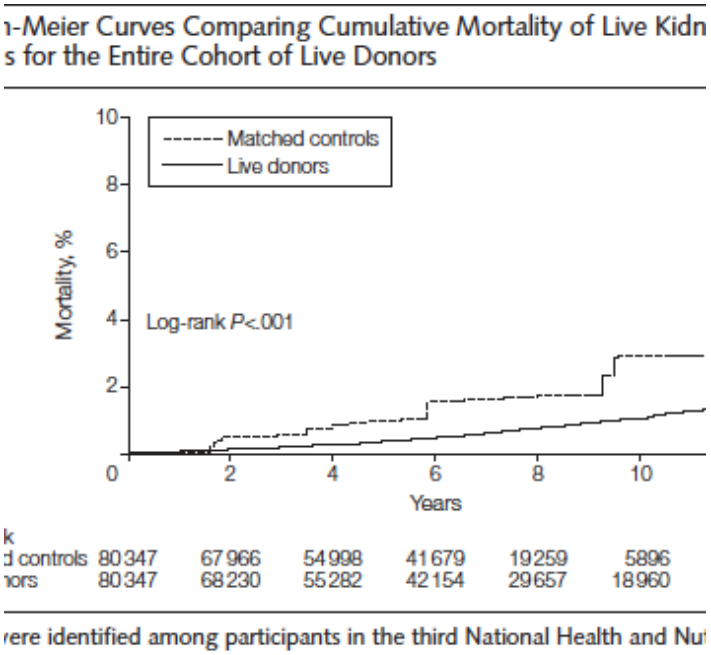
Limitations
Relative Risk Estimates

- 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

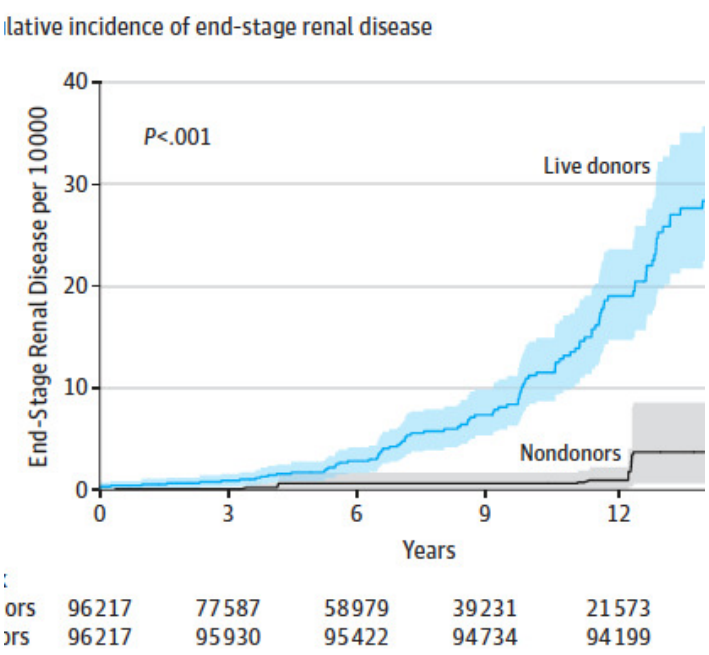
Perspectives Can Change Over Time

Same control group
Different Terminology

Segev 2010



Muzaale 2014



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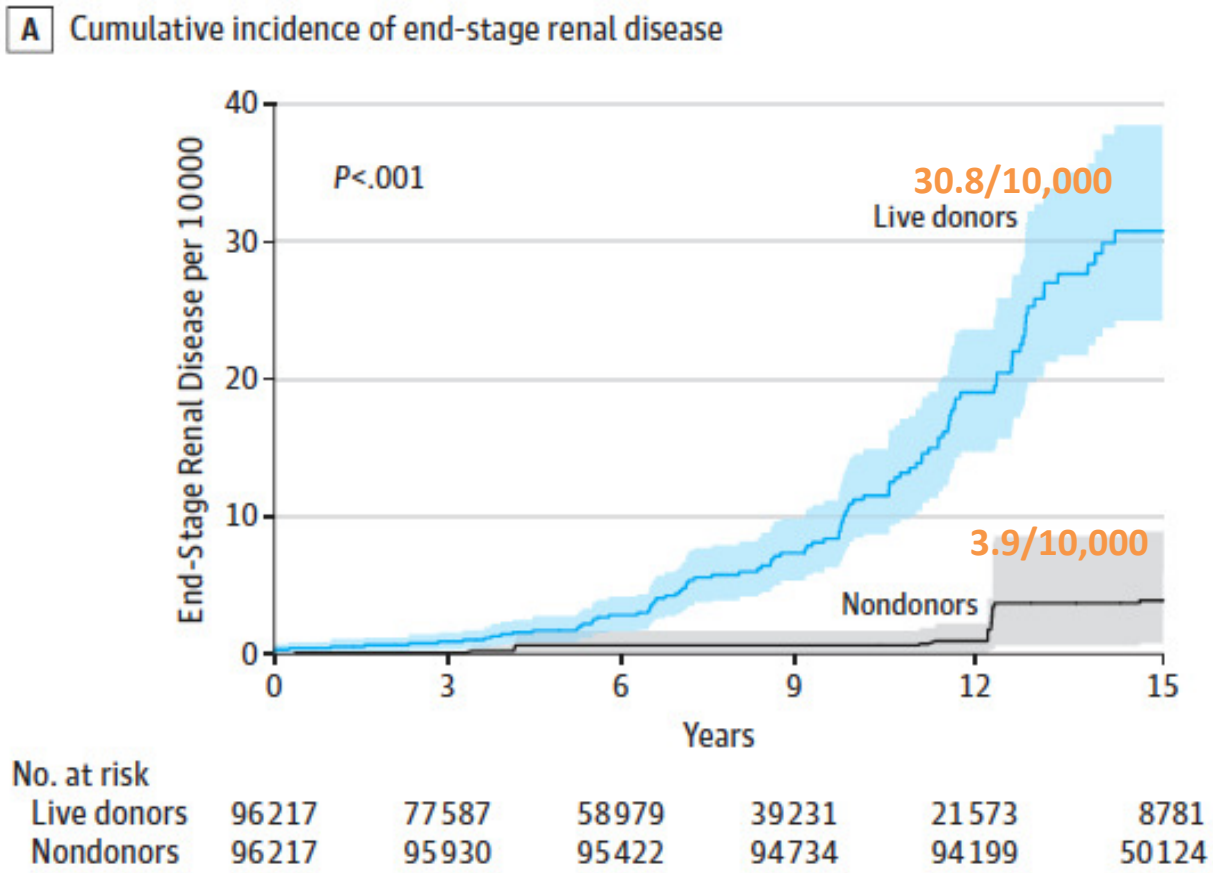
	Number	Years	ESRD Outcome Source	Median Maximum Follow Up	Crude ESRD Incidence
Donors reported to OPTN	96,217	April 1, 1994 – Nov 30, 2011	CMS 2728 Activation to transplant Waiting List	7.6 years 15 years	99 cases 10.3 per 10,000
Controls NHANES III Healthy sub-set	20,024 9,364	1988 – 1994	CMS 2728	15 years 15 years	17 cases 18.2 per 10,000

