Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. N Engl J Med 2016;374:411-21. DOI: 10.1056/NEJMoa1510491

(PDF last updated December 15, 2016.)

Supplement to: Kidney Failure Risk Projection for the Living Kidney Donor Candidate

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List of CKD-PC Investigators and Collaborators

CKD-PC investigators/collaborators (study acronyms/abbreviations are listed in Section 5)**:**
ARIC: Josef Coresh, MD, PhD, Johns Hopkins University, United States; Kunihiro Matsushita, MD, PhD, Johns Hopkins University, United States; Yingying Sang, MS, Johns Hopkins University, United States; Casey M Rebholz, PhD, MHS, MPH, Johns Hopkins University, United States; **Geisinger:** Jamie Green, MD, MS, Geisinger Medical Center, United States; H Les Kirchner, PhD, Geisinger Medical Center, United States; Alexander Chang, MD, MS, Geisinger Medical Center, United States; **ICES KDT:** Amit X Garg, MD, PhD, Institute for Clinical Evaluative Sciences Kidney, Dialysis and Transplantation Program, Canada; Eric McArthur, MSc, Institute for Clinical Evaluative Sciences Kidney, Dialysis and Transplantation Program, Canada; S Joseph Kim, MD, PhD, Institute for Clinical Evaluative Sciences Kidney, Dialysis and Transplantation Program, Canada; Ngan N Lam, MD, Institute for Clinical Evaluative Sciences Kidney, Dialysis and Transplantation Program, Canada; **Maccabi:** Gabriel Chodick, PhD, Maccabi Healthcare Services, Israel; Varda Shalev, MD, Maccabi Healthcare Services and Tel Aviv University, Israel, Inbal Goldshtein, MSc, Maccabi Healthcare Services, Israel; Nachman Ash ; Sarah S. Moser ; **Mt Sinai Bio*Me*:** Erwin P Bottinger, MD, Icahn School of Medicine at Mount Sinai, United States; Girish N Nadkarni, MD, Icahn School of Medicine at Mount Sinai, United States; Stephen B Ellis, Icahn School of Medicine at Mount Sinai, United States; Rajiv Nadukuru, Icahn School of Medicine at Mount Sinai, United States; **NHANES:** Morgan Grams, MD PhD, Johns Hopkins University, United States, Dorry L Segev, MD, PhD, Johns Hopkins University, United States, Abimereki D. Muzaale, MD, MPH, Johns Hopkins University, United States; Allan B. Massie, PhD, Johns Hopkins University, United States; Eric K. Chow, MSc, Johns Hopkins University, United States; **OPTN:** Bertram Kasiske, MD, Hennepin County Medical Center and University of Minnesota, United States; Krista L Lentine, MD, PhD, Saint Louis University School of Medicine, United States; **VA:** Csaba P Kovesdy, MD, Memphis Veterans Affairs Medical Center and University of Tennessee Health Science Center, United States; Miklos Z Molnar, MD, PhD, University of Tennessee Health Science Center, United States

CKD-PC Steering Committee: Josef Coresh (Chair), MD, PhD, Johns Hopkins University, United States; Paul E de Jong, MD, PhD, University Medical Center Groningen, The Netherlands; Ron T Gansevoort, MD, PhD, University Medical Center Groningen, The Netherlands; Morgan Grams, MD PhD, Johns Hopkins University, United States; Stein Hallan, MD, PhD, Norwegian University of Science and Technology and St Olav University, Norway; Csaba P Kovesdy, MD, Memphis Veterans Affairs Medical Center and University of Tennessee Health Science Center, United States; Andrew S Levey, MD, Tufts Medical Center, United States; Kunihiro Matsushita, MD, PhD, Johns Hopkins University, United States; Varda Shalev, MD, Maccabi Healthcare Services and Tel Aviv University, Israel; Mark Woodward, PhD, George Institute, Australia

CKD-PC Data Coordinating Center: Shoshana H Ballew (Coordinator), PhD, Johns Hopkins University, United States; Josef Coresh (Principal investigator), MD, PhD, Johns Hopkins University, United States; Morgan Grams (Director of Nephrology Initiatives), MD, PhD, Johns Hopkins University, United States; Kunihiro Matsushita (Director), MD, PhD, Johns Hopkins University, United States; Yingying Sang (Lead programmer), MS, Johns Hopkins University, United States; Mark Woodward (Senior statistician), PhD, George Institute, Australia

The KDIGO Living Kidney Donor Workgroup contributed to the formulation of the research questions (members: Amit X Garg (Co-Chair), Krista L Lentine (Co-Chair), Patricia Adams, Josefina Alberu, Mohamed Bakr, Josep Campistol, Lorenzo Gallon, Cathy Garvey, Sandeep Guleria, Andrew S Levey, Philip KT Li, Jose Osmar Medina-Pestana, Dorry Segev, Faissal AM Shaheen, Sandra J Taler, Kazunari Tanabe, Linda Wright, Martin Zeier).

Study Design and Oversight: MG, ASL, KM, JC, DLS, BLK, KLL, and AXG conceived of the study concept and design. The CKD Prognosis Consortium (CKD-PCC) Data Coordinating Center (DCC; MG, YS, KM, SB, JC) and the CKD-PC investigators/collaborators listed in the Supplementary Appendix materials acquired the data. The DCC members analyzed the data. MG and JC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and all authors had final responsibility for the decision to submit for publication, informed by discussions with collaborators. MG, YS, ASL, KM, SB, JC, KLL, and AXG drafted the manuscript, and ARC, EKC, BLK, CPK, GNN, VS, and DLS provided critical revisions of the manuscript. All collaborators shared data and were given the opportunity to comment on the manuscript. JC obtained funding for CKD-PC and individual cohort and collaborator support is listed in the Supplementary Appendix.

Section 1: Analytic notes for the individual studies

Overview:
As previously described,[1,2] the collaborating cohorts were asked to compile a dataset with approximately 30 variables (key exposures [serum creatinine to estimate GFR and albuminuria], covariates [e.g., age, sex, race/ethnicity, diabetes, hypertension], and end-stage renal disease outcome [event variable and corresponding follow-up times]). To be consistent across cohorts, the CKD-PC Data Coordinating Center sent definitions for those variables to participating cohorts.

For 3 of the 7 studies, the Data Coordination Center at Johns Hopkins University had the data and conducted the analyses in-house; the remainder ran the standard code written in STATA by the Data Coordinating Center and shared the output with the Data Coordinating Center. The standard code was designed to automatically save all estimates and variance-covariance matrices needed for the meta-analysis. Then, the Data Coordinating Center meta-analyzed the estimates across cohorts using STATA. Cohorts with fewer than 20 outcomes in any particular analysis were excluded. OPTN was also analyzed at the Data Coordinating Center but only used to calculate risks. Thus, no outcome was required in this study.

As detailed in our previous reports,[1,2] we used creatinine measured using a standard IDMS traceable method (Geisinger, ICES KDT, VA) or calibrated to that method (NHANES, ARIC) where possible.
We calculated eGFR using the CKD-EPI equation: $eGFR_{CKD\text{-}EPI} = 141 \times (\text{minimum of standardized serum creatinine [mg/dL]}/\kappa \text{ or } 1)^{\alpha} \times (\text{maximum of standardized serum creatinine [mg/dL]}/\kappa \text{ or } 1)^{-1.209} \times 0.993^{age} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$, where κ is 0.7 if female and 0.9 if male and α is -0.329 if female and -0.411 if male.[5] The selection of knots – in other words, values above and below which we allowed the slope of the association to change – for eGFR and BMI was based on clinical thresholds.[6] For eGFR, we added a knot at 120, since J-shaped associations of creatinine-based eGFR and clinical outcomes have been observed.[2] Zero values of ACR were replaced with 0.1 for log transformation.

Notes for individual studies:

ARIC: This study is a population-based cohort of 15,792 persons from four recruitment sites: Washington County, Maryland; Forsyth County, North Carolina; suburban Minneapolis, Minnesota, and Jackson, Mississippi. The study enrolled persons ages 45 to 65 years selected by probability sampling in 1987-1989 and is thus considered representative of the corresponding community population. For the purpose of this study, visit 4 (1995-1998) was used as baseline, when participants were between 54 and 74 years of age. This visit was chosen because it was the first time albuminuria was quantified. Medication use was determined by self-report. In sensitivity analyses, we also evaluated risk factor associations over the entire 25 years of follow-up, with similar results.

Geisinger: This study includes all persons 18 years or older as of index date who received outpatient care within the Geisinger Health System, a large health system located in rural Pennsylvania, and thus is considered representative of the insured population in that community. Covariates obtained most closely to index date within the past year were included in models. Medication use was obtained by provider order entry. Participants with un-tested urine protein were assumed to have ACR <300 mg/g. Urine dipstick values were coded as 0, 30, 100, 300, 600, and 2000 mg/g and thus the low-risk subgroup was restricted to values <300 mg/g. Urine protein-to-creatinine ratios were converted to ACR by dividing by 2.655 for women and 1.7566 for men, as previously described.[3] Data were available from 1996 to 2014.

Maccabi: This study includes all Maccabi primary care recipients, 18 years or older as of index date, and thus is considered representative of the insured population in that region. Covariates obtained most closely to index date within the past year were included in models. Anti-hypertension medication use was obtained by pharmacy fill. Participants with un-tested urine protein were assumed to have ACR <300 mg/g. Data were available from 2001 to 2015.

Mt Sinai BioMe Biobank: This study includes outpatients in the Mount Sinai health system, 18 years or older as of index date recruited non-selectively from primary care and subspecialty clinics. Covariates obtained most closely to index date within the past year were included in models. Medication use was obtained by provider order entry. Participants with un-tested urine protein were assumed to have ACR <300 mg/g. Urine dipstick values were coded as 0.2, 1, 30, 100, and 500 mg/g and thus the low-risk group was restricted to values <500 mg/g. Urine protein-to-creatinine ratios were converted to ACR by dividing by 2.655 for women and 1.7566 for men as above. Data were available from 2003 to 2014.

NHANES: These cohorts are nationally representative cross-sectional surveys of civilian, non-institutionalized persons. NHANES III occurred between 1988-1994; continuous NHANES occurred between 1999-2010. Follow-up for ESRD was until 2008. Medication use was obtained by self-report. All analyses used sample weights as described in the analytic guidelines.

OPTN: This dataset represents living kidney donors who donated between January 1, 2005, and July 2, 2014, with available serum creatinine and systolic blood pressure. Urine protein-to-creatinine ratios were available in 1,381 donors and converted to ACR by dividing by 2.655 for women and 1.7566 for men as above. ACR was imputed as 4 mg/g for those with "negative," "not done," or "unknown" urinalysis, and 30 mg/g for those with "positive" urinalysis. Smoking status was reported to the OPTN as "history of cigarette use" or "other tobacco used"; we categorized a positive response to either question as former smoker. BMI was not available for the majority of donors and was assigned a value of 26 kg/m^2 for all donors.

