EDITORIAL

# The Risks of Living Kidney Donation

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Only candidates with an apparent low risk of kidney disease are accepted as living kidney donors. Postdonation studies that extend up to 12 years have shown rates of end-stage renal disease (ESRD) among donors that are similar to those observed in the general population, which suggests minimal risk from the inevitable reduction in the glomerular filtration rate (GFR) that occurs at donor nephrectomy.[1] However, a recent 7.6-year study in the United States showed that the incidence of ESRD was 8 times as high among donors as among well-selected nondonor controls.[2] A similar 15.2-year study in Norway showed that the risk was 11 times as high.[3] The magnitude of these relative risks has been debated, but when predonation risks of ESRD are multiplied by the relative risk of donation, significantly greater absolute postdonation risks are predicted. However, the absolute rates of ESRD were low in both studies, which reinforced the prevailing "low risk" characterization of donation.

The low estimates of long-term risk in these recent studies as well as in earlier donor-outcome studies may well have been underestimated because of their methodologic approach.[4] The lifetime risk of ESRD in the general population is roughly 3%; approximately 90% of cases occur after 44 years of age, and half the cases occur after 64 years of age.[5,6] Many diseases that will cause ESRD in later life will not be present in young candidates, and screening will not detect them. The design of past postdonation studies would not have detected ESRD due to kidney diseases that developed in later life in young donors or ESRD due to kidney diseases that began within a given study interval but progressed to ESRD outside it.[4] The latter limitation would not be overcome by adding the rates of ESRD over a 7.6-year period in successively older cohorts, as was done in the above-mentioned U.S. study to arrive at a 1% postdonation risk of ESRD among donors who would live to be 80 years of age.[2]

A thoughtful study whose results are now published in the *Journal* attempts to quantify the long-term risks of ESRD in the absence of donating a kidney among low-risk persons who might be considered to be acceptable donors.[7] Predominantly middle-aged adults were drawn from seven large cohorts and followed for an average of 6.4 years. Among the exclusion criteria were insulin-dependent diabetes mellitus, an estimated, size-normalized GFR (eGFR) of less than 45 ml per minute per 1.73 $m^2$ of body-surface area, severe hypertension, and a urinary albumin-to-creatinine ratio of 300 mg or more of albumin per gram of creatinine or approximately 1+ or greater albumin by dipstick (macroalbuminuria). ESRD was most strongly predicted by the presence of non–insulin-dependent diabetes and by graded associations with an eGFR of less than 90 ml per minute per 1.73 $m^2$, hypertension, and microalbuminuria. The risk factors for ESRD were weighted and then applied to project the risk of ESRD over longer intervals. As the authors advise, there are limitations to this new method of deriving long-term estimates from shorter-term data.

For example, the study does not account for the risk of progressive diabetic nephropathy, which causes almost half the cases of ESRD in the United States each year and is the dominant threat to donors.[4,6] Diabetes becomes increasingly prevalent after 30 years of age; after approximately 15 years of diabetes, macroalbuminuria often

develops, yet it was an exclusion criterion in the current study. Once macroalbuminuria occurs, the eGFR decreases at a rate of approximately 40 ml per minute per 1.73 $m^2$ per decade, resulting in ESRD after 15 or more years.[4-6] Currently, postdonation diabetes is poorly predicted in donor candidates, even with the use of focused, traditional criteria[8] rather than the nonspecific risk factors used in the current study. Furthermore, ESRD would not have developed in any patient with classically progressing diabetic nephropathy during the study interval. Similar concerns would apply if ESRD due to other kidney diseases was not well represented in the cohorts that were used to develop the risk projections in the present study.

In the current study, kidney diseases had to progress quickly in order to be counted, but most kidney diseases progress slowly. For example, in one study, approximately 25% of 5627 patients with 1+ to 4+ albumin by dipstick, but in whom GFR was not determined, had progression to ESRD within 17 years.[9] In the present study, participants who began with an eGFR of 100 ml per minute per 1.73 $m^2$ would have to have had a reduction of approximately 90 ml per minute per 1.73 $m^2$ over a period of 6.4 years in order for ESRD to be identified. In postdonation studies, such quickly progressing diseases are predominantly glomerulonephritides.[3]

Because of the relatively short study interval, kidney diseases that progressed to ESRD would have been more likely to develop in participants near the beginning of the study than at a later point, and very low grade albuminuria and hypertension would probably have been part of the disease process. In the general population, these two factors predict a reduction in the eGFR of only 1 to 2 ml per minute per 1.73 $m^2$ per decade.[5,10] They are not recognized predictors of specific diseases that are entirely absent at study entry, such as IgA nephropathy or bladder-outlet obstruction. In summary, the predictive associations in the present study may well have been less strong if the cohorts had been followed for longer periods of time, during which ESRD from diabetes and other similarly unpredicted kidney diseases would have continued to appear. Although the present study tested the derived projected risks against outcome data from living donors, those outcome data may have had similar limitations.

