

Donation from Old Living Donors

How safe is it?

Safe for recipient or donor?

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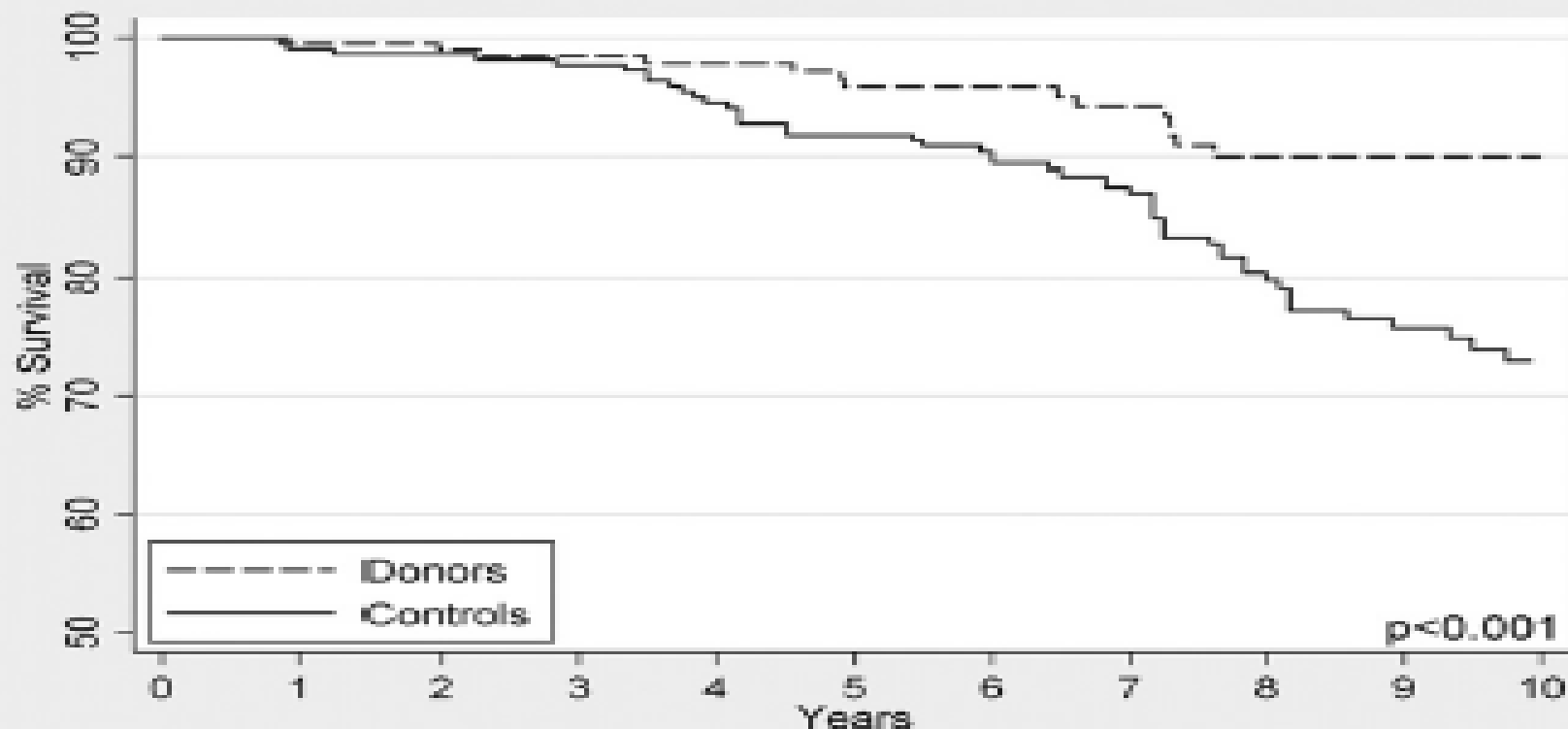
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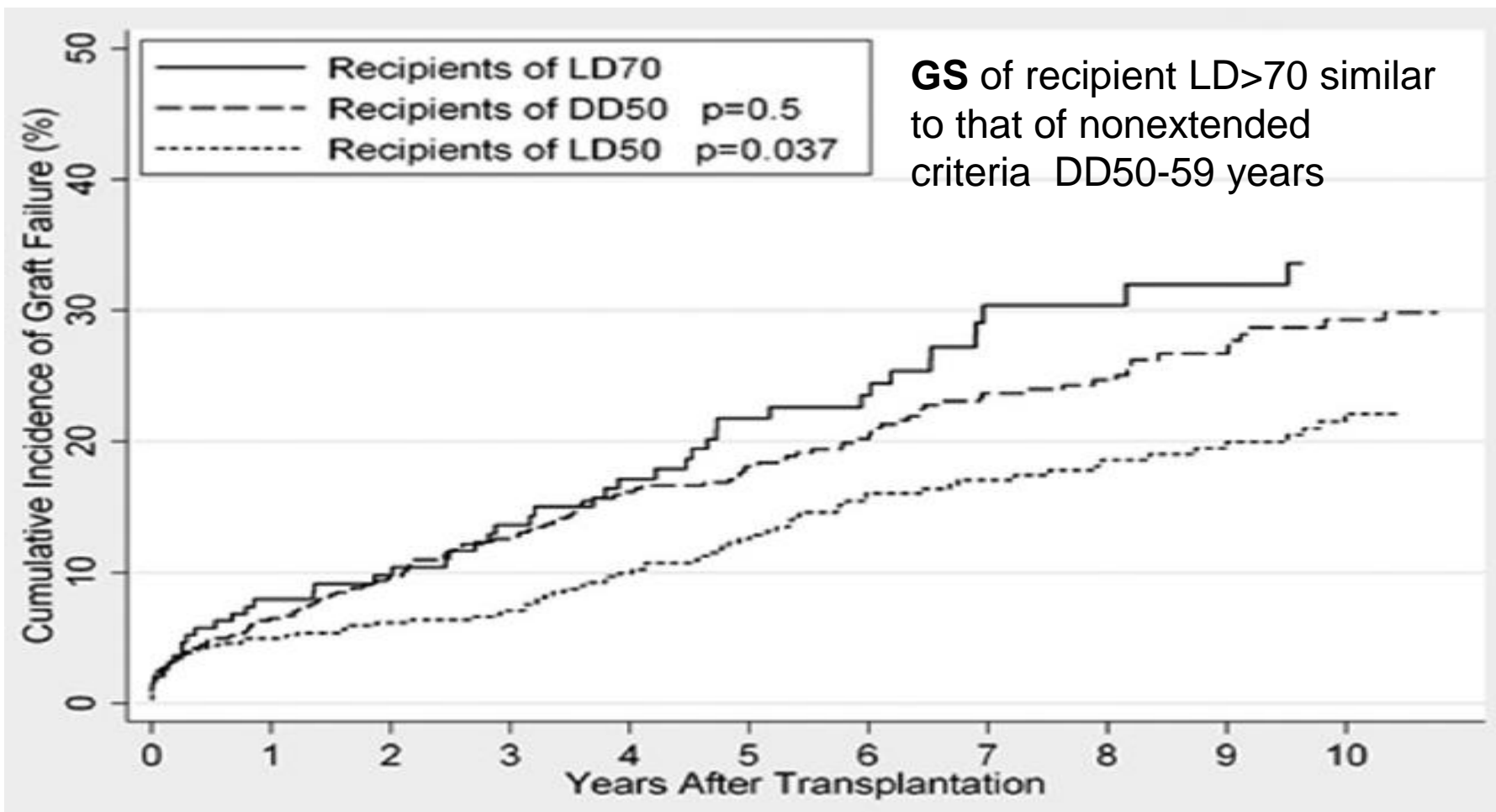
Living kidney Donors ages 70 and Older: Recipient and Donor outcomes (1)



| At Risk | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|
| Donors | 219 | 202 | 185 | 172 | 156 | 140 | 127 | 114 | 93 | 78 | 66 |
| Controls | 219 | 217 | 216 | 214 | 207 | 201 | 198 | 172 | 126 | 98 | 71 |

Patient survival: live kidney donors aged >70, compared with matched healthy controls drawn from the National Health and Nutrition Examination Survey cohort.

Living kidney Donors ages 70 and Older: Recipient and Donor outcomes (2)



219 donors aged > 70, matched to 50-59 old live donors from NHANES III

Age: how is an old living-donor (LD) ?

- Median age for live-kidney donors varies.
 - Pakistan (Karachi) 34 years
 - Norway (Oslo) 47 years
 - Japan (Tokyo) 52 years
- Old LD?, older than:
 - 50, 55, 60, 65, 70....?
- Reports on old living donors: median follow-up time is usually very short

How to assess donor safety for old LD?

- Risks?
 - Mortality, ESRD, hypertension, diabetes, proteinuria, low eGRF, LVH,
- Compare risk in different age intervals within a donor cohort
- Compare risk in age intervals to corresponding age intervals in “control” cohorts
- Control (background) cohorts are problematic

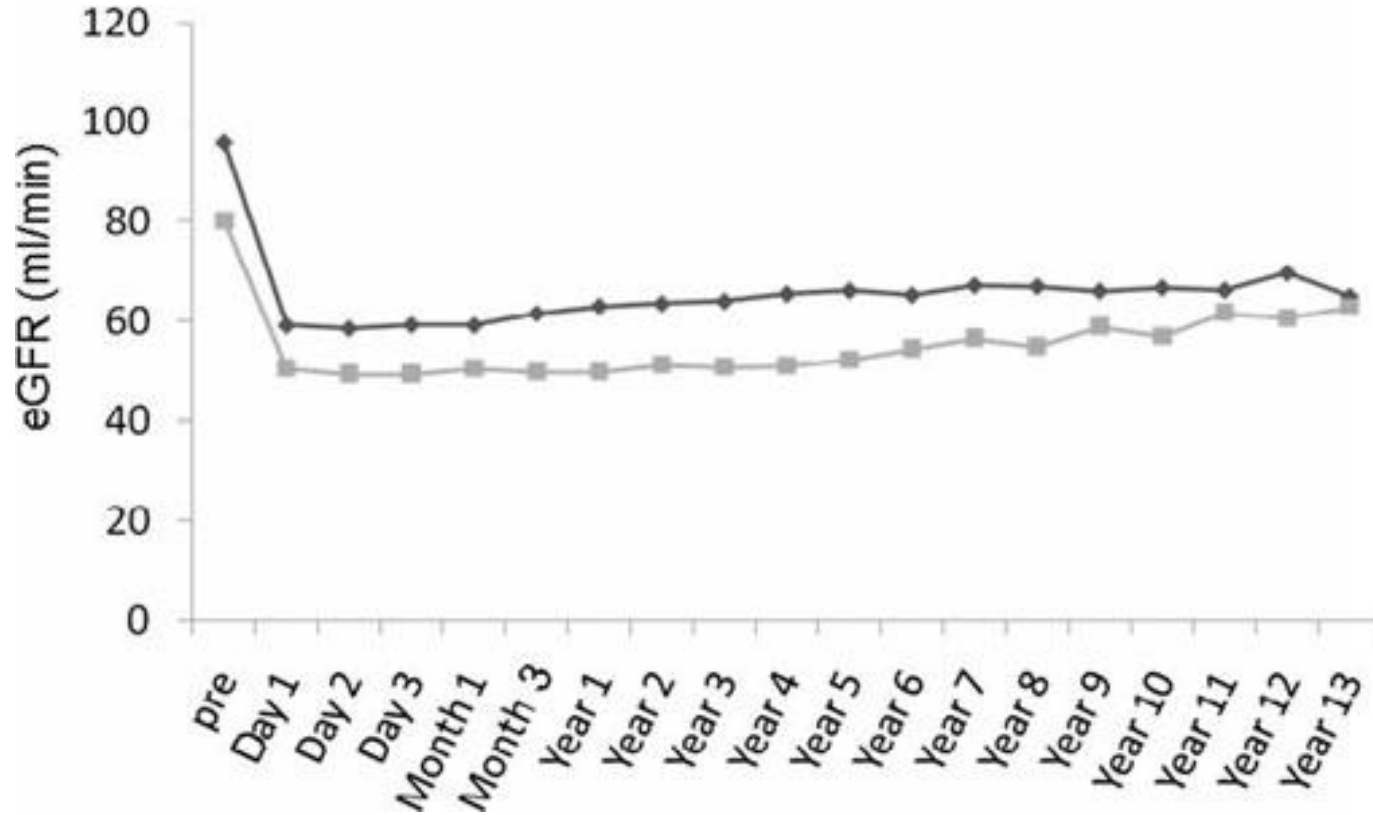
Short-term risks for living donors

- Perioperative mortality: 0.03%
 - Matas et al. Am J Transplant 2003;3;830 (2 for 10,000 donors)
 - Segev et al. JAMA 2010;303:959 (3.1 for 10,000 donors)
 - 25 deaths within 90 days. Surgical mortality higher in:
 - women,
 - black versus hispanic and white,
 - hypertension vs non-hypertension.
 - **Not age.**
 - In the Nordic countries, LD from 1969: no perioperative deaths