ICES KDT: These are all persons 18 years of age and older in the province of Ontario who had an outpatient serum creatinine measurement performed by a large commercial provincial laboratory (Gamma Dynacare) or outpatient measurements from 12 hospitals in Southwestern Ontario. The date of this measurement served as the start date for follow-up. The cohort is considered representative of the Ontario province. Insulin use was not available in all persons and systolic blood pressure values were not available; thus the lower population excluded all persons with diabetes or hypertension and Ontario was not included in the determination of the proportion of events occurring in the low-risk cohort. Participants with un-tested urine protein were assumed to have ACR <300 mg/g. The presence of diabetes or hypertension was assessed with all available healthcare database records prior to cohort entry. Other baseline characteristics were assessed reviewing records in the year prior to cohort entry.

VA: This cohort represents all patients in the VA system with eGFR ≥60 ml/min/1.73 m^2 measured between October 1, 2004 and September 30, 2006. Thus, the cohort is considered representative of US veterans without CKD. Insulin use was not available in all persons; thus, the lower risk population excluded all persons with diabetes and the VA was not included in the determination of the proportion of events occurring in the low-risk subgroup. Covariates obtained most closely to index date within the past year were included in models. Anti-hypertension medication use was obtained by pharmacy fill. Participants with un-tested urine protein were assumed to have ACR <300 mg/g.

Section 2: Overall Population ESRD Incidence Calculations

Annual estimates of ESRD incidence were previously published in Grams et al "Lifetime Incidence of CKD Stages 3-5 in the United States".[4] Residual lifetime risks used in the current study are directly from this paper, and 15-year risks were calculated by compounding annual risk over a 15-year time period.

In the original study, the overall probability of developing end-stage renal disease were estimated for the US population by category of age (by decade), sex, and race (black or white) using methods put forth by Kiberd and Clase.[5] Two estimates were used: the annual probability of dying prior to ESRD ($QnoESRD_x$, where x denotes given age, sex, and race), and the annual probability of developing ESRD ($pESRD_x$). The probability $pESRD_x$ was derived from the US Renal Data System 2009 Annual Report, which reports the age-, gender-, and race-specific ESRD incidence rate per million population ($rESRD_x$). Probability was calculated from this estimate as $pESRD_x = rESRD_x/(1+0.5([rESRD_x])$. $QnoESRD_x$ was calculated as $QnoESRD_x = 1- (1-q_x)^{(dx - dESRDx)/dx}$, where qx represents the overall mortality derived from the National Vital Statistics Report, d_x is the total deaths, and $dESRD_x$ is the total excess deaths from ESRD. The excess deaths from ESRD were calculated as the probability of dying with ESRD during the interval multiplied by the proportion of patients with ESRD, where the probability of dying with ESRD is estimated from the rate of excess ESRD mortality (observed ESRD mortality – general population mortality). These were used in a Markov model (ESRD and death were treated as absorbing states) with a simulated cohort of 10,000 individuals of specified age, race, and sex for Monte Carlo simulations, with a lifetime horizon capped at 90 years and a cycle length of one year. Markov models are subject to many limitations, but perhaps the most salient is the assumption of constant rates and distribution in the population over time.

Life expectancy (years) and residual lifetime until age 90 and 15-year risk (%) of ESRD by race, sex, and decade of age

Baseline age	20 years	30 years	40 years	50 years	60 years	70 years	80 years
Life Expectancy (years)							
Black Men	72	73	74	75	78	82	88
Black Women	78	79	79	80	82	85	89
White Men	77	78	78	79	81	84	88
White Women	81	82	82	83	84	86	89
Residual Lifetime Risks of ESRD (%)							
Black Men	8.7	8.8	8.4	7.9	6.9	5.1	2.9
Black Women	7.9	7.7	7.5	7.1	6.3	4.6	2.4
White Men	3.4	3.3	3.2	3.2	3.0	2.5	1.6
White Women	2.3	2.2	2.2	2.1	1.9	1.4	0.7
15-Year Risks of ESRD (%)							
Black Men	0.4	1.1	2.0	3.2	4.4	4.4	2.9
Black Women	0.3	0.7	1.3	2.3	3.8	3.9	2.4
White Men	0.1	0.2	0.4	0.8	1.6	2.1	1.6
White Women	0.1	0.1	0.3	0.6	1.0	1.2	0.7

Section 3: Calculation of Incidence of ESRD For a Base-Case Candidate of Given Age, Sex, and Race (H_x)

Step 1: Define the "low-risk" group in NHANES (i.e., exclude persons with known contraindications to kidney donation)

Exclude persons with one or more absolute contraindications to kidney donation: estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2, insulin-dependent diabetes mellitus, the use of 4 or more anti-hypertensive medications, systolic/diastolic blood pressure ≥160/90 mmHg with medication or ≥170/100 mmHg without medication, random urine albumin-to-creatinine ratio ≥300 mg/g, or a history of coronary heart disease, stroke, congestive heart failure, or peripheral arterial disease.

Step 2: Select relevant "base-case" scenario (estimated from age-specific average US kidney donor characteristics)

Age Group	Race	Sex	eGFR
15-25	Black/White	Male/Female	114
26-34	Black/White	Male/Female	106
35-44	Black/White	Male/Female	98
45-54	Black/White	Male/Female	90
55-64	Black/White	Male/Female	82
65-74	Black/White	Male/Female	74
75-84	Black/White	Male/Female	66

Other covariates in the base-case were fairly uniform in the US donor population and thus an overall average was used: systolic blood pressure 120 mmHg, albumin-to-creatinine ratio 4 mg/g, no diabetes, no antihypertension medication, non-smoker and BMI 26.

Step 3: Convert baseline covariates in NHANES to the functional forms used in equations, centered on base-case values

For eGFR: 4 splines with knots at 60, 90, and 120 ml/min/1.73 m^2 (knots refer to the point at which the slope is allowed to change)

eGFR1 = [60 -min(eGFR,60))]/ 15
eGFR2 = [min(eGFRbase, 90) – max(min(eGFR,90),60)] /15
eGFR3 = [max(eGFRbase,90) – max(min(eGFR,120),90)] /15
eGFR4 = [120 - max(eGFR, 120)] /15

For BMI: 2 splines with knots at 30 kg/m^2

BMI1 = min (BMI – 26, 5)/5
BMI2 = max (BMI – 30, 0) /5

Step 4: Calculate linear function for each NHANES Participant *i* in a given age decade, race, sex subgroup using meta-analyzed β coefficients (Table 2)

B_i = 1.8879 × eGFR1 + 0.4884× eGFR2 + 0.0203 × eGFR3 – 0.2420 × eGFR4 + 0.3500 × (SBP – 120) /20 + 0.3012 (if use anti-hypertensive medications) – 0.0241 × BMI1 + 0.1474 × BMI2 + 1.1008 (if diabetes) + 1.0772 × ($\log_{10}$ACR- $\log_{10}$4) + 0.3700 (if former smoker) + 0.5680 (if current smoker)

Step 5: Estimate the overall incidence of ESRD in the low-risk subgroup

Use previously estimated general population estimates (Section 2) and developed multiplier (30%; Table S1) to determine overall incidence of ESRD (R) over a given time period in given subgroup of age, sex and race (denoted x). For example, for the low-risk 20-year-old black male population, the overall lifetime estimate would be R_{20BM}=8.7%*30% = 2.61%.

Step 6: Define the base-case risk in subgroup x as the overall risk in subgroup x divided by the product-sum of the centered linear functions and their prevalence (P_i) in subgroup x of the low-risk population

$H_x = R_x/\sum(e^{Bi}*P_i)$

Section 4: Project an Individual's Incidence of ESRD

Step 1: Select relevant "base-case" scenario (estimated from age-specific average US kidney donor characteristics)

Age Group	Race	Sex	eGFR
15-25	Black/White	Male/Female	114
26-34	Black/White	Male/Female	106
35-44	Black/White	Male/Female	98
45-54	Black/White	Male/Female	90
55-64	Black/White	Male/Female	82
65-74	Black/White	Male/Female	74
75-84	Black/White	Male/Female	66

Other covariates in the base-case: systolic blood pressure 120 mmHg, albumin-to-creatinine ratio 4 mg/g, BMI 26 kg/m^2, no diabetes, no antihypertension medication, non-smoker.

Step 2: Convert baseline covariates in NHANES to the functional forms used in equations, centered on base-case values

For eGFR: 4 splines with knots at 60, 90, and 120 ml/min/1.73 m^2 (knots refer to the point at which the slope is allowed to change)

eGFR1 = [60 -min(eGFR,60))]/ 15
eGFR2 = [min(eGFRbase, 90) – max(min(eGFR,90),60)] /15
eGFR3 = [max(eGFRbase,90) – max(min(eGFR,120),90)] /15
eGFR4 = [120 - max(eGFR, 120)] /15

For BMI: 2 splines with knots at 30 kg/m^2

BMI1 = min (BMI – 26, 5)/5
BMI2 = max (BMI – 30, 0) /5

Step 3: Calculate linear function for individual participant using meta-analyzed β coefficients (Table 2)

B = 1.8879 × eGFR1 + 0.4884× eGFR2 + 0.0203 × eGFR3 – 0.2420 × eGFR4 + 0.3500 × (SBP – 120) /20 + 0.3012 (if use anti-hypertensive medications) – 0.0241 × BMI1 + 0.1474 × BMI2 + 1.1008 (if diabetes) + 1.0772 × ($\log_{10}$ACR- $\log_{10}$4) + 0.3700 (if former smoker) + 0.5680 (if current smoker)

Step 4: Use the base-case risk for given age, sex, and race x (Hx)

A) For 15-Year Risk (%, 95% Confidence Interval)

Age Group	Black Man	Black Woman	White Man	White Woman
15-25	0.08 (0.05, 0.10)	0.05 (0.02, 0.09)	0.02 (0.01, 0.02)	0.01 (0.01, 0.02)
26-34	0.16 (0.08, 0.21)	0.09 (0.04, 0.15)	0.04 (0.02, 0.04)	0.03 (0.01, 0.04)
35-44	0.24 (0.12, 0.33)	0.15 (0.06, 0.23)	0.06 (0.03, 0.08)	0.04 (0.02, 0.06)
45-54	0.27 (0.12, 0.43)	0.16 (0.06, 0.31)	0.08 (0.04, 0.12)	0.06 (0.03, 0.09)

55-64	0.32 (0.12, 0.56)	0.18 (0.08, 0.35)	0.13 (0.06, 0.21)	0.08 (0.03, 0.13)
65-74	0.14 (0.05, 0.34)	0.19 (0.07, 0.36)	0.12 (0.04, 0.23)	0.07 (0.03, 0.14)
75-84	0.12 (0.05, 0.24)	0.06 (0.02, 0.13)	0.05 (0.02, 0.12)	0.03 (0.01, 0.06)

