Association of Single Measurements of Dipstick Proteinuria, Estimated Glomerular Filtration Rate, and Hematocrit with 25-Year Incidence of End-Stage Renal Disease in the Multiple Risk Factor Intervention Trial

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The incidence of ESRD is increasing rapidly. Limited information exists regarding early markers for the development of ESRD. This study aimed to determine over 25 yr the risk for ESRD associated with proteinuria, estimated GFR (eGFR), and hematocrit in men who did not have identified kidney disease and were randomly assigned into the Multiple Risk Factor Intervention Study (MRFIT). A total of 12,866 men who were at high risk for heart disease were enrolled (1973 to 1975) and followed through 1999. Renal replacement therapy was ascertained by matching identifiers with the United States Renal Data System's data; vital status was from the National Death Index. Men who initiated renal replacement therapy or died as a result of kidney disease were deemed to have developed ESRD. Dipstick urine for proteinuria, eGFR, and hematocrit were related to development of ESRD. During 25 yr, 213 (1.7%) men developed ESRD. Predictors of ESRD were dipstick proteinuria of 1+ or ≥2+ (hazard ratio [HR] 3.1 [95% confidence interval (CI) 1.8 to 5.4] and 15.7 [95% CI 10.3 to 23.9] respectively) and an eGFR of <60 ml/min per 1.73 m^2 (HR 2.4; 95% CI 1.5 to 3.8). Correlation between eGFR and serum creatinine was 0.9; the risk for ESRD with a 1-SD difference of each was identical (HR 1.21). Bivariate analysis demonstrated a 41-fold increase in ESRD risk in those with an eGFR <60 ml/min per 1.73 m^2 and ≥2+ proteinuria (95% CI 15.2 to 71.1). There was no association between hematocrit and ESRD. Other baseline measures that independently predicted ESRD included age, cigarette smoking, BP, low HDL cholesterol, and fasting glucose. Among middle-aged men who were at high risk for cardiovascular disease but had no clinical evidence of cardiovascular disease or significant kidney disease, dipstick proteinuria and an eGFR value <60 ml/min per 1.73 m^2 were strong predictors of long-term development of ESRD. It remains unknown whether intervention for proteinuria or early identification of those with chronic kidney disease reduces the risk for ESRD.

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The incidence of ESRD has increased rapidly in the past decade, and the number of people with ESRD is projected to double by the year 2010 (1). Despite this rapid increase, limited information exists regarding early markers for the development of ESRD. Previous groups have studied either individuals with established chronic kidney disease (CKD) or unknown baseline kidney function. Most studies of individuals with established kidney disease have had short durations of follow-up and used surrogate markers for ESRD, such as change in GFR or doubling of serum creatinine in addition to ESRD as end points (2–6). Whether these markers are useful in identifying individuals who are at high risk for developing ESRD over the long term is uncertain. Other studies, including investigations of the cohort of men who were screened for the Multiple Risk Factor Intervention Trial (MRFIT), have followed individuals for a long time (7–13). These studies established BP, diabetes, and black race as major risk factors for ESRD, but they did not include assessment of renal function at baseline. Recognizing the limitations of previous studies, we aimed to determine over 25 yr the risk for ESRD associated with casual dipstick proteinuria, estimated GFR (eGFR), and hematocrit in individuals who did not have identified kidney disease at baseline and were randomly assigned in the MRFIT study.

Materials and Methods

MRFIT was a multicenter, randomized trial to study the effect of an intervention program that was designed to lower BP, to decrease serum cholesterol by dietary changes and to achieve smoking cessation in men who were at high risk for cardiovascular disease (CVD). Details concerning the screening have been published (14–16). Briefly, between

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1973 and 1975, 361,662 men aged 35 to 57 yr were screened by 22 clinical centers in 18 U.S. cities for entry into the trial. Of those who were screened, 12,866 men were randomly assigned. The randomly assigned men are the focus of this report.