Nonetheless, the present study by Grams et al. is a noteworthy attempt to address quantitatively the growing perception that donor candidates have markedly varied risks of ESRD, and some candidates who are currently considered to be at unacceptably high risk may have lower risks than others who are currently deemed to be at acceptable risk. Past efforts to address this pressing problem have lacked the precision that we all desire.[4] The present study initiates an approach that may improve the defensible selection and counseling of the admirable persons who are considering kidney donation.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

# Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate

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## ABSTRACT

### BACKGROUND

Evaluation of candidates to serve as living kidney donors relies on screening for individual risk factors for end-stage renal disease (ESRD). To support an empirical approach to donor selection, we developed a tool that simultaneously incorporates multiple health characteristics to estimate a person's probable long-term risk of ESRD if that person does not donate a kidney.

### METHODS

We used risk associations from a meta-analysis of seven general population cohorts, calibrated to the population-level incidence of ESRD and mortality in the United States, to project the estimated long-term incidence of ESRD among persons who do not donate a kidney, according to 10 demographic and health characteristics. We then compared 15-year projections with the observed risk among 52,998 living kidney donors in the United States.

### RESULTS

A total of 4,933,314 participants from seven cohorts were followed for a median of 4 to 16 years. For a 40-year-old person with health characteristics that were similar to those of age-matched kidney donors, the 15-year projections of the risk of ESRD in the absence of donation varied according to race and sex; the risk was 0.24% among black men, 0.15% among black women, 0.06% among white men, and 0.04% among white women. Risk projections were higher in the presence of a lower estimated glomerular filtration rate, higher albuminuria, hypertension, current or former smoking, diabetes, and obesity. In the model-based lifetime projections, the risk of ESRD was highest among persons in the youngest age group, particularly among young blacks. The 15-year observed risks after donation among kidney donors in the United States were 3.5 to 5.3 times as high as the projected risks in the absence of donation.

### CONCLUSIONS

Multiple demographic and health characteristics may be used together to estimate the projected long-term risk of ESRD among living kidney-donor candidates and to inform acceptance criteria for kidney donors. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others.)

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*A complete list of the members of the Chronic Kidney Disease Prognosis Consortium is provided in the Supplementary Appendix, available at NEJM.org.

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Nearly 30,000 people worldwide become living kidney donors each year.[1-3] Traditionally, living donors have been selected on the basis of an absence of risk factors for poor outcomes after donation and without a comprehensive assessment of individualized long-term risk. Although kidney donation is considered to be safe in healthy, low-risk persons, donation has lifelong implications, and the most direct effect may be an increased long-term risk of end-stage renal disease (ESRD).[4-7] A tool to predict a donor candidate's long-term risk of ESRD that incorporates the combined effect of multiple demographic and health characteristics before donation could help make the criteria by which a potential kidney donor is accepted or declined more empirical and transparent.

In the absence of a robust epidemiologic framework for the assessment of long-term risk, acceptance criteria for living kidney donation have varied widely among transplantation centers.[8-10] Controversy exists over whether donor candidates with certain health characteristics, such as older age or hypertension, should be accepted for kidney donation. Some transplantation centers use more stringent criteria for younger donors than for middle-aged donors, given the long postdonation life expectancy during which complications may develop.[11] Race is also a consideration in the evaluation of donor candidates; the risk of ESRD is higher among blacks than among whites both in the general U.S. population and in the donor population.[2,5,12-14]

We developed an online risk tool to help evaluate, counsel, and accept living kidney-donor candidates (www.transplantmodels.com/esrdrisk). Using population-based data, we derived equations that quantify the combined effect of 10 routinely available demographic and health characteristics to estimate the risk of ESRD among kidney-donor candidates over a 15-year time horizon. These estimates do not incorporate any added risk that is attributable to kidney donation. Kidney donation probably increases the risk of ESRD, but the increase in risk according to predonation characteristics is difficult to quantify reliably with the use of existing data.[15-17] We compared risk projections with the observed 15-year incidence of ESRD among living kidney donors, hypothesizing, on the basis of recent reports,[5,6] that the incidence of ESRD among persons who donate kidneys would be at least four times as high as the projected incidence in the absence of donation. Because many kidney donors are young, we also projected the lifetime risk of ESRD, with the caveat that these lifetime estimates lack precision and were based on relatively short follow-up data.

## METHODS

### STUDY PROTOCOL

We developed risk equations to estimate the long-term risk of ESRD in the absence of kidney donation according to a person's demographic and health characteristics. Source data included the annual incidence of ESRD in the overall U.S. population and the associations of health characteristics with ESRD in seven general population studies (Section 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol, with the statistical analysis plan, is available at NEJM.org.

### INCIDENCE OF ESRD IN THE U.S. POPULATION

The annual incidence of ESRD, defined as the need for long-term dialysis or a kidney transplant, was previously estimated in the U.S. population within the categories of age, sex, and race.[14] These estimates were derived with the use of actual ESRD incidence and mortality data collected by the U.S. Renal Data System and overall mortality data from the U.S. Census (Section 2 in the Supplementary Appendix).[18] Annual rates were compounded to determine the absolute risk over the desired time horizon.

