



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Living Kidney Donation: Assessing Renal Risk

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**Medical School:**

University College Cork, Ireland

Residency:

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Fellowship:

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Clinical Interests:

Renal transplantation, live kidney donation, CVD in CKD

Academic Interests:

CV disease in CKD & transplantation

Education and scientific research training

Transplantation immunology



Disclosures

Editorial Director – nephSAP, American Society of Nephrology

Lexicon Pharmaceuticals – research support

Alexion Pharmaceuticals, Vera Therapeutics, Astra Zeneca – consulting

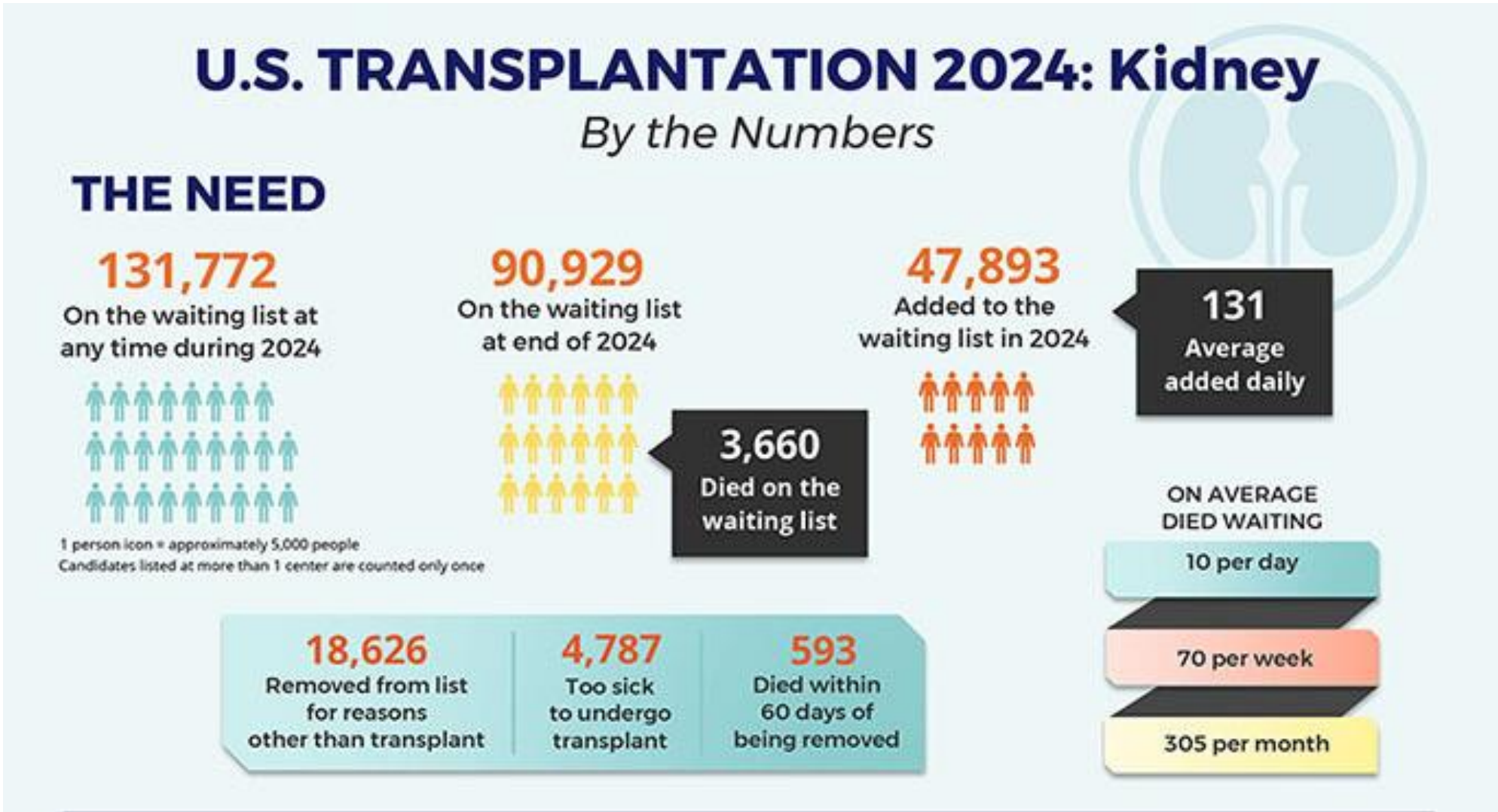


Objectives

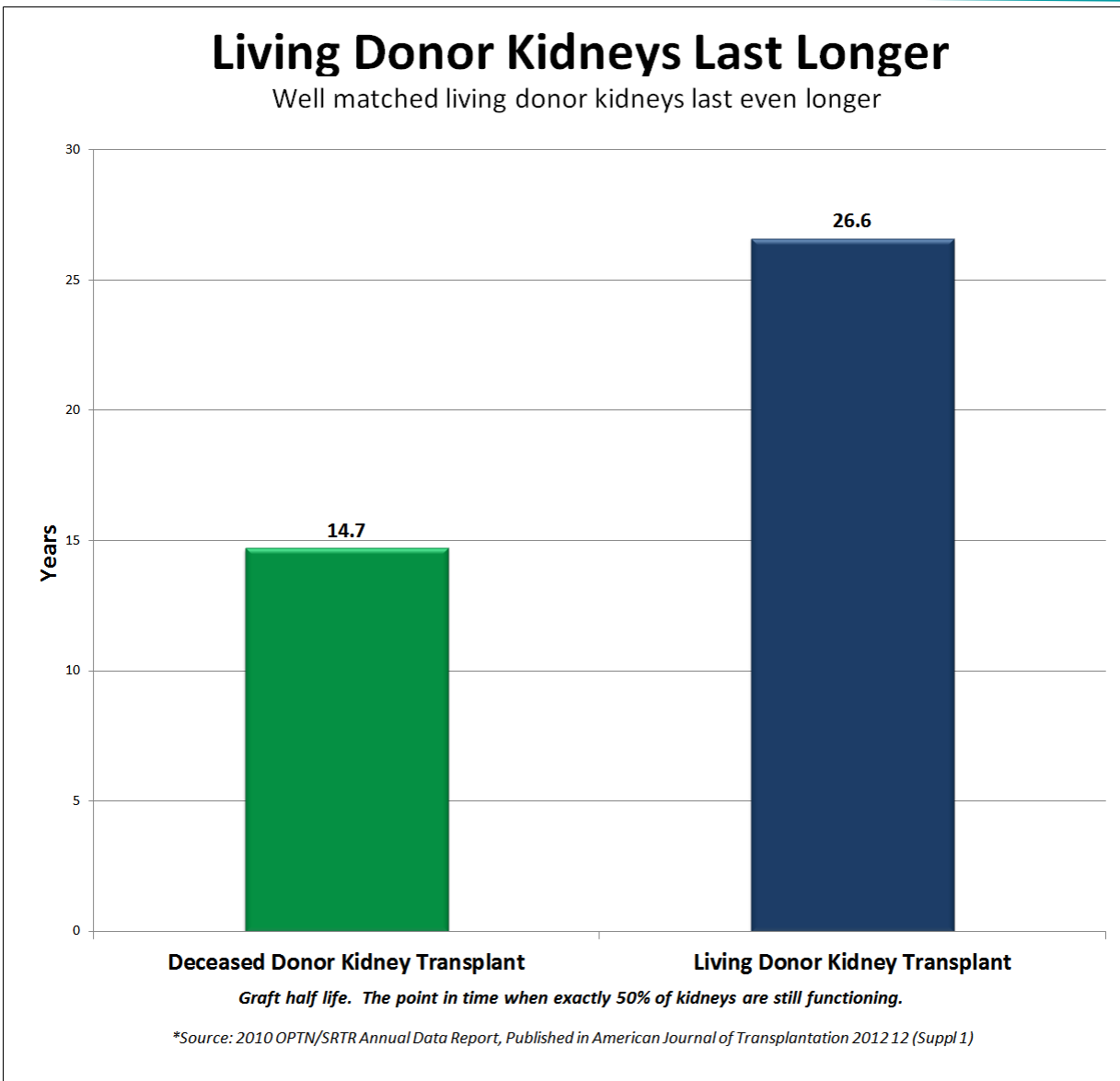
1. Review physiological changes after kidney donation
2. Discuss the risk of CKD/ESKD after donation
3. Describe methods of predicting risk of ESKD in donors
4. Review special populations – young donors, older donors, ApoL1 risk genotypes