Perioperative and postoperative complications (1)

- 539 LD in Netherlands 1994-2006
- Living donors above 60 versus living donor below 60 years of age
- Difference in:
 - Blood loss (230 vs. 180 mL)
 - Hospital stay: 4 days vs 3 days
- No difference in:
 - Minor or major intraoperative and postoperative complications

Perioperative and postoperative complications (2)

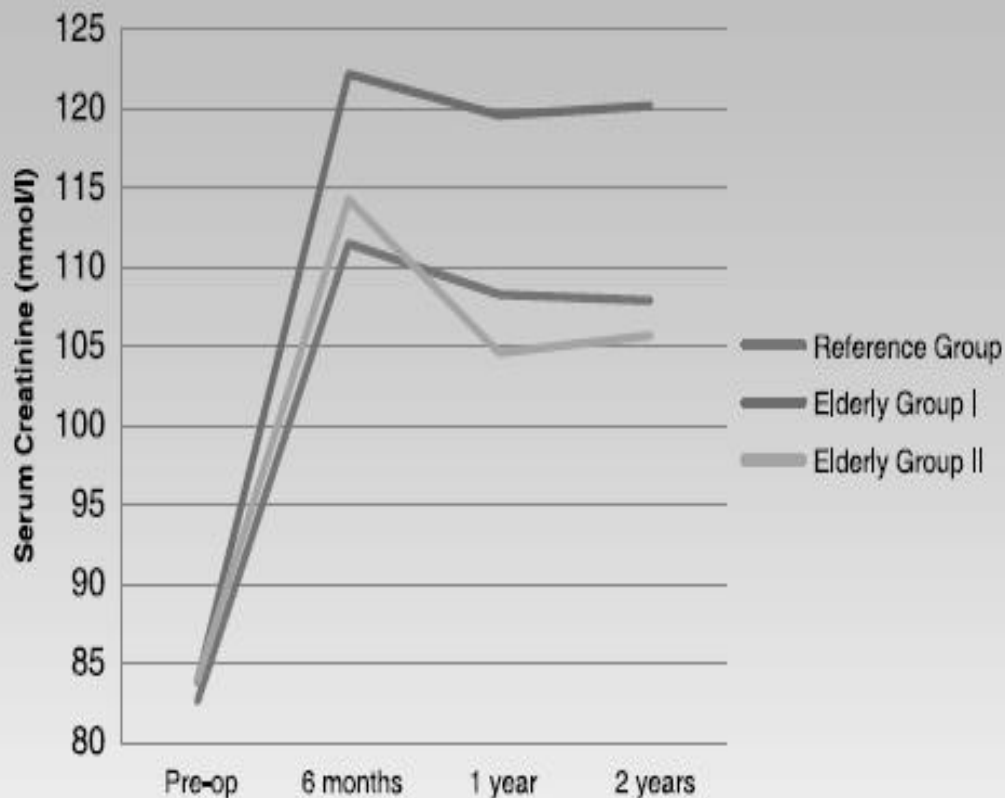
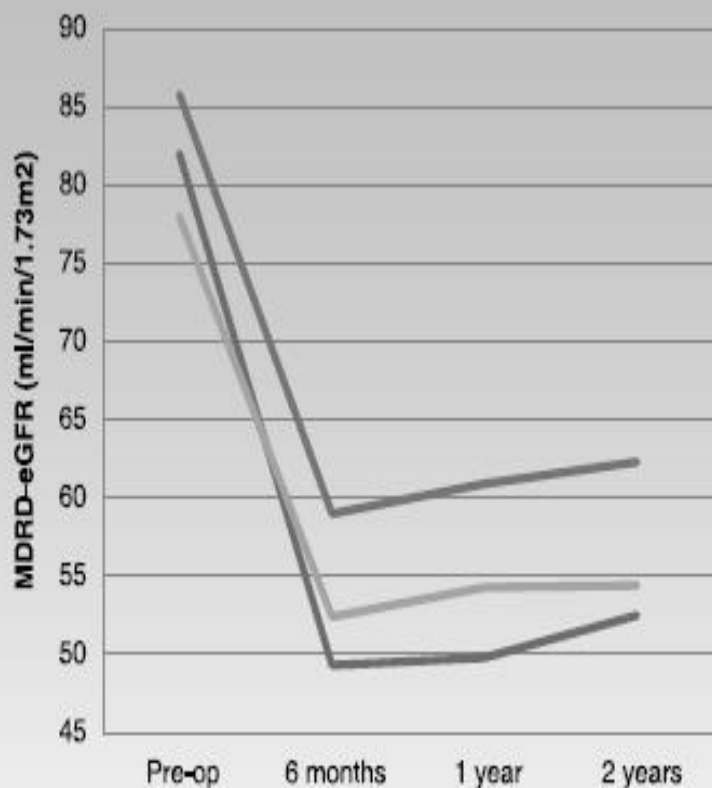


Median estimated glomerular filtration rate (eGFR) of 539 live kidney donors divided into two age groups. (Black line indicates <60; gray line indicates ≥ 60.)

Expanding the donor pool : living donor nephrectomy in the elderly and the overweight (1)

- Three groups of elderly: 60-65 y (62) and BMI < 30) and > 65 y (68) and BMI < 30; > 60y and BMI > 30; reference group: age < 60y (42) and BMI < 30.
- No difference in:
 - Operative time
 - Length of hospital stay
 - Estimated blood loss
 - Early postoperative complications

Expanding the donor pool : living donor nephrectomy in the elderly and the overweight (2)



Estimated glomerular filtration rate (eGFR) and serum creatinine pre- and postnephrectomy.

O'Brien et al Transplantation 2012;93:1158
(West London Renal and Transplant centre)

Surgical complications?

- 1,022 LD nephrectomies in Norway (24% laparoscopic nephrectomy):no mortality; **2.90% major surgical complications**

TABLE 5. Odds ratios for wound infection n=37/951

| Risk factor | Unadjusted odds ratio | Adjusted odds ratio | 95% CI Lower–upper | <i>P</i> |
|------------------------|-----------------------|---------------------|--------------------|----------|
| Age >60 yr | 0.45 | 0.56 | 0.17–1.91 | 0.36 |
| Smoking | 4.38 | 4.78 | 2.30–9.96 | <0.001 |
| BMI >25 | 3.47 | 4.03 | 1.80–9.04 | 0.001 |
| Laparoscopic surgery | 0.17 | 0.24 | 0.06–1.03 | 0.06 |
| Antibiotic prophylaxis | 0.36 | 0.52 | 0.15–1.78 | 0.30 |

***Peri- and postoperatively
procedures seems not to indicate
an increased risk for old donors***

Donation from Old Living Donors

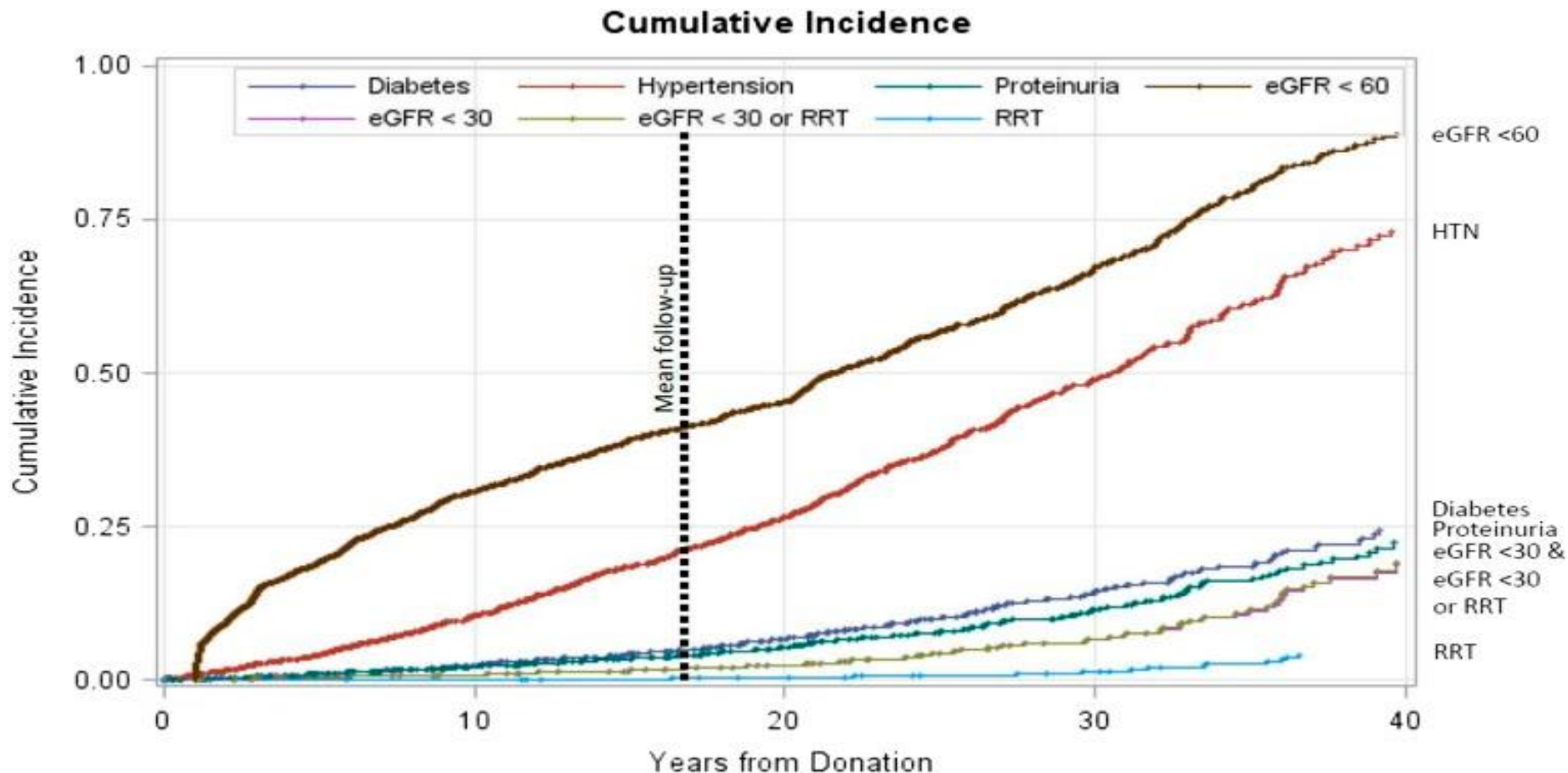
How safe is it?