We partitioned the population incidence of ESRD into a high-risk subgroup (ineligible for kidney donation) and a low-risk subgroup (potentially eligible for kidney donation), with the latter subgroup specified to exclude persons with one or more of the following absolute contraindications to kidney donation: an estimated glomerular filtration rate (eGFR) of less than 45 ml per minute per 1.73 $m^2$ of body-surface area, insulin-dependent diabetes mellitus, the use of four or more antihypertensive medications, a blood pressure of 160/90 mm Hg or more while the person was taking medication or 170/100 mm Hg or more while the person was not taking medication, a urinary albumin-to-creatinine ratio of 300 or more (as measured in milligrams of albumin to grams of creatinine), or a history of coronary heart disease, stroke, congestive

heart failure, or peripheral arterial disease (Table S1 in the Supplementary Appendix).

### ASSOCIATIONS OF INDIVIDUAL HEALTH CHARACTERISTICS WITH ESRD

We quantified the associations between health characteristics and ESRD in the low-risk subgroups of seven general population cohorts that were assembled by the Chronic Kidney Disease Prognosis Consortium[19]: the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994), the Atherosclerosis Risk in Communities (ARIC) Study, the Geisinger Health System, the Maccabi Health System, the Veterans Health Administration (VA), the Mount Sinai BioMe cohort, and the Institute for Clinical Evaluative Sciences Ontario Kidney, Dialysis, and Transplantation Program. To ensure model stability, cohorts were required to have data on at least 20 ESRD events in the low-risk subgroup.

We considered 13 distinct demographic and health characteristics: age, race, sex, eGFR, urinary albumin-to-creatinine ratio, systolic blood pressure, the presence or absence of noninsulin-dependent diabetes mellitus, the use or nonuse of antihypertensive medication, smoking status, body-mass index (BMI; the weight in kilograms divided by the square of the height in meters), total cholesterol level, low-density lipoprotein (LDL) cholesterol level, and history of kidney stones. All the models were adjusted for an interaction between age and race.

Risk associations were estimated with the use of multivariable Cox proportional-hazards models individually in each cohort and then combined with the use of a random-effects meta-analysis. Multiple imputation was used for missing data on health characteristics. Missing data ranged from less than 1% for all variables in the ARIC cohort to more than 99% for measures of albuminuria in the VA cohort (Table S2 in the Supplementary Appendix). Coefficients that were based on data missing more than 20% of the time were not used in the meta-analysis. The discrimination of coefficients resulting from the meta-analysis was evaluated in the individual cohorts (Table S3 in the Supplementary Appendix).

### ESTIMATING THE LONG-TERM INCIDENCE OF ESRD IN THE BASE-CASE SCENARIO

We applied the coefficients derived from the meta-analysis to the low-risk subgroups of the NHANES III and continuous NHANES (1999–2010) cohorts using sample weights according to analytic guidelines.[20] A base-case scenario was defined by the average health characteristics of the living donor population in the United States: a systolic blood pressure of 120 mm Hg, a urinary albumin-to-creatinine ratio of 4 (as measured in milligrams of albumin to grams of creatinine), a BMI of 26, no smoking, no diabetes or use of antihypertensive medication[5] (characteristics that were fairly uniform among donors, regardless of age), and an average eGFR within subgroups of age (Section 3 in the Supplementary Appendix).

The linear function for each participant was centered on that of the base-case scenario within each category of age (in 10-year increments), sex, and race.[21] We calibrated this risk to the estimated incidence of ESRD in the low-risk population over the given time periods (15 years and lifetime) by dividing the overall estimate by the sum of the product of the prevalence of each low-risk participant's health profile and the exponentiated linear function (Section 4 in the Supplementary Appendix).

### PROJECTED RISKS IN THE DONOR POPULATION

We applied the risk equations to 57,508 living kidney donors assembled from the U.S. Organ Procurement and Transplantation Network between January 1, 2005, and July 2, 2014. After the exclusion of 4510 donors who were missing predonation data on serum creatinine level or systolic blood pressure, 52,998 donors were included.

The urinary albumin-to-creatinine ratio was imputed as 4 (measured in milligrams of albumin to grams of creatinine) for participants with urinalysis results reported as "negative," "not done," or "unknown" and as 30 for those with results reported as "positive." Smoking status was imputed as former smoker if "history of cigarette use" or "other tobacco used" was reported. In total, 2.5% of the donors had missing data regarding BMI, 1.7% had missing data regarding diabetes mellitus, and 97.5% had missing data regarding use of antihypertensive medication. Missing values were imputed as follows: 26 for BMI, no diabetes mellitus for status with respect to diabetes mellitus, and no antihypertensive medication for status with respect to antihypertensive medication use.