B) For Lifetime Risk (%, 95% Confidence Interval)

Age Group	Black Man	Black Woman	White Man	White Woman
15-25	1.62 (1.00, 2.09)	1.23 (0.50, 2.08)	0.58 (0.39, 0.72)	0.35 (0.17, 0.57)
26-34	1.33 (0.70, 1.73)	1.03 (0.45, 1.65)	0.53 (0.34, 0.67)	0.38 (0.22, 0.54)
35-44	1.00 (0.49, 1.37)	0.85 (0.37, 1.35)	0.43 (0.19, 0.58)	0.29 (0.13, 0.47)
45-54	0.66 (0.30, 1.04)	0.50 (0.18, 0.95)	0.31 (0.14, 0.47)	0.21 (0.11, 0.32)
55-64	0.49 (0.19, 0.87)	0.31 (0.13, 0.59)	0.26 (0.12, 0.42)	0.15 (0.06, 0.24)
65-74	0.17 (0.05, 0.40)	0.22 (0.09, 0.43)	0.15 (0.05, 0.28)	0.08 (0.03, 0.15)
75-84	0.12 (0.05, 0.25)	0.06 (0.02, 0.13)	0.06 (0.02, 0.13)	0.03 (0.01, 0.06)

Step 5: Project ESRD Incidence for an individual

ESRD Incidence Over a Given Time = $(1 – (1 – H_x / 100)^{e\text{^}B}) \times 100$

Risk calculator available at www.transplantmodels.com/esrdrisk

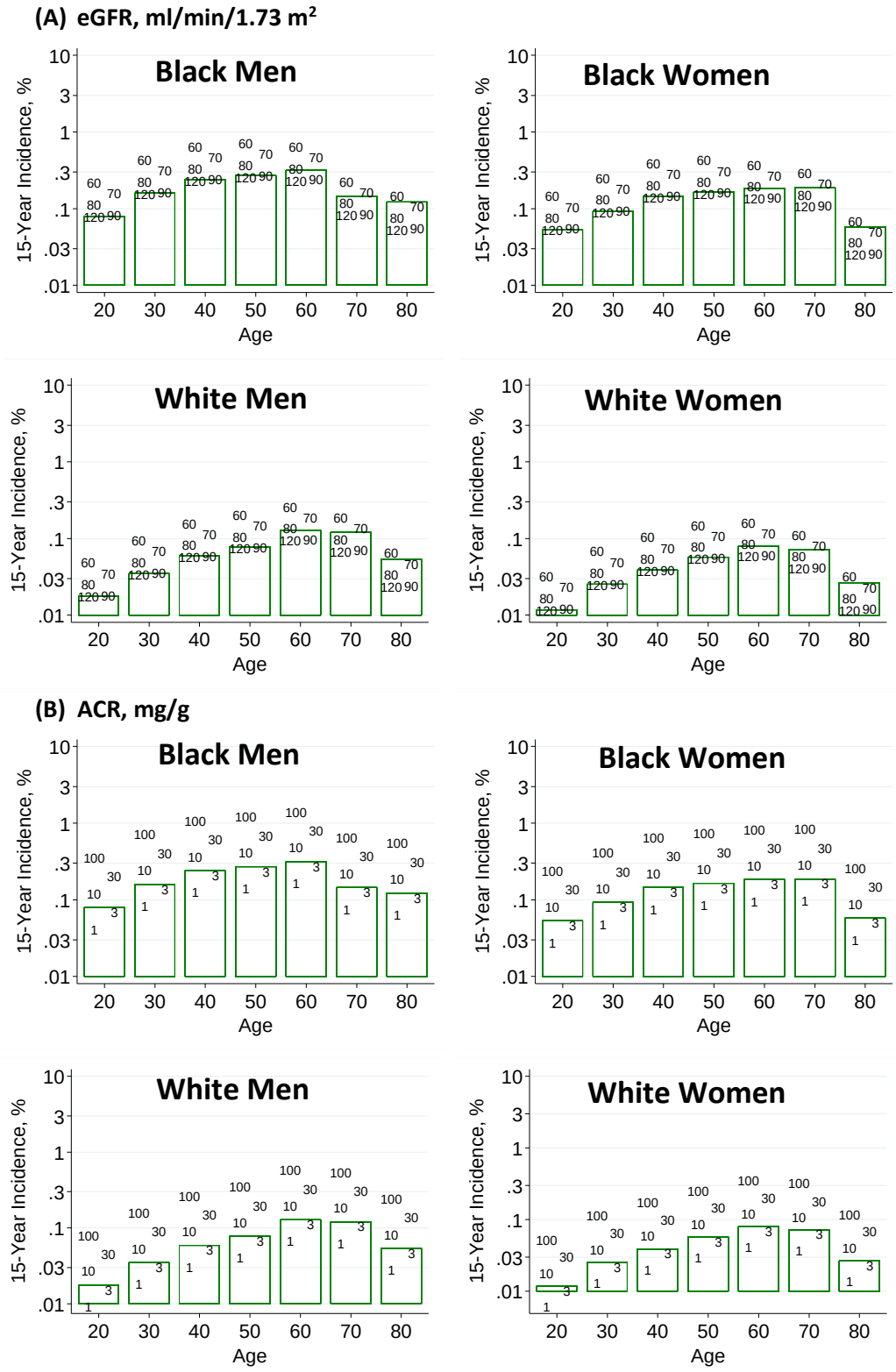
Section 5: Acronyms or abbreviations for studies included in the current report and their key references linked to the Web references

ARIC:	Atherosclerosis Risk in Communities Study[6]
Geisinger:	Geisinger Health System[7]
Maccabi:	Maccabi Health System[8]
Mt Sinai BioMe:	Mount Sinai BioMe Biobank Platform[9]
NHANES III:	Third US National Health and Nutrition Examination Survey[10]
OPTN:	Organ Procurement and Transplantation Network
ICES KDT:	Ontario Institute for Clinical Evaluative Sciences, Provincial Kidney, Dialysis and Transplantation program (ICES KDT)
VA:	Veterans Administration Study[11]

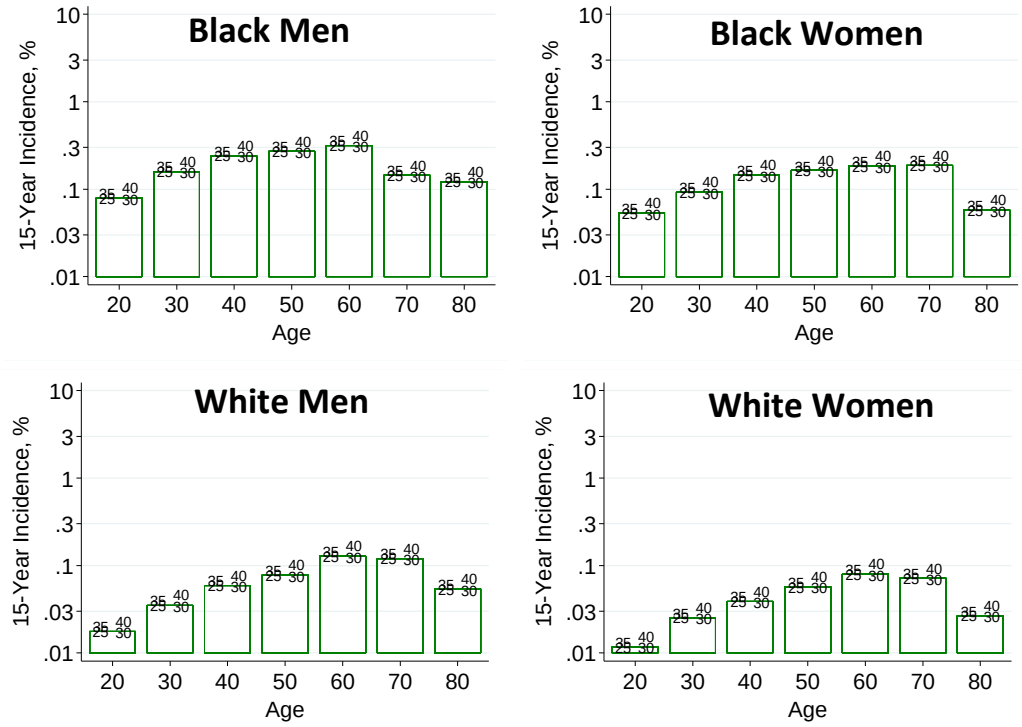
Section 6: Acknowledgements and funding for collaborating cohorts

Study	List of sponsors
ARIC	The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The authors thank the staff and participants of the ARIC study for their important contributions.
Geisinger	Geisinger Clinic
Maccabi	
Mt. Sinai BioMe	
NHANES III	United States Center for Disease Control
OPTN	
ICES KDT	The Institute for Clinical Evaluative Sciences (ICES) Kidney, Dialysis and Transplantation Program is supported by an operating grant from the Canadian Institutes of Health Research. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Parts of the material in the current report are based on data and information compiled and provided by the Canadian Institute of Health Information (CIHI). The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, the Ontario MOHLTC or CIHI is intended or should be inferred.
VA	This study was supported by grant R01DK096920 and by resources from the US Department of Veterans Affairs. Support for VA/CMS data is provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (Project Numbers SDR 02-237 and 98-004). Opinions expressed in this paper are those of the authors' and do not represent the official opinion of the US Department of Veterans Affairs.

