Predictors of New-Onset Kidney Disease in a Community-Based Population

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Hypertension and diabetes are the leading causes of end-stage renal disease (ESRD). Among individuals who develop ESRD, the risk of cardiovascular disease is 10 to 20 times higher than the general population, and increased risks are evident even in mild kidney disease. There are approximately 275,000 patients with ESRD in the United States and it is estimated that an additional 8 million US adults have kidney disease (defined as a glomerular filtration rate [GFR] of <60 mL/min per 1.73 m²). Because kidney disease often progresses to ESRD and its attendant complications, the identification of precursors of kidney disease is important, with the belief that interventions will prevent or delay the progression to ESRD.

We previously reported that age, treatment for hypertension, and diabetes were associated with elevated creatinine levels in a cross-sectional analysis. Dyslipidemia, obesity, and smoking have also been shown to be associated with kidney disease. However, much of the prior research examining risk factors for kidney disease have focused on patients who subsequently developed ESRD. To better understand the continuum of kidney disease, especially at an earlier stage when interventions may delay or prevent sequelae, we sought to examine predictors of incident kidney disease in a community-based sample.

METHODS

Study Sample
The Framingham Heart Study began in 1948 with the enrollment of 5209 men and women aged 28 to 62 years, with participants undergoing examinations every 2 years. In 1971, 5124 men and women were enrolled into the Framingham Offspring Study, which included the children or spouses of the children of the original cohort. Offspring participants underwent examinations approximately every 4 years; the design and 

Context Kidney disease is associated with an increased risk for the development of cardiovascular disease and end-stage renal disease; however, risk factors for kidney disease have not been well studied.

Objective To identify predictors of the development of new-onset kidney disease.

Design, Setting, and Participants A community-based, longitudinal cohort study of 2585 participants who attended both a baseline examination in 1978-1982 and a follow-up examination in 1998-2001, and who were free of kidney disease at baseline.

Main Outcome Measures Kidney disease was assessed by the Modification of Diet in Renal Disease Study equation and defined by a glomerular filtration rate (GFR) in the fifth or lower percentile (<59.25 mL/min per 1.73 m² in women, ≤64.25 mL/min per 1.73 m² in men). Stepwise logistic regression was used to determine the impact of risk factors on the occurrence of new-onset kidney disease. Baseline and long-term, 12-year, averaged risk factor models were explored.

Results At baseline, there were 1223 men and 1362 women, with a mean age of 43 years, who were free of preexisting kidney disease. After a mean follow-up of 18.5 years, 244 participants (9.4%) had developed kidney disease. In multivariable models, baseline age (odds ratio [OR], 2.36 per 10-year increment; 95% confidence interval [CI], 2.00-2.78), GFR (<90 mL/min per 1.73 m²; OR, 3.01; 95% CI, 1.98-4.58; 90-119 mL/min per 1.73 m²; OR, 1.84; 95% CI, 1.16-2.93), body mass index (OR, 1.23 per 1 SD; 95% CI, 1.08-1.41), diabetes (OR, 2.60; 95% CI, 1.44-4.70), and smoking (OR, 1.42; 95% CI, 1.06-1.91) were related to the development of kidney disease. In addition to baseline age and GFR, the long-term, averaged risk factors that were predictive of kidney disease included hypertension (OR, 1.57; 95% CI, 1.17-2.12), high-density lipoprotein cholesterol level (OR, 0.80 per 1 SD; 95% CI, 0.69-0.92), and diabetes (OR, 2.38; 95% CI, 1.45-3.92). Compared with a normal GFR (≥120 mL/min per 1.73 m²), a mildly reduced GFR (<90 mL/min per 1.73 m²) predicted a 3-fold odds of progression to kidney disease (OR, 2.95; 95% CI, 1.94-4.49).

Conclusions Established cardiovascular disease risk factors are associated with the development of new-onset kidney disease. Patients with a mildly reduced GFR should be monitored for progression to kidney disease.

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methods have been previously described. The current investigation is composed of participants from the Framingham Offspring Study who attended a baseline examination in 1978-1982 and returned for a follow-up examination in 1998-2001. Of the 3867 participants who attended the baseline examination, 2738 (71%) attended the follow-up examination. Participants excluded from this sample were older and more likely to be hypertensive, smoke, or have diabetes compared with participants included in the analysis. There were no differences in serum creatinine level or GFR. The institutional review board at Boston Medical Center approved the study, and all participants gave written informed consent.