**Table 1. Characteristics of the Low-Risk Subgroups in the General Population Cohorts.***

| Characteristic | NHANES | ARIC | VA† | ICES KDT‡ | Maccabi | Mount Sinai | Geisinger |
|---|---|---|---|---|---|---|---|
| Country | U.S. | U.S. | U.S. | Canada | Israel | U.S. | U.S. |
| Low-risk population — no. of participants (% of total cohort)§ | 8775 (81) | 8155 (72) | 1,362,620 (52) | 2,120,427 (52) | 1,149,058 (90) | 8844 (73) | 275,435 (80) |
| ESRD event — no. of participants (%) | 38 (0.4) | 81 (1.0) | 845 (0.1) | 1146 (0.1) | 1355 (0.1) | 69 (0.8) | 366 (0.1) |
| Follow-up — yr | | | | | | | |
| Median | 16 | 14 | 6 | 6 | 8 | 4 | 8 |
| Interquartile range | 14–18 | 13–15 | 6–7 | 3–8 | 4–11 | 2–6 | 4–12 |
| Age | | | | | | | |
| Mean — yr | 41±16 | 63±6 | 56±15 | 40±15 | 40±15 | 49±15 | 46±17 |
| Distribution — % of participants¶ | | | | | | | |
| 18–24 yr | 16 | 0 | 3 | 17 | 16 | 5 | 12 |
| 25–34 yr | 25 | 0 | 8 | 22 | 24 | 16 | 17 |
| 35–44 yr | 23 | 0 | 13 | 25 | 25 | 18 | 21 |
| 45–54 yr | 14 | 6 | 23 | 21 | 18 | 24 | 21 |
| 55–64 yr | 11 | 57 | 29 | 10 | 10 | 22 | 15 |
| 65–74 yr | 8 | 36 | 15 | 4 | 5 | 11 | 10 |
| 75–84 yr | 3 | 0 | 10 | 1 | 2 | 3 | 4 |
| Women — % of participants | 52 | 57 | 9 | 58 | 56 | 60 | 59 |
| Black race — % of participants | 12 | 20 | 18 | NA‖ | 0 | 46 | 2 |
| eGFR — ml/min/1.73 $m^2$ | 102±19 | 88±14 | 87±16 | 103±18 | 95±21 | 92±22 | 97±20 |
| Urinary albumin-to-creatinine ratio** | | | | | | | |
| Median | 6 | 3 | 5 | NA | 0 | 7 | 12 |
| Interquartile range | 4–9 | 2–7 | 3–11 | NA | 0–12 | 3–22 | 5–29 |
| Systolic blood pressure — mm Hg | 119±14 | 124±16 | 130±14 | NA | 119±14 | 123±14 | 124±14 |
| Antihypertensive drug use — % of participants | 17 | 33 | 23 | NA | 6 | 15 | 12 |
| Noninsulin-dependent diabetes mellitus — % of participants | 8 | 11 | NA | NA | 8 | 11 | 7 |
| Body-mass index†† | | | | | | | |
| Mean | 26±5 | 28±5 | 28±5 | NA | 26±5 | 28±9 | 30±7 |
| >30 — % of participants | 20 | 32 | 32 | NA | 18 | 30 | 41 |
| >35 — % of participants | 8 | 11 | 10 | NA | 6 | 14 | 19 |

| Smoking status — % of participants | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Current smoker | 25 | 15 | NA | NA | 23 | 14 | 25 | |
| Former smoker | 35 | 42 | NA | NA | 2 | 18 | 22 | |

* Plus–minus values are means ±SD. The cohorts included the Atherosclerosis Risk in Communities Study (ARIC), the Geisinger Health System (Geisinger), the Maccabi Health System (Maccabi), the Mount Sinai BioMe cohort (Mount Sinai), the Third National Health and Nutrition Examination Survey (NHANES), the Institute for Clinical Evaluative Sciences Ontario Kidney, Dialysis and Transplantation Program (ICES KDT), and the Veterans Health Administration (VA). The term eGFR denotes estimated glomerular filtration rate, ESRD end-stage renal disease, NA not available, and U.S. United States.

† This cohort did not supply information on insulin use, so the low-risk subgroup excluded all persons with diabetes.

‡ This cohort did not supply information on systolic blood pressure or insulin use, so the low-risk cohort excluded all persons with diabetes and hypertension.

§ The low-risk subgroup excluded persons with an eGFR of less than 45 ml per minute per 1.73 $m^2$, insulin-dependent diabetes mellitus, the use of four or more antihypertensive medications, blood pressure of 160/90 mm Hg or more while the participant was taking medication or 170/100 mm Hg or more while the participant was not taking medication, urinary albumin-to-creatinine ratio of 300 or more (as measured in milligrams of albumin to grams of creatinine), and a history of coronary heart disease, stroke, congestive heart failure, or peripheral arterial disease.

¶ Percentages do not always sum to 100 owing to rounding.

‖ Data on race were not available in this cohort, but it was estimated that approximately 3% of the population in Ontario is black.

** The albumin-to-creatinine ratio was measured in milligrams of albumin to grams of creatinine.

†† The body-mass index is the weight in kilograms divided by the square of the height in meters.