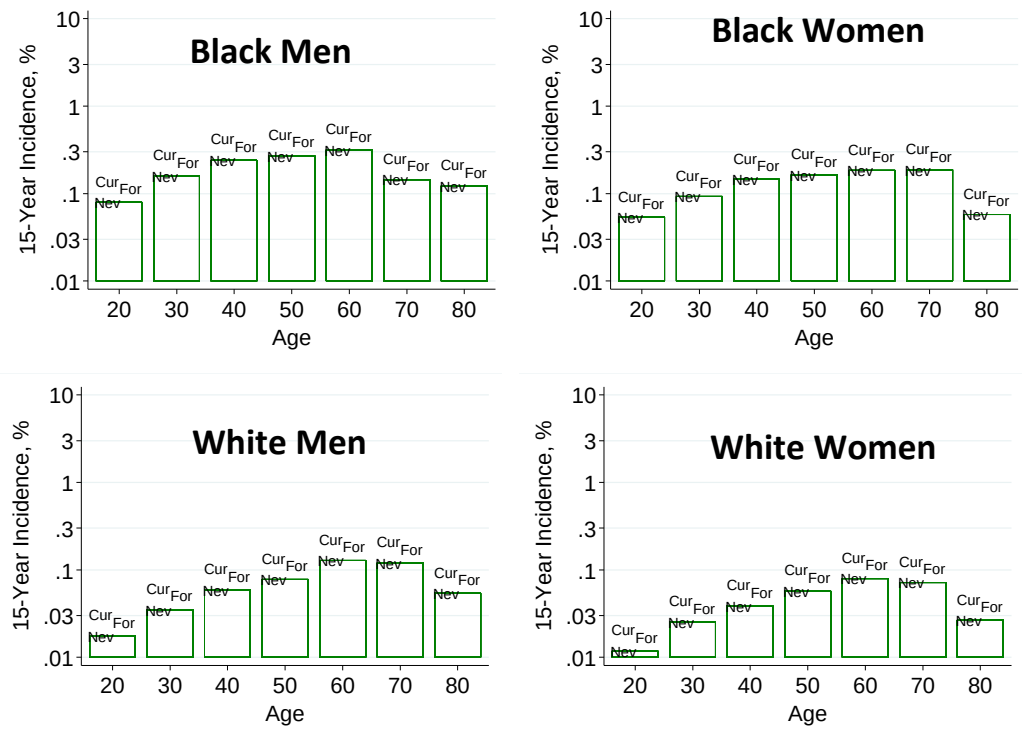
Figure S1: 15-Year incidence (%) of ESRD in the United States in the absence of kidney donation for the "base-case" scenario (green bars) with alteration of a single risk factor



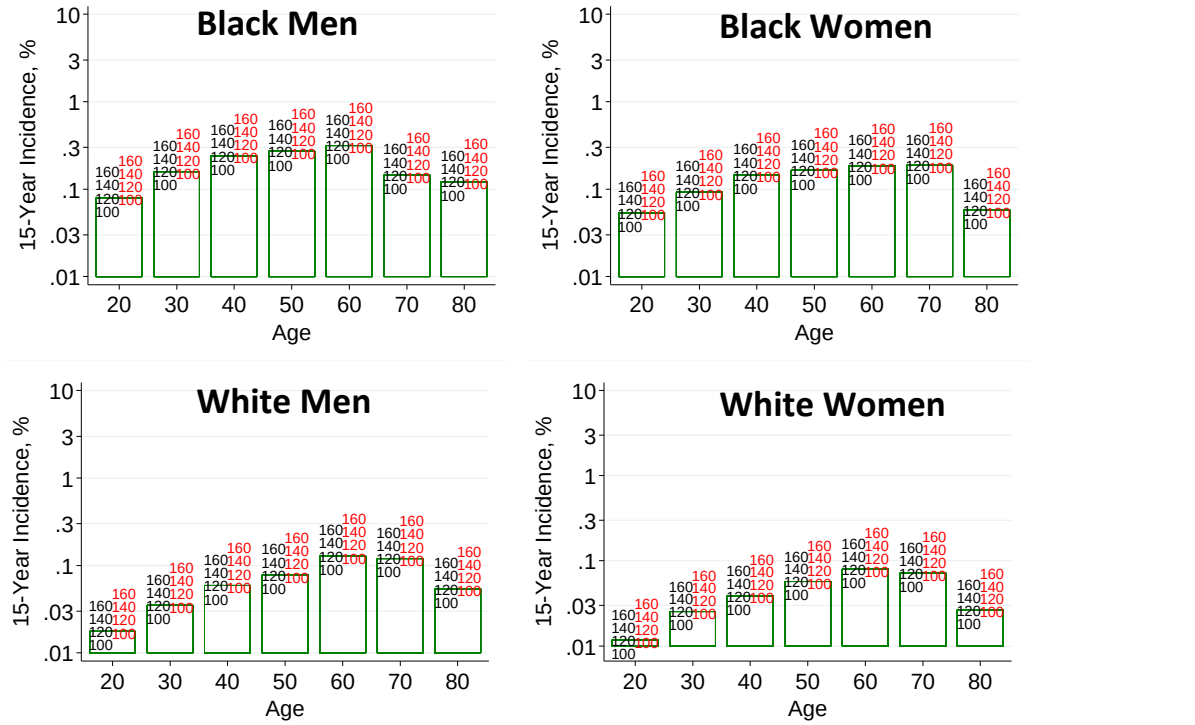
(C) BMI, kg/m²



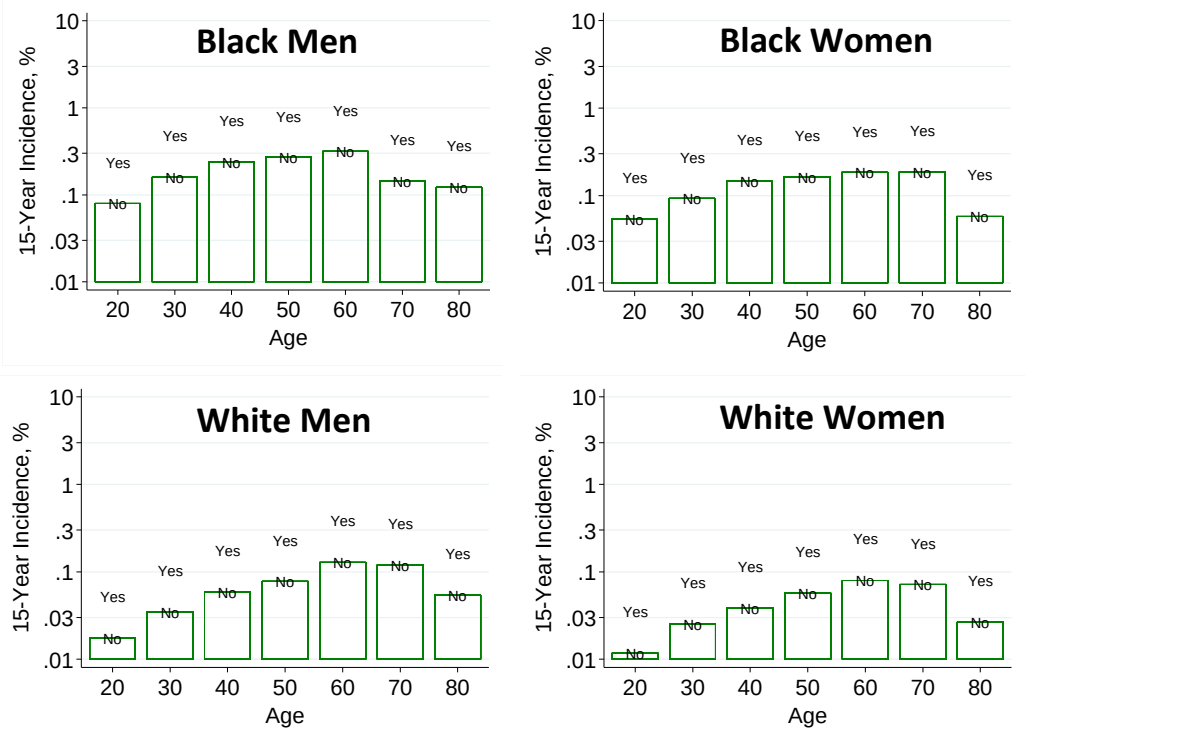
(D) Smoking status, current (Cur), former (For), and Never (Nev)



(E) Systolic blood pressure, mmHg without (black) and with (red) antihypertension medication



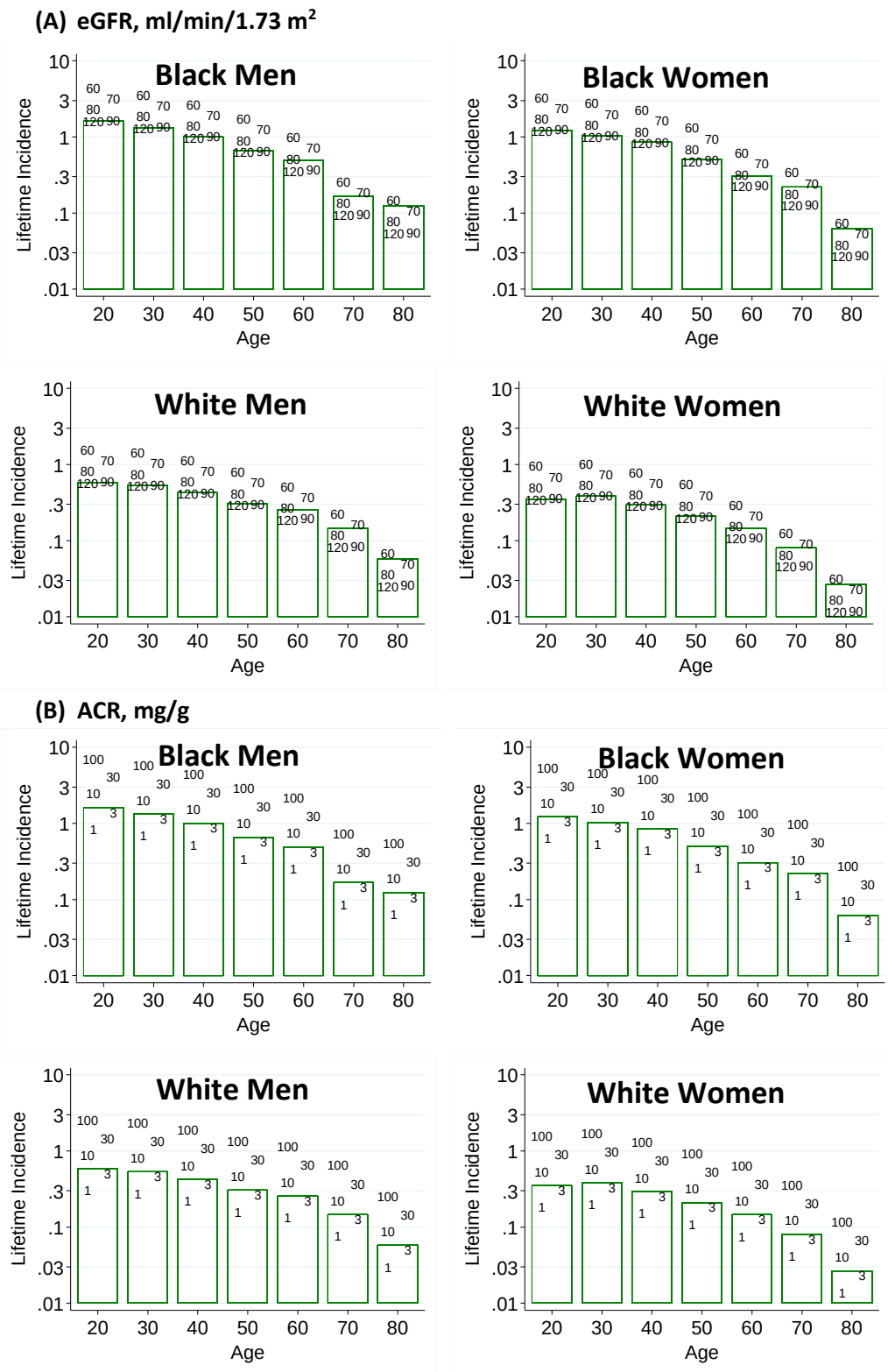
(F) Non-insulin Dependent Diabetes Mellitus