Screening and Baseline Measurements

Screening occurred at three visits. At the first, risk for coronary heart disease was assessed using measurements of serum cholesterol, diastolic BP, and self-reported cigarette smoking. Men who were in the upper 15% (changed to 10% after one third of the screening was completed) of risk were invited to attend a second screening visit. Men were excluded at the first screening visit when they had a diastolic BP ≥115 mmHg, had serum cholesterol >9.05 mmol/L (350 mg/dl), were taking medication for diabetes, or were previously hospitalized for a heart attack for 2 wk or more.

At the second screening visit, a blood sample was taken after an overnight fast. The blood was analyzed at a central laboratory at the Institute of Medical Sciences in San Francisco using a protocol that was described previously (17). Serum creatinine, glucose, uric acid, and potassium were measured; plasma lipid levels also were determined. Quality control procedures and the precision of the laboratory measurements have been published (15,17). Urine dipstick (Ames Labstix or equivalent) for proteinuria, blood and pH, and hematocrit and white blood cell count were measured locally at the second screening visit. Proteinuria was read by a technician 1 min after dipping and assessed as none, trace, 1+, 2+, 3+, or 4+ (17).

Men with a serum creatinine <2.0 mg/dl and without evidence of cardiovascular or other life-threatening diseases were invited to attend a third screening visit. At this visit, eligible men who consented to the trial were randomly assigned to a special intervention ($n = 6428$) or usual care ($n = 6438$) group.

BP were measured in a seated position at the second and third screening visits (three measurements each) by a trained observer with a random-zero sphygmomanometer. Baseline BP was defined as the average of the second and third readings recorded at the second and third screening visits (18).

Outcome

The primary outcome for this analysis was ESRD from any cause, defined as initiation of renal replacement therapy (RRT; hemodialysis, peritoneal dialysis, or having a kidney transplant), or death from renal failure, through December 31, 1999. Individuals who initiated RRT were ascertained by matching MRFIT identifiers with data from the United States Renal Data System (USRDS). The latter is a stand-alone database that combines dialysis data from the Centers for Medicare and Medicaid (CMS) Renal Beneficiary and Utilization System and kidney transplant data from the United Network for Organ Sharing transplant database (19). The CMS ESRD program was initiated on January 1, 1973. Starting on April 1, 1995, all individuals who started RRT in the United States have been required to register with the CMS ESRD program. In a prospective cohort that was carried out from 1989 to 1993, the USRDS correctly identified 95.4% of individuals who initiated RRT and were found through study follow-up. In addition, the date of initiation was within 120 d for 97% of individuals (20). The United Network for Organ Sharing transplant registry began collecting information on kidney transplant recipients in 1987. Matching was performed with the following variables: Social Security number, full name, date of birth, gender (all MRFIT participants were men), race, and date of death (if the individual had died). In addition to formulaic matching, all matches were visually inspected to confirm their accuracy.

Vital status through the end of the trial on February 28, 1982, was determined by MRFIT clinical centers, which ascertained deaths and obtained death documentation. From March 1, 1982, through December 31, 1999, vital status was determined using the National Death Index (21). For deaths that occurred through 1990, death certificates were obtained and centrally coded by a trained nosologist using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Starting in 1991, the National Death Index Plus Service was used to obtain the primary cause of death, either ICD-9 or ICD-10. ICD-9 codes that defined renal failure in MRFIT have been given (11,13). Corresponding codes for ICD-10 were used for deaths that occurred in 1999.

Statistical Analyses

Time-to-event methods were used to estimate the incidence of ESRD and study the association of baseline risk factors with time to first event of ESRD or death from kidney disease. These associations were similar for the special intervention and usual care groups; therefore, these groups were combined. Estimates of cumulative percentage of participants who developed ESRD were obtained using the Kaplan-Meier method. Proportional hazards regression (Cox) models were used to quantify the association of dipstick proteinuria, serum creatinine, eGFR, hematocrit, and other baseline measures with ESRD (22). eGFR was calculated using the simplified Modification of Diet in Renal Disease equation (23); for Asian and Hispanic participants, the equation for white individuals was used. eGFR was categorized as <60, 60 to 75, and ≥75 ml/min per 1.73 m^2. Proteinuria was categorized as negative/trace, 1+, and ≥2+. Hematocrit was analyzed by categories that corresponded to normal ranges (<42, 42 to 54, and ≥55%). Creatinine, eGFR, and hematocrit also were considered as continuous variables in Cox models. For each marker, three Cox models were constructed. The first was a univariate model. The second adjusted for the following