### STATISTICAL ANALYSIS

We compared recently published data regarding the 15-year risk of ESRD among kidney donors[5] with the projected risk in the absence of donation in a hypothetical group of age-matched donor candidates and assessed the relative risk. We conducted various sensitivity analyses. First, we varied by ±33% the estimated proportion of events occurring in the low-risk subgroup, and second, we projected the long-term risk of ESRD with the use of coefficients derived from a literature review.[22,23] Because the coefficients in our meta-analysis were similar to those that have been published previously for all variables except BMI, the sensitivity analyses that were based on a literature review focused on BMI. All the analyses were performed with the use of Stata/MP software, version 13.1 (StataCorp).

## RESULTS

### CHARACTERISTICS OF THE PARTICIPANTS AT BASELINE

Overall, there were 8,325,115 participants in the seven cohorts, of whom 4,933,314 had no health conditions that were deemed to be absolute contraindications to kidney donation. In this subgroup, there were 3900 ESRD events over a period of 31,321,064 person-years of follow-up; the median follow-up ranged from 4 years in the Mount Sinai cohort to 16 years in the NHANES cohort (Table 1). The average age of the participants at cohort entry ranged from 40 years in the ICES KDT cohort to 63 years in the ARIC cohort. The proportion of women ranged from 9% in the VA cohort to 52 to 60% in the remaining cohorts.

### ASSOCIATIONS OF HEALTH CHARACTERISTICS WITH ESRD

There was a graded association between lower eGFR and higher risk of ESRD at levels of less than 90 ml per minute per 1.73 $m^2$; at levels of 90 ml per minute per 1.73 $m^2$ or more, there was no significant association (Table 2). Other characteristics that were associated with a higher risk of ESRD included noninsulin-dependent diabetes (adjusted hazard ratio for the comparison with no diabetes, 3.01; 95% confidence interval [CI], 1.91 to 4.74), higher systolic blood pressure (hazard ratio per increase of 20 mm Hg, 1.42; 95% CI, 1.27 to 1.58), use of antihypertensive

medication (hazard ratio for the comparison with no use, 1.35; 95% CI, 1.01 to 1.82), former smoking (hazard ratio for the comparison with never smoking, 1.45; 95% CI, 1.23 to 1.71), current smoking (hazard ratio for the comparison with never smoking, 1.76; 95% CI, 1.29 to 2.41), and higher urinary albumin-to-creatinine ratio (hazard ratio per increase of 10×, 2.94; 95% CI, 0.99 to 8.75). There was a relatively weak association between BMI and the risk of ESRD; a small graded association was observed with a BMI of more than 30 (hazard ratio per increase of 5 above 30, 1.16; 95% CI, 1.04 to 1.29). Findings regarding total cholesterol level, LDL cholesterol level, and history of kidney stones were not significant and thus were excluded from the final model.

### INDIVIDUALIZED ESRD RISK PROJECTIONS

The 15-year predonation projection of the risk of ESRD for the average kidney-donor candidate varied according to age, sex, and race; the highest risks were among middle-aged black men (Fig. 1A). For a 20-year-old base-case candidate, the 15-year projected risk was 0.08% among black men, 0.05% among black women, 0.02% among white men, and 0.01% among white women. The corresponding estimates for a 40-year-old base-case candidate were 0.24%, 0.15%, 0.06%, and 0.04%; for a 60-year-old base-case candidate, the estimates were 0.32%, 0.18%, 0.13%, and 0.08%, respectively. As expected, the model-based lifetime projections were generally higher than the 15-year projections, especially among younger persons, although the risks were less than 2% for all base-case scenarios (Fig. 1B).

The projected risk of ESRD was higher among persons with additional risk factors, particularly a high albumin-to-creatinine ratio, than among those without additional risk factors (Table 3). Current smoking was also a strong risk factor (Fig. S1 in the Supplementary Appendix). Risk factors had a larger effect on model-based lifetime projections among young persons than among older persons (Fig. S2 in the Supplementary Appendix). The relationships were similar in most sensitivity analyses (Fig. S3 in the Supplementary Appendix), with the exception of the lifetime projected risks among young persons with obesity, in whom projected risks that were based on coefficients derived from the literature review were higher than those in the developed model (Table S4 in the Supplementary Appendix).

### RISK PROJECTIONS AMONG KIDNEY DONORS

When the predonation projections of risk of ESRD were applied to the donor population in the United States, 99% of the donors had a projected 15-year predonation risk of ESRD of less than 3%, 98% had a projected incidence of less than 2%, and 94% had a projected incidence of less than 1% (Fig. S4 in the Supplementary Appendix). Predonation estimates of more than 3% were most common among black donors who were 53 to 68 years of age.