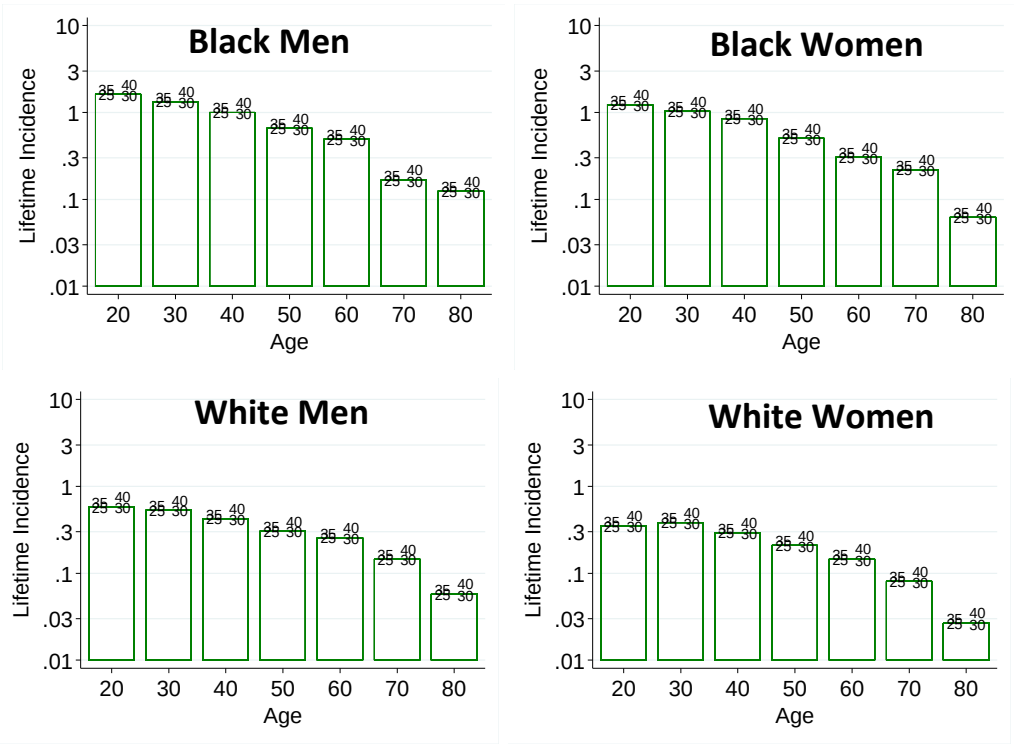
*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m^2 for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine

ratio (ACR) 4 mg/g (0.4 mg/mmol), BMI 26 kg/m^2, and no diabetes mellitus or anti-hypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age.

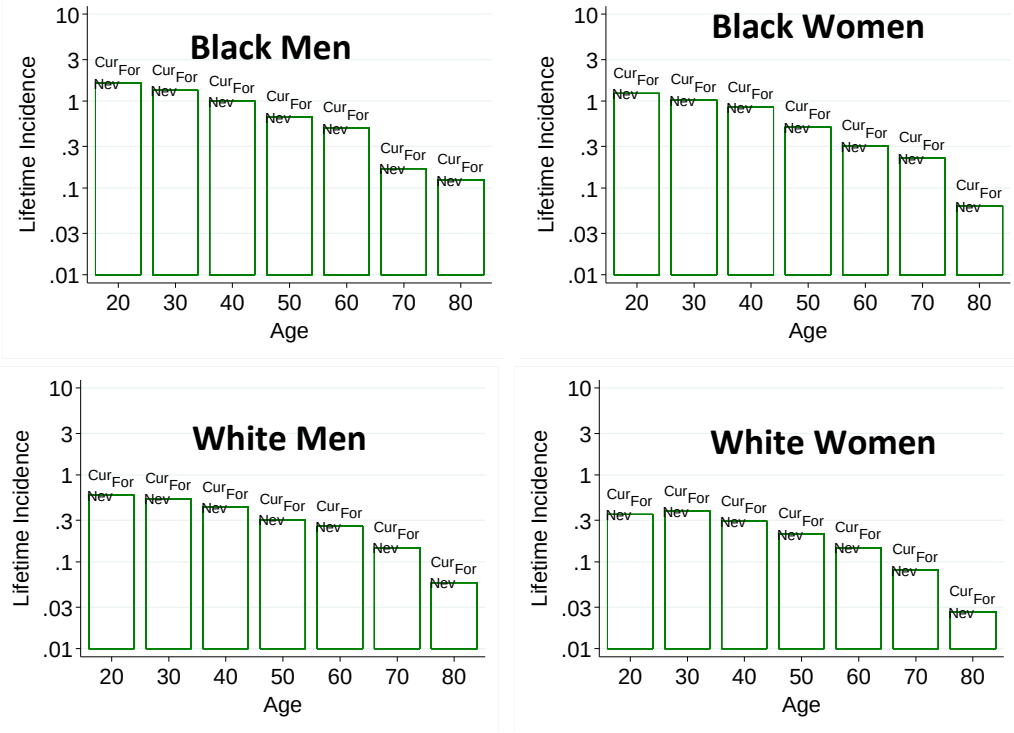
Figure S2: Lifetime incidence (%) of ESRD in the United States in the absence of kidney donation for the "base-case" scenario (green bars) with alteration of a single risk factor



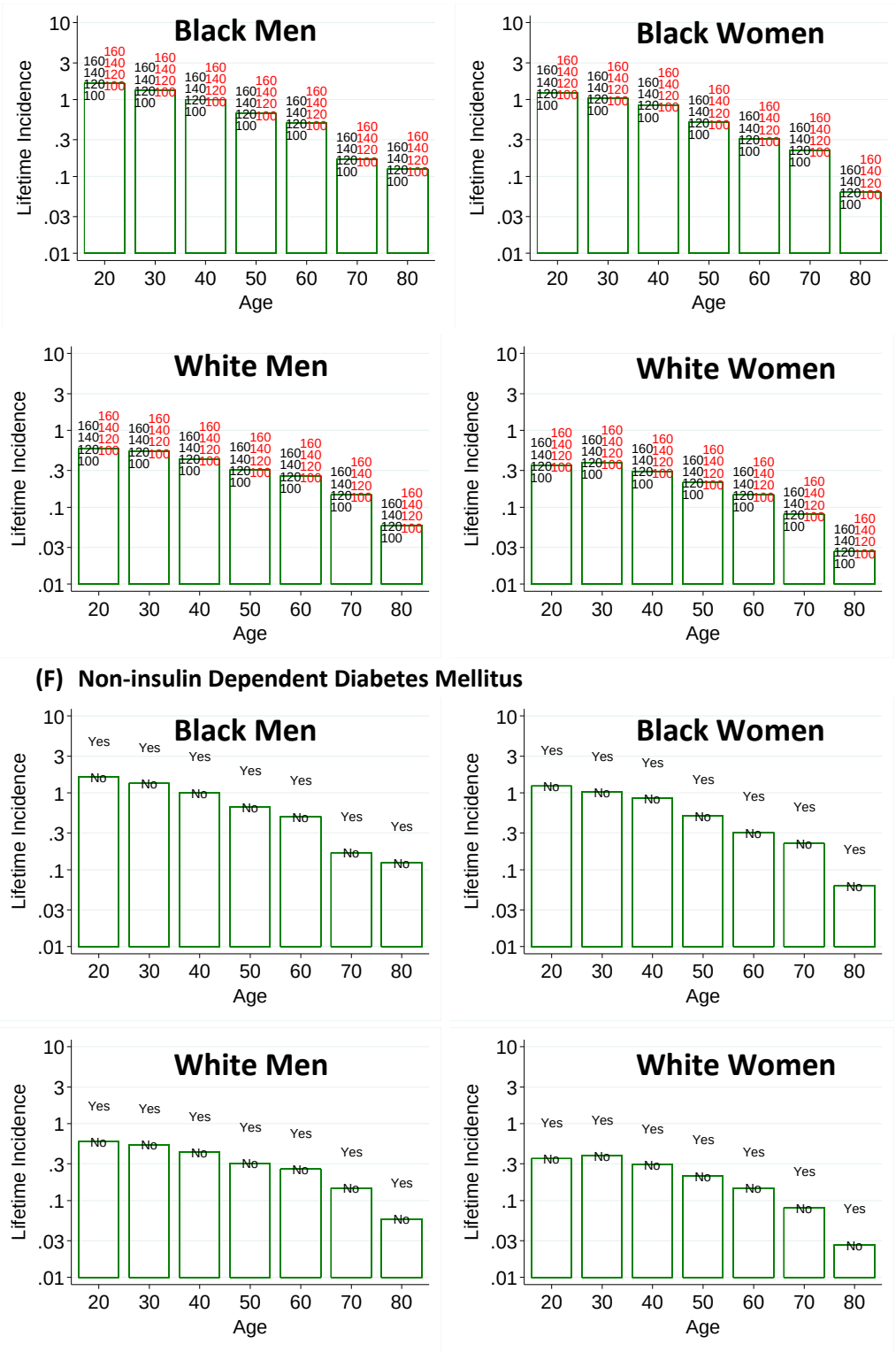
(C) BMI, kg/m²



(D) Smoking status, current (Cur), former (For), and Never (Nev)



(E) Systolic blood pressure, mmHg without (black) and with (red) antihypertension medication