Incidence of ESRD in Donors Versus Controls



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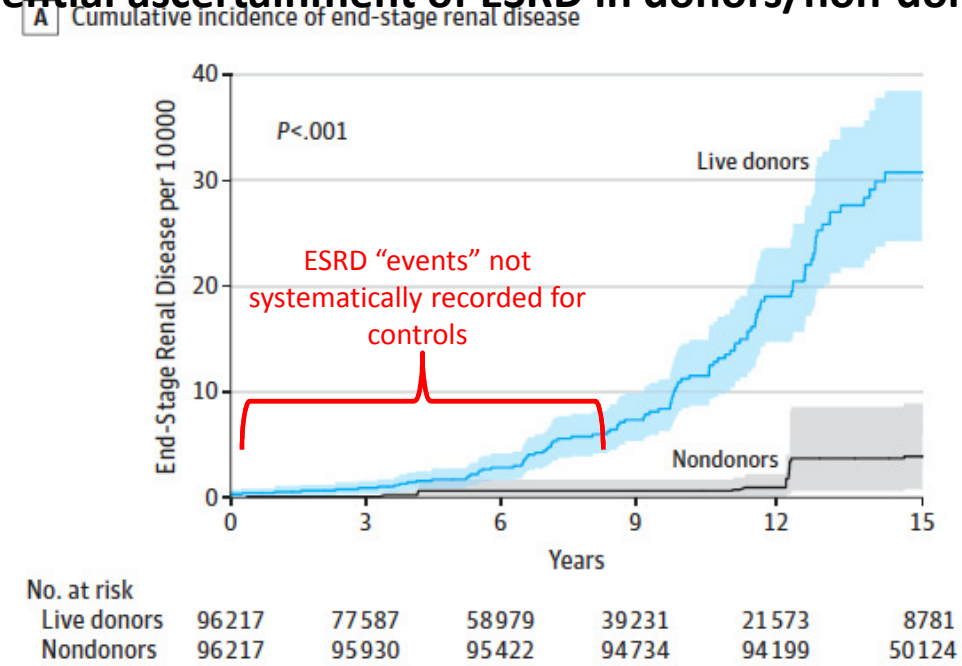
Different Outcome Assessment

Limitation

Differential ascertainment of ESRD in donors/non-donors



- NHANES cohort 1988-94 versus donors 1994 -2011
- 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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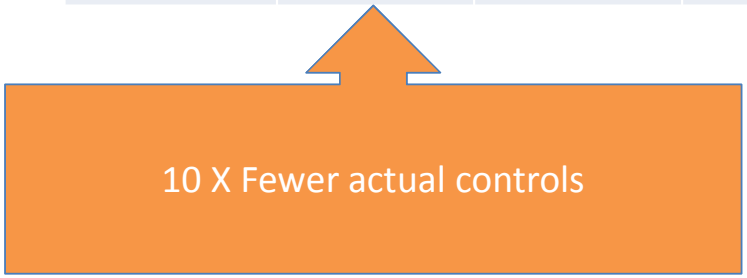
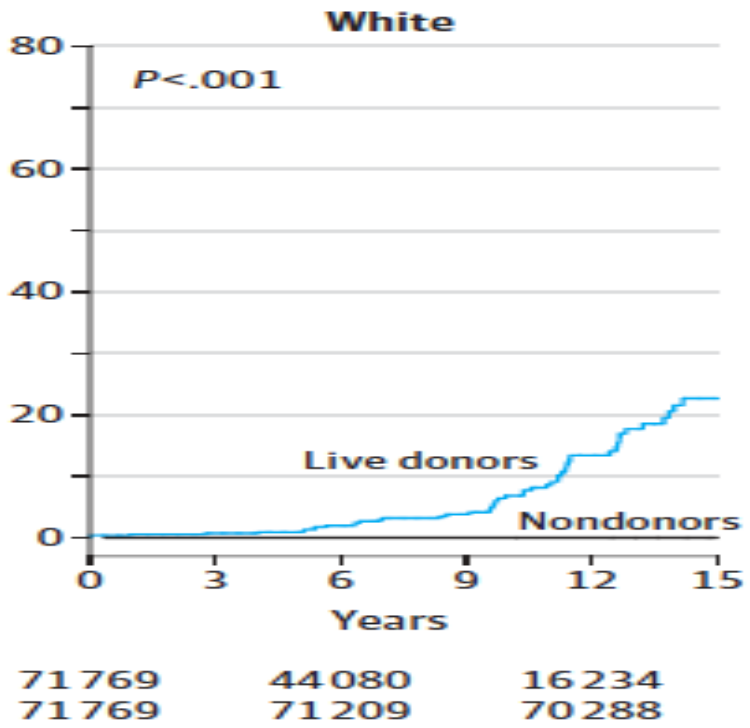