- End-stage renal disease
- Intermediary endpoints: low GFR; proteinuria

Renal Function Profile in White Kidney Donors: The first 4 Decades (1)

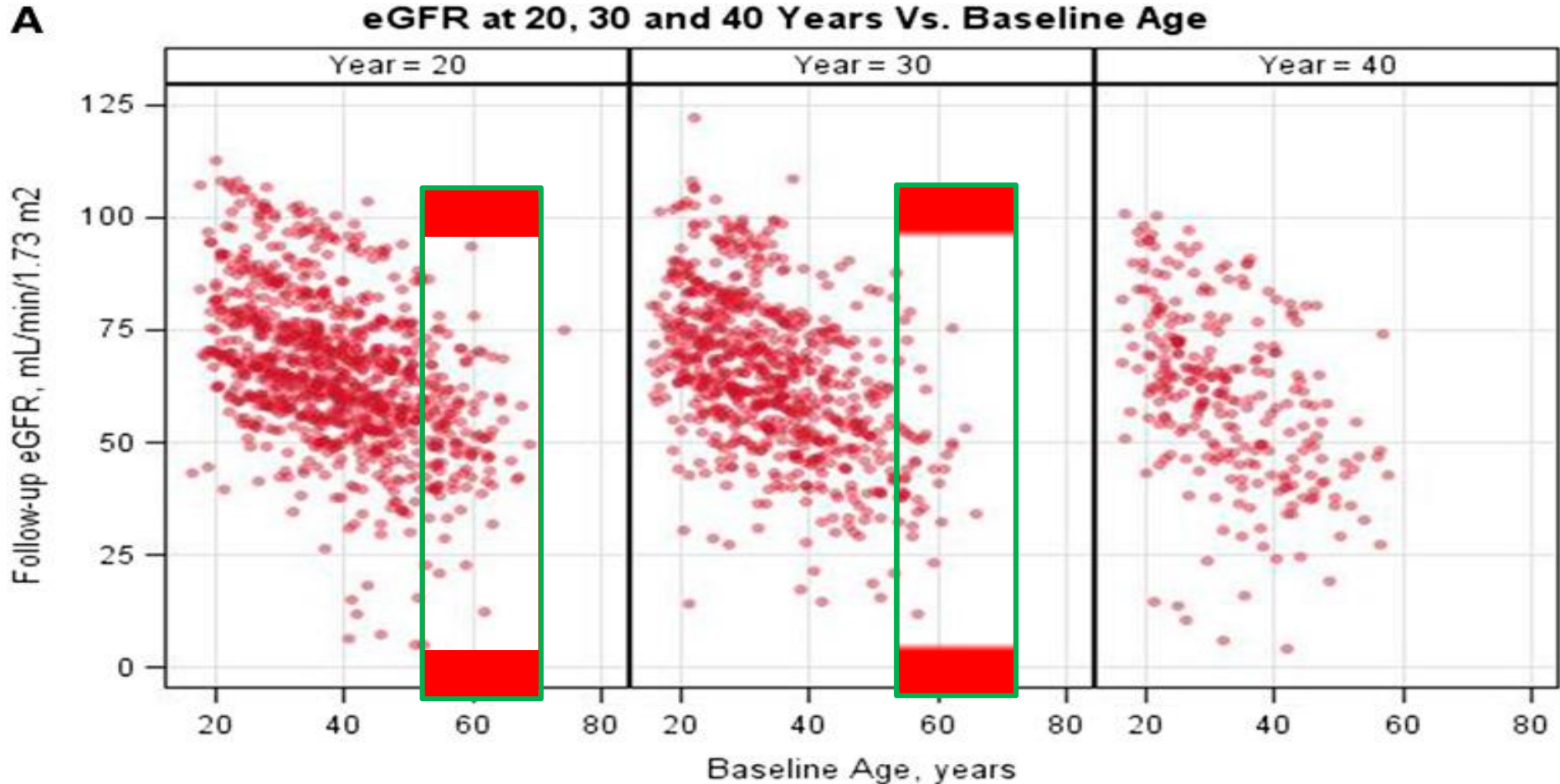
- Single-center study (1963-2013), Minneapolis; mean 16 years of follow-up of 3,956 white live-kidney donors
- Severe reduction in GFR and ESRD after kidney donation were uncommon and were highly associated with post-donation diabetes and hypertension.
- eGFR < 30 mL/min or ESRD was though associated with age, hypertension and systolic BP

Renal Function Profile in White Kidney Donors: The first 4 Decades (2)



Cumulative risk of reduced GFR and proteinuria. Kaplan–Meier time to development of hypertension, proteinuria, eGFR,60ml/min per 1.73 m², eGFR,30ml/min per 1.73 m², eGFR,30ml/min per 1.73 m² or ESRD, and ESRD alone.

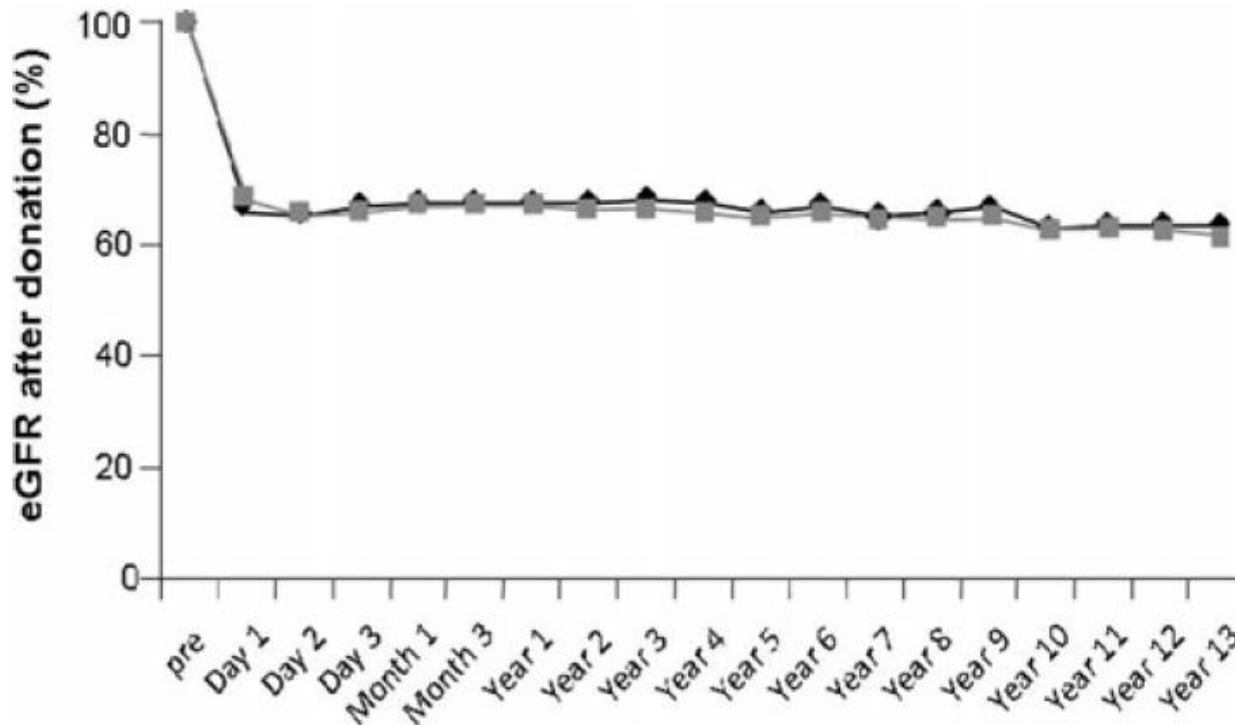
Renal Function Profile in White Kidney Donors: The first 4 Decades (3)



Higher baseline eGFR and younger age were highly associated with a better postdonation eGFR.
(A) Relationship between age at donation and eGFR at 20, 30, and 40 years postdonation.

“As kidney function does not progressively decline, live-kidney donation is considered safe”

Dols et al.



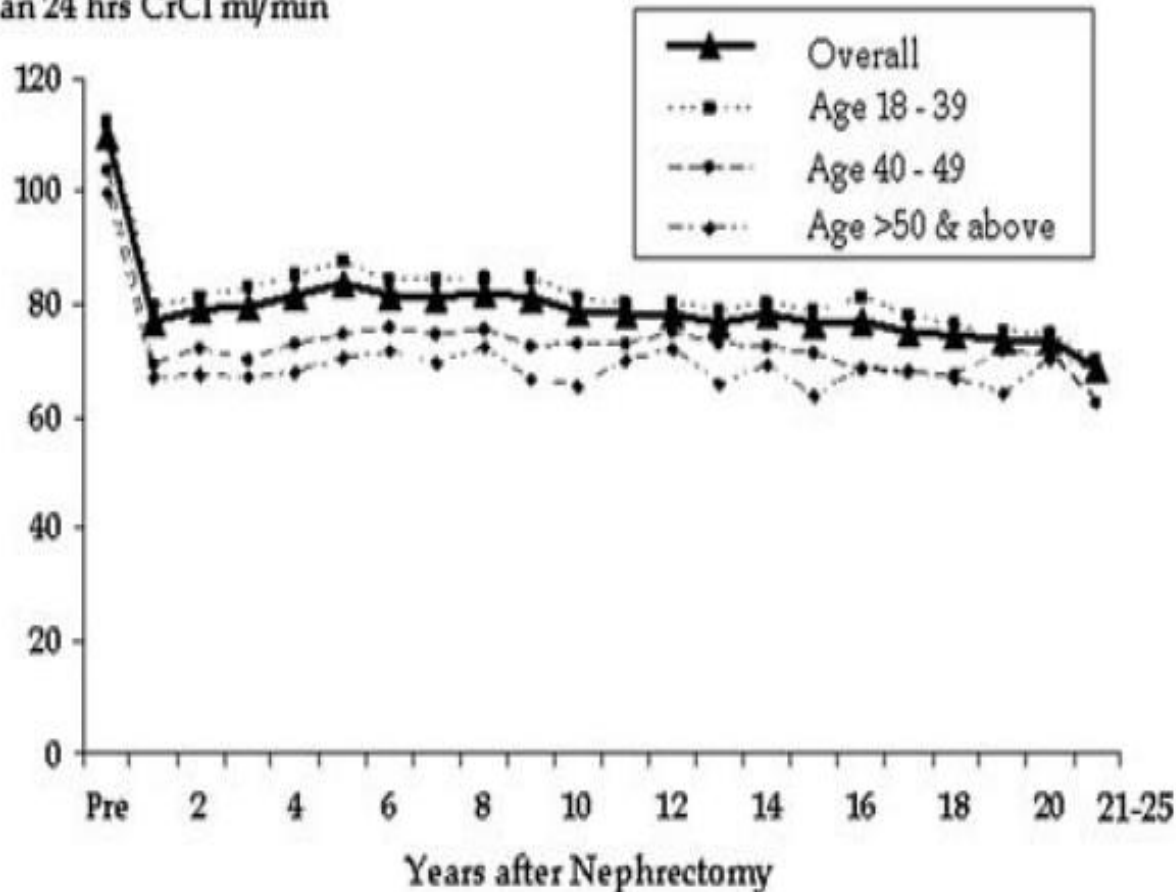
Percent difference in eGFR in donors > 60 y (65y; n=117) versus < 60 y (46y; n=422)

No difference in proteinuria, and hypertension; no donors with GFR<30 mL/min.

25 donors > 70y (74): outcomes similar to those < 70y, except for initial hospital stay.

Long-term safety of living kidney donation in an emerging country (Pakistan)

Mean 24 hrs CrCl ml/min



A “small” control group (n=70) of non-donor siblings.

