

# Marginal donors: Young vs. Old

Why we should prefer older donors

**Geir Mjøen, Oslo, Norway**

- Long term risks in kidney donors
- Interpretation
- Consequences
- Recommendation

# Kidney donors

- Donors are healthy at the time of donation.
- Mean age is usually around 40 years.
- Donors have been examined physically, with blood tests and radiology, and declared healthy.

# Follow-up time

- Long follow-up time is needed to uncover long-term risks after donation
- Harmful effects may take decades

# Mortality

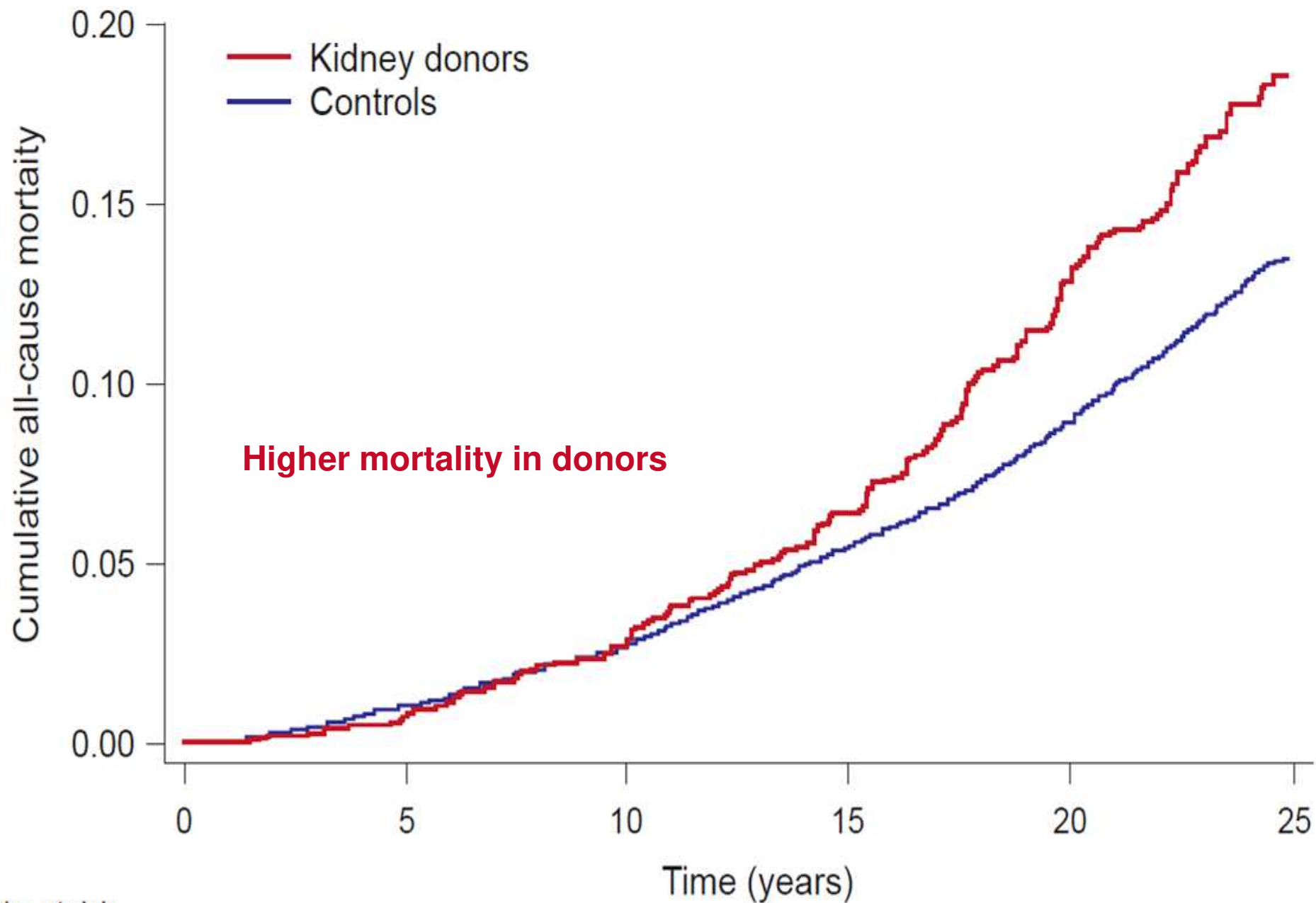
<http://www.kidney-international.org>

clinical investigation

© 2013 International Society of Nephrology

## Long-term risks for kidney donors

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



No. at risk	
Donors	1,901      1,686      1,296      951      699      293
Controls	31,575      31,405      30,700      29,864      28,743      12,600