Matching

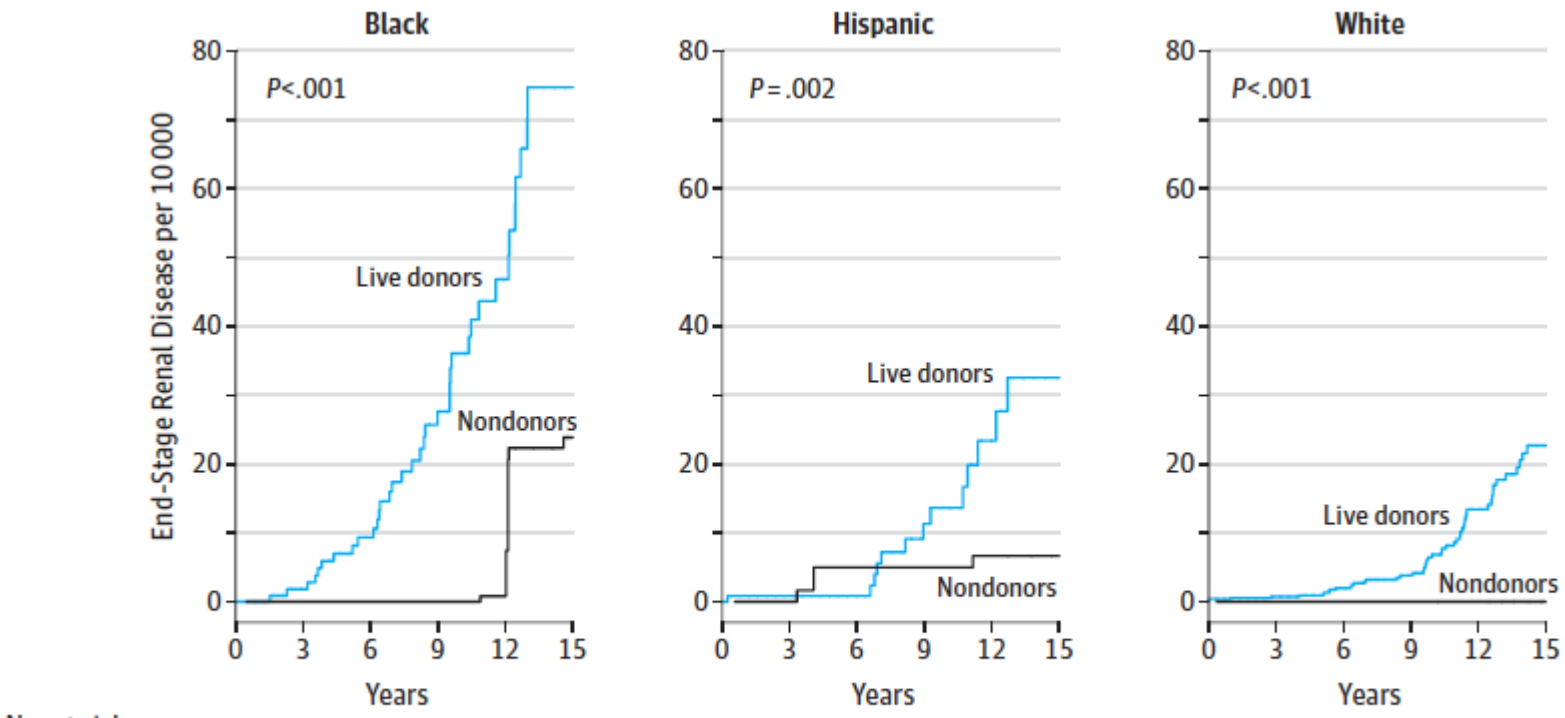
- When matching with replacement, because the matched controls are no longer independent–some are in the matched sample more than once and this needs to be accounted for in the outcome analysis, for example by using frequency weights.

- 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



No. at risk									
Live donors	12 387	7910	2887	12 061	6989	2452	71 769	44 080	16 234
Nondonors	12 387	12 256	12 093	12 061	11 957	11 818	71 769	71 209	70 288