OPTN/SRTR 2024 Annual Data Report: Kidney



Benefits of Live Donor Kidney Transplantation



Pre-emptive transplantation:
Best kidney & recipient outcomes

Median Survival:
Live donor Tx: 19 years
Deceased donor Tx: 12 years

Poggio et al AJT 2021
Schaubel et al JAMA 2022

Benefits of Live Donor Kidney Transplantation

Faster access to transplant

Opportunity to avoid dialysis entirely

Potential for a better matched kidney

Lower rates of delayed graft function

Flexibility in finding a donor: Exchange programs/Advanced donation



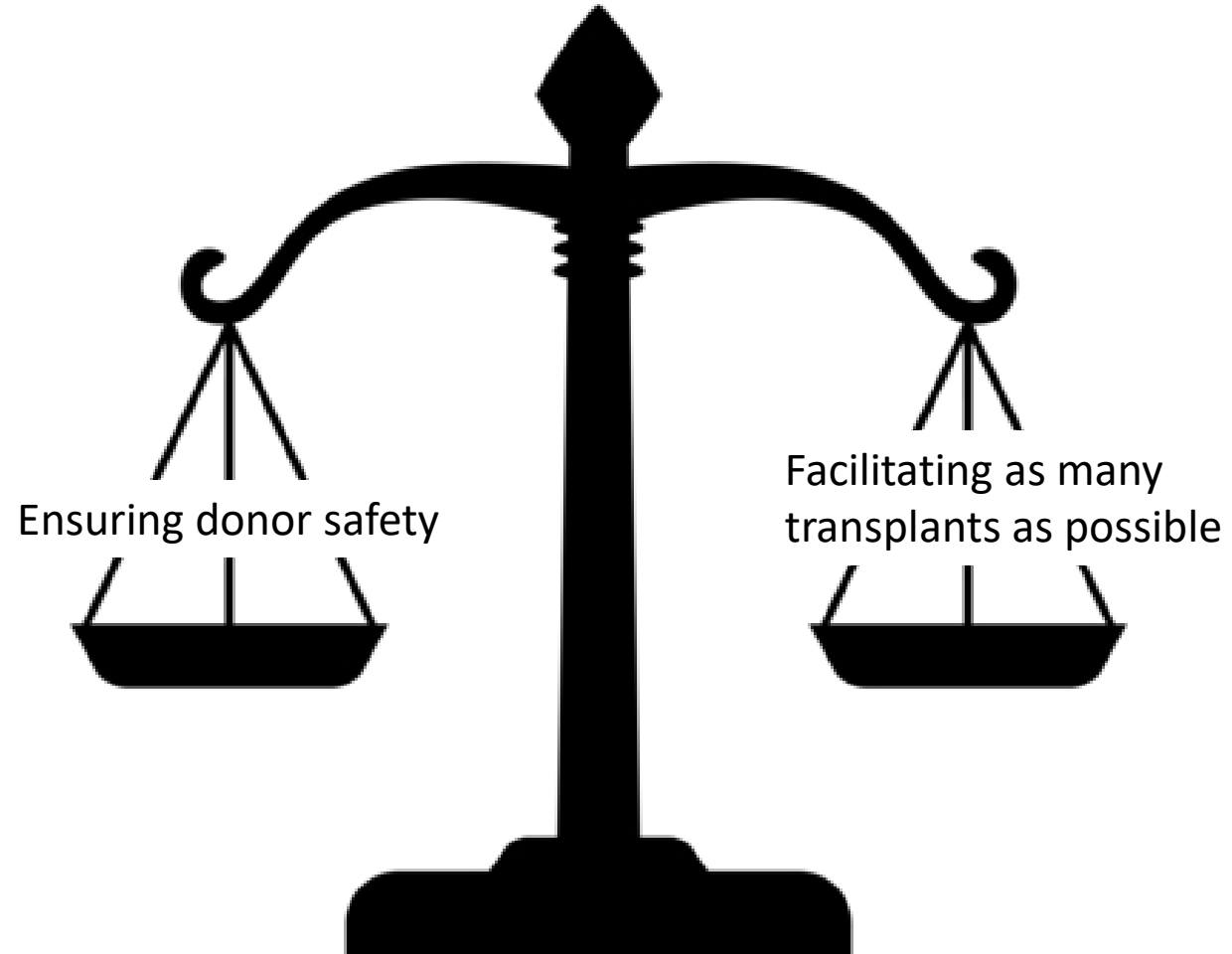
Candidate Selection: Assessing renal function



Evaluating Kidney Donors



Evaluating Kidney Donors



Factors to consider in accepting a candidate

Screening to confirm health rather than exclude disease

Risks of future ESKD

- Demographic risks (age, race, sex)
- Risk related to health characteristics (BP, BMI, smoking, FHx etc)
- Donation-attributable risk

Substantial uncertainty, especially across patient subgroups



KDIGO Guidelines: Care of the Renal Donor

Kidney function should be assessed as GFR
eGFR based on creatinine should be used for initial assessment

Ideal:

- Measured creatinine clearance, by iothalamate, inulin, radioisotope clearance

Alternatives:

- 24hr urine for creatinine clearance
- Repeated measured of eGFR
- Estimates from creatinine and cystatin



KDIGO Guidelines: Donor selection

Acceptable: Creatinine clearance $>90\text{mls/min/1.73m}^2$

CrCl $60\text{-}89\text{mls/min/1.73m}^2$ - individualized decision-making based on acceptable risk threshold

Urine albumin/creatinine ratio $<30\text{mg/g}$ (regardless of GFR)



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Counsel patients of increase in risk of ESKD following donation, but the absolute risk out to 15 years remains low

Donors with hypertension controlled to $<140/90\text{mmHg}$ on 1-2 antihypertensives and without end organ damage, may be suitable to donate



Nephron Endowment and Kidney Donation



Distribution of glomerular number in autopsy studies *Hoy et al. KI 2003*

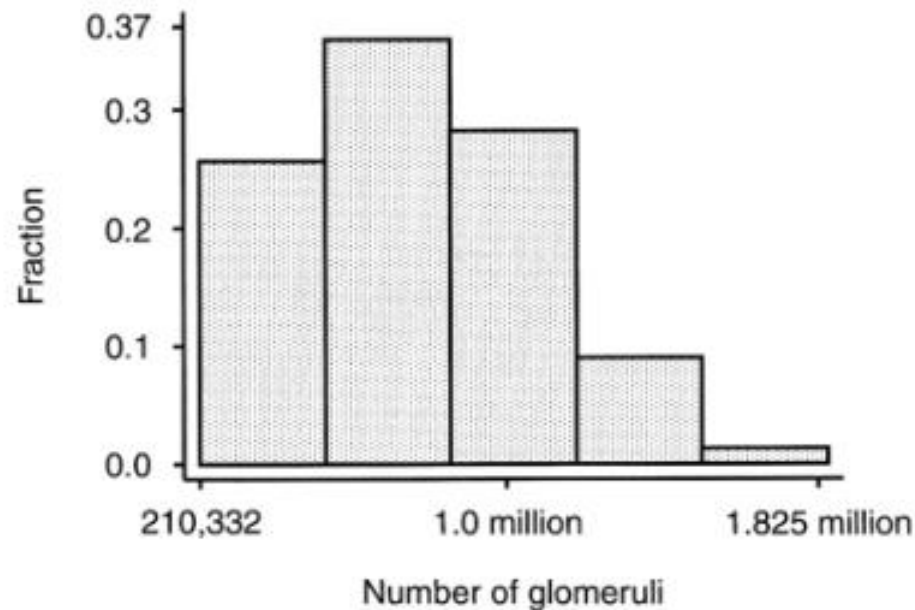


Fig. 3. Distribution of total number of glomeruli, and thereby nephrons, in kidneys (all subjects).