The 15-year risks of ESRD that have been observed among kidney donors in the United States were 3.5 to 5.3 times as high as the projected risks among nondonors, with similar patterns of risk according to race and sex in the absence of donation and in the presence of donation (Table S5 in the Supplementary Appendix). For example, the projected 15-year risk (in the absence of donation) for the average black male donor candidate was 0.21% and the observed risk (after donation) was 0.96%. The corresponding projected and observed 15-year risks among black women were 0.12% and 0.59%; the risks among white men were 0.07% and 0.34%, respectively, and the risks among white women were 0.04% and 0.15%, respectively.

## DISCUSSION

We estimated the long-term risk of ESRD according to 10 predonation demographic and health characteristics assessed together. We then developed an online risk tool to help evaluate and counsel living kidney-donor candidates and improve the acceptance process. We found substantial variation in the projected risks of ESRD according to age, sex, and race. For the base-case candidate, a scenario reflecting the average kidney donor in the United States, the highest 15-year risks were among middle-aged black men. In model-based lifetime projections, young persons, particularly those of black race, were at the highest risk. Many older persons had low estimates of the long-term risk of ESRD, even in the presence of health characteristics that are often considered to be contraindications to donation, such as low eGFR or mild hypertension.

**Table 2. Meta-Analysis of Multivariable-Adjusted Hazard Ratios That Estimate the Association of Baseline Characteristics with ESRD.***

| Characteristic | Hazard Ratio (95% CI) | β±SE | Population Cohort | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | NHANES | ARIC | VA | ICES KDT | Maccabi | Mount Sinai | Geisinger |
| eGFR per decrease of 15 ml/min/1.73 $m^2$ | | | | | | | | | |
| <60 ml/min/1.73 $m^2$ | 6.61 (4.87–8.96) | 1.89±0.16 | 12.82 (0.35–463.68) | 6.66 (1.85–23.97) | NA | 10.47 (6.75–16.24) | 6.00 (4.74–7.60) | 2.47 (0.64–9.55) | 5.50 (3.25–9.30) |
| 60–89 ml/min/1.73 $m^2$ | 1.63 (1.53–1.74) | 0.49±0.03 | 1.05 (0.33–3.36) | 1.51 (1.01–2.25) | 1.50 (1.32–1.70) | 1.59 (1.39–1.82) | 1.72 (1.54–1.93) | 1.65 (1.03–2.64) | 1.85 (1.51–2.26) |
| 90–119 ml/min/1.73 $m^2$ | 1.02 (0.85–1.23) | 0.02±0.09 | 0.83 (0.32–2.14) | 1.67 (0.87–3.20) | 0.98 (0.81–1.17) | 0.77 (0.68–0.88) | 0.96 (0.81–1.15) | 1.35 (0.81–2.27) | 1.27 (0.99–1.62) |
| ≥120 ml/min/1.73 $m^2$ | 0.79 (0.56–1.10) | −0.24±0.17 | 1.18 (0.47–2.94) | NA | 0.50 (0.34–0.72) | 1.62 (1.04–2.52) | 0.72 (0.52–1.00) | 0.82 (0.45–1.47) | 0.59 (0.47–0.75) |
| Systolic blood pressure, per increase of 20 mm Hg | 1.42 (1.27–1.58) | 0.35±0.06 | 2.90 (1.74–4.82) | 1.40 (1.04–1.88) | 1.27 (1.15–1.41) | NA | 1.45 (1.33–1.57) | 1.29 (0.91–1.84) | 1.47 (1.25–1.72) |
| Antihypertensive drug use | 1.35 (1.01–1.82) | 0.30±0.15 | 0.31 (0.07–1.31) | 1.18 (0.74–1.88) | 1.17 (1.01–1.36) | NA | 1.90 (1.68–2.16) | 2.04 (1.19–3.49) | 1.16 (0.90–1.49) |
| Noninsulin-dependent diabetes mellitus | 3.01 (1.91–4.74) | 1.10±0.23 | 9.73 (2.97–31.88) | 2.95 (1.79–4.85) | NA | NA | 2.21 (1.97–2.48) | 1.49 (0.79–2.81) | 4.50 (3.45–5.88) |
| Body-mass index, per 5-point increase | | | | | | | | | |
| ≤30 | 0.98 (0.81–1.17) | −0.02±0.09 | 2.40 (1.11–5.21) | 1.20 (0.74–1.95) | 0.91 (0.80–1.02) | NA | NA | 0.94 (0.62–1.40) | 0.87 (0.71–1.08) |
| >30 | 1.16 (1.04–1.29) | 0.15±0.05 | 0.95 (0.40–2.24) | 1.30 (0.95–1.79) | 1.26 (1.13–1.40) | NA | NA | 0.99 (0.83–1.18) | 1.18 (1.06–1.30) |
| Smoking status | | | | | | | | | |
| Former smoker | 1.45 (1.23–1.71) | 0.37±0.08 | 1.98 (0.73–5.37) | 1.75 (1.02–3.00) | NA | NA | 1.35 (1.03–1.79) | 1.12 (0.62–2.02) | 1.51 (1.18–1.94) |
| Current smoker | 1.76 (1.29–2.41) | 0.57±0.16 | 4.44 (1.49–13.27) | 3.51 (1.81–6.78) | NA | NA | 1.35 (1.17–1.56) | 1.42 (0.77–2.63) | 1.60 (1.22–2.09) |
| Urinary albumin-to-creatinine ratio, per increase of 10× | 2.94 (0.99–8.75) | 1.08±0.56 | 5.48 (2.37–12.71) | 1.80 (1.26–2.56) | NA | NA | NA | NA | NA |

* CI denotes confidence interval, and SE standard error. The analysis was additionally adjusted for age, race, and sex. The reference category for use of antihypertensive drugs was no use of antihypertensive drugs. The reference category for noninsulin-dependent diabetes mellitus was no diabetes. The reference category for smoking status was never smoked.