### Baseline Measurements and Definitions

Kidney function was estimated by GFR, which was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation, defined as follows: GFR = 186.3 × (serum creatinine)^(-1.154) × age^(-0.203) × (0.742 for women). The outcome variable of interest was based on the National Kidney Foundation Kidney Disease Outcome Initiative working group definition of kidney disease (GFR < 60 mL/min per 1.73 m²). This particular cutoff was chosen by Kidney Disease Outcome Quality Initiative because of the increased prevalence of hypertension, anemia, derangements in calcium-phosphorous metabolism, reduction in serum albumin, and reductions in functional status that occur below this cutoff. The use of a GFR cut point of less than 60 mL/min per 1.73 m² classified 50% more women as having kidney disease than men; therefore, we modified the Kidney Disease Outcome Quality Initiative definition and reclassified kidney disease as a GFR at or below the sex-specific fifth percentile (59.25 mL/min per 1.73 m² in women and 64.25 mL/min per 1.73 m² in men). The outcome of interest was the development of a GFR below these cut points at the follow-up examination. Serum creatinine was measured by using the modified Jaffe method. Because the measure of creatinine can vary across different laboratories, creatinine was calibrated by using a 2-step process. First, National Health and Nutrition Examination Survey III creatinine values were calibrated to the Cleveland Clinic Laboratory, requiring a correction factor of 0.23 mg/dL (20.3 μmol/L). Then, mean creatinine values from Framingham Offspring Study, by sex-specific age groups (20-39, 40-59, 60-69, ≥70 years), were aligned with the corresponding corrected National Health and Nutrition Examination Survey III age-specific and sex-specific means.

### Assessment of Risk Factors

Details regarding the methods of risk factor measurement and laboratory analyses have been previously described. Each examination included a cardiovascular disease assessment and blood testing. Participants with a fasting glucose level of 126 mg/dL (6.99 mmol/L) or higher and/or who were receiving oral hypoglycemic or insulin treatment for diabetes were defined as diabetic. Impaired fasting glucose was defined as a fasting glucose level between 110 and 125 mg/dL (6.11-6.94 mmol/L) in the absence of diabetes. Participants with a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher (mean of 2 readings taken by the examining physician) or receiving medication for treatment of hypertension were defined as hypertensive. Fasting lipid measures included total cholesterol and high-density lipoprotein cholesterol (HDL-C). Smoking status was defined as smoking 1 or more cigarettes per day in the year preceding the examination. Participants with systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher and/or who were receiving oral hypoglycemic or insulin treatment for diabetes were defined as diabetic. Impaired fasting glucose was defined as a fasting glucose level between 110 and 125 mg/dL (6.11-6.94 mmol/L) in the absence of diabetes. Participants with a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher (mean of 2 readings taken by the examining physician) or receiving medication for treatment of hypertension were defined as hypertensive. Fasting lipid measures included total cholesterol and high-density lipoprotein cholesterol (HDL-C). Smoking status was defined as smoking 1 or more cigarettes per day in the year preceding the examination. Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters.

### Statistical Analysis

The primary outcome of interest was the development of kidney disease at the follow-up examination. Covariates included age, sex, hypertension, impaired fasting glucose level, diabetes, baseline GFR (categorized as <90 mL/min per 1.73 m² and 90-119 mL/min per 1.73 m²), BMI, total cholesterol and HDL-C levels, and cigarette smoking. A secondary analysis used systolic blood pressure and hypertension treatment in place of hypertension.

Covariates were assessed at the baseline examination and at the next 3 examinations. Long-term, averaged analyses were performed by using covariate data from the baseline examination and the subsequent 3 examination cycles, spanning a 12-year period. For long-term, averaged analyses involving continuous data, the mean of all available measurements was taken. For long-term, averaged analyses involving discrete data, we divided the number of times the risk factor was present by the total number of examinations attended. If this number was 0.5 or higher, reflecting presence of the condition at half or more of the examinations attended, then the long-term, averaged predictor was considered present.

Baseline and long-term, averaged predictors were examined in association with the outcome variable. Stepwise logistic regression was used. P < .05 was necessary for inclusion in the model; age and sex were forced into all multivariable models. Continuous variables were standardized by sex-specific standard deviation units for ease of interpretation. A secondary analysis was conducted by using logistic regression to examine the number of risk factors present at baseline (0, 1, 2, ≥3) and the odds of developing kidney disease; 0 risk factors at baseline served as the referent group. Selected risk factors included hypertension, diabetes, current smoking, and obesity (BMI > 30); results were age-adjusted and sex-adjusted.