# Mortality

- Hazard ratio (HR) for all-cause death was 1.30 (95% confidence interval [CI] 1.11-1.52,  $p=0.001$ ).
- HR for cardiovascular death (HR 1.40, 95% CI 1.03-1.91,  $p=0.03$ )

# Mortality differs from other studies

- Other studies have not found increased mortality.
- However, follow-up time was shorter

## 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 to estimate short-term operative risk in various strata of live donors, and to compare 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 national registry of 80 347 live kidney donors in the United States between April 1, 2005, and March 31, 2009. Median (interquartile range) follow-up was 6.3 (3.2) years. A matched cohort was drawn from 9364 participants of the third National Health and Medical Examination Survey.

BMJ

BMJ 2012;344:e1203 doi: 10.1136/bmj.e1203 (Published 1 March 2012)

Page 1 of 10

RESEARCH

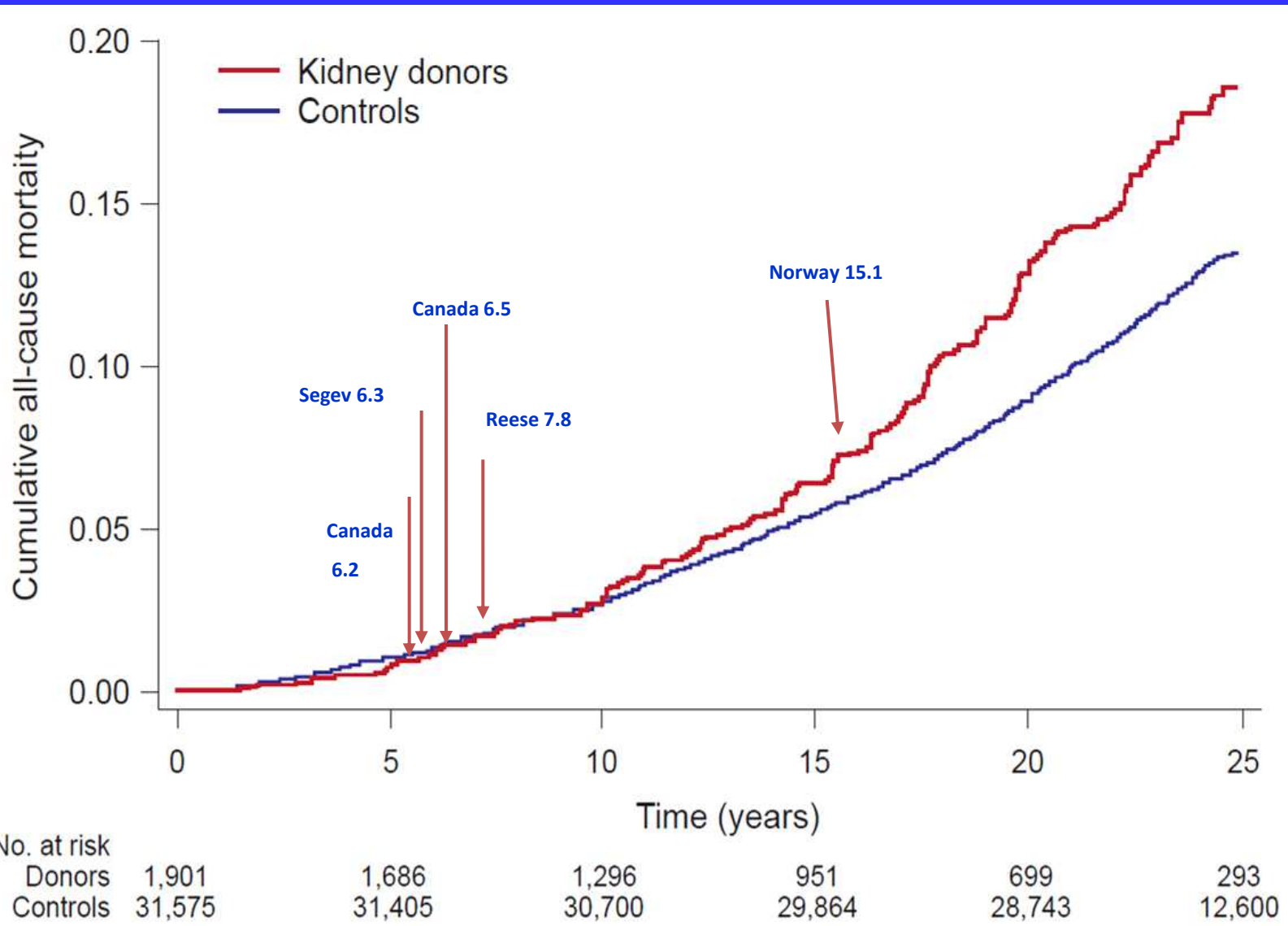
## Cardiovascular disease in kidney donors: matched cohort study