Higher fasting glucose and hypertension in non-donor

Single-center study, 1985-2012: 3,748 LD; of these 2,696 donors followed-up for up to 27 years (median 5.6 years)
ESDR : 6 (0.2%)

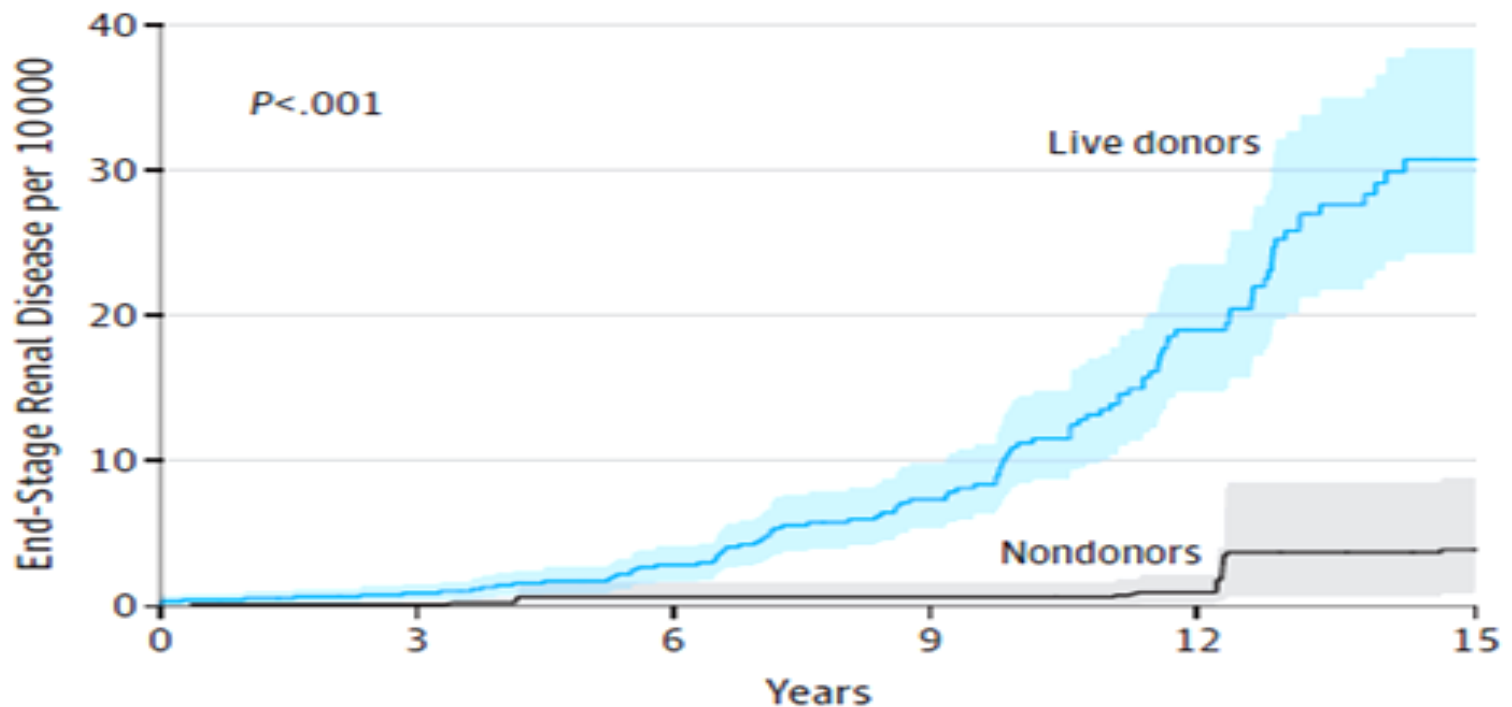
ESDR after live-kidney donation

Risk of end-stage renal disease following live kidney donation (1)

- Included 96,217 US living-kidney donors
- Compared to 9,364 healthy subjects (participants in NHANES III) who could have been kidney donors
- Estimated risk of ESRD in donors at 15 years after donation 30.8 per 10,000 in donors and 3.9 per 10,000 in matched healthy non-donor counterpart.

Risk of end-stage renal disease following live kidney donation (2)

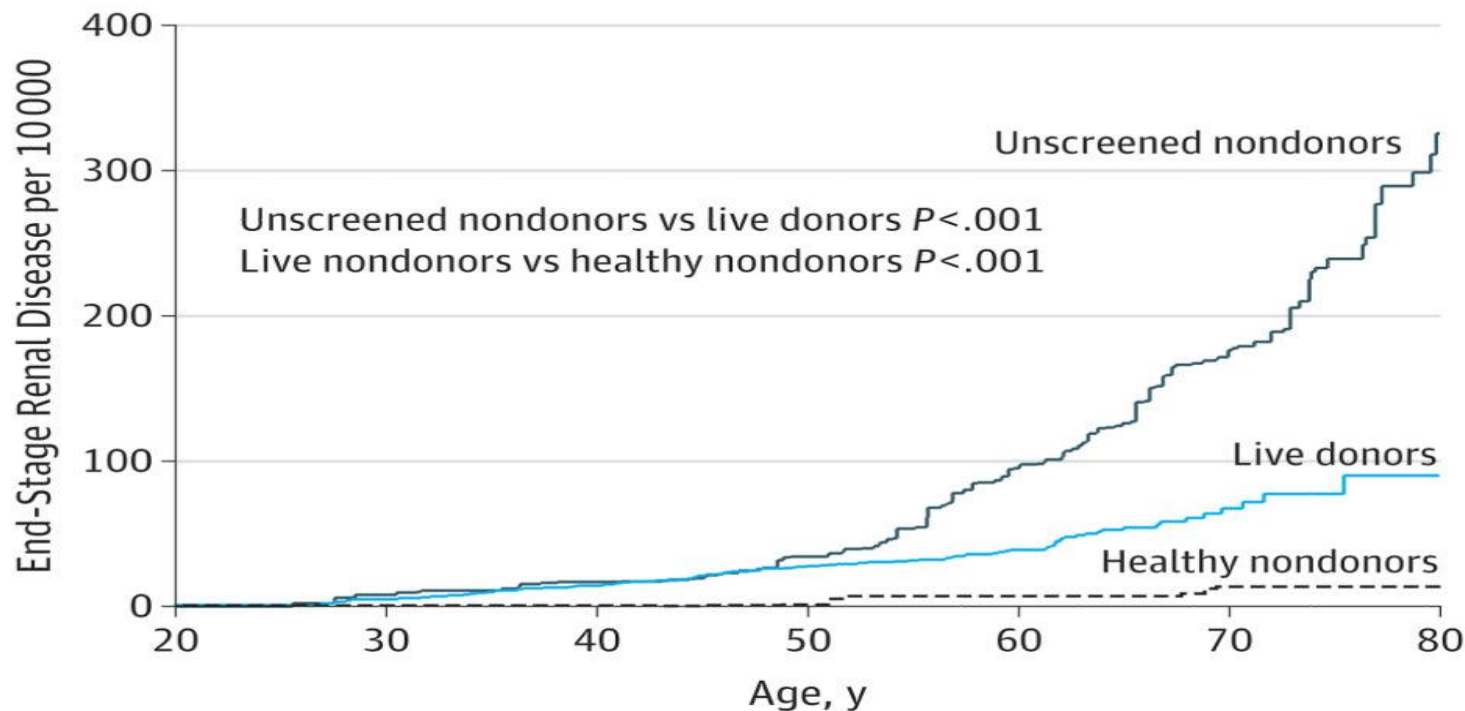
A Cumulative incidence of end-stage renal disease



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 |

Risk of end-stage renal disease following live kidney donation (3)

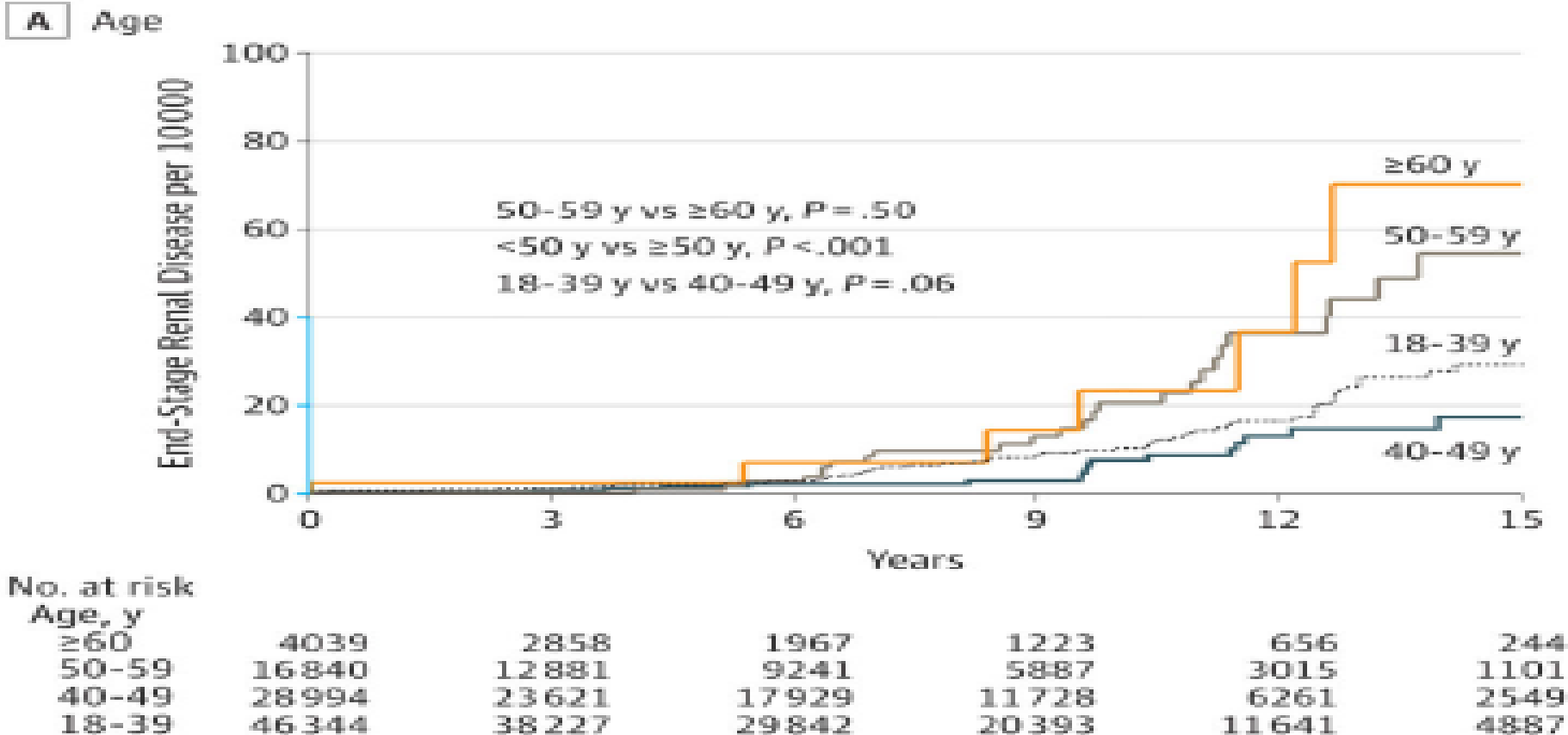


| No. at risk | 20 | 30 | 40 | 50 | 60 | 70 | 80 |
|---------------------|------|-------|-------|-------|-------|------|-----|
| Unscreened nondonor | 1296 | 18436 | 36272 | 40863 | 26982 | 7990 | 647 |
| Live donor | 1143 | 13144 | 22647 | 22944 | 12151 | 2575 | 218 |
| Healthy nondonor | 1306 | 18487 | 36397 | 40961 | 28358 | 9011 | 870 |

Estimated Lifetime Risk of End-Stage Renal Disease in Matched But Unscreened Nondonors, Live Kidney Donors, and Matched Healthy Nondonors

Nondonors were identified among participants in the third National Health and Nutrition Examination Survey. Healthy nondonors were a subset of unscreened nondonors. Comparisons were made by bootstrapping.