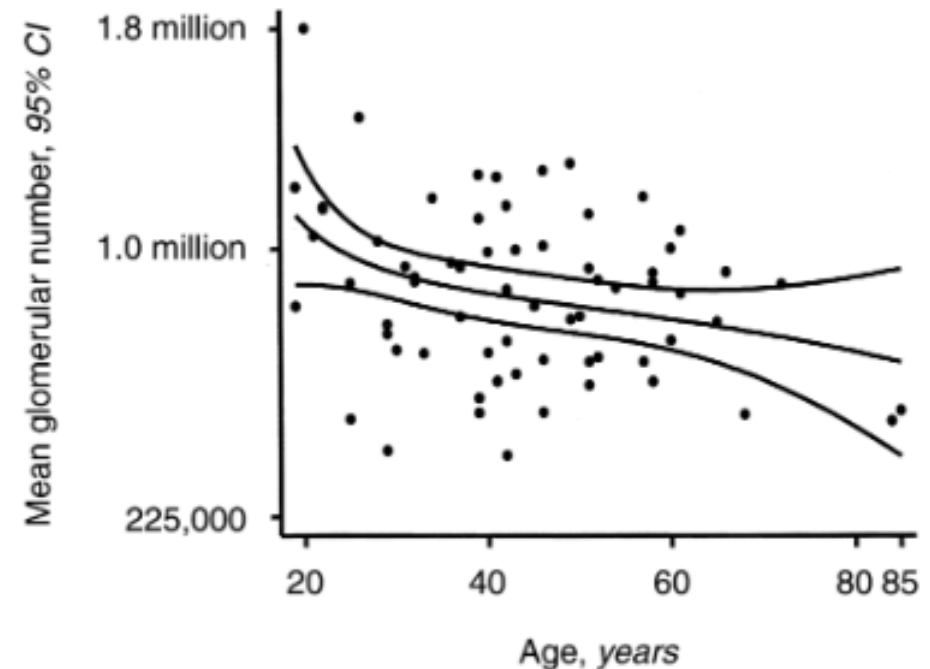


Fig. 4. Effect of age on total glomerular number. Individual values are shown together with the mean and 95% confidence intervals. Values are adults (18+ years) only and adjusted for sex.

Kidney weight, glomerular volume and glomerular mass increase with increased BSA; but glomerular number does not



Single Nephron GFR in Healthy Adults.

Denic et al, *NEJM* 2017;376:2349-57

Age-Group Differences in Number of Nephrons per Kidney, the Single-Nephron GFR, and Total GFR among 1388 Living Kidney Donors.

Table 2. Age-Group Differences in the Number of Nephrons per Kidney, the Single-Nephron GFR, and Total GFR among 1388 Living Kidney Donors.				
Age Group	No. of Donors	No. of Nephrons	Single-Nephron GFR <i>nl/min</i>	Total GFR <i>ml/min</i>
18–29 yr	190	970,000±430,000	79±42	127±25
30–39 yr	339	930,000±350,000	77±36	124±24
40–49 yr	417	850,000±360,000	81±42	114±23
50–59 yr	300	810,000±360,000	80±40	106±20
60–64 yr	73	750,000±310,000	79±36	101±18
65–69 yr	56	720,000±260,000	76±33	95±17
70–75 yr	13	480,000±170,000	110±44	96±25



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70–75 yr	13	480,000±170,000	110±44	96±25



Nephron endowment and donation:

Wide variations in nephron endowment

- Factors to consider include birth weight, body size, FHx ESKD

Lower glomerular density is associated with glomerular hypertrophy

- Risk factors include higher BMI, FHx ESKD, male, older age, higher albumin excretion

Wide variations in single nephron GFR

- Determinant of post donation GFR



Changes after Kidney Donation



Physiologic changes post kidney donation

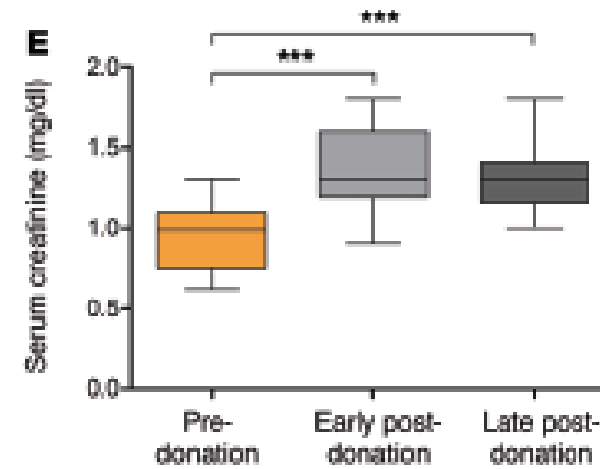
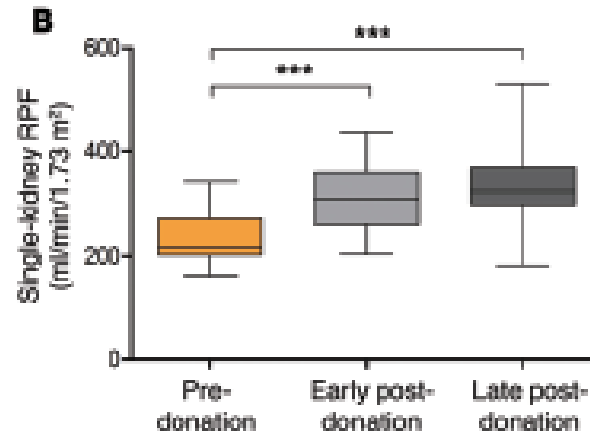
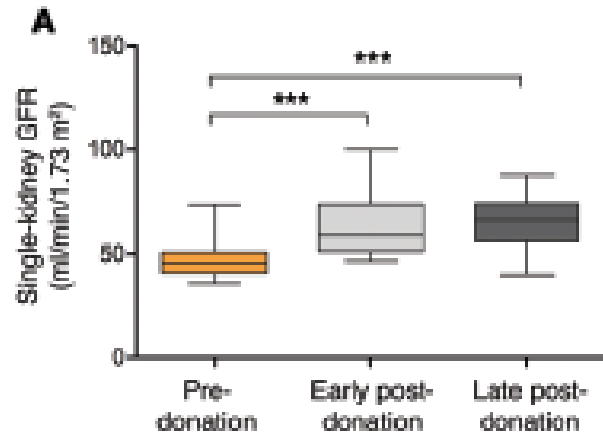
Nephron mass decreases by 50% after donation

GFR in remaining kidney increases by 20-40% by 2 weeks post donation

- Increase in single nephron GFR
- Predominantly hemodynamic
- 'Adaptive hyperfiltration'

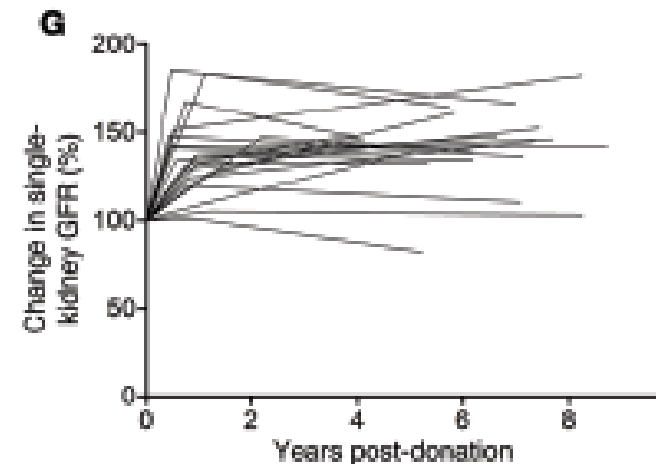


Physiologic changes following kidney donation



Early: <1yr
Late: ~6yrs

Increase in GFR without evidence of glomerular hypertension.