OPEN ACCESS

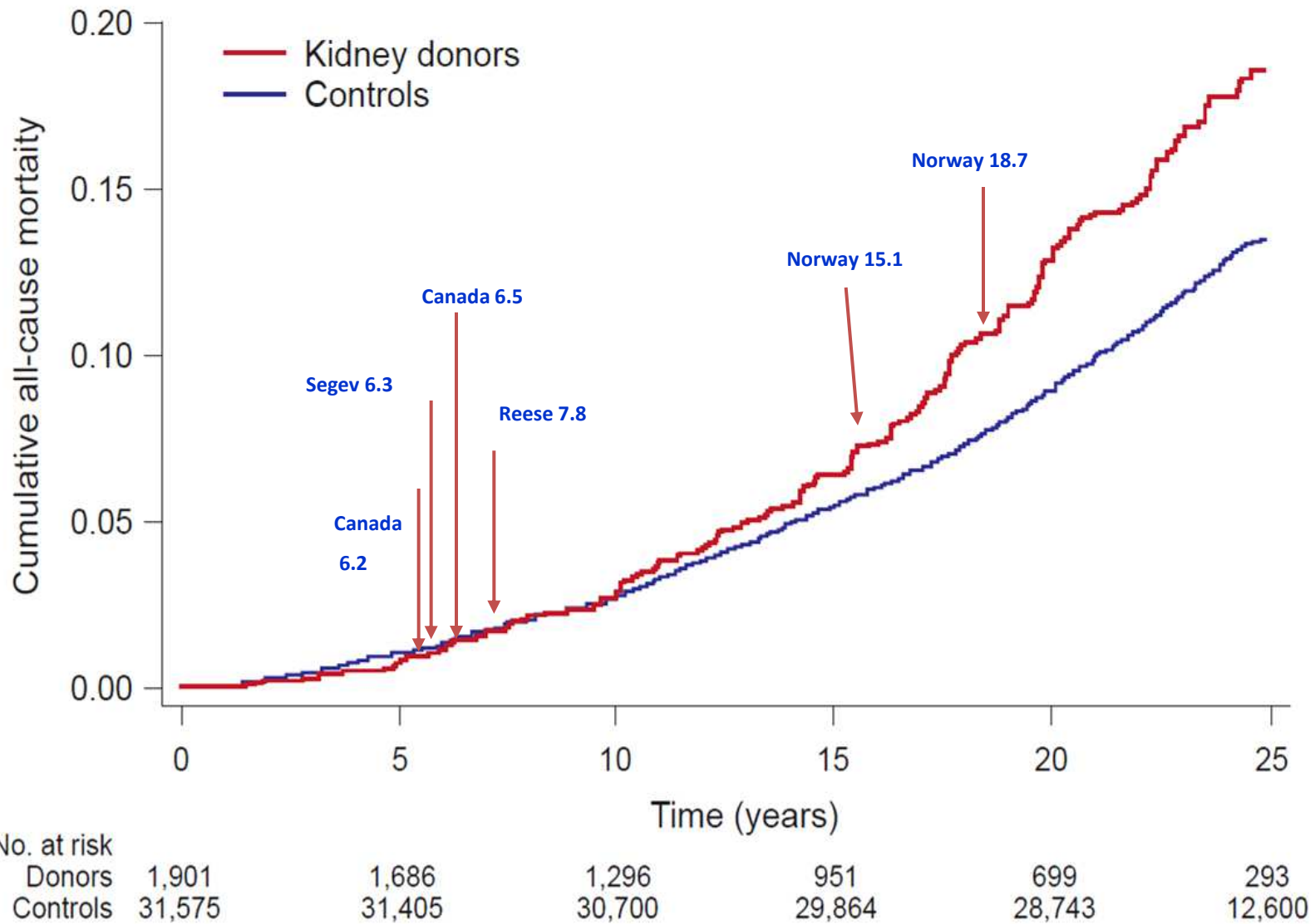
Amit X Garg *professor*<sup>1,2,3</sup>, Aizhan Meirambayeva *epidemiology student*<sup>1,2</sup>, Anjie Huang *biostatistician*<sup>3</sup>, Joseph Kim *assistant professor*<sup>3,4</sup>, G V Ramesh Prasad *associate professor*<sup>4</sup>, Greg Knoll *professor*<sup>5</sup>, Neil Boudville *associate professor*<sup>6</sup>, Charmaine Lok *associate professor*<sup>4</sup>, Philip M. Fine *professor*<sup>4</sup>, *et al.*