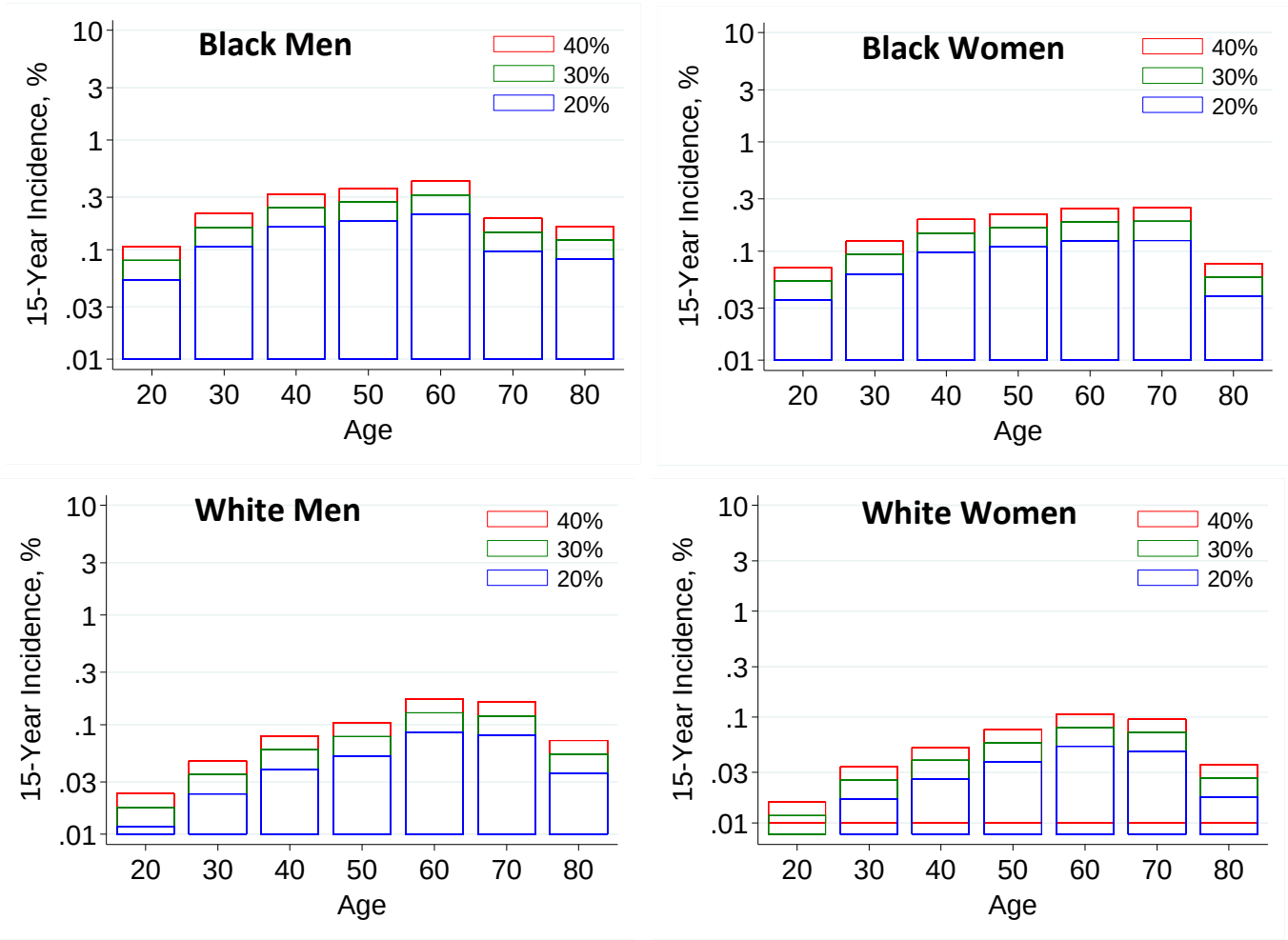
(F) Non-insulin Dependent Diabetes Mellitus

*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m^2 for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, urine albumin-creatinine

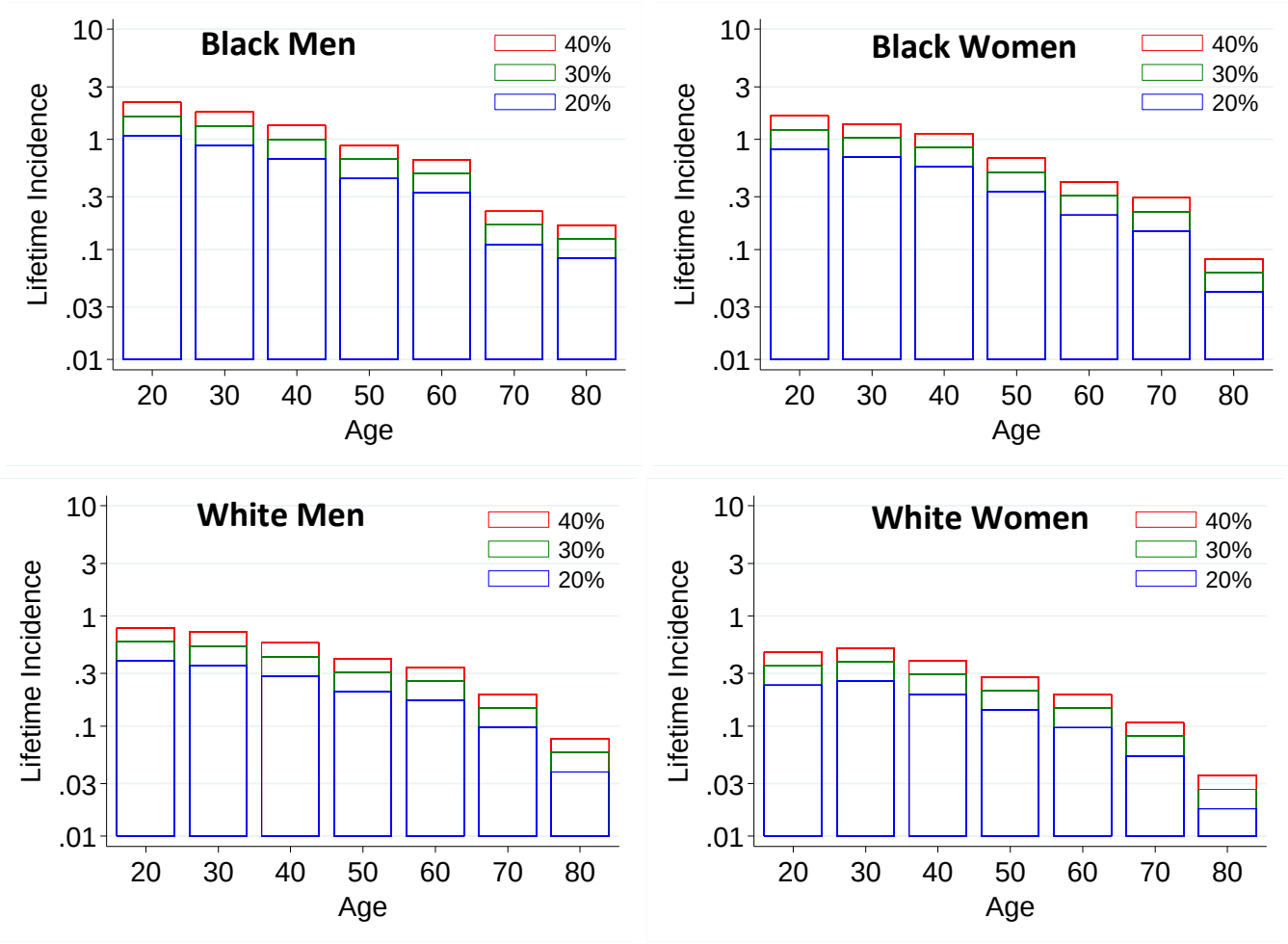
ratio (ACR) 4 mg/g (0.4 mg/mmol), BMI 26 kg/m^2, and no diabetes mellitus or anti-hypertensive medication use. These were selected as being representative of recent US living kidney donors where, with the exception of eGFR, there was little variation in health characteristics by age. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESRD in the low-risk population, and thus are likely imprecise.

Figure S3: 15-Year incidence (%) (A) and lifetime incidence (%) (B) of ESRD in the United States in the absence of donation by age, race, and sex for the "base-case" scenario, with estimated proportion of events occurring in the low-risk population set to 30% (primary analysis) and sensitivity analyses to lower (20%) and higher (40%) proportions