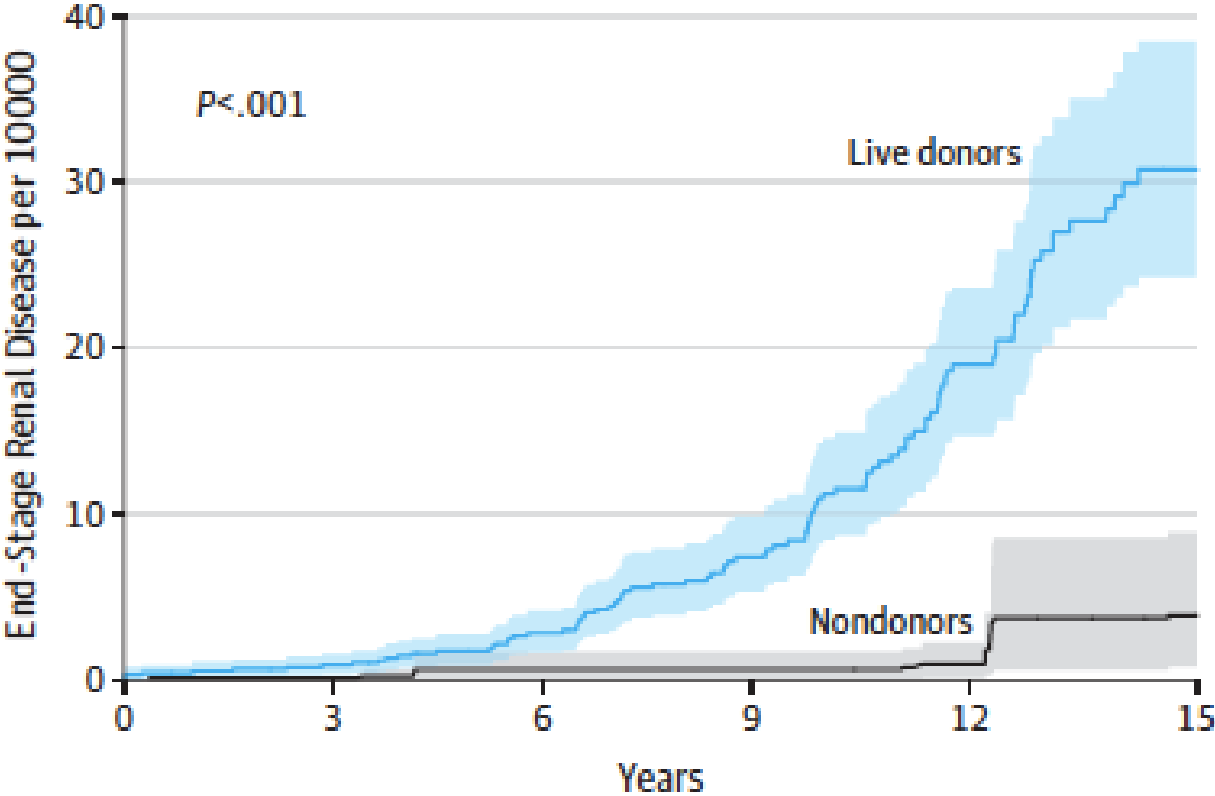
CKD/ESKD after Kidney Donation



Risk of End Stage Renal Disease Following Live Kidney Donation.

Muzaale et al. *JAMA* 2014; 311:(6)579-586

A Cumulative incidence of end-stage renal disease



1994-2011

96,217 kidney donors

20,024 matched controls from
NHANES III

Median follow up:

7.6 years (IQR 3.9-11.5 yrs)
donors

15 years (IQR 13.7-15.0
yrs) non donors

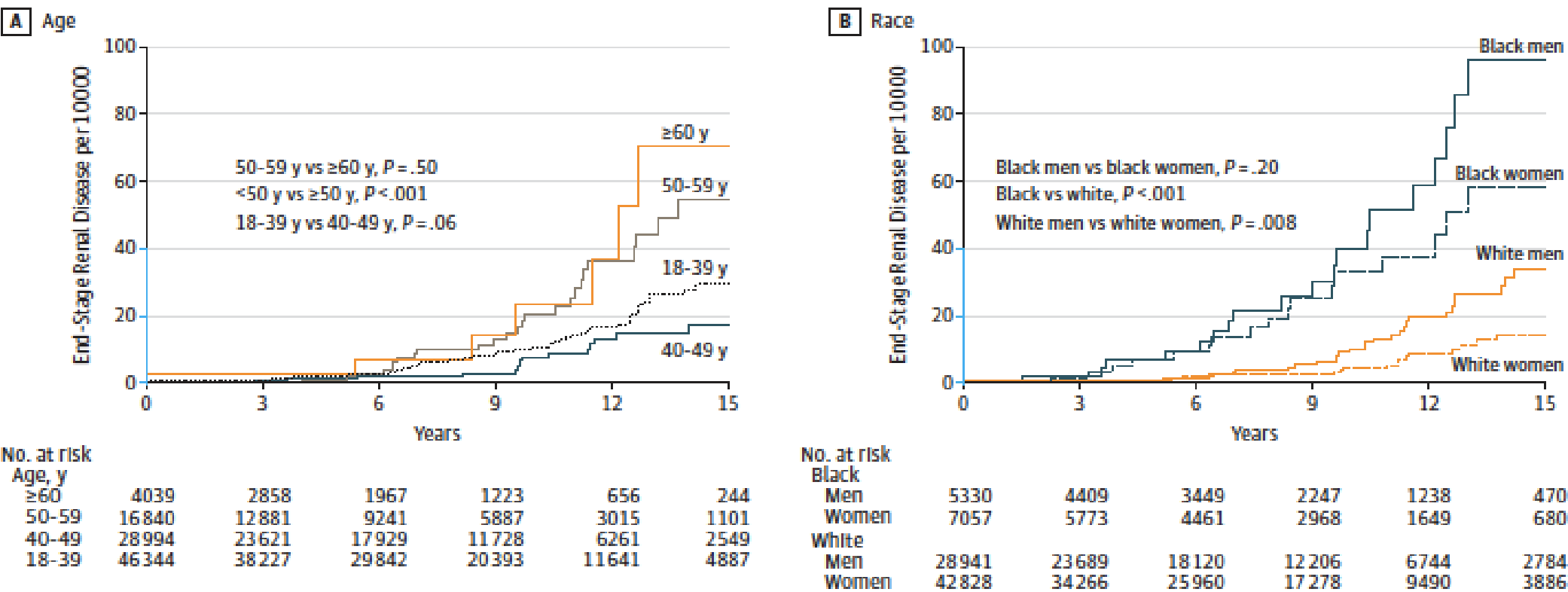
No. at risk

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.

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Figure 2. Cumulative Incidence of End-Stage Renal Disease in Live Kidney Donors



99 cases of ESKD; 50 were 18-39 years. Greatest risk in black men



Risk of End Stage Renal Disease Following Live Kidney Donation.

Muzaale et al. *JAMA* 2014; 311:(6)579-586

Est. cumulative incidence of ESRD at 15 years:

- 30.8/10,000 in donors
- 3.9/10,000 in healthy non-donors

Est. lifetime risk of ESRD, by age 80 years:

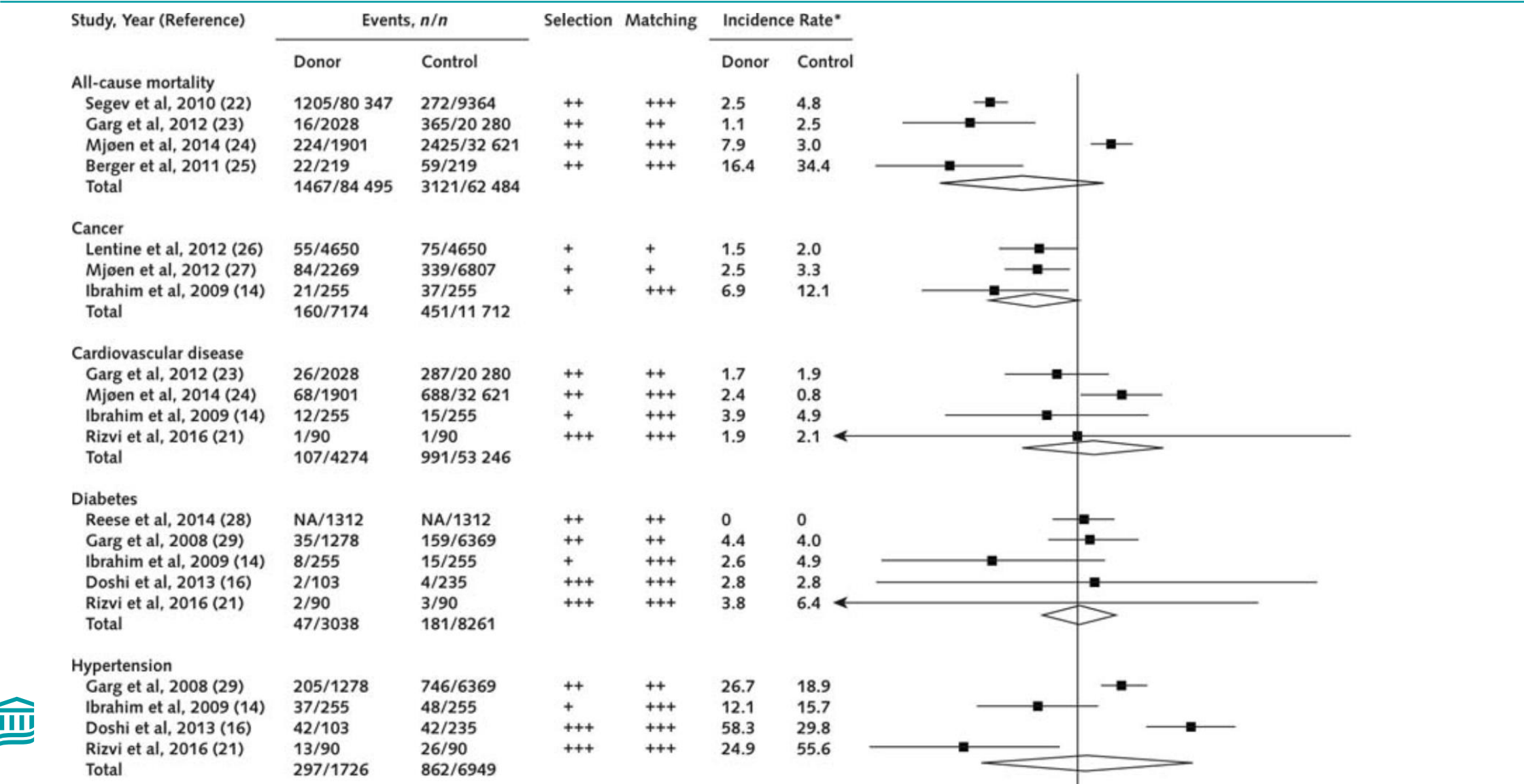
- 90/10,000 donors
- 14/10,000 healthy non donors

6-8 fold increase in relative risk of ESKD in donors

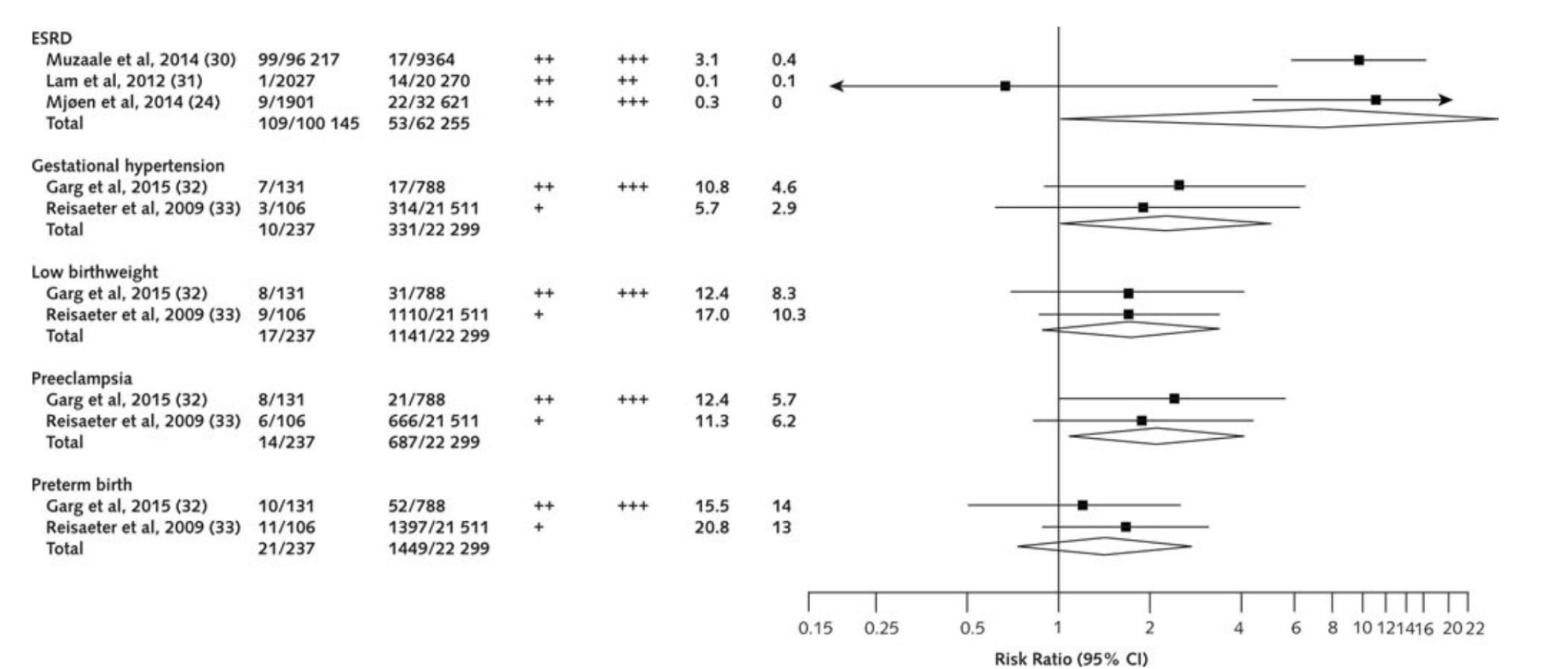
Absolute risks remain low and is well below that of general population



Mid- and Long-Term Health Risks in Living Kidney Donors: A Systematic Review and Meta-analysis. Ann Intern Med. O’Keeffe et al. doi:10.7326/M17-1235



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Risk Prediction



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

Grams et al. *NEJM* 2016

Tool to predict a donor candidate's long-term risk of ESKD

5 million healthy participants

- Low-risk subgroups of general population cohorts
- *Potentially eligible to donate*

Median follow up of 4-16 years

Projected risk of ESKD based on:

- Demographic risks (age, race, gender)
- Risk related to health characteristics (BP, BMI, smoking etc)

Compared risk projections to observed incidence of ESKD at 15 year post kidney donation in 53,000 donors



Projected Incidence of ESRD in the United States among Hypothetical Donor Candidates in the Absence of Kidney Donation.

Table 3. Projected Incidence of ESRD in the United States among Hypothetical Donor Candidates in the Absence of Kidney Donation.*

Scenario	Age yr	Race	eGFR <i>ml/min/1.73 m²</i>	Urinary Albumin: Creatinine Ratio†	Systolic Blood Pressure <i>mm Hg</i>	Smoking Status	15-Yr Projection (95% CI)	Model-Based Lifetime Projection (95% CI)
1	20	Black	115	4	130	Never	0.1 (0.1–0.1)	1.9 (1.2–2.5)
2	20	Black	115	4	130	Current	0.2 (0.1–0.2)	3.4 (2.0–4.8)
3	20	Black	115	4	140‡	Current	0.3 (0.1–0.4)	5.4 (2.9–8.5)
4	20	Black	115	30	140‡	Current	0.7 (0.2–1.5)	13.3 (4.8–27.0)
5	60	White	80	4	140	Never	0.2 (0.1–0.3)	0.4 (0.2–0.6)
6	60	White	60	4	140	Never	0.4 (0.2–0.6)	0.7 (0.3–1.2)
7	60	White	60	4	140‡	Never	0.5 (0.2–0.8)	1.0 (0.5–1.7)
8	60	White	60	30	140‡	Current	2.2 (1.1–3.6)	4.4 (2.1–7.0)

* The online risk tool is available at www.transplantmodels.com/esrdrisk. Lifetime projections are based on 15 years of follow-up data and calibrated to the incidence of ESRD in the U.S. low-risk population; thus they are imprecise. All estimates reflect the population average for unmeasured characteristics; individual risk may be higher or lower. Projections shown are for a man with the specified characteristics and with a BMI of 25 and no diabetes. Confidence intervals were obtained from simulations sampled from the distribution of hazard ratios in the meta-analysis.

† Urinary albumin-to-creatinine ratio was measured in milligrams of albumin to grams of creatinine.