# Different follow-up time may explain different findings



# Update with longer follow-up – Similar results



# ESRD

- HR for ESRD was greatly increased (11.38, 95% CI 4.37-29.63,  $p < 0.001$ )

## Long-term risks for kidney donors

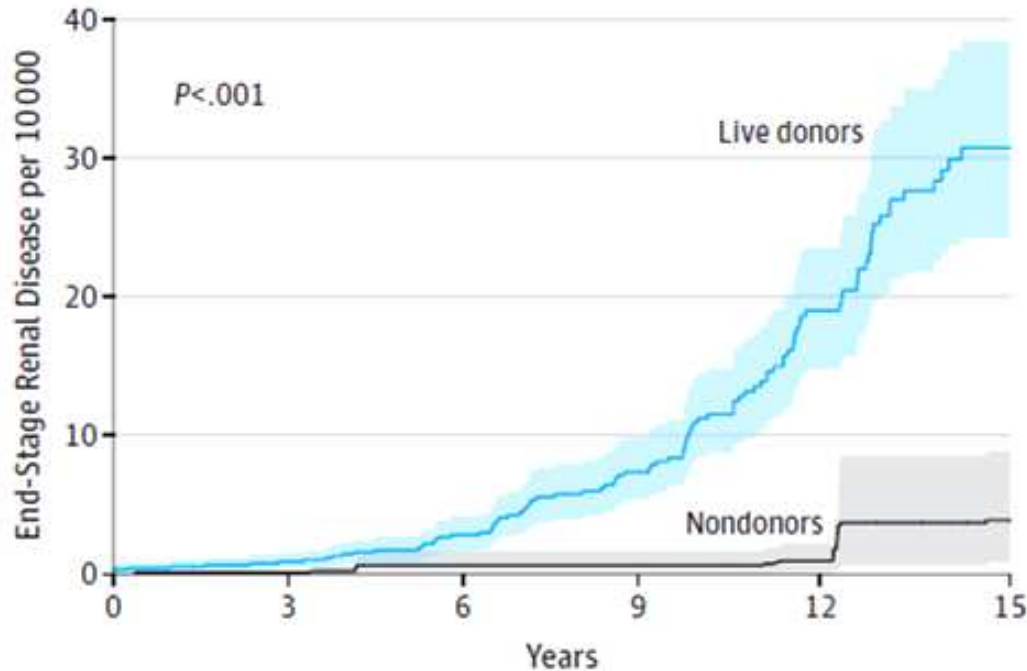
Geir Mjøen<sup>1</sup>, Stein Hallan<sup>2,3</sup>, Anders Hartmann<sup>1</sup>, Aksel Foss<sup>1</sup>, Karsten Midtvedt<sup>1</sup>, Ole Øyen<sup>1</sup>, Anna Reisæter<sup>1</sup>, Per Pfeffer<sup>1</sup>, Trond Jenssen<sup>1</sup>, Torbjørn Leivestad<sup>4</sup>, Pål- Dag Line<sup>1</sup>, Magnus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