Table 1. Cumulative percentage of RRT, overall and by cause; renal mortality; and ESRD (RRT or renal mortality)[a]

Renal End Point	Total Events	Cumulative % at Year				
		5	10	15	20	25
RRT as a result of	176	0.016	0.073	0.247	0.811	1.804
diabetes (ICD-9 2550)	50	0.000	0.000	0.009	0.114	0.506
hypertensive renal disease (ICD-9 4039)	59	0.008	0.033	0.112	0.336	0.604
other causes	67	0.008	0.040	0.126	0.363	0.705
Renal death	62	0.000	0.033	0.103	0.346	0.644
ESRD (renal death or RRT)	213	0.016	0.106	0.341	1.030	2.161

[a]ICD-9, *International Classification of Diseases, Ninth Revision*; RRT, renal replacement therapy.

baseline variables: Age, race (black *versus* nonblack), triglycerides, LDL-C, HDL-C, smoking status (current smoker *versus* nonsmoker), family history of diabetes (yes/no), serum glucose, uric acid, body mass index, and systolic BP (all of these variables were significantly associated with ESRD in univariate analyses or were used to select participants for MRFIT). The third model included all of the baseline variables plus eGFR, proteinuria, and hematocrit. A Cox model that considered the association of bivariate categories of eGFR and proteinuria with ESRD, adjusted for other baseline factors, also was considered to quantify the additive effect of both risk factors on ESRD. Failure times were defined as the time elapsed from randomization to the development of ESRD (initiation of RRT or renal death). Individuals without ESRD were censored at the end of follow-up (December 31, 1999) or date of (nonrenal) death.

All analyses were performed with SAS 8.2 (SAS Institute, Cary NC). All tests are presented with two sided P values; $P < 0.05$ was considered significant. The Hennepin County Medical Center and University of Minnesota Human Subjects Research Committee approved this study.

Results

Over 25 yr of follow-up, 213 (1.7%) men developed ESRD; 176 initiated RRT, and 37 died from renal diseases (without known previous RRT; 25 men died of renal disease after initiating RRT). Table 1 outlines the causes of ESRD in the MRFIT cohort. More than one half (52%) of the ESRD events occurred after 20 yr of follow-up.

Table 2 compares baseline characteristics of individuals with and without ESRD. As a consequence of risk eligibility criteria for MRFIT, men, on average, had elevated BP and serum cholesterol and a large percentage smoked cigarettes compared with the general population.

Table 3 summarizes the results of a multivariate analysis. Older age, black race, lower HDL concentrations, being a smoker, greater systolic BP, greater fasting blood glucose and uric acid concentrations, and a family history of diabetes were associated with an increased risk for ESRD.

This model was repeated to exclude participants with proteinuria and/or eGFR <60. Associations were largely unchanged. Relationships between ESRD and race, history of diabetes, and uric acid were in the same direction but attenuated, with the last two covariates becoming nonsignificant with $P = 0.07$ and 0.08, respectively.

Table 2. Baseline characteristics for MRFIT randomized men with and without ESRD through December 31, 1999[a]