### RESULTS

After excluding participants with kidney disease at the baseline examination (n = 153), 2589 participants were...
available for analysis (1223 men and 1362 women). The mean follow-up time was 18.5 years (range, 16-22 years). The mean ages at the baseline and follow-up examinations were 43 and 61 years, respectively. Figure 1 displays the relationship between baseline and follow-up GFR.

Baseline characteristics are shown in Table 1. Overall, the 244 participants (9.4%) who developed kidney disease at follow-up were more likely to be older. They also had a higher mean BMI, a higher total cholesterol level, and a higher prevalence of diabetes and hypertension. These differences were mirrored in the long-term, averaged covariates. Participants with hypertension were older, were more likely to have diabetes, and had a lower GFR at follow-up, although there was no difference in baseline GFR. Forty-one percent and 49% of those individuals with baseline and long-term, averaged hypertension were treated with at least 1 medication. At baseline, 75% of participants received diuretics and 26% received β-blockers. During the long term, 41% were treated with diuretics, 46% were treated with β-blockers, 12% were treated with calcium channel blockers, and 17% were treated with angiotensin-converting enzyme inhibitors. Those participants treated with angiotensin-converting enzyme inhibitors (n=69) had similar baseline GFR values but higher follow-up GFR values; they also had lower total cholesterol levels and were less likely to smoke.

Fourteen percent, 8%, and 4% of participants with a baseline GFR of less than 90 mL/min per 1.73 m², 90 to 119 mL/min per 1.73 m², and 120 mL/min per 1.73 m² or higher, respectively, developed kidney disease during follow-up. Age-adjusted and sex-adjusted individual baseline predictors of developing kidney disease included age, systolic blood pressure, hypertension, hypertension treatment, BMI, HDL-C level (inverse relationship), smoking, and diabetes (Table 2). A baseline GFR of less than 90 mL/min per 1.73 m² was associated with a nearly 3-fold increase in the odds of developing kidney disease, and a baseline GFR between 90 and 119 mL/min per 1.73 m² was associated with a 77% increase in the odds of developing kidney disease. The odds increased steadily with increasing number of risk factors at baseline (Figure 2).

Baseline multivariable predictors of the development of kidney disease included age (odds ratio [OR], 2.36 per 10-year increment; 95% confidence interval [CI], 2.00-2.78) and diabetes (OR, 2.60; 95% CI, 1.44-4.70), which were associated with more than a doubling of the odds of developing kidney disease (Table 2). Body mass index increased the odds of developing kidney disease by 23% (OR, 1.23; 95% CI, 1.08-1.41) per SD unit, and smoking increased the odds by 42% (OR, 1.42; 95% CI, 1.06-1.91). A GFR between 90 and 119 mL/min per 1.73 m² was associated with an 84% increase in the odds of developing kidney disease (OR, 1.84; 95% CI, 1.16-2.93), whereas a GFR of less than 90 mL/min per 1.73 m² was associated with a 3-fold increase in the odds of progressing to kidney disease (OR, 3.01; 95% CI, 1.98-4.58). Using

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**Table 1.** Baseline and Long-term, Averaged Characteristics Stratified by Kidney Disease Status After a Mean of 18.5 Years of Follow-up†

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline</th>
<th>Long-term, Averaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42 (9)</td>
<td>50 (9)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>1104 (47)</td>
<td>119 (49)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.79 (0.22)</td>
<td>0.88 (0.20)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.83 (0.17)</td>
<td>1.38 (0.72)</td>
</tr>
<tr>
<td>GFR, mL/min per 1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>112 (57)</td>
<td>91 (28)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>91 (23)</td>
<td>51 (10)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>120 (15)</td>
<td>127 (17)</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>417 (18)</td>
<td>91 (37)</td>
</tr>
<tr>
<td>Hypertension treatment, No. (%)</td>
<td>168 (7)</td>
<td>42 (17)</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>25.3 (4.2)</td>
<td>28.6 (4.2)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>229 (45)</td>
<td>243 (51)</td>
</tr>
<tr>
<td>HDL</td>
<td>49 (13)</td>
<td>47 (14)</td>
</tr>
<tr>
<td>Smoking, No. (%)</td>
<td>775 (33)</td>
<td>85 (35)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>48 (2)</td>
<td>21 (9)</td>
</tr>
<tr>
<td>Impaired fasting glucose, No. (%)</td>
<td>172 (7)</td>
<td>24 (10)</td>
</tr>
</tbody>
</table>

Abbreviations: GFR, glomerular filtration rate; HDL, high-density lipoprotein; NA, not applicable.