# Other studies on ESRD

- “Risk of End-Stage Renal Disease Following Live Kidney Donation” Muzaale et al, JAMA 2014
  - Around 8 – 10 times increased risk for ESRD
- Reese et al. et al. “Mortality, Cardiovascular and End-Stage Disease outcomes among Older Live Kidney Donors” JASN 2013; 24: 71A
  - Around 7 – 8 times increased risk for ESRD

Figure 1. Cumulative Incidence of End-Stage Renal Disease in Live Kidney Donors and Matched Healthy Nondonors

A Cumulative incidence of end-stage renal disease



No. at risk						
Live donors	96 217	77 587	58 979	39 231	21 573	8 781
Nondonors	96 217	95 930	95 422	94 734	94 199	50 124

# Time to ESRD?

- Norwegian study mean time to ESRD was 18 years
- Study by Matas et al (AJT 2018) mean time to ESRD 27 years
- Developing ESRD depends on a “second hit”. New disease developing after donation.

# Hypertension

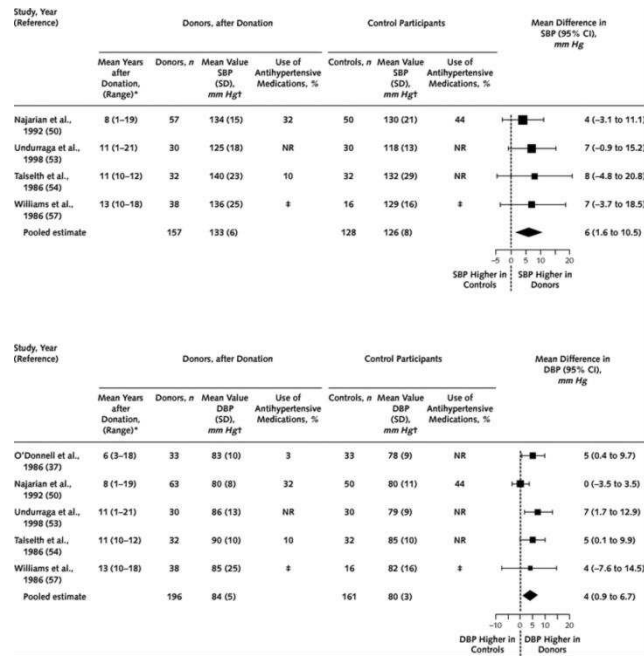
# Hypertension

- Meta analysis of available studies on blood pressure and hypertension
- "Kidney donors may have a 5-mm Hg increase in blood pressure within 5 to 10 years after donation over that anticipated with normal aging."



## From: Meta-Analysis: Risk for Hypertension in Living Kidney Donors

Ann Intern Med. 2006;145(3):185-196. doi:10.7326/0003-4819-145-3-200608010-00006



### Figure Legend:

Meta-analysis of controlled studies of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at least 5 years after kidney donation.

The size of each square is inversely proportional to the variability of the study estimate. NR = not reported. \*Studies are arranged by the average number of years after donation. †A summary of various methods to assess blood pressure are presented in the Results section. ‡Study reported that a percentage of donors were taking antihypertensive medication but did not quantify the amount.

# Time to Hypertension?

- Sanchez et al AJT 2018
- Hypertension developed in 4% 10% and 51% at 5, 10 and 40 years after donation

ORIGINAL ARTICLE

AJT

## Hypertension after kidney donation: Incidence, predictors, and correlates

Otto A. Sanchez<sup>1</sup> | Laine K. Ferrara<sup>1</sup> | Sarah Rein<sup>1</sup> | Danielle Berglund<sup>2</sup> |  
Arthur J. Matas<sup>3</sup> | Hassan N. Ibrahim<sup>4</sup>

<sup>1</sup>Division of Renal Diseases and Hypertension, University of Minnesota, Minneapolis, MN, USA

<sup>2</sup>Informatics Services for Research and

Incidence of postdonation hypertension, risk factors associated with its development, and impact of type of treatment received on renal outcomes were determined in 2700 kidney donors. Using Cox proportional hazard model, adjusted hazard ratios

# Preeclampsia

- Higher incidence of preeclampsia in donors (Garg et al 2015)
- Two studies found increased preeclampsia in pregnancies after donation vs. before (Reisæter et al. 2009; Ibrahim et al 2009)

# Maternal and Fetal Outcomes of Pregnancies after Cohort Entry in Living Kidney Donors and Matched Nondonors.

**Table 3.** Maternal and Fetal Outcomes of Pregnancies after Cohort Entry in Living Kidney Donors and Matched Nondonors.