	Men with ESRD	Men without ESRD	*P*
Demographics/behavior			
age (y)	48.2 ± 5.6	46.1 ± 6.0	<0.001
% black	15.0	7.1	<0.001
education (yr)	13.5 ± 3.0	13.8 ± 2.9	0.176
income (1974 to 1976; in $1000)	20.1 ± 9.7	21.5 ± 9.5	0.079
% cigarette smokers	64.3	63.7	0.817
alcoholic drinks per week (*n*)	10.9 ± 10.1	12.6 ± 12.4	0.053
BMI (kg/m^2)	28.4 ± 3.7	27.7 ± 3.5	0.002
% family history of diabetes	26.3	18.6	0.004
Plasma lipids			
total plasma cholesterol (mg/dl)	245.4 ± 38.8	240.4 ± 36.8	0.035
triglycerides (mg/dl)	235.9 ± 198.4	193.6 ± 143.7	<0.001
HDL cholesterol (mg/dl)	40.0 ± 10.8	42.1 ± 11.8	0.009
LDL cholesterol (mg/dl)	156.9 ± 39.0	160.1 ± 36.0	0.252
Serum chemistries/urinalysis			
uric acid (mg/dl)	7.2 ± 1.5	6.8 ± 1.3	<0.001
potassium (mg/dl)	4.4 ± 0.5	4.4 ± 0.4	0.888
creatinine (mg/dl)	1.2 ± 0.2	1.1 ± 0.1	<0.001
eGFR (ml/min per 1.73 m^2)	76.5 ± 15.0	79.7 ± 12.9	<0.001
hematocrit (volume %)	46.3 ± 3.5	46.5 ± 3.8	0.463
fasting glucose (mg/dl)	105.7 ± 24.6	99.3 ± 15.5	<0.001
% proteinuria 1+ or higher	18.8	3.4	<0.001
% proteinuria 2+ or higher	12.2	0.9	<0.001
BP-related			
diastolic BP (mmHg)	93.9 ± 10.2	90.7 ± 8.7	<0.001
systolic BP (mmHg)	142.6 ± 16.5	135.3 ± 14.2	<0.001
% prescribed BP medication	24.4	19.3	0.055
% hypertensive (medications or BP ≥90/140 mmHg)	77.5	65.7	<0.001
No. of men	213	12653	

[a]BMI, body mass index; eGFR, estimated GFR; MRFIT, Multiple Risk Factor Intervention Trial.

Table 3. Multivariate association between baseline factors and risk for developing ESRD among men randomly assigned in MRFIT[a]

	HR	95% CI	*P*
Demographics/behavior			
age (per 10 yr older)	1.97	1.51 to 2.58	<0.001
black (*versus* white race)	2.73	1.75 to 4.25	<0.001
current smoker (*versus* nonsmoker)	1.84	1.35 to 2.51	<0.001
BMI (per 5 kg/m^2 greater)	1.17	0.95 to 1.44	0.14
% family history of diabetes	1.45	1.06 to 1.98	0.02
Plasma lipids			
triglycerides (per 25 mg/dl higher)	1.01	0.99 to 1.03	0.22
HDL cholesterol (per 5 mg/dl lower)	1.25	1.09 to 1.44	0.002
LDL cholesterol (per 10 mg/dl higher)	1.01	0.97 to 1.05	0.62
Serum chemistries/urinalysis			
uric acid (per 1 mg/dl higher)	1.16	1.04 to 1.29	0.006
fasting glucose (per 10 mg/dl higher)	1.10	1.03 to 1.17	0.003
BP related			
systolic BP (per 10 mmHg higher)	1.31	1.19 to 1.43	<0.001

[a]Also included in the full model are GFR, hematocrit, and urine proteinuria concentration, which are not shown. CI, confidence interval; HR, hazard ratio.

Baseline Proteinuria and Risk for ESRD

Proteinuria was present as 1+ in 335 (2.5%) men and as ≥2+ in 139 (1.0%) men at baseline. Of individuals with negative or trace proteinuria, 1.4% developed ESRD, compared with 4.2% of those with 1+ proteinuria and 18.7% of those with ≥2+ proteinuria. Compared with those with no proteinuria or trace, hazard ratios (HR) for 1+ and ≥2+ proteinuria were 3.1 (95% confidence interval [CI] 1.78 to 5.42) and 15.7 (95% CI 10.33 to 23.87), respectively (Table 4). The multivariate risk for developing ESRD was slightly reduced with adjustment for baseline factors (Table 4). The pattern of incidence of ESRD over time was similar in men with ≥2+ and 1+ proteinuria, with a steep rise in incidence in the ≥2+ group starting after approximately 10 yr of follow-up and a steep rise in the 1+ group starting after approximately 20 yr of follow-up (Figure 1A).