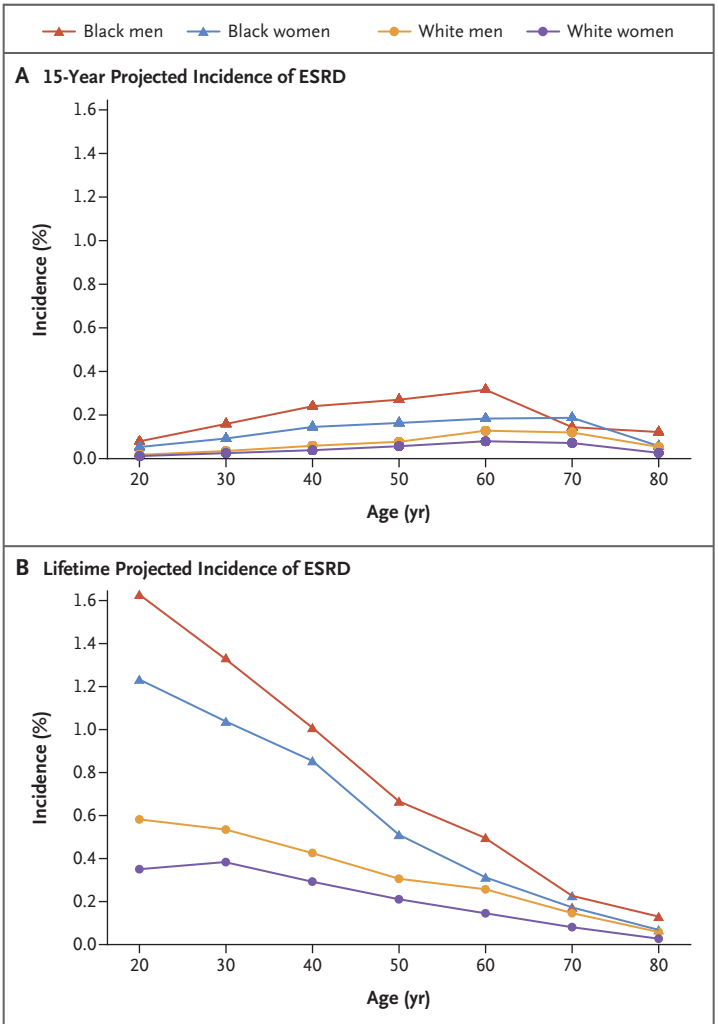


**Figure 1. Projections of the Incidence of End-Stage Renal Disease (ESRD) in the United States According to Age, Race, and Sex for the Base-Case Scenario.**

The base-case scenario (a scenario reflecting the average kidney donor in the United States) for the 15-year projected risk (Panel A) is the following: an age-specific estimated glomerular filtration rate (114, 106, 98, 90, 82, 74, and 66 ml per minute per 1.73 $m^2$ for an age of 20, 30, 40, 50, 60, 70, and 80 years, respectively), systolic blood pressure of 120 mm Hg, a urinary albumin-to-creatinine ratio of 4 (as measured in milligrams of albumin to grams of creatinine), a body-mass index (the weight in kilograms divided by the square of the height in meters) of 26, and no diabetes mellitus or use of antihypertensive medication. These factors were selected as being representative of living kidney donors in the United States. The lifetime projections (Panel B) were based on 15 years of follow-up data and were calibrated to the incidence of ESRD in the low-risk population in the United States and thus lack precision. All the estimates reflect the U.S. population average for unmeasured characteristics; individual risk may be higher or lower. Confidence intervals for each of the estimates are provided in Section 4 in the Supplementary Appendix. Confidence intervals were obtained from simulations that were sampled from the distribution of coefficients derived from the meta-analysis.

This study generates estimates of long-term risk of ESRD among low-risk persons, in which a combination of individual demographic and health characteristics were considered together. Our estimates leveraged data from more than 31 million person-years of follow-up and included persons with health characteristics that are not well captured in current populations of living kidney donors.

Use of the online risk tool in kidney donor–acceptance protocols may help to minimize the number of living kidney donors in whom ESRD develops after donation, support donation among people whose long-term risk was previously misunderstood, and enhance informed consent and shared decision making with donor candidates.[24] Although the risk tool was developed specifically for the United States, the methods that we used to generate robust estimates may be adapted to other countries with the use of local data sources.