Outcome	Pregnancies in Donors (N=131)	Pregnancies in Nondonors (N=788)	Odds Ratio (95% CI)	P Value*
	<i>no. of events (%)</i>			
Primary outcome: gestational hypertension or preeclampsia	15 (11)	38 (5)	2.4 (1.2–5.0)	0.01
Secondary outcomes				
Gestational hypertension†	7 (5)	17 (2)	2.5 (0.9–6.5)	0.06
Preeclampsia	8 (6)	21 (3)	2.4 (1.0–5.6)	0.05
Cesarean section	41 (31)	224 (28)	1.2 (0.7–2.1)	0.44
Postpartum hemorrhage	≤5 (≤4)‡	24 (3)	0.9 (0.3–2.9)	0.91
Preterm birth with gestation of <37 wk	10 (8)	52 (7)	1.2 (0.5–2.5)	0.70
Low birth weight of <2500 g	8 (6)	31 (4)	1.7 (0.7–4.0)	0.21

\* P values were derived from random-effects logistic-regression models for binary outcome data, accounting for the correlation structure within matched sets and in women with multiple pregnancies.

† When diagnostic codes for both gestational hypertension and preeclampsia were present in a given pregnancy, the outcome was counted as a diagnosis of preeclampsia.

‡ To comply with privacy regulations for minimizing the chance of identification of a study participant, numbers of participants are suppressed in the case of 5 or fewer participants (reported as ≤5).

What about donors with mild hypertension?

# Donors with mild hypertension

- Donors with available blood pressure data in the period 1963-2007 were included.
- Hypertension was defined retrospectively as BP > 140/90 or use of medication.
- Does mild hypertension at donation affect long-term survival?

# Methods

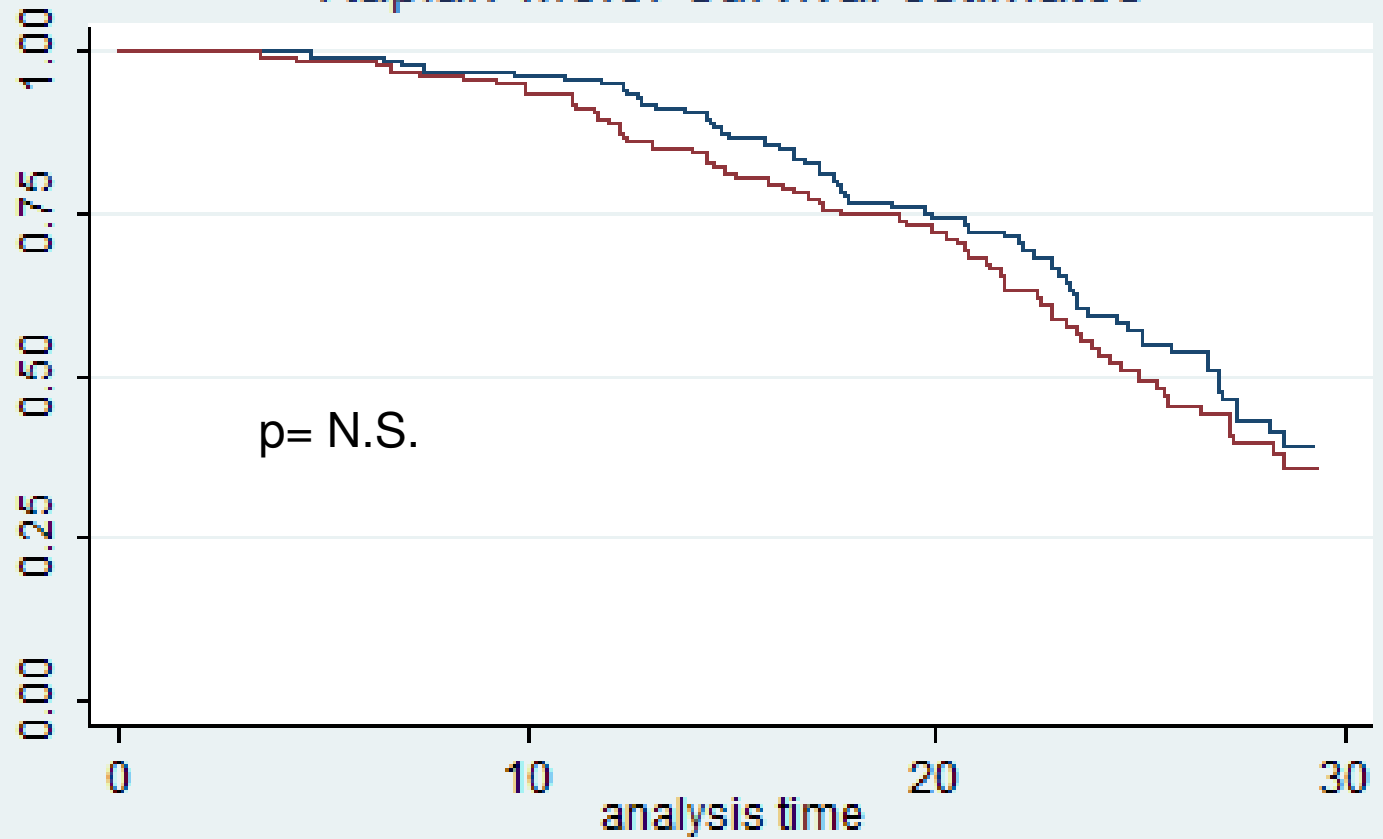
- Hypertensive and normotensive donors were matched 1:1 for age, gender and time of donation.