Risk of end-stage renal disease following live kidney donation (4)



Cumulative Incidence of End-Stage Renal Disease in Live Kidney Donors

Estimates obtained using Kaplan-Meier methods and compared using log-rank tests. The y-axis scale shown in blue indicates the range from 0 to 40 events per 10 000.

Muzaale AD, et al. JAMA, 2014;311:579-86

Long-term risks for kidney donors (ESRD)

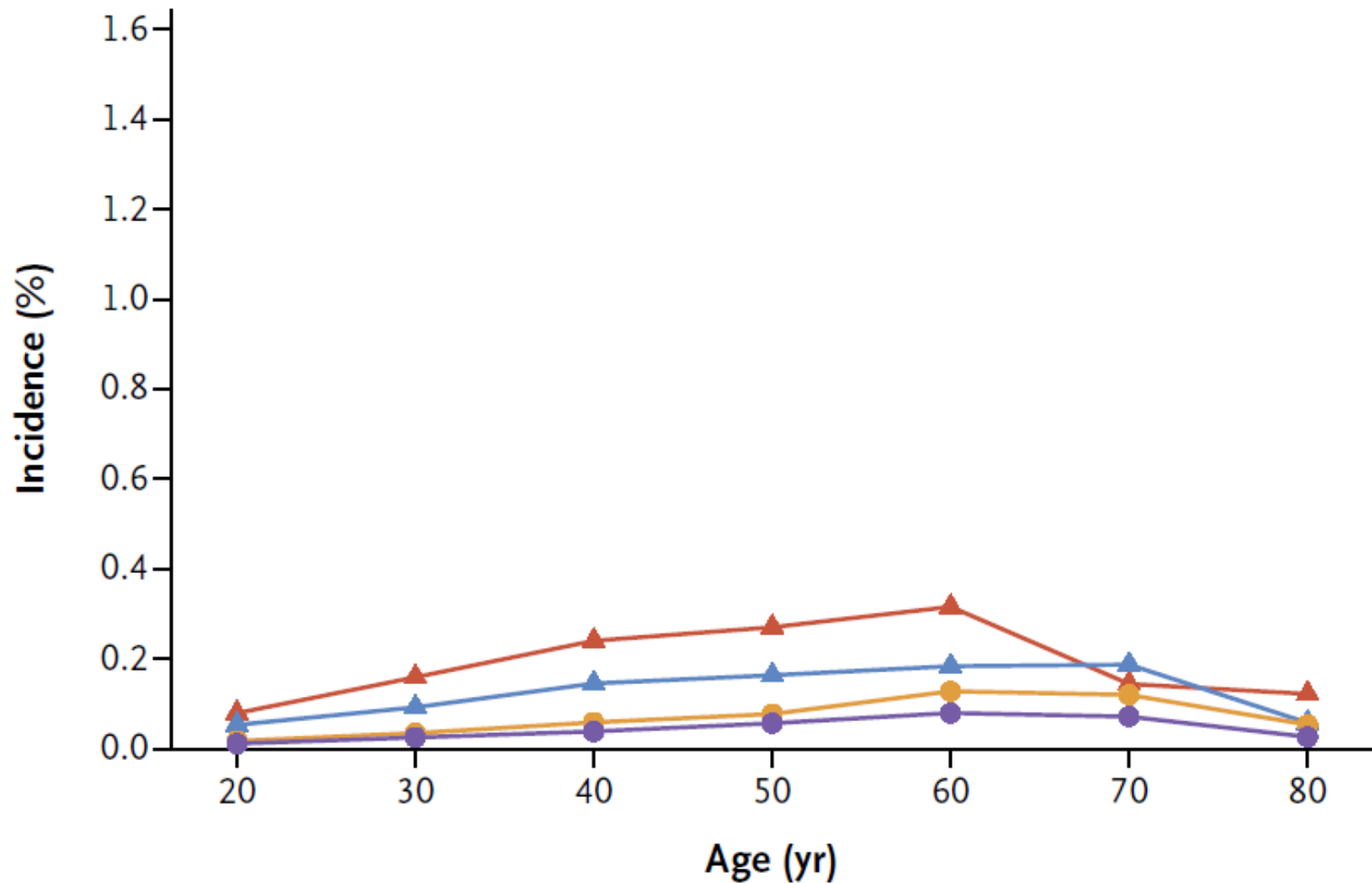
- 1,901 Norwegian live-kidney donors
- Median follow-up: 15 years
- 32,621 controls from HUNT study
- HR for ESRD was greatly increased (11.38, 95% CI 4.37-29.63, $p < 0.001$)

Kidney-failure risk projection for the living kidney-donor candidate

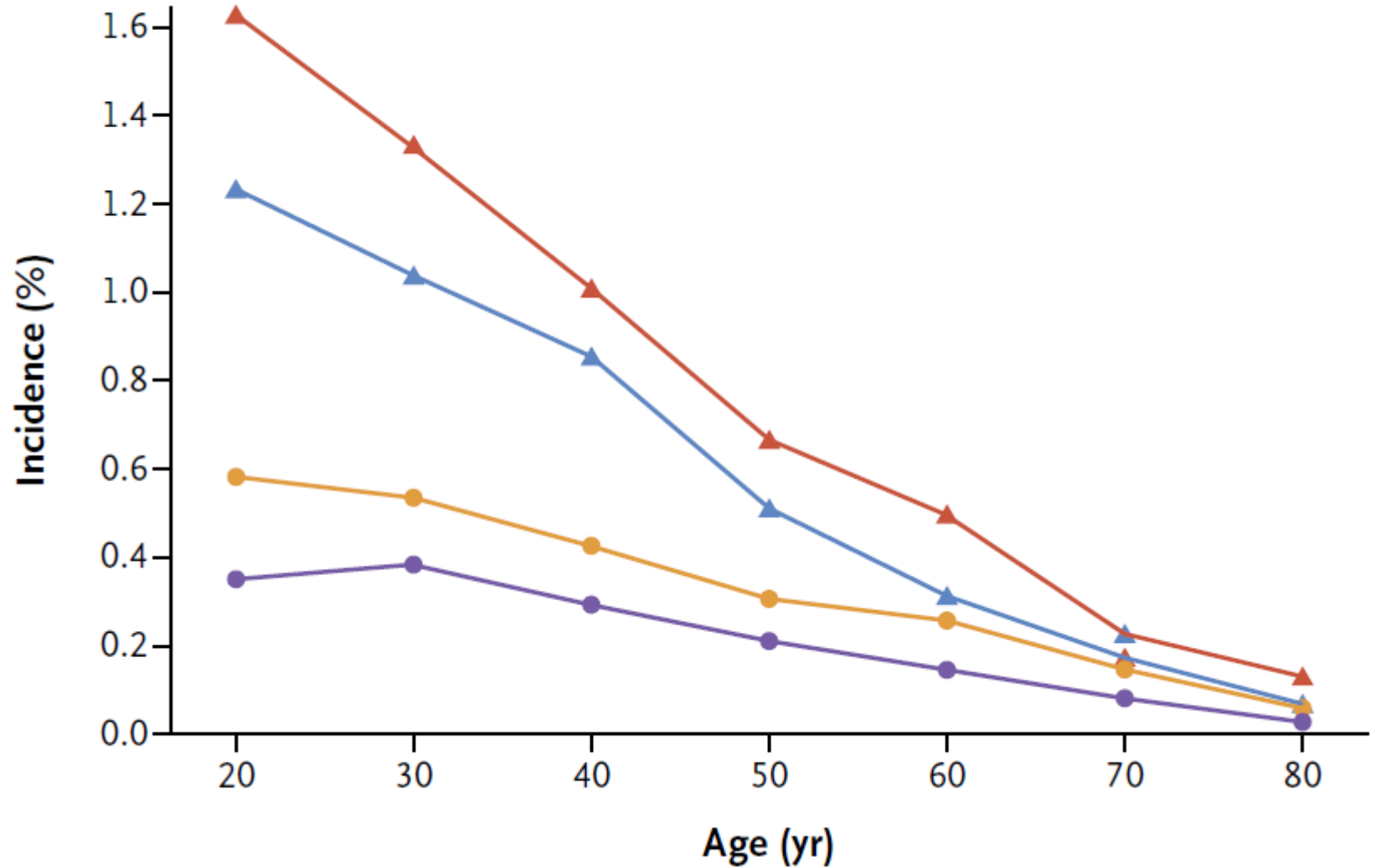
- A total of 4 933 314 participants (7 cohorts) were followed of median of 4 to 16 years. In the absence of donation 15 years risk for ESRD varied from 0.04% to 0.24%
- The 15-year ESRD risk after donation among 52,998 kidney donors was 3.5 to 5.3 times higher as the projected risk in the absence of donation

Black men Black women White men White women

A 15-Year Projected Incidence of ESRD



B Lifetime Projected Incidence of ESRD



- Only 2.8% of US living-kidney donors were 65 years or older
 - Their estimates suggest that “healthy older adults may be appropriate donor candidates with respect to their future ESRD risk”.
- In the model-based life time projections the risk was highest in youngest age groups, particularly among young blacks
- “Many older persons had low long-term risk of ESRD, even in the presence of health characteristics that are often considered to be contraindications to donation, such as low GFR or mild hypertension.”

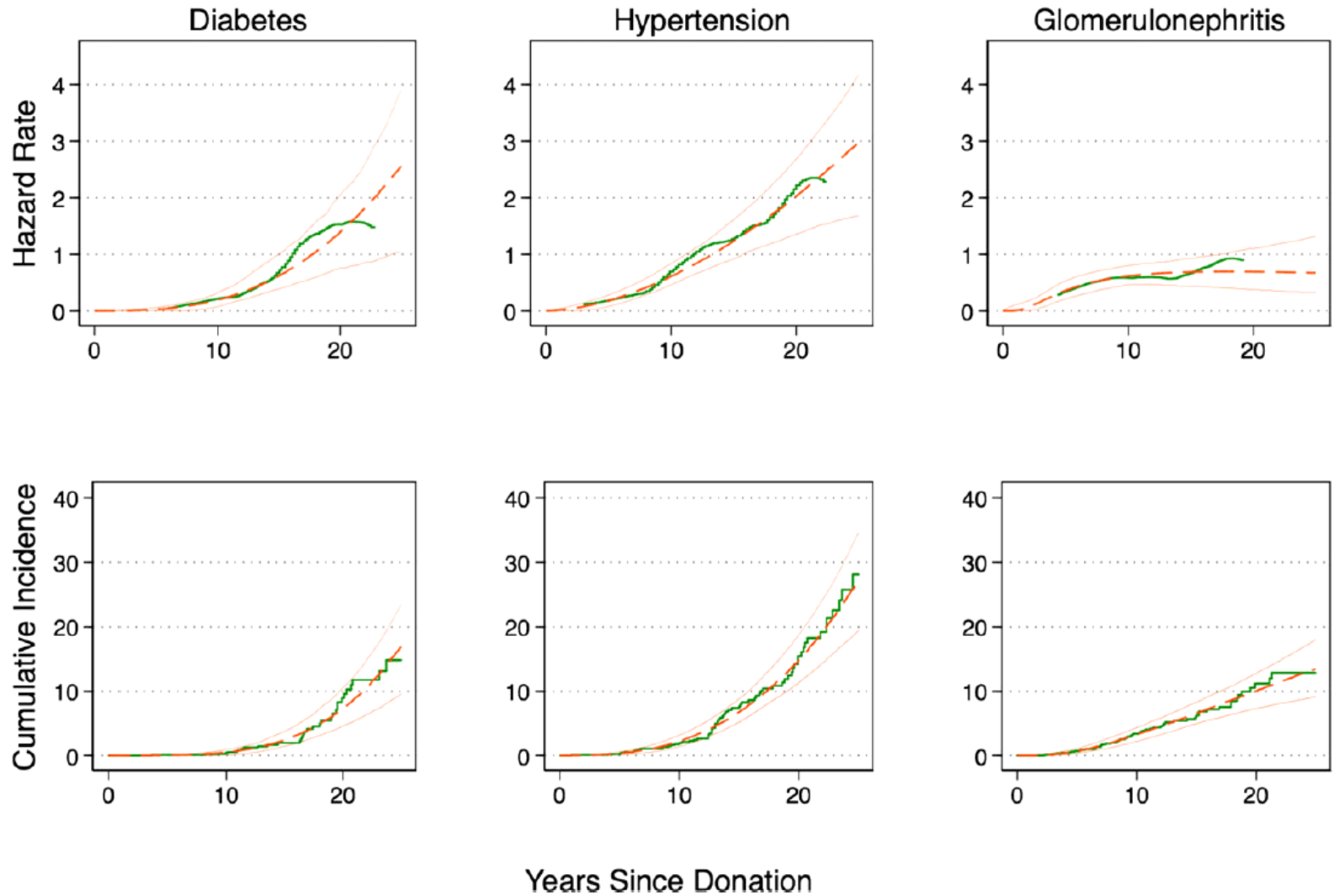
ESRD in donor compared to a “healthy” population