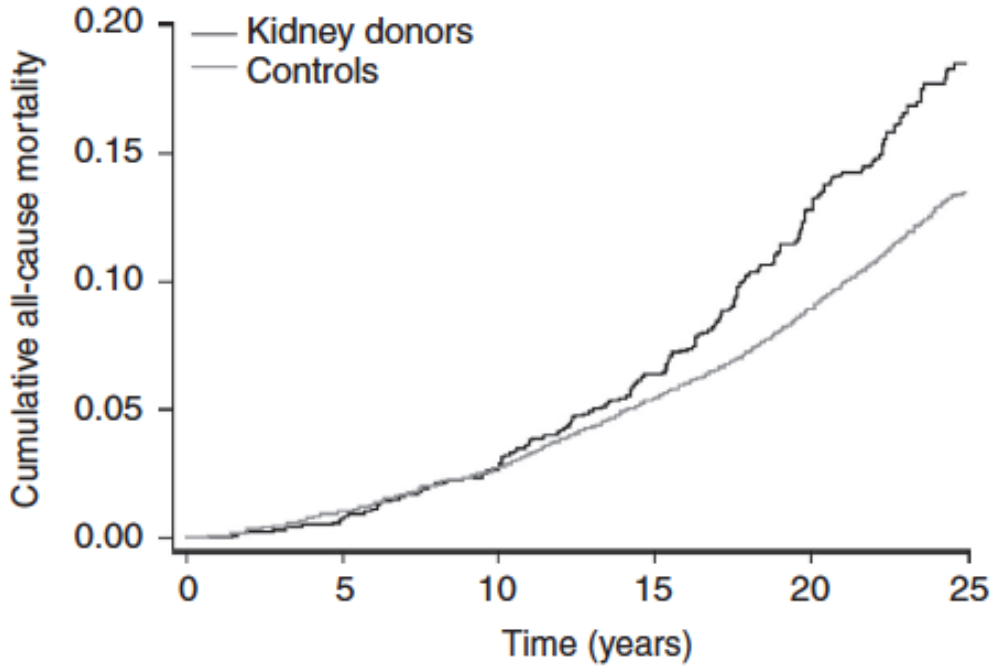
Segev -2010 JAMA

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 Mjøen[1], Stein Hallan[2,3], Anders Hartmann[1], Aksel Foss[1], Karsten Midtvedt[1], Ole Øyen[1], Anna Reisæter[1], Per Pfeffer[1], Trond Jenssen[1], Torbjørn Leivestad[4], Pål- Dag Line[1], Magnus Øvrehus[2], Dag Olav Dale[1], Hege Pihlstrøm[1], Ingar Holme[5], Friedo W. Dekker[6] and Hallvard Holdaas[1]

Kidney International 2014 86: 162-7



Hazard Ratio All Cause Mortality
1.31 (1.11 – 1.52)

American Journal of Transplantation 2014; 14: 1715–1716
Wiley Periodicals Inc.