(A) 15-year incidence



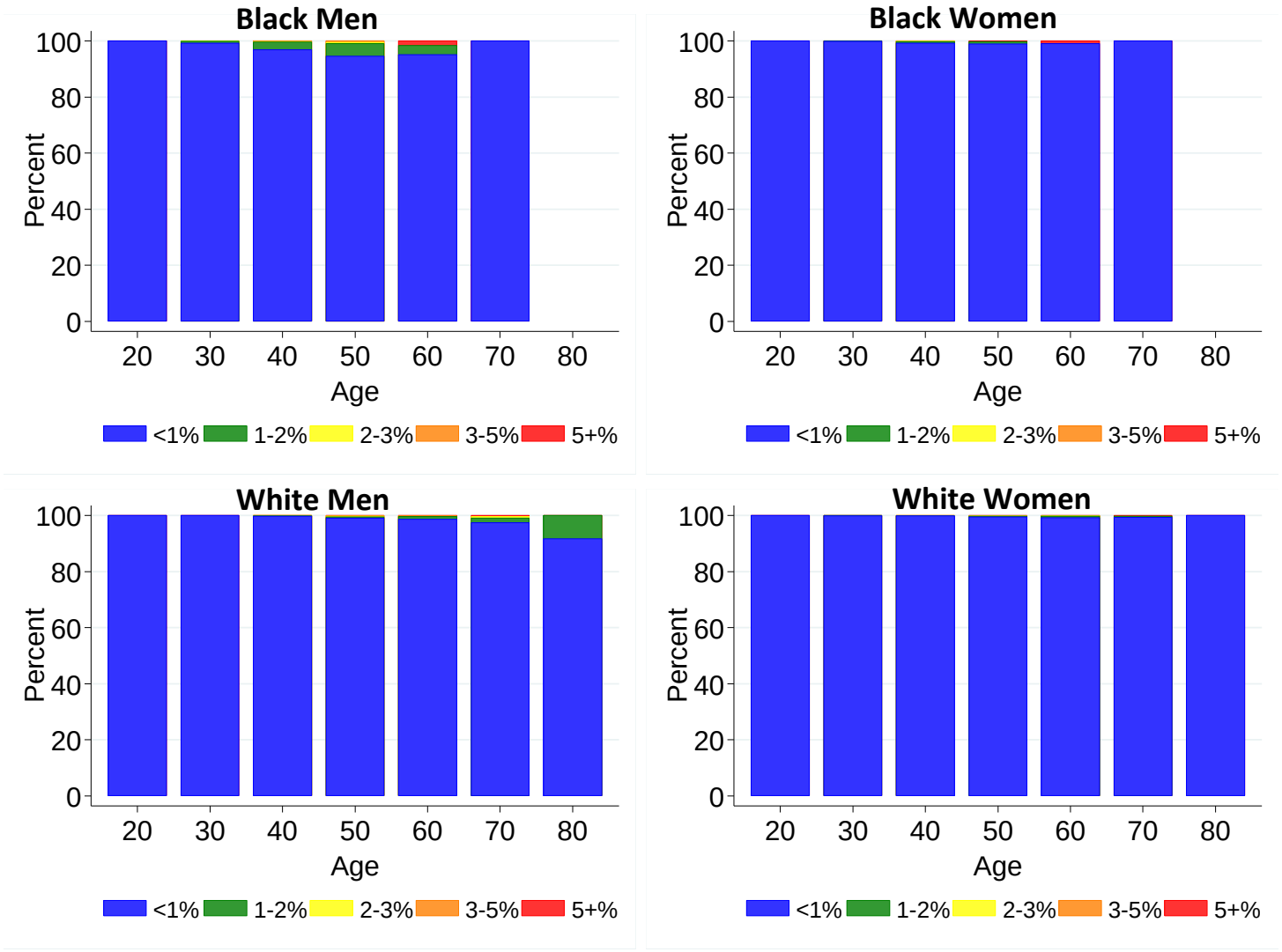
(B) Lifetime incidence



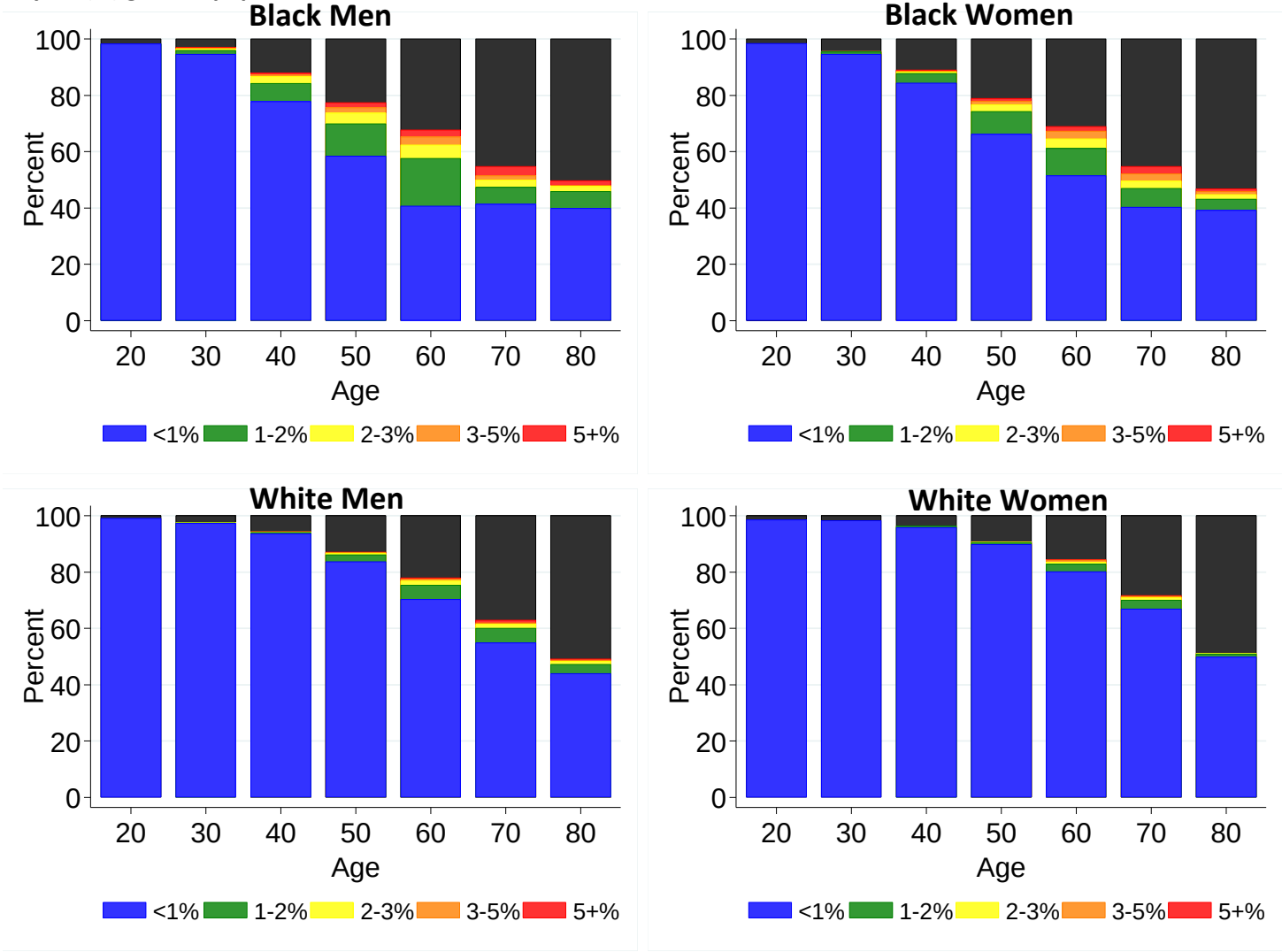
*The base-case scenario is the following: age-specific eGFR (114, 106, 98, 90, 82, 74, and 66 ml/min/1.73 m^2 for ages 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure 120 mmHg, ACR 4 mg/g (0.4 mg/mmol), BMI 26 kg/m^2, and no diabetes or anti-hypertension medication use. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESRD in the low-risk population, and thus are likely imprecise.

Figure S4: Distribution of projected 15-Year (%) (A-B) and lifetime (%) (C-D) ESRD risk in the United States and in absence of donation according to pre-donation risk characteristics in the US donor population (N=52,998) and US general population