- Norwegian experience, Mjøen/Holdaas KI 2014;86:162
 - Around 11 times increased risk for ESRD
- “Risk of End-Stage Renal Disease Following Live-Kidney Donation” Muzaale/Segev, JAMA 2014
 - Around 8 – 10 times increased risk for ESRD
- “Mortality, Cardiovascular and End-Stage Disease outcomes among Older Live-Kidney Donors” Reese et al JASN 2013; 24: 71A
 - Around 7 – 8 times increased risk for ESRD
- “Kidney-Failure Risk Projection for the Living-Kidney Donor Candidates” Grams et al. NEJM, 2016
 - 15 year observation period, estimated a 3.5 – 5.3 times increased risk of ESRD

Patterns of End-stage Renal Disease Caused by Diabetes, hypertension and Glomerulonephritis in Live Kidney Donors

- Observed 125,427 donors for a median of 11 years and linked to ESRD registry data
- Early post-donation ESRD associated with glomerulonephritis.
- Late post-donation ESRD associated with diabetes and hypertension
 - 7.7 fold risk of developing diabetic ESRD late (10-25 years) post donation versus early (<10 years) post-donation
 - 2.6 fold risk of developing hypertensive ESRD late than early.

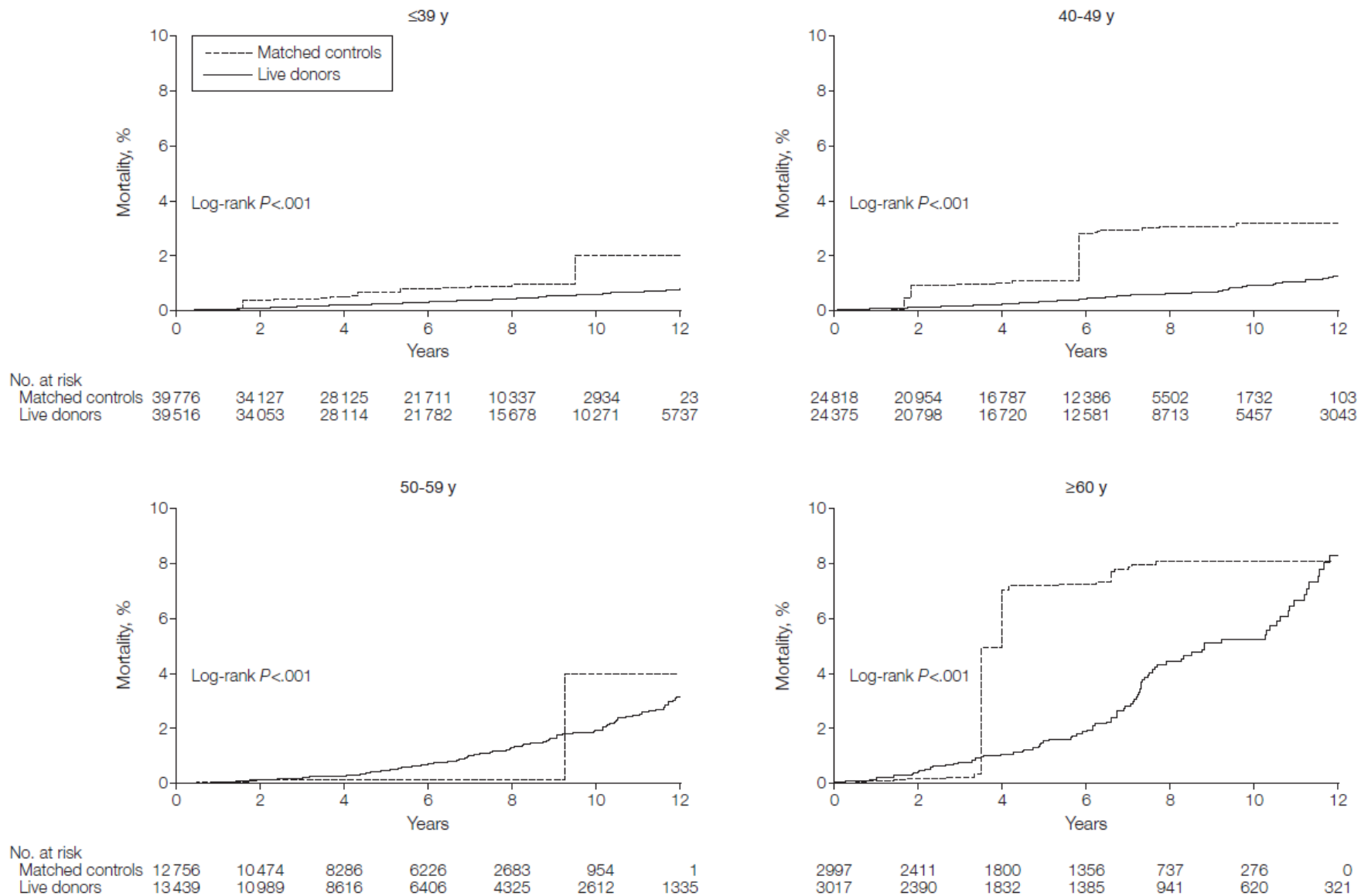
Cause-Specific Risk of ESRD per 10,000 Donors



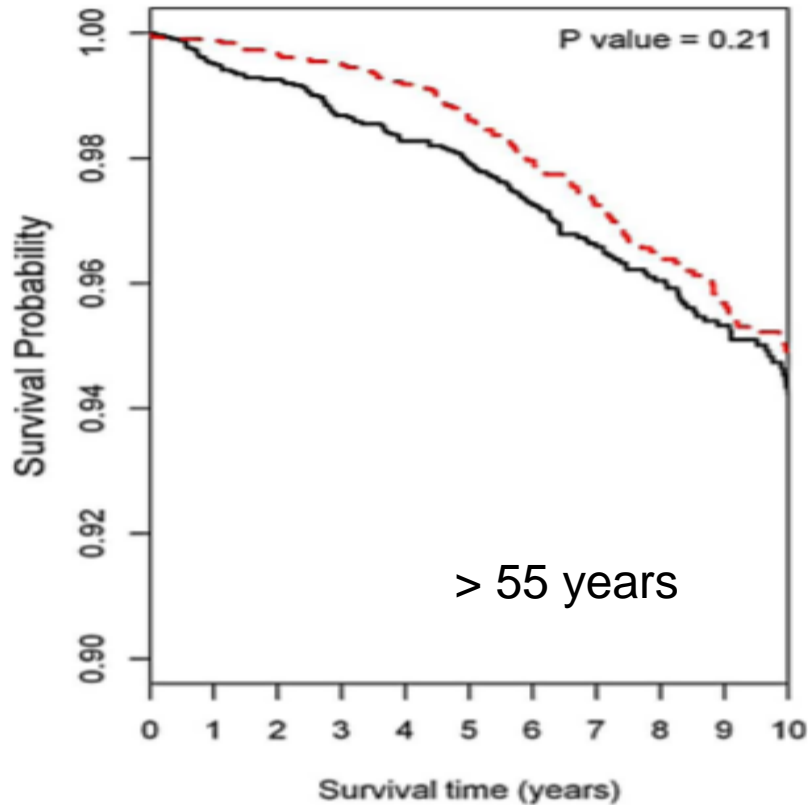
- Donor loses 30% renal function as a result of nephrectomy Therefore has less reserve.
- All else being equal, a donor will have a low GFR years before a matched non donor. Therefore with normal loss of GFR or with development of disease, a donor has increased risk.
- The majority of kidney disease begins in middle age:
 - normal young donors are at more increased long-term risk than normal older donors
 - low normal GFR is a risk for ESRD when kidney disease starts

Long-term live-donor mortality

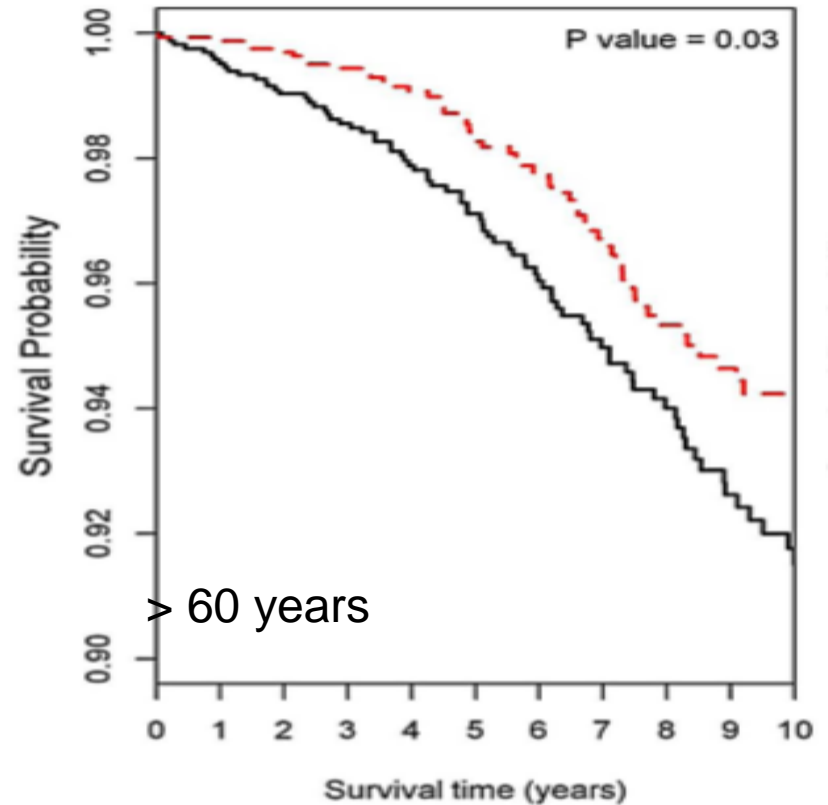
Figure 2. Kaplan-Meier Curves Comparing Cumulative Mortality of Live Kidney Donors and Matched Controls by Age Category



Matched controls were identified among participants in the third National Health and Nutrition Examination Survey.