SI conversion factors: To convert creatinine to µmol/L, multiply by 88.4; total and HDL cholesterol to mmol/L, multiply by 0.0259.

*Data are mean (SD) unless otherwise indicated.
†Calculated as weight in kilograms divided by the square of height in meters.
‡See “Methods” section for definition.
systolic blood pressure and hypertension treatment instead of hypertension in the multivariable model did not change the results. Excluding participants with either a myocardial infarction or congestive heart failure at baseline (n=104) did not change the results.

Long-term, averaged individual and multivariable predictors are presented in Table 3. In the multivariable model, in addition to age and baseline category of GFR, results for diabetes were similar to those of the baseline model. Long-term, averaged hypertension increased the odds of developing kidney disease by 57% (OR, 1.57; 95% CI, 1.17-2.12) and higher long-term, averaged levels of HDL-C (per SD unit) decreased the odds of developing kidney disease by 20% (OR, 0.80; 95% CI, 0.69-0.92). When systolic blood pressure and hypertension treatment were included in place of hypertension, hypertension treatment entered the model with similar results. The results of long-term, averaged models also remained similar when participants with myocardial infarction or congestive heart failure at baseline were excluded.

**COMMENT**

In a large community-based sample of participants free of kidney disease at baseline, established cardiovascular disease risk factors predicted the development of kidney disease. In addition, a mildly reduced GFR at baseline increased the odds of developing kidney disease. Our data indicate that among unselected participants, diabetes, hypertension, obesity, smoking, low HDL-C level, and a mild reduction in GFR are important risk factors for the development of new-onset kidney disease.

This study has the advantage of a large sample of participants free of kidney disease at baseline, a long follow-up period, and the ability to study disease at its inception. We are also able to study models composed of baseline and long-term, averaged risk factors. Both models offer unique and complementary insights into risk factors for kidney disease. The baseline risk factor model is advantageous because risk factors clearly precede outcome, whereas the long-term, averaged model allows us to account for changes in risk factors over time.

Diabetes is a key risk factor for the development of ESRD. The incidence rate of ESRD among persons with diabetes is nearly 200 per 100 000 person-years compared with 14 per 100 000 person-years in persons without diabetes. Data from double-blind randomized controlled trials have shown that pharmacological interventions can slow the progression of diabetic nephropathy.

Not surprisingly, our data also show that diabetes is a risk factor for new-onset kidney disease, although our odds ratios are lower than reported among persons with ESRD. This difference may be from the changing definition of diabetes over time, as well as the identification of a more severe disease outcome (ESRD compared with moderate kidney disease). Most clinical trials looking at the progression of diabetic nephropathy have been conducted in patients with more severe kidney disease or in those with concomitant hypertension. Given that diabetes was such a strong risk factor for the development of kidney disease in our study sample, additional clinical trials may be needed to understand if patients with diabetes will benefit from interventions initiated earlier in their disease course.

We indicate that hypertension is a predictor for the development of incident kidney disease. In the epidemiological literature, a graded, continuous relationship exists between blood pressure and ESRD, as well as between long-term, averaged individual and multivariable predictors of developing kidney disease after a mean of 18.5 years of follow-up.