# Results

- Mean age among hypertensive donors was 57.7 years and 44,3 % were male. During a median follow-up of 16.9 years there were 96 deaths among donors with hypertension.
- Mean BP 147/89 mmHg vs. 124/77 mmHg



# Kaplan-Meier survival estimates



Number at risk

HT = 0 141

133

83

16

HT = 1 141

128

79

17



All cause mortality risk in HT donors vs normotensive donors is similar

# Results

- We found no difference in long-term survival among older/middle-aged donors with and without mild hypertension
- Due to limited observation time and mean age of 56 years old these results are not applicable to young donors.

# Interpretations

## Personal Viewpoint Forum

# Risk Appreciation for Living Kidney Donors: Another New Subspecialty?

**Robert W. Steiner\***

*Department of Medicine, University of California at San Diego, School of Medicine, San Diego, CA*

*\*Corresponding author: Robert W. Steiner,  
rsteiner@UCSD.edu*

The lack of explicit quantification of risk, however, complicates both formulation of center policy and communication with donor candidates. Particularly for donors with IMA's, by using population screening studies and end stage renal disease (ESRD) epidemiologic data (4,5) we can defensibly estimate the risks associated with the IMA that such

# Interpretation

- Kidney donation may be associated with long-term risks to the donor
- Absolute risks seem relatively small, at least in low risk populations (middle aged caucasians).
- Not all populations are low risk (for example young afro-americans)
- Long observation period before risks appear

Steiner et al, AJT, 14:538-44

Donor loses 30% renal function as a result of nephrectomy. Therefore has less reserve.

All else being equal, a donor will have a low GFR years before a similar non-donor.

Therefore with normal loss of GFR or with development of disease, a donor has increased risk.

American Journal of Transplantation 2014; 14: 538-544  
Wiley Periodicals Inc.

© Copyright 2014 The American Society of Transplantation  
and the American Society of Transplant Surgeons

doi: 10.1111/ajt.12625

Personal Viewpoint

## Estimating Risks of *De Novo* Kidney Diseases After Living Kidney Donation

R. W. Steiner<sup>1,\*</sup>, J. H. Ix<sup>1,2,3</sup>, D. E. Rifkin<sup>1,2,3</sup>  
and B. Gert<sup>4,5,6</sup>

<sup>1</sup>Division of Nephrology, Department of Medicine, UC  
San Diego School of Medicine, San Diego, CA

### Introduction

Transplant centers often refuse candidates for living kidney donation with hematuria or increased diabetic risk because they are at increased risk of chronic pyelonephritis or diabetes.

# Steiner et al, AJT, 14:538-44

The majority of kidney disease begins in middle age:

- normal young donors are at increased long-term risk than normal older donors
- low normal GFR is a risk for ESRD when kidney disease starts

American Journal of Transplantation 2014; 14: 538-544  
Wiley Periodicals Inc.