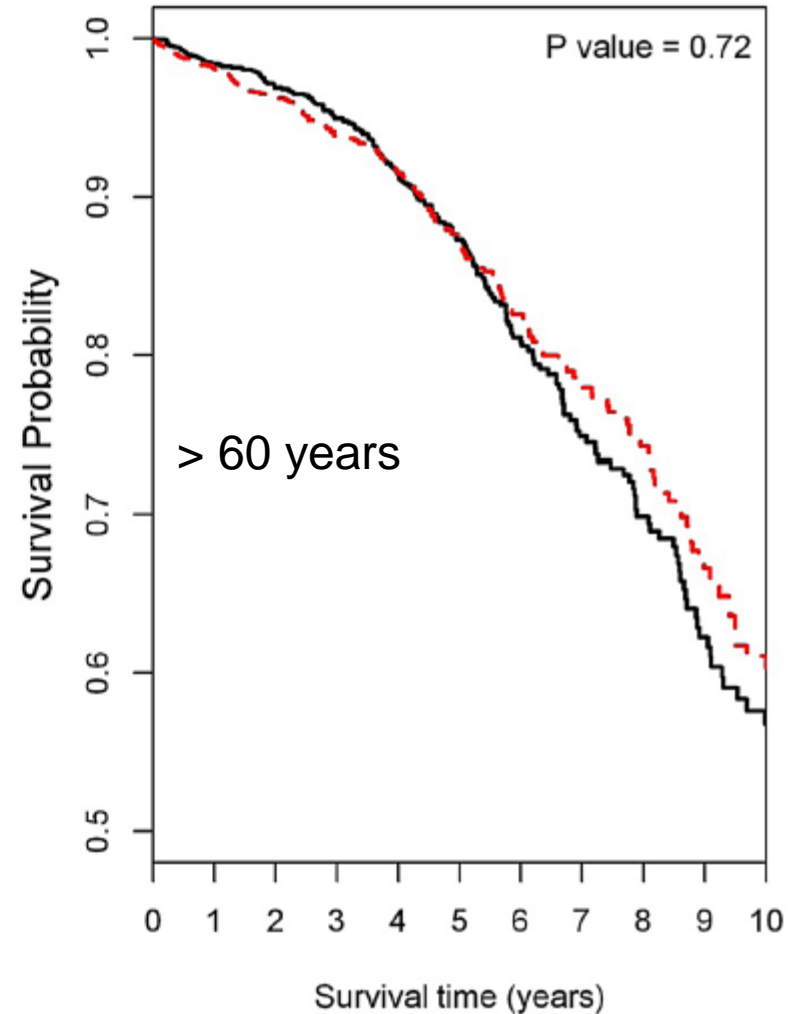
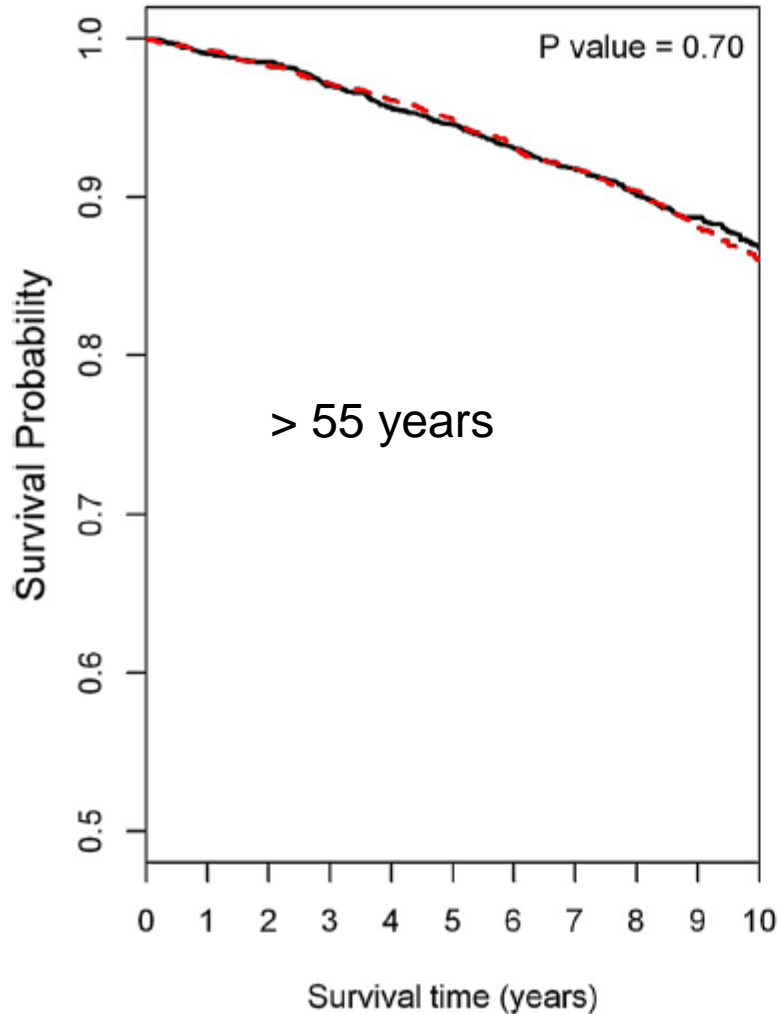
— Non-donor
 3368 3352 3338 3036 2797 2541 2249 1948 1623 1286 915
 - - - Donor
 3368 3365 3352 3059 2821 2555 2263 1962 1631 1287 921



— Non-donor
 1648 1641 1632 1423 1242 1068 903 755 611 478 369
 - - - Donor
 1648 1647 1644 1436 1260 1085 921 769 620 489 377

Matched 3368 older (>55, mean age 59 years) live donors matched to carefully selected healthy older individuals in the Health and Retirement study. **Primary outcome:** mortality.

Mortality and CV events among Old Live Kidney donors



Living kidney Donors aged 70 and Older: Recipient and Donor outcomes

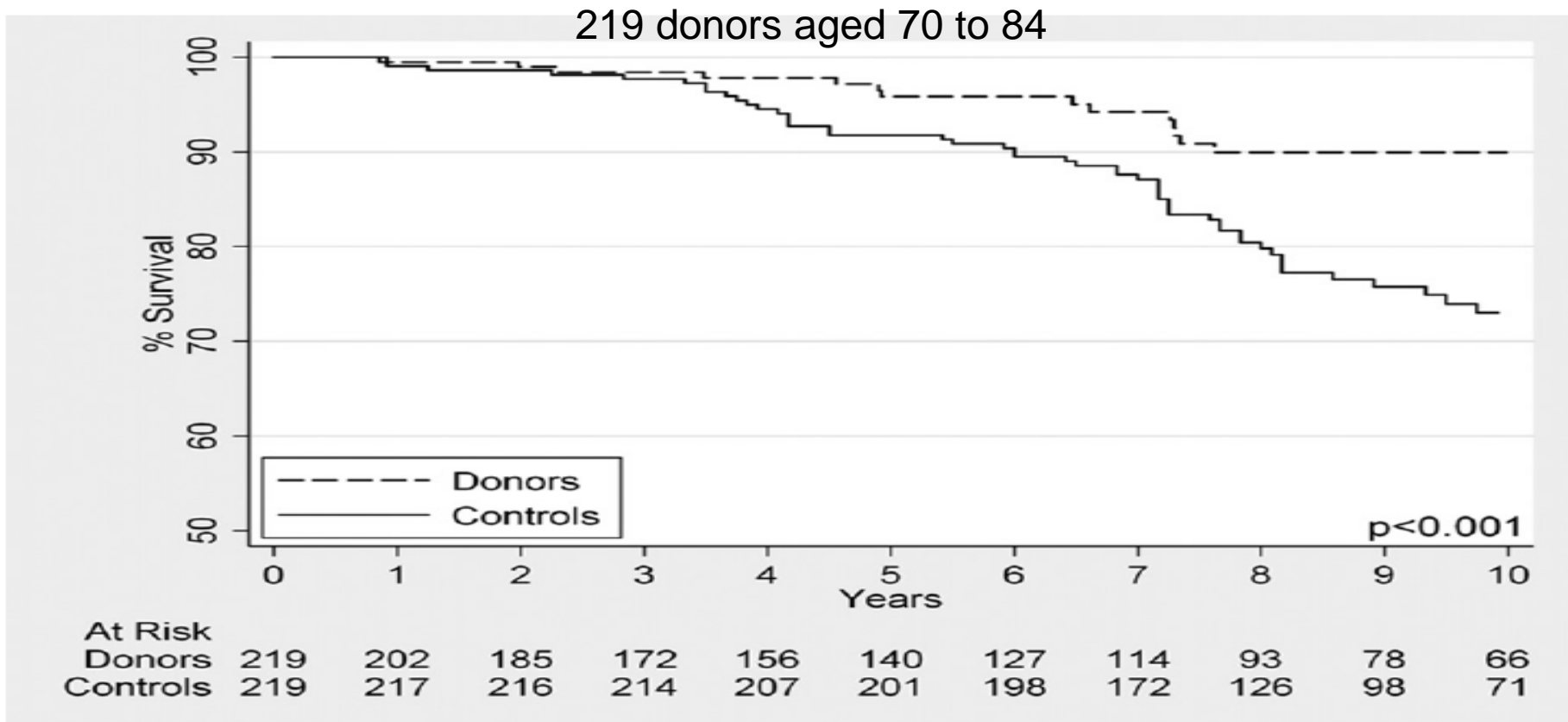
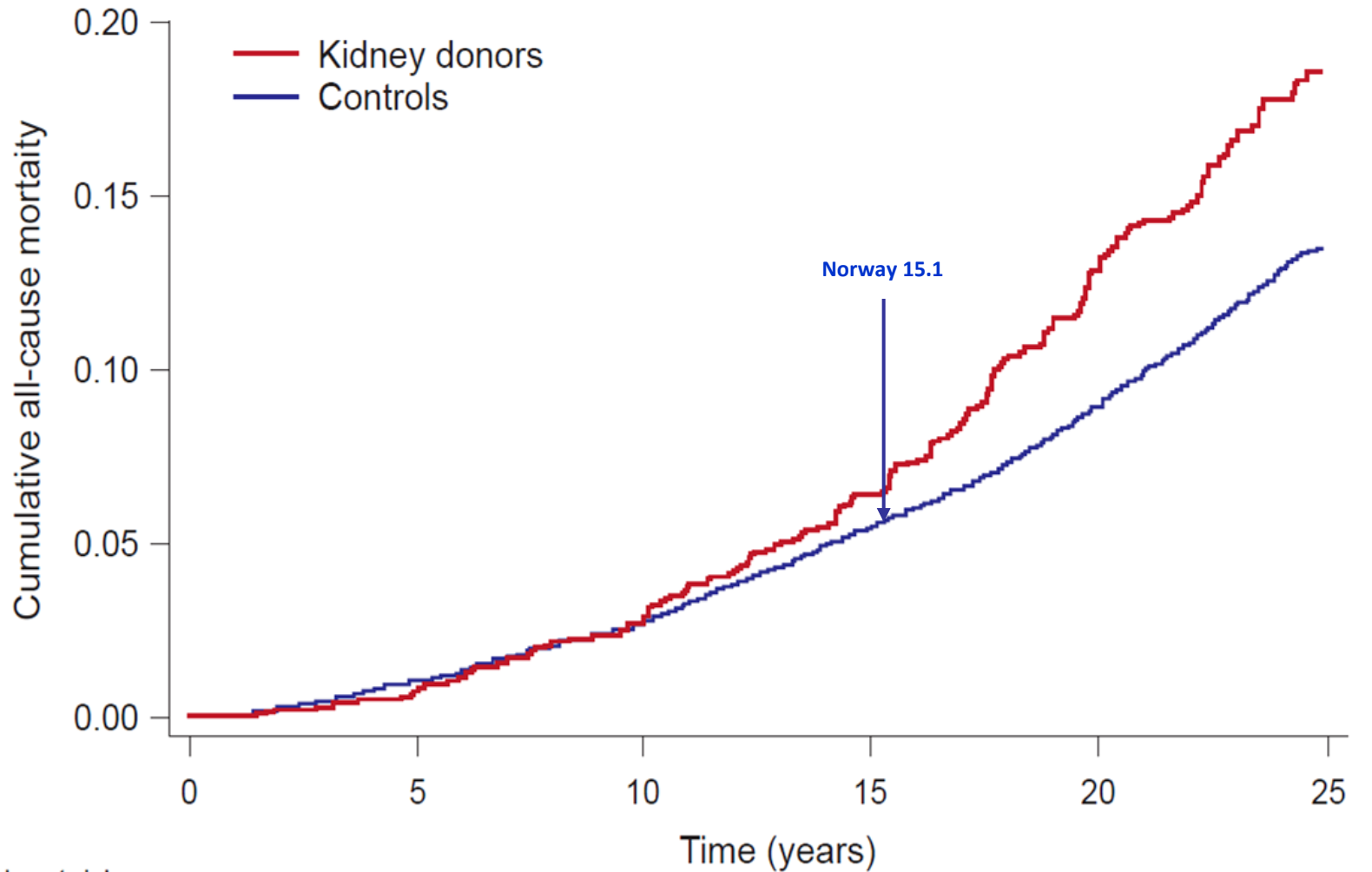


Figure 3. | Kaplan-Meier survival curve of live kidney donors aged ≥ 70 , compared with matched healthy controls drawn from the National Health and Nutrition Examination Survey cohort.