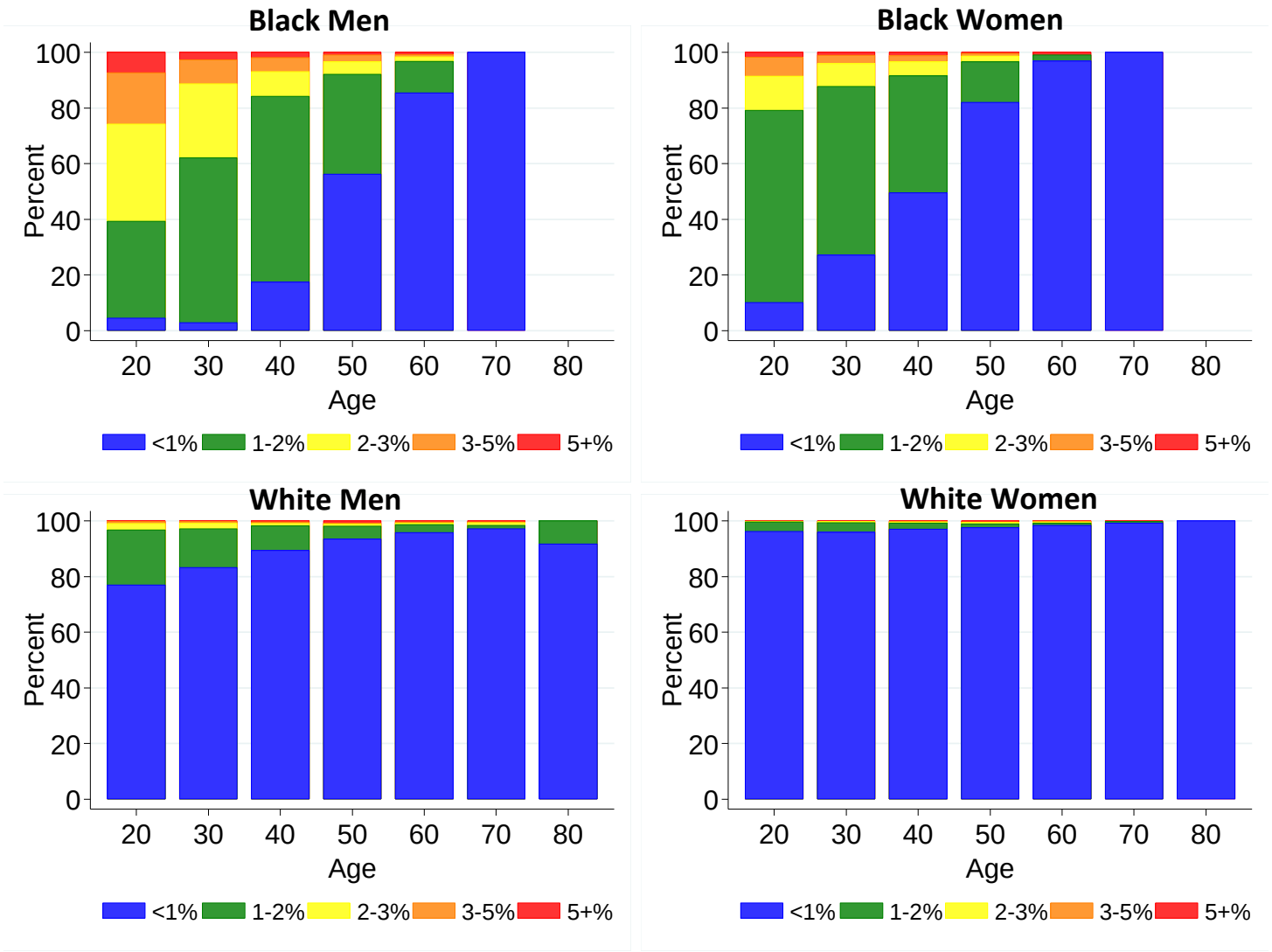
(A) 15-year (%) donor



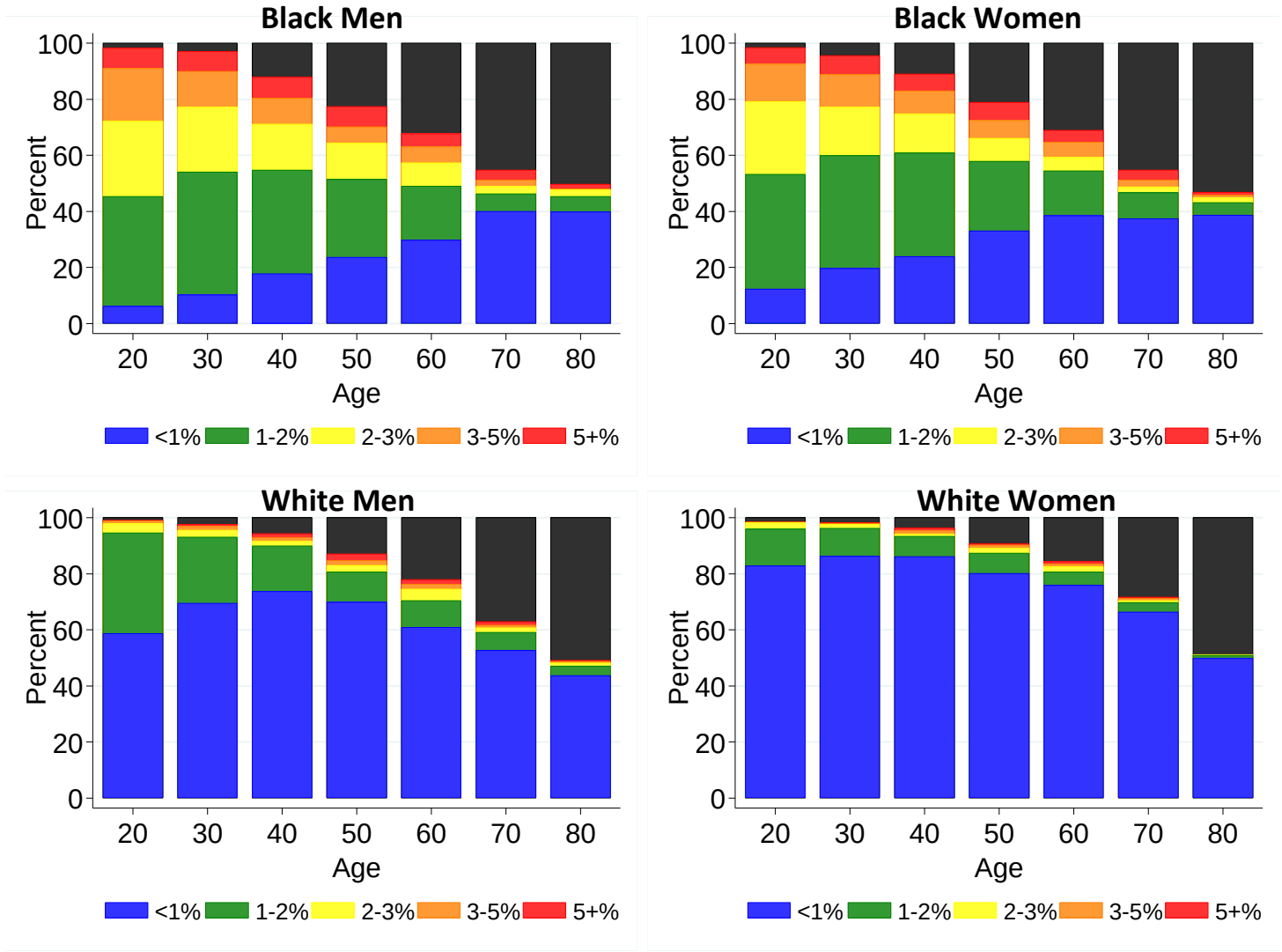
(B) 15-year (%) general population



(C) Lifetime (%) donor



(D) Lifetime (%) general population



The donor population consisted of white and black living kidney donors from 2005-2014 as reported to the Organ Procurement and Transplantation Network. Projected risks estimate 15-year and lifetime incidence of ESRD in the absence of donation. Prevalence in the general population was determined from NHANES III and the continuous NHANES (1999-2010). The black bar represents persons considered “high risk” and likely ineligible for kidney donation with one or more of the following risk factors: estimated

glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2, insulin-dependent diabetes mellitus, the use of 4 or more antihypertensive medications, systolic blood pressure ≥160/90 mmHg on medication or ≥170/100 mmHg off medication, random urine albumin-to-creatinine ratio (ACR) ≥300 mg/g (≥ 34 mg/mmol), and a history of coronary heart disease, stroke, congestive heart failure, or peripheral arterial disease. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESRD in the low-risk population, thus should be interpreted cautiously. There were no black donors in the 80-year age group.

Table S1: Estimates of the proportion of ESRD events in the low risk population

Low risk proportion	ARIC			Geisinger			Maccabi			BioMe			NHANES		
	HR	Prv	Risk	HR	Prv	Risk	HR	Prv	Risk	HR	Prv	Risk	HR	Prv	Risk
Overall, at mean age	5.50	30%	43%	16.7	20%	24%	17.4	10%	39%	14.4	27%	22%	16.1	12%	35%
Age 18-44				28.5	7%	34%	21.0	2.5%	67%	20.7	13%	27%	23.1	3%	61%
Age 45-54				16.1	17%	28%	11.7	11%	46%	14.9	25%	22%	15.3	12%	38%
Age 55-64	6.26	26%	42%	11.0	27%	27%	7.9	20%	42%	12.0	32%	22%	11.7	21%	30%
Age 65-74	4.24	36%	46%	7.48	39%	29%	5.3	32%	42%	9.60	40%	23%	8.86	38%	25%
Age 75+				5.10	54%	31%	3.6	50%	43%	7.71	57%	21%			

*HR, hazard ratio of high-risk status; Prev, prevalence of high-risk status; Proportion, the proportion of the ESRD risk in the low-risk subgroup. Proportion of the ESRD risk in the low-risk subgroup was calculated as the inverse of the sum of the prevalence of low-risk status and the product term of risk ratio associated with high-risk status and prevalence of high-risk status (e.g., $1/[\text{risk ratio}_{\text{high-risk}}*\text{prevalence}_{\text{high-risk}} + \text{prevalence}_{\text{low-risk}}]$). The risk ratio of high-risk status was approximated using the hazard ratio of high-risk status, which was determined using Cox proportional hazards models fit in the full population with the following covariates: age, sex, race, risk subgroup (low or high), a product term between age and race, and 3 additional product terms between risk subgroup and age, sex, and race. High-risk status was determined as estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2, insulin-dependent diabetes, the use of 4 or more antihypertensive medications, systolic blood pressure ≥160/90 mmHg on medication or ≥170/100 mmHg off medication, random urine albumin-to-creatinine ratio (ACR) ≥300 mg/g (≥34 mg/mmol), and a history of coronary heart disease, stroke, congestive heart failure, or peripheral arterial disease. Based on the results, in primary analysis, we estimated that 30% of ESRD events occurred in the low-risk subgroup; in sensitivity analyses, we varied the proportion of events to 20% and 40%.

Table S2: Proportion missing data in 7 general population cohorts and the living kidney donor cohort

	Cohorts used in Meta-Analysis*								For Risk Distribution in Recent Donors
Cohort	**NHANES**	**ARIC**	**VA**	**ICES KDT**	**Maccabi**	**Mount Sinai**	**Geisinger**		**OPTN**
Diabetes, %	0.06%	0.4%	NA	NA	NA	0%	0%		1.7%
Body-mass index, %	0.03%	0.1%	8.7%	NA	54.8%	15.5%	4.0%		2.1%
Smoking Status, %	0%	0.4%	NA	NA	0%	0%	1.5%		2.5%
Urine albumin-to-creatinine ratio, %	1.7%	0.8%	99.3%	NA	95.4%	94.8%	95.8%		9.4%**

*Variables with <2% missing were not imputed. Variables missing >2% in the general cohorts were imputed using multiple imputation with the exception of Maccabi due to very large sample size. In this cohort, the Cox model did not include BMI and ACR. In the meta-analysis of general population cohorts, variables with >20% imputed values were used for adjustment only and not included in the meta-analyzed coefficients. Other covariates do not have missing values.

** Refers to the presence of dipstick testing or albuminuria testing

Table S3: Discrimination of meta-analyzed coefficients in individual cohorts

Cohort	C-statistic, 95% CI
ARIC	0.821 (0.776, 0.865)
NHANES	0.889 (0.838,0.941)
Geisinger*	0.787 (0.759, 0.816)
Maccabi*	0.806 (0.789, 0.822)
Mount Sinai*	0.711 (0.629, 0.793)
VA*	0.675 (0.656, 0.695)

Harrel's C-statistic was performed on cohorts by applying the meta-analyzed beta coefficients to the values of the variables. C-statistics were calculated at the median of follow-up time in each cohort. An asterisk indicates that the study does not have data on one or more key variables for risk prediction; thus, the C-statistic is likely an underestimate. With the exception of ARIC and NHANES, all studies were missing albumin-to-creatinine ratio for the majority of participants. Diabetes, BMI, and smoking status were also commonly unavailable (see Table 2 & S2).

Table S4. Sensitivity analyses using coefficients for body mass index (BMI) derived from two published studies

(A) 15-Year ESRD Risk Projections

15-year risk of ESRD (%)	Age	Using coefficients from developed risk equations		Using meta-analyzed BMI coefficient from two published studies[12,13]	
		BMI 35 kg/m^2	BMI 40 kg/m^2	BMI 35 kg/m^2	BMI 40 kg/m^2
Black men	20	0.09	0.10	0.16	0.31
	40	0.27	0.32	0.33	0.62
	60	0.36	0.42	0.43	0.81
Black women	20	0.06	0.07	0.08	0.16
	40	0.16	0.19	0.17	0.32
	60	0.21	0.24	0.21	0.39
White men	20	0.02	0.02	0.04	0.07
	40	0.07	0.08	0.09	0.16
	60	0.15	0.17	0.17	0.31
White women	20	0.01	0.02	0.03	0.05
	40	0.04	0.05	0.05	0.10
	60	0.09	0.11	0.10	0.19

C) Lifetime ESRD Risk Projections

Lifetime risk of ESRD (%)	Age	Using coefficients from developed risk equations		Using meta-analyzed BMI coefficient from two published studies[12,13]	
		BMI 35 kg/m^2	BMI 40 kg/m^2	BMI 35 kg/m^2	BMI 40 kg/m^2
Black men	20	1.84	2.13	3.28	6.07
	40	1.14	1.32	1.38	2.58
	60	0.56	0.65	0.67	1.24

Black women	20	1.39	1.61	1.92	3.57
	40	0.96	1.12	0.99	1.86
	60	0.35	0.40	0.35	0.65
White men	20	0.66	0.77	1.26	2.36
	40	0.48	0.56	0.63	1.18
	60	0.29	0.34	0.33	0.62
White women	20	0.40	0.46	0.78	1.46
	40	0.33	0.39	0.40	0.76
	60	0.17	0.19	0.18	0.34

*Predicted risks reflect the base-case scenario with the value for BMI set to 35 and 40 kg/m^2. Estimates for the sensitivity analyses were derived using the same procedure as detailed in Sections 3 and 4 but treating BMI as a categorical value (<25 kg/m^2, 25-29.9 kg/m^2, 30-34.9 kg/m^2, and 35+ kg/m^2) with the following coefficients meta-analyzed from the Hsu et al and Vivante et al studies[12,13]: 0.7991 for BMI 25-30 kg/m^2, 1.5317 for BMI 30-35 kg/m^2 and 2.1622 for BMI 35+ kg/m^2. Lifetime risk projections are based on 15 years of follow-up data and calibrated to the incidence of ESRD in the low-risk population, and thus are likely imprecise.

Table S5. Comparison of 15-year risk projections (in the absence of donation) to observed risk (after donation) in US kidney donors

	ESRD risk projection in the absence of donation (15-years)*	Observed ESRD risk in live kidney donors (15-years) (N=96,217)**	Relative risk of ESRD in donors vs. prediction in the absence of donation***
Black men	0.21%	0.96%	4.8
Black women	0.12%	0.59%	4.9
White men	0.067%	0.34%	5.3
White women	0.045%	0.15%	3.5

*Calculated as detailed in Sections 2-3. Risks were calculated using the observed distribution of ages in the US donor population and the average donor scenario by race and sex.

**Actual risks obtained from Muzaale et al.[14]

*** Muzaale et al[14] report the incidence of ESRD to be 30.8 per 10 000 (95% CI, 24.3-38.5) in donors and 3.9 per 10 000 (95%CI, 0.8-8.9) in NHANES matched non-donors. The estimated relative risk overall was 7.9 with a bootstrapped estimated 95% confidence interval of 4.6-8.1. In Mjoen et al,[15] the estimated relative risk was 11.38 (95% CI: 4.37–29.6).

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