### Table 2. Baseline Individual and Multivariable Predictors of Developing Kidney Disease After a Mean of 18.5 Years of Follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Individual Predictors</th>
<th>Multivariable Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10-year increment</td>
<td>2.56 (2.18-2.99)</td>
<td>2.36 (2.00-2.78)</td>
</tr>
<tr>
<td>Sex (women vs men)</td>
<td>0.92 (0.70-1.20)</td>
<td>0.89 (0.67-1.18)</td>
</tr>
<tr>
<td>Baseline GFR, mL/min per 1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90</td>
<td>2.84 (1.88-4.30)</td>
<td>3.01 (1.98-4.58)</td>
</tr>
<tr>
<td>90-119</td>
<td>1.77 (1.12-2.80)</td>
<td>1.84 (1.16-2.93)</td>
</tr>
<tr>
<td>Body mass index, per SD unit</td>
<td>1.28 (1.12-1.45)</td>
<td>1.23 (1.08-1.41)</td>
</tr>
<tr>
<td>Smoking (yes vs no)</td>
<td>1.34 (1.01-1.79)</td>
<td>1.42 (1.06-1.91)</td>
</tr>
<tr>
<td>Diabetes (yes vs no)</td>
<td>2.74 (1.56-4.82)</td>
<td>2.60 (1.44-4.70)</td>
</tr>
<tr>
<td>Systolic blood pressure, per SD unit</td>
<td>1.16 (1.02-1.32)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (yes vs no)</td>
<td>1.57 (1.16-2.12)</td>
<td>†</td>
</tr>
<tr>
<td>Hypertension treatment (yes vs no)</td>
<td>1.58 (1.07-2.32)</td>
<td>†</td>
</tr>
<tr>
<td>Cholesterol, per SD unit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.03 (0.90-1.19)</td>
<td>†</td>
</tr>
<tr>
<td>HDL</td>
<td>0.82 (0.71-0.94)</td>
<td>†</td>
</tr>
<tr>
<td>Impaired fasting glucose (yes vs no)</td>
<td>1.04 (0.65-1.66)</td>
<td>†</td>
</tr>
</tbody>
</table>

Abbreviations: GFR, glomerular filtration rate; HDL, high-density lipoprotein.

†Did not enter the multivariable model.

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Table 3. Long-term, Averaged Individual and Multivariable Predictors of Developing Kidney Disease After 18.5 Years of Follow-up

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Individual Predictors*</th>
<th>Multivariable Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10-year increment</td>
<td>†</td>
<td>2.18 (1.84-2.58)</td>
</tr>
<tr>
<td>Sex (women vs men)</td>
<td>†</td>
<td>0.96 (0.72-1.27)</td>
</tr>
<tr>
<td>Baseline GFR, mL/min per 1.73 m²</td>
<td>†</td>
<td>2.95 (1.94-4.49)</td>
</tr>
<tr>
<td>&lt;90</td>
<td>†</td>
<td>1.87 (1.18-2.98)</td>
</tr>
<tr>
<td>90-119</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>HDL-C, per SD unit</td>
<td>0.76 (0.66-0.88)</td>
<td>0.80 (0.69-0.92)</td>
</tr>
<tr>
<td>Diabetes (yes vs no)</td>
<td>2.73 (1.69-4.41)</td>
<td>2.38 (1.45-3.92)</td>
</tr>
<tr>
<td>Hypertension (yes vs no)</td>
<td>1.76 (1.32-2.36)</td>
<td>1.57 (1.17-2.12)</td>
</tr>
<tr>
<td>Smoking (yes vs no)</td>
<td>1.29 (0.95-1.76)</td>
<td>†</td>
</tr>
<tr>
<td>Systolic blood pressure, per SD unit</td>
<td>1.17 (1.01-1.35)</td>
<td>†</td>
</tr>
<tr>
<td>Hypertension treatment (yes vs no)</td>
<td>1.65 (1.20-2.25)</td>
<td>†</td>
</tr>
<tr>
<td>Body mass index, per SD unit</td>
<td>1.21 (1.06-1.39)</td>
<td>†</td>
</tr>
<tr>
<td>Total cholesterol, per SD unit</td>
<td>1.01 (0.88-1.17)</td>
<td>†</td>
</tr>
<tr>
<td>Impaired fasting glucose (yes vs no)</td>
<td>1.08 (0.64-1.82)</td>
<td>†</td>
</tr>
</tbody>
</table>

Abbreviations: GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol.

*All predictors are age-adjusted and sex-adjusted, except for age, which is sex-adjusted, and sex, which is age-adjusted.

†Data obtained from baseline examination only.

‡Did not enter the multivariable model.

Long-term, Averaged Individual and Multivariable Predictors of Developing Kidney Disease After 18.5 Years of Follow-up

We demonstrate that lower HDL-C levels are associated with the development of kidney disease. Lipid abnormalities are common in patients with ESRD,11 and dyslipidemia has been shown to be associated with the progression of kidney disease in patients with chronic renal insufficiency.12 Similarly, other studies13,14 have demonstrated an inverse association of HDL-C with progression of kidney disease. Analyses of lipid-lowering trial data are warranted to determine if control of dyslipidemias can prevent or delay the progression of kidney disease.