‡ The projected incidence of ESRD is among persons who are taking antihypertensive medication.

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Transplant Models

The Epidemiology Research Group for Organ Transplantation is a research group focused on organ transplantation at the Johns Hopkins School of Medicine. Below are some of the decision models we have developed.

For more information, please visit our website, www.transplantepi.org

Living Kidney Donor Risk Index (LKDPI)

This model predicts recipient risk of graft loss after living donor kidney transplantation based on donor characteristics, on the same scale as the KDPI ...

Massie AB, Leanza J, Fahmy LM, Chow EK et al. A Risk Index for Living Donor Kidney Transplantation. *AJT* 2016 (epub ahead of print)

[Continue to model »](#)

ESRD Risk Tool for Kidney Donor Candidates

This model is intended for low-risk adults considering living kidney donation in the United States. It provides an estimate of 15-year and lifetime incidence of end-stage renal disease...

Grams ME, Sang Y, Levey AS, Matsushita K, Ballew S, Chang AR et al. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. *NEJM* 2015 (epub ahead of print)

[Continue to model »](#)

Infectious Risk Donors

When a patient with end stage renal disease (ESRD) on the waitlist for a kidney is offered an Infectious Risk Donor (IRD) kidney, they need to decide whether they will accept the IRD kidney and the associated infectious risk, or if they will decline it and continue to wait for the next available infectious-risk free kidney ...

Chow, E. K. H., Massie, A. B., Muzaale, A. D., Singer, A. L., Kucirka, L. M., Montgomery, R. A., ... & Segev, D. L. (2013). Identifying appropriate recipients for CDC infectious risk donor kidneys. *American Journal of Transplantation*, 13(5), 1227-1234.

[Continue to model »](#)

Transplant Candidacy for Patients 65+

This prediction model is intended for adults with ESRD on dialysis aged 65 and above; it provides the predicted probability of 3-year survival after kidney transplantation (KT). Patients with predicted 3-year post-KT survival in the top quintile are deemed "excellent" candidates ...

Pediatric Transplant: Living or deceased donor first?

Most pediatric kidney transplant recipients live long enough to require retransplantation. The most beneficial timing for living donor transplantation in candidates with one living donor is not clear...

Postdonation Risk of ESRD in Living Kidney Donors

Risk estimation is critical for appropriate informed consent and varies substantially across living kidney donors.

Massie, Allan B., et al. "Quantifying Postdonation Risk of ESRD in Living



www.transplantmodels.com

ESRD Risk Tool for Kidney Donor Candidates

Projected Incidence of End-Stage Renal Disease:

0.06% Pre-Donation 15-Year*	0.43% Pre-Donation Lifetime*
? Post-Donation 15-Year**	? Post-Donation Lifetime**

blue: < 1%, green: 1-2%, yellow: 2-3%, orange: 3-5%, red: >5%

The pre-donation risks represent projections if a person does not donate a kidney. Details about estimating post-donation risk are provided below.

[reset](#)

[print summary](#)

Patient Characteristics:

Age (18-80yrs)

40

Gender

Male

Race (White or Black)

White

eGFR (mL/min/1.73m²)

90

Systolic Blood Pressure (mmHg)

120

Hypertension Medication

No Medication

BMI (kg/m²)

25

Non-Insulin Dependent Diabetes

No Diabetes

Urine Albumin to Creatinine (mg/g)

4

click on units to change between mg/g and mg/mmol

Smoking History

Non-Smoker

* Pre-donation projected risk of end-stage renal disease (in the



Obstacles to estimates of ESRD risks of young living kidney donors. Steiner *AJT* 2019 and *AJT* Feb 2014

Only 10% of ESKD occurs by age 40 years, 50% after age 65

Incidence of ESKD aged 20: 30/million/year

Incidence of ESKD aged 75: 1,560/million/year

Can ESKD be predicted by an algorithm that does not predict any specific disease?



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Can ESKD be predicted by an algorithm that does not predict any specific disease?

ESKD was modeled as a lifetime risk, where donors were considered at linear risk throughout their lives.

However, ESKD occurs at increasing incidence with advancing age, mostly occurring >65 years



Obstacles to estimates of ESRD risks of young living kidney donors. Steiner *AJT* 2019 and *AJT* Feb 2014

Significant lag time from the development of kidney disease to progression to ESKD

Donation is associated with 25-40ml/min loss in GFR

Significance of GFR loss is dependent on the rate of progression of subsequent kidney disease

Slowly progressive conditions, where GFR loss is lower, greater predicted effect of donation

Calculators may significantly underestimate lifetime risk of ESKD in younger donors due to short follow up



Schematic of GFR decline in live kidney donors

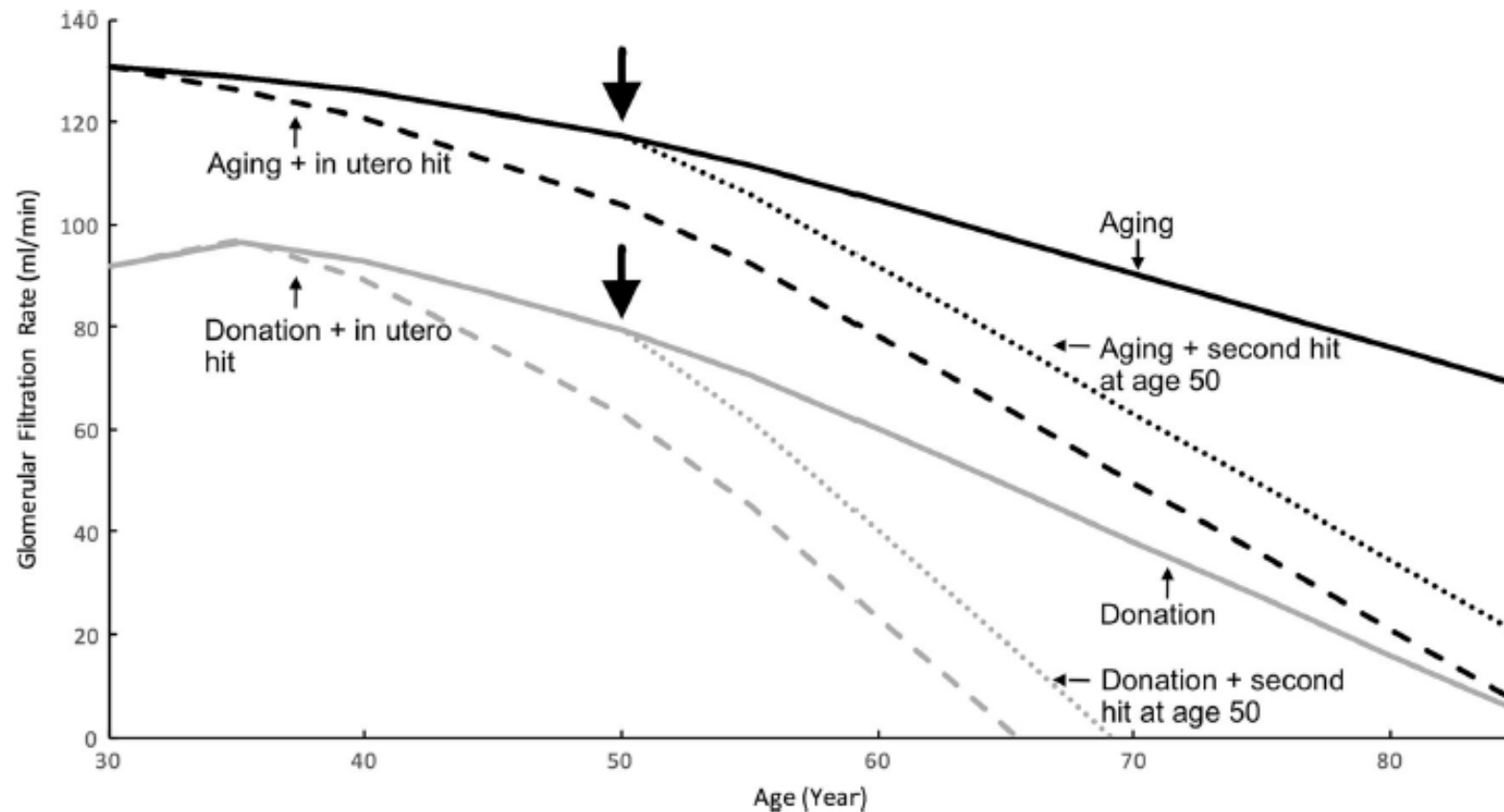


Fig. 2 A schematic presentation of the multiple-hit hypothesis of kidney disease progression in living donors. A hypothetical 30-year-old candidate contemplates kidney donation with three possible scenarios: (1) without donation and with perfect health, glomerular filtration rate (GFR) declines gradually with age (black solid line, adopted from [1]). With donation, adaptive compensation keeps GFR at ~70% of baseline

level (gray solid line). (2) A “first hit” exists (in utero insult or genetic predisposition), and GFR declines at 2× the normal rate, with and without donation (hashed lines). (3) A medical risk factor develops at age 50 and causes GFR to decline at 2X the normal rate, with and without donation (dotted lines). In scenarios 2) and 3), the donor’s time to ESKD is significantly shortened by donation