doi: 10.1111/ajt.12804

Editorial

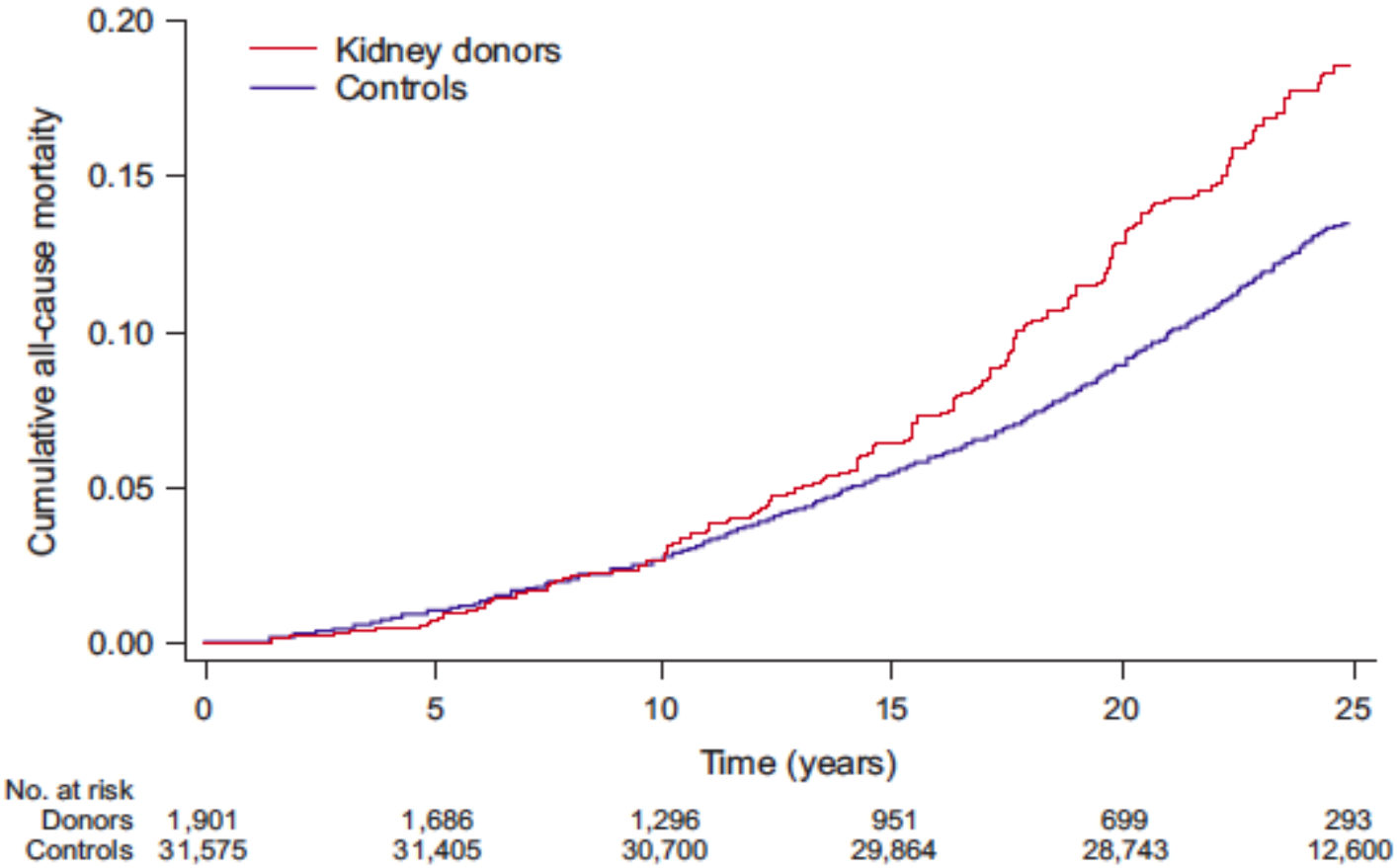
Quantifying Risk of Kidney Donation: The Truth Is Not Out There (Yet)

Table 1 | Baseline characteristics of kidney donors and controls 1901 32,601

	Kidney donors	Controls
Age, years	46.0 ± 11.5 *n* = 1901	37.6 ± 11.7 *n* = 32,621
Male gender, %	41.0 *n* = 1901	46.9 *n* = 32,621
Current smoking, %	41.5 *n* = 1375	39.5 *n* = 25,993
Systolic BP, mm Hg	123.3 ± 10.0 *n* = 1768	121.4 ± 10.4 *n* = 31,398
Diastolic BP, mm Hg	77.4 ± 7.2 *n* = 1768	77.2 ± 7.9 *n* = 31,394
BMI, kg/m^2	24.2 ± 2.8 *n* = 1558	23.5 ± 2.6 *n* = 31,421

Controls were matched for age using a matching algorithm

American Journal of Transplantation 2014; 14: 2671–2672
Wiley Periodicals Inc.



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

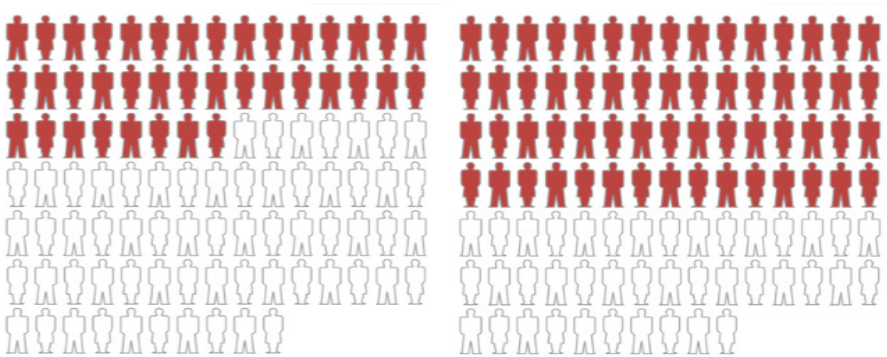
- The above limitations reduce confidence in the author's finding of an attributable mortality risk

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