In our data, higher BMI was associated with an increased risk of kidney disease. Limited epidemiologic data exist linking obesity to kidney disease.15,16 Pathologic evidence obtained from kidney biopsy specimens has documented the emergence of an obesity-related glomerulopathy,15 and epidemiologic data suggest that obese individuals have a 45% increased risk of developing proteinuria.16 Because of the inherent association among body weight, muscle mass, and serum creatinine, more research is necessary to better understand the relationship between measures of obesity and kidney disease, independent of body weight. Given the increasing prevalence of overweight and obesity, an understanding of their impact on kidney disease is necessary.

Smoking has been shown to be a predictor of incident kidney disease.16-20 In the Cardiovascular Health Study cohort,20 the number of cigarettes smoked per day was related to an increase in serum creatinine level. Another study19 showed that current smoking was related in a dose-dependent manner to both albuminuria and kidney disease but inferences regarding causality were limited by its cross-sectional design. Much of the literature documenting an association between smoking and kidney disease is limited by relatively short-term follow-up periods.16,17,20 as well as the use of samples enriched for hypertension.17 To our knowledge, our study is among the first large, prospective, epidemiologic studies to show that smoking is a risk factor for the development of kidney disease in an unselected population.
This study has advantages over prior studies that have examined risk factors for the development of kidney disease. The Framingham Heart Study is a population-based sample in which selection bias is inherently low. We have the ability to investigate the effects of long-term follow-up with multiple interim visits, allowing us to compute long-term, averaged risk factors. We have an interval of nearly 20 years from the baseline examination to follow-up.

There are some limitations to our study. Kidney disease was defined by a single creatinine measure. It is not possible to determine whether participants who fulfilled outcome criteria did so for at least a 3-month period. However, misclassification of participants would be likely to bias our results toward the null. The GFR was estimated by using the MDRD Study equation. The MDRD Study equation has been validated in participants with a GFR of less than 90 mL/min per 1.73 m²; values outside this range are extrapolated. However, we were able to increase the accuracy of the MDRD Study equation by performing an indirect calibration to the laboratory that developed the equation. Our study sample is not nationally representative or ethnically diverse. However, the relationships of risk factors to coronary heart disease outcomes observed in Framingham Offspring Study have recently been validated in 6 ethnically and geographically diverse cohorts, and they were found to be applicable in other populations.

Although our use of long-term, averaged risk factors allows for the integration of mean risk factor exposure over time, one cannot assume that they preceded the development of kidney disease. We have tried to reduce this possibility of reverse causality by limiting our assessment of long-term, averaged risk factors to the 12-year period following the baseline examination. Lastly, we may have observed a survival bias, because participants had to attend both the initial and follow-up examinations. It is possible that those individuals with the most severe risk factor burden would have died or developed significant disability in the interim; this would likely bias our results toward the null.

The results of this study highlight several risk factors for kidney disease. These results are novel because much of the previous work has focused on risk factors that lead to ESRD, whereas we describe risk factors that lead to new-onset kidney disease. In addition, we have shown that those with a baseline GFR of less than 90 mL/min per 1.73 m² have a 3-fold increase in the odds of developing kidney disease, suggesting that these individuals be considered at high risk for the development of kidney disease.

We have shown that established cardiovascular disease risk factors are predictors of the development of kidney disease. Further research is necessary to better understand these relationships. Whether risk factor modification can slow the progression of kidney disease warrants further investigation.

Author Contributions: Dr Fox had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Fox, Larson, Culleton, Levey. Acquisition of data: Wilson. Analysis and interpretation of data: Fox, Larson, Leip, Wilson, Levey.

Drafting of the manuscript: Fox. Critical revision of the manuscript for important intellectual content: Larson, Leip, Culleton, Wilson, Levey.


Study supervision: Levey.

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Role of the Sponsors: The National Heart, Lung, and Blood Institute participated in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, and approval of the manuscript.

Acknowledgment: We thank Josef Coresh, MD, PhD, for his aid in preparation of the manuscript.

REFERENCES


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PREDICTORS OF KIDNEY DISEASE


“I will not cease from mental fight,” Blake wrote. Mental fight means thinking against the current, not with it. . . . It is our business to puncture gas bags and discover the seeds of truth.
—Virginia Woolf (1882-1941)