Schematic of GFR decline in live kidney donors

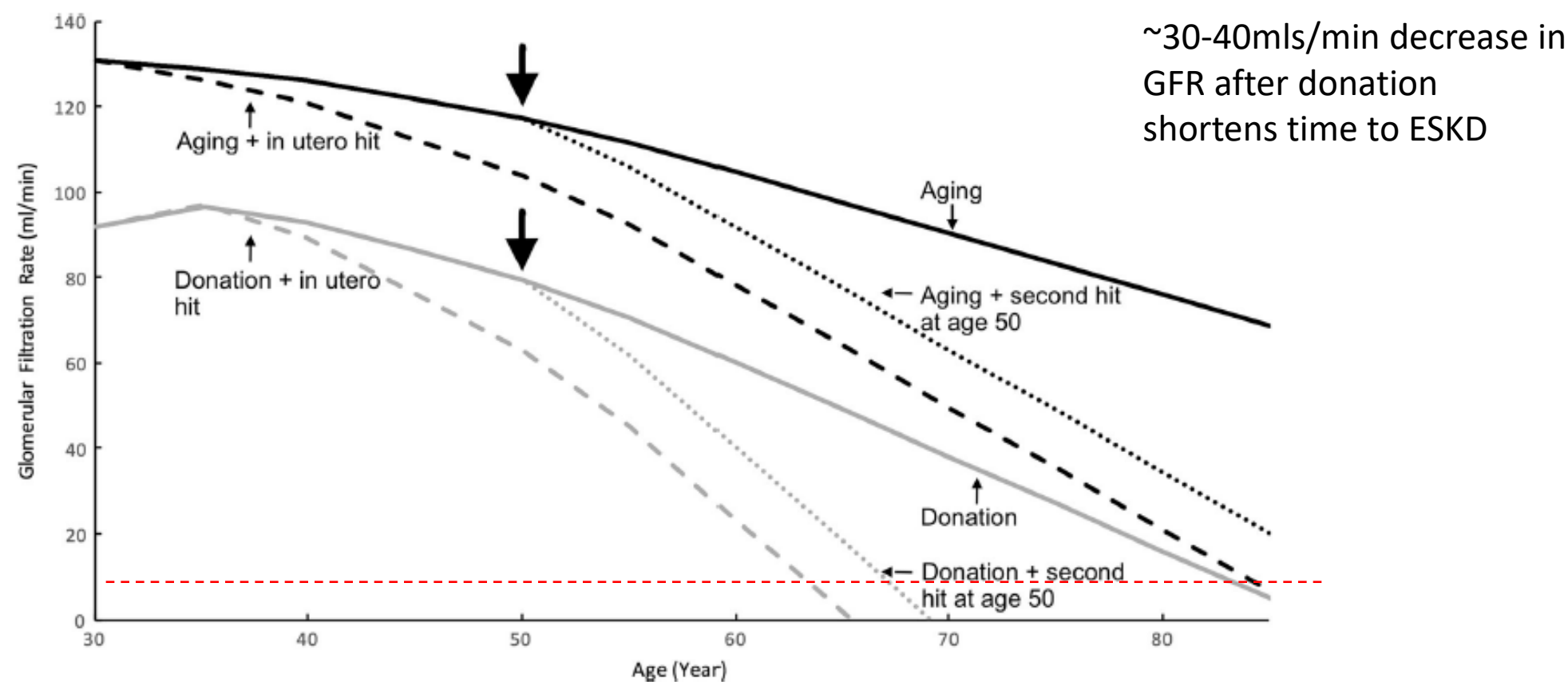


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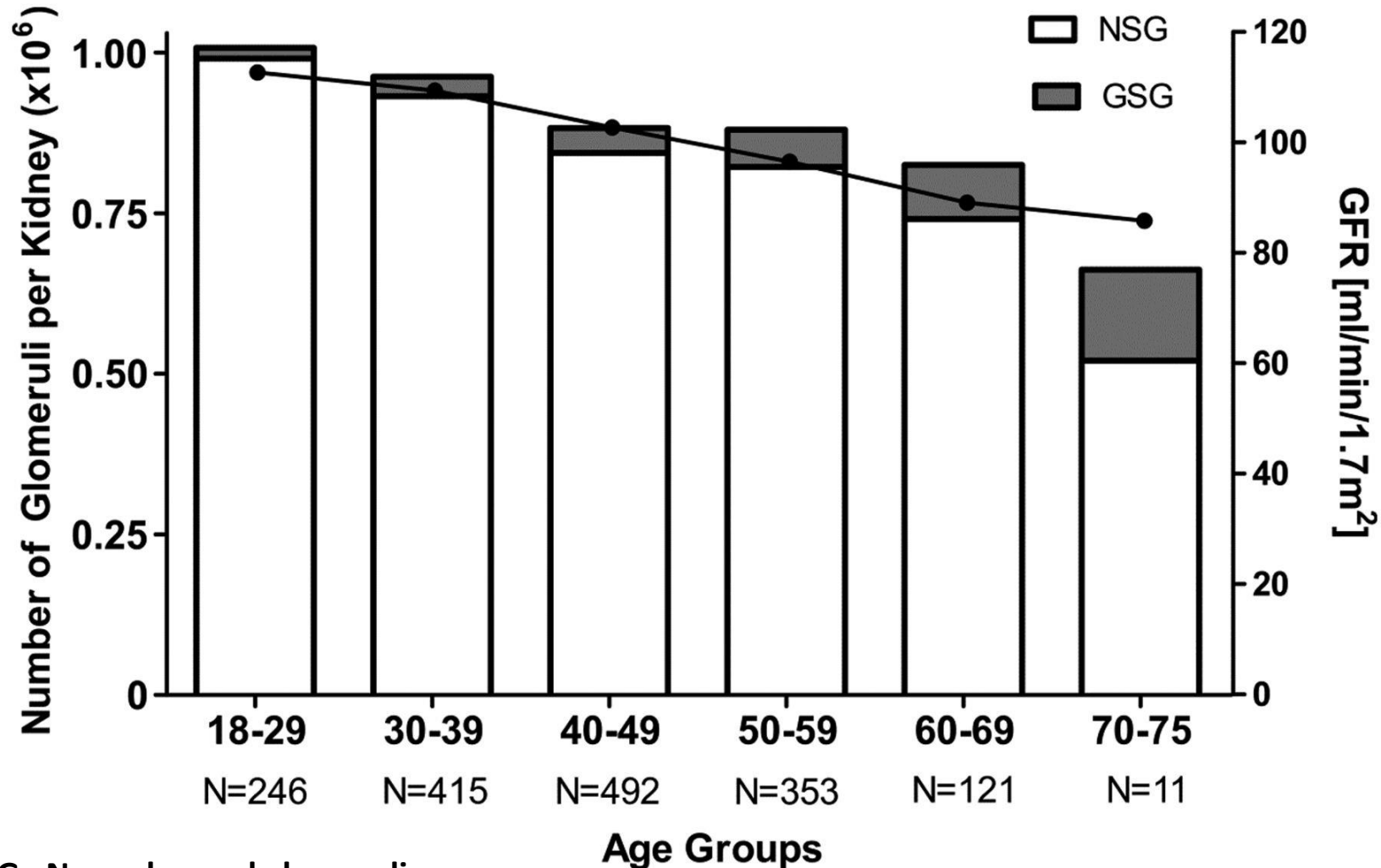


What About Older Donors?