© Copyright 2014 The American Society of Transplantation  
and the American Society of Transplant Surgeons

doi: 10.1111/ajt.12625

Personal Viewpoint

## Estimating Risks of *De Novo* Kidney Diseases After Living Kidney Donation

R. W. Steiner<sup>1,\*</sup>, J. H. Ix<sup>1,2,3</sup>, D. E. Rifkin<sup>1,2,3</sup>  
and B. Gert<sup>4,5,6</sup>

<sup>1</sup>Division of Nephrology, Department of Medicine, UC  
San Diego School of Medicine, San Diego, CA

### Introduction

Transplant centers often refuse candidates for living kidney donation with hematuria or increased diabetic risk because they are at increased risk of chronic kidney disease or diabetes.

# Donor risks and remaining lifespan

- 20 year old healthy donor has 60 remaining years to live
- 60 years old donor with hypertension, has 20 years
- Long-term risk is likely to be proportional to remaining lifespan



# Steiner AJT 10:737-741

- Some older donors with isolated medical abnormality such as mild hypertension will be at lower or about the same overall baseline lifetime risk for ESRD as young «normal» candidates.

*American Journal of Transplantation* 2010; 10: 737–741  
Wiley Periodicals Inc.

© 2010 The Author  
Journal compilation © 2010 The American Society of  
Transplantation and the American Society of Transplant Surgeons

Personal Viewpoint

doi: 10.1111/j.1600-6143.2010.03023.x

## **'Normal for Now' or 'At Future Risk': A Double Standard for Selecting Young and Older Living Kidney Donors**

R. W. Steiner

a donor when an isolated medical abnormality (IMA) such as mild hypertension, nephrolithiasis, idiopathic isolated

# Steiner AJT 10:737-741

- To remain ethically consistent, transplant centers who accept any young donor can not refuse older donors with IMAs.

*American Journal of Transplantation* 2010; 10: 737-741  
Wiley Periodicals Inc.

© 2010 The Author  
Journal compilation © 2010 The American Society of  
Transplantation and the American Society of Transplant Surgeons

Personal Viewpoint

doi: 10.1111/j.1600-6143.2010.03023.x

## **'Normal for Now' or 'At Future Risk': A Double Standard for Selecting Young and Older Living Kidney Donors**

R. W. Steiner

a donor when an isolated medical abnormality (IMA) such as mild hypertension, nephrolithiasis, idiopathic isolated

# Consequences

- Inform donors, change written information
- Change criteria for older donors

# Written information

- All donors receive written information
- Used to be "studies have shown that donors live longer....."
- Now it has changed



For You who have  
been asked to  
donate a kidney

# For You who are asked to donate a kidney

There has been a concern that the remaining kidney may be susceptible to long-term damage due to reduced renal function.

Two studies, one in Norway with 2000 kidney donors, and one in USA, have shown that donors might have a small **increased risk** for renal replacement therapy

# For You who are asked to donate a kidney

In the Norwegian study we also found that there may be an **increased long-term risk for cardiovascular mortality** compared to a healthy population.

We inform of our study so potential donors might take the results into account when deciding whether to donate a kidney. This also reinforces the importance of participating in the regular follow-up after donation.

# Renal function in potential living donor

## Measured GFR by age brackets

Age	(mL/min/1.73m <sup>2</sup> )
Below 50	90
50-70	130-age
Above 70	60



# Blood pressure requirements

Office BP  $\leq$  140/90 mmHg or 24 h ambulatory BP  $\leq$  130/80 .

Donors above 60 years of age with “mild” hypertension are accepted using one BP medication

# Diabetes/Impaired glucose tolerance

Diabetics are not accepted as donors

Donors above 60 years of age are accepted with impaired glucose tolerance

Donors below the age of 60 must have normal OGTT

# Proteinuria

Donors with albuminuria are not accepted.

Donors above 60 years may have  
microalbuminuria

# Summary living donor

- All donors face long term risks.
- The predictive value of a normal donor evaluation is low in younger donors, since most diseases will occur later in life.
- Older donors are relatively healthier, and have a shorter remaining lifespan.
- Choose older donors when possible

Thank you