Our risk projections focused on ESRD in the absence of donation over a 15-year time horizon. These estimates may not fully capture the relevant risks among young donors, who may have more than 60 years of remaining life. For this reason, we also provided projected lifetime risks of ESRD, with the caveat that these estimates lack precision and use data from cohorts with relatively short follow-up time. Although we did not specifically model the incidence of risk factors such as diabetes and hypertension, our projections incorporate the community-observed rate of disease development in a given subgroup of the population, thereby incorporating all disease pathways to ESRD. However, the projections should be considered to be the population average. If a person has a higher risk of diabetes than does a peer with identical demographic and health characteristics (blood pressure, eGFR, albuminuria, BMI, and smoking status), the actual risk of ESRD may be higher than our projected risk.

Similarly, the magnitude of the added risk from donation and the variation in this risk according to health characteristics such as obesity remain uncertain. In two recent studies,[5,6] the ratio of the risk of donation as compared with nondonation was estimated to be 7.9 (95% CI, 4.6 to 8.1) and 11.4 (95% CI, 4.4 to 9.6). Our 15-year risk projections in the absence of donation appear to be consistent with these estimates[5,6]

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

| Scenario | Age | Race | eGFR | Urinary Albumin: Creatinine Ratio† | Systolic Blood Pressure | Smoking Status | 15-Yr Projection (95% CI) | Model-Based Lifetime Projection (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | *yr* | | *ml/min/1.73 m²* | | *mm Hg* | | | |
| 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.

and also show similar patterns of risk variation according to sex and race.[12,13]

The relative associations used in our online tool were derived from seven cohorts, with median follow-up periods ranging from 4 to 16 years. These estimates in the meta-analysis were, for the most part, very similar to those that have been published previously in a cohort with 25-year follow-up.[22] The risk of ESRD was higher among blacks than among whites and slightly higher among men than among women — findings that are similar to estimates in the general population.[14,18] Racial variation in the risk of ESRD may relate to the incidence of hypertension and diabetes,[13,25] access to care and other unmeasured environmental factors, and the distribution of kidney-disease risk alleles such as *APOL1*; our estimates incorporate only the population-average exposure to these factors. However, two studies with long-term follow-up have suggested much stronger risk associations between BMI and ESRD than we observed.[22,23] Sensitivity analyses suggest that an underestimate of the risk association between BMI and ESRD would be significant primarily among the youngest donor candidates. Thus, we suggest that caution be used in evaluating obese donor candidates, particularly when they are young.

Despite excellent outcomes in recipients of kidneys from older living donors,[26-28] only 2.8% of the living kidney donors in the United States were 65 years of age or older in 2014.[3] Our estimates suggest that healthy older adults may be appropriate donor candidates with respect to their risk of ESRD. It is relatively unlikely that ESRD would develop in a healthy older adult, who has lived to an older age without the development of high-risk health conditions, even in the presence of suboptimal health characteristics such as a low eGFR or mild hypertension. Other studies have shown the safety of kidney donation by older adults with respect to postdonation outcomes, such as perioperative death or cardiovascular events.[26-28]

To model the risk of ESRD in the absence of donation, the current study used established methods, risk estimates derived from the actual incidence in the United States, and data from millions of persons. However, certain assumptions must be emphasized, particularly with regard to the lifetime projections. First, the projections were calibrated to the incidence rates of ESRD from U.S. population data. Annual incidence was derived with the use of life-table methods, which assume a constant age-, sex-, and race-specific incidence of ESRD over periods

of decades and a static population substructure. Second, information on certain health characteristics of interest was not available. Our estimates reflect the population average for unmeasured characteristics. Persons with higher socioeconomic status than the population average may have a lower risk of ESRD, and persons with lower socioeconomic status may have a higher risk.

Third, our models to estimate the 15-year and lifetime risks were based on cohorts of low-risk persons who were followed for a median of 4 to 16 years. Fourth, random-effects meta-analysis takes into account potential heterogeneity, but precision is limited. Fifth, our study focused on a single outcome — ESRD treated with long-term dialysis or transplantation. We did not assess untreated low eGFR, a condition that is particularly common among older persons,[29,30] nor did we assess the risk of other diseases, such as hypertension or preeclampsia, that have been linked to kidney donation.[31,32] Finally, we made no estimate of the age at which ESRD would develop in a donor candidate or the duration of ESRD before death, nor did we assess the risk of perioperative or other complications from donation, which may vary according to baseline characteristics such as obesity.[13,31-33]

In conclusion, our online risk tool incorporates multiple baseline demographic and health characteristics to project a donor candidate's 15-year risk of ESRD in the absence of kidney donation and may be useful in the evaluation and counsel of living kidney-donor candidates. Future estimates may be improved by the incorporation of data from cohorts with longer follow-up time and from other countries and by the addition of the risk of donation according to multiple predonation health characteristics.

The views expressed in this article are those of the authors and in no way should be seen as an official policy or interpretation of the U.S. government.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

## APPENDIX

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