Substantial Loss of Nephrons in Healthy Human Kidneys with Aging.

JASN 2017;28:313-320



NSG= Non sclerosed glomeruli
GSG= Globally sclerosed glomeruli



Living Kidney Donors: Impact of Age on Long-Term Safety. *AJT* 2011 11;(4):737-742

539 live kidney donors in Netherlands

Age <60 yrs: 432 pts, >60 yrs: 117 pts

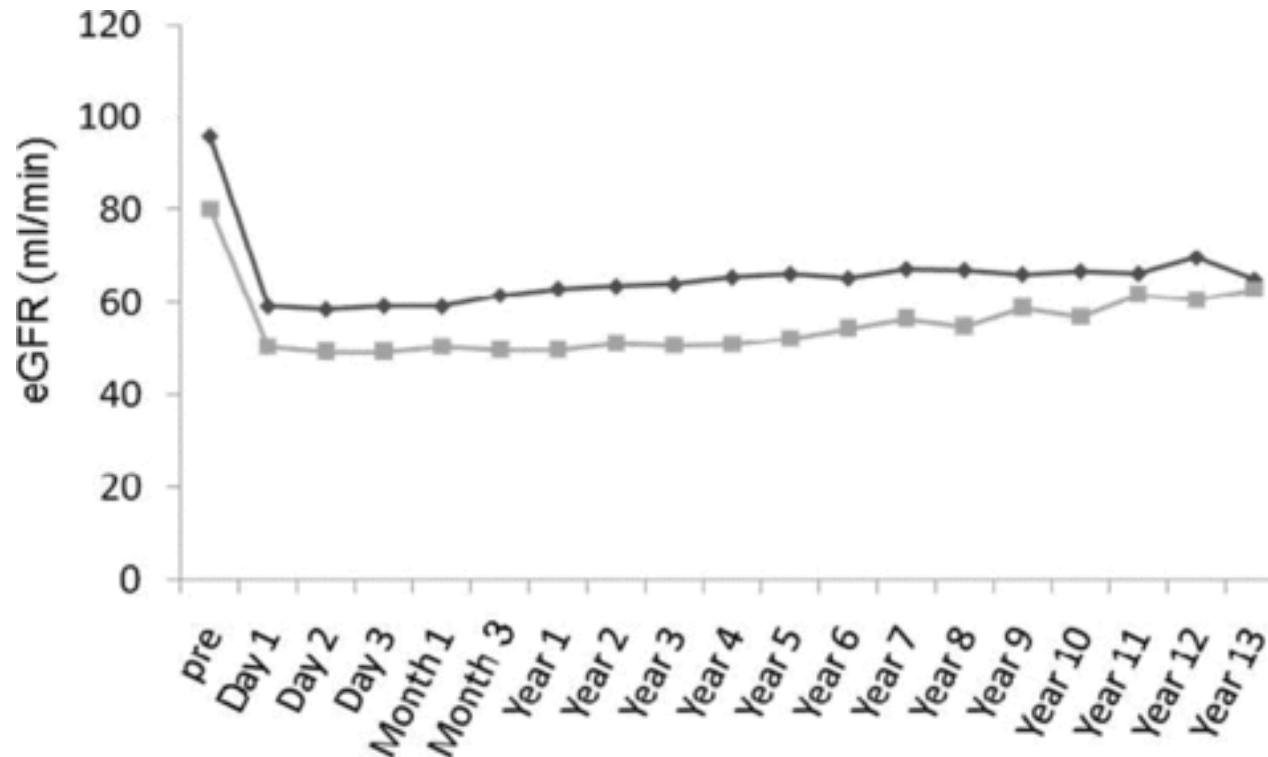
Pre-donation eGFR: 96mls/min vs 80mls/min

Median follow up 5.5 years

Black line: <60yrs
Gray line $\geq$ 60yrs

eGFR<60mls/min:
80% vs 31%

No eGFR
<30mls/min



Risks of ESKD in older live kidney donors with hypertension. Al Ammary et al. *CJASN* 2019

2265 donors >50 years with pre-existing hypertension

15 year risk of ESKD:

- Hypertensive 0.8%
- Normotensive 0.2%

No increased mortality

Similar studies showing no increased risk of CV disease/mortality



Need for age-appropriate GFR thresholds for donation?

KDIGO 2017:

- GFR >60mls/min

BTS 2018:

- Baseline GFR should be >2 standard deviations above mean for age
- >90mls/min for donors <30 years

CTS 2018:

- >90mls/min for < 30years
- >85mls/min for 31-40 years,
- >80mls/min for 41-65 years, >75mls/min for >66 years



CKD in African Americans post donation: Role of *APO L1* risk alleles



APOL1 and Kidney Transplantation

13% of individuals of near-African ancestry carry 2 *APOL1* risk alleles

Up to 20% in family members of those with ESKD

Elevated lifetime risk of ESKD

Renal transplants from donors with 2 risk alleles appear to have increased risk of graft failure

74% graft survival at 5 years, 54% at 10 years



APOL1 Genotype and Renal Function in Black Living Kidney Donors. Doshi et al, *JASN* Apr 2018

136 Black donors with *APOL1* high risk alleles

12 year follow up

Lower baseline eGFR (98mls/min vs. 108mls/min)

Lower post donation GFR (57mls/min vs. 67mls/min)

Faster decline in GFR (1.19mls/min/yr vs. 0.4mls/min/yr)

2 cases of ESKD



Apolipoprotein L1 Gene Genotype and Kidney Outcomes After Living Kidney Donation. JAMA Intern Med 2026;186;(8):943-950.

Table 2. Study Outcomes and Clinical Characteristics at the Study Visit Among Black Kidney Donors With and Without *APOL1* High-Risk Genotypes^a

Characteristic	Black donors, No. (%)		Relative risks (95% CI)	
	With <i>APOL1</i> high-risk genotypes (n = 68)	Without <i>APOL1</i> high-risk genotypes (n = 377)	Unadjusted (445 Black donors)	Adjusted for predonation eGFR (426 Black donors)
Primary outcome				
eGFR <45 mL/min/1.73 m ^{2b}	10 (14.7)	24 (6.4)	2.31 (1.16 to 4.61)	1.91 (0.90 to 4.03)
P value	NA	NA	.02	.09
Other outcomes				
ESKD	1 (1.5)	2 (0.5)	2.77 (0.25 to 30.15)	2.84 (0.27 to 29.56)
eGFR <60 mL/min/1.73 m ^{2b}	40 (58.8)	148 (39.3)	1.50 (1.18 to 1.90)	1.34 (1.08 to 1.67)
Urinary albumin-creatinine ratio ≥30 mg/g [No.] ^b	15 (23.1) [65]	62 (16.6) [374]	1.39 (0.85 to 2.29)	1.47 (0.88 to 2.43)
Urinary albumin-creatinine ratio ≥300 mg/g [No.] ^b	4 (6.2) [65]	6 (1.6) [374]	3.84 (1.11 to 13.22)	3.89 (1.20 to 12.65)
Hypertension ^{b,c}	39 (57.4)	172 (45.6)	1.26 (0.996 to 1.59)	1.30 (1.02 to 1.64)

Study visits 18.5 (16.9-20.5) years after donation

APO L1 Long-Term Kidney Transplant Outcomes Network (APOLLO)



APOL1 risk alleles and Living Kidney Donation

Balancing donor risk with access to transplantation

Lack of predictive value of Apo L1 risk allele testing

Prospective APOLLO study results pending

Discussions regarding appropriate use of genetic testing

Opportunities for patient counselling and shared decision-making



Summary



Take Home Points:

ESKD following live kidney donation remains a rare event

Significant variability in risk across patient groups

Other long term risks: hypertension, pre-eclampsia, gout, changes in LV mass

Risk factors for adverse outcomes: low nephron endowment, lower GFR at donation, ApoL1 risk alleles, and others.



Take Home Points:

Younger donors may have elevated lifetime risk of ESKD due to unpredictable events

Prognosis for older donors appears dependent on GFR at time of donation – slope of GFR loss is similar to younger donors

Risk calculators may have some predictive value

Selected donors with lower GFRs may be safe to donate, however more data is needed.



Thank you!