Mortality

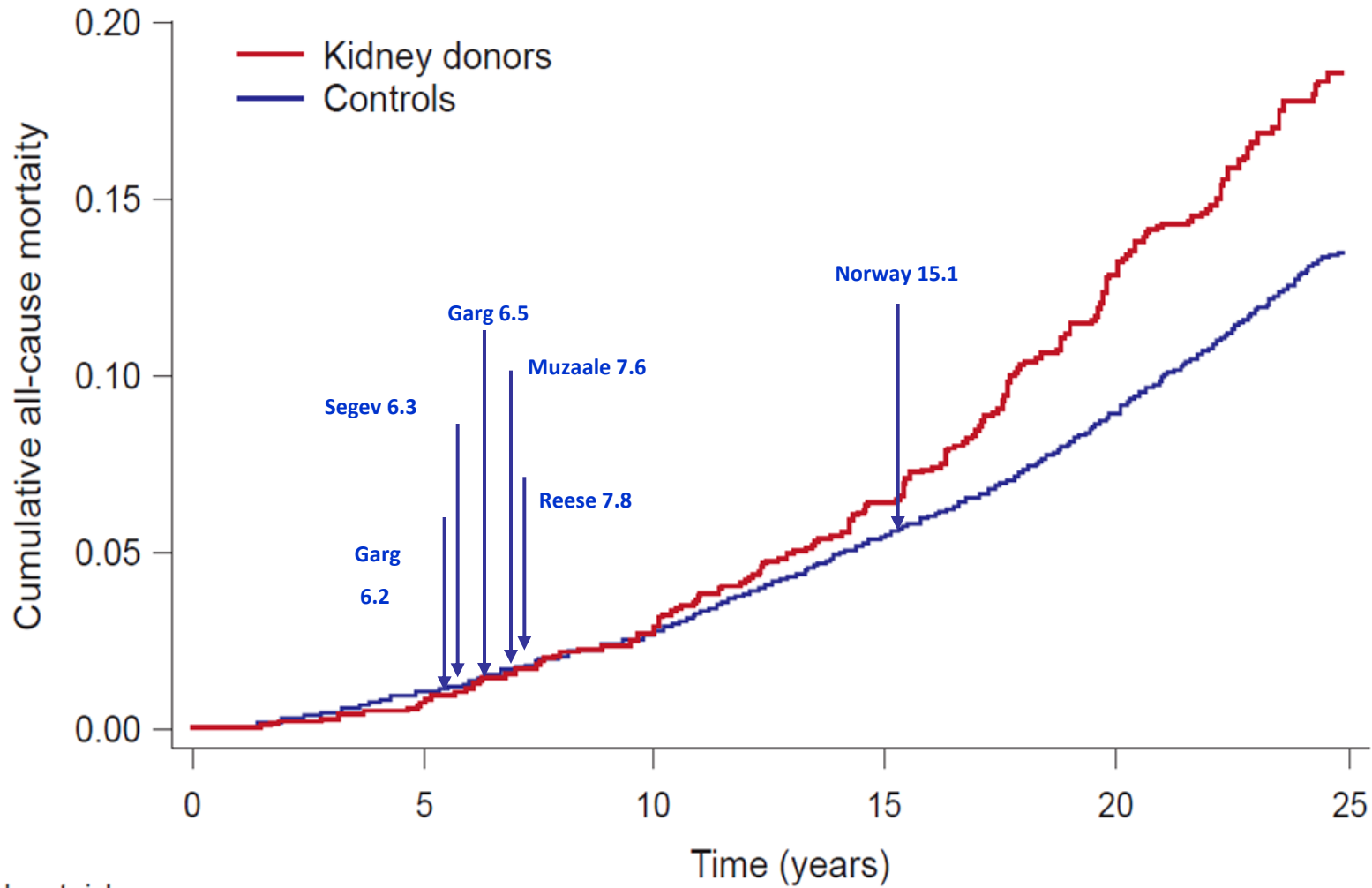
- Hazard ratio (HR) for all-cause death was 1.30 (95% confidence interval [CI] 1.11-1.52, $p=0.001$).
- HR for cardiovascular death (HR 1.40, 95% CI 1.03-1.91, $p=0.03$)

Mortality vs. years of follow-up

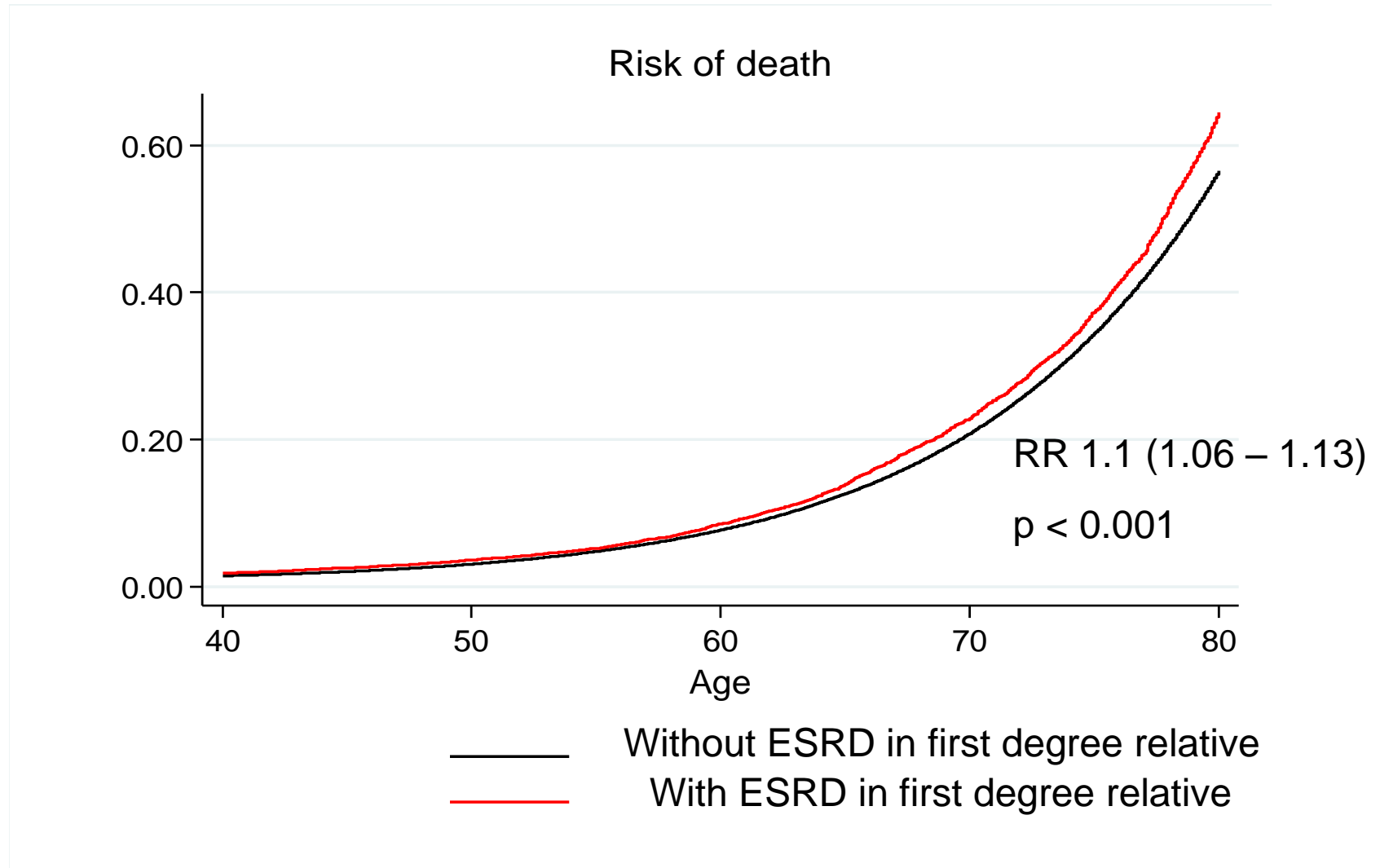


| No. at risk | 0 | 5 | 10 | 15 | 20 | 25 |
|-------------|--------|--------|--------|--------|--------|--------|
| Donors | 1,901 | 1,686 | 1,296 | 951 | 699 | 293 |
| Controls | 31,575 | 31,405 | 30,700 | 29,864 | 28,743 | 12,600 |

Mortality vs. years of follow-up



5 119 134 subjects included, 8203 developed ESRD, 27 046 had first degree relative with ESRD (1960 – 2009)



Healthy old donors need healthy old controls

- Kidney donors are healthy
- To estimate actual risks attributable to donation, we need donors who are equally healthy at the time of the kidney donor`s nephrectomy
- Available information on comorbidities, blood pressure, BMI, albuminuria, renal function to ensure that controls are healthy enough and to allow for adjusted analyses to reduce confounding factors.

Previous studies

- Early studies have compared kidney donors with controls from the general population
- That might be an inadequate comparison since kidney donors are healthy
- More recent studies have used more appropriate control groups

Young/old donors

- Young kidney donors are very healthy at donation
 - «Normal for now»
- Long follow-up time is needed
- «Harmful effects» may take decades
- Old donors are healthy at donation, shorter exposure time for «harmful effects»

Summary living donor

- Living donors are needed
- Most important message: we need for long-term follow-up
 - Continue to promote LD
 - However, balanced information, especially to “young” donors
 - Older donor, more “relaxed” about “minor” co-morbidity

Older donors

- Older donors have a lower life expectancy than younger ones
- «Younger donors therefore have potential to develop and be exposed to renal and cardiovascular risk factors for a longer period of time than older donors, resulting in an increased life time risk of developing ESRD or premature mortality». (Clayton et al. Transplantation June 2016)
- Consequently these risks will be less in older donors.

The classical selection of live kidney donors

- It is a request that donors are "healthy enough".
 - Some are qualified; others are dismissed
- Any risk factors will stop donation
- Old age per se is not a risk

Renal function requirement for potential living donor

GFR should be assessed by isotope-clearance/iotholamate technique.

Estimated/calculated GFR or creatinine clearance is not acceptable.

Cut-off values for measured GFR in order to be qualified as a potential donor

| Age | (mL/min/1.73m²) |
|-----------------|-----------------------------------|
| Below 50 | 90 |
| 50 – 60 | 80 |
| 60 – 70 | 70 |
| 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 1 antihypertensive medication or 1 antihypertensive medication with diuretics.

Diabetes/Impaired glucose tolerance

Patients with diabetes are not accepted as donors

Donors above 60 years of age are accepted with elevated OGTT

Donors below the age of 60 must have normal OGTT

Proteinuria

Patient with macroalbuminuria is not accepted as donors

Donors above 60 years may have microalbuminuria

Microalbuminuria for donors below the age of 60 are excluded

Summary

- «Old» Donors compared to «young» donors
 - No or minimal increased perioperative complications
 - Seems to be no difference for increased risk for ERSD
 - No increased long-term mortality attributable to donor nephrectomy

Donation from Old Living Donors

How safe is it?

Reasonably safe

Thank you for your attention