Separate analyses were carried out for the outcome of initiation of RRT. The fully adjusted HR in Table 4 for this end point were 2.7 and 14.9 for 1+ and ≥2+ proteinuria, respectively.

eGFR and Risk for ESRD

The majority of men had eGFR values ≥60 ml/min per 1.73 m^2 at baseline (4128 men between 60 and 75 and 8241 men ≥75 ml/min per 1.73 m^2); 497 (3.9%) men had an eGFR <60 ml/min per 1.73 m^2 (mean 55 ml/min per 1.73 m^2; SD 4). Figure 1B gives the cumulative incidence of ESRD according to baseline eGFR. The 25-yr incidence of ESRD was the same for men with eGFR values of between 60 and 75 and ≥75 ml/min per 1.73 m^2 (1.5%). However, men with a baseline eGFR <60 ml/min per 1.73 m^2 were more likely to develop ESRD (5.6%; Table 4). With the fully adjusted model, the HR for developing ESRD in those with eGFR <60 ml/min per 1.73 m^2 was 2.4 (95% CI 1.5 to 3.8) *versus* those with an eGFR ≥75 ml/min per 1.73 m^2. Separate analyses were carried out for the outcome of initiation of RRT. The fully adjusted HR for those with eGFR <60 ml/min per 1.73 m^2 *versus* those with an eGFR ≥75 ml/min per 1.73 m^2 was 3.0 for this end point.

When eGFR was modeled as a continuous variable, the HR for ESRD associated with a 1-SD lower eGFR was 1.30 (95% CI 1.11 to 1.52) after adjustment for baseline variables and 1.21 (95% CI 1.04 to 1.41) when proteinuria and hematocrit also were considered. There was a strong correlation between eGFR and serum creatinine at baseline ($r = -0.90$). When creatinine was used in place of eGFR as the marker of baseline kidney function, results were similar (Table 4). Modeled as a continuous variable, the HR for ESRD associated with a 1- SD higher creatinine was 1.33 (95% CI 1.17 to 1.52) after adjustment for baseline variables and 1.21 (95% CI 1.07 to 1.37) when proteinuria and hematocrit also were considered.

Bivariate Relationship of Proteinuria and eGFR to ESRD

The combined influence of eGFR and proteinuria on risk for ESRD is shown in Table 5. The majority of men had eGFR values ≥75 ml/min per 1.73 m^2 and negative/trace proteinuria (61.7%). For these men, the cumulative percentage of men who developed ESRD was 1.3%. For each category of eGFR, increasing levels of proteinuria were associated with an increased risk for developing ESRD. Likewise, for each category of proteinuria, risk generally increased with decreasing eGFR values. Men with 2+ proteinuria and eGFR values <60 ml/min per 1.73 m^2 were at especially high risk for ESRD (41%), although the number of men in this category was small ($n = 22$). The multivariate HR for ESRD was 32.9 (95% CI 15.2 to 30.3) in these men compared with men with eGFR ≥75 ml/min per 1.73 m^2 and no/trace proteinuria at baseline. The effects of eGFR and proteinuria were additive, and there was no evidence of an interaction ($P = 0.34$ for interaction).

Interaction tests also were carried out between both eGFR

Table 4. Number of men with ESRD in MRFIT by proteinuria, eGFR, and hematocrit levels at baseline and summary of Cox regression analysis[a]

Labstix Result	No. of Men	No. with ESRD	Cox Regression Summary (HR [95% CI])		
			Unadjusted	Adjusted[b]	Adjusted[c]
Negative/trace	12380	173 (1.4%)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1+	335	14 (4.2%)	3.10 (1.78 to 5.42)	2.31 (1.29 to 4.15)	2.30 (1.28 to 4.13)
2+ or higher	139	26 (18.7%)	15.70 (10.33 to 23.87)	15.15 (9.83 to 23.37)	14.21 (9.16 to 22.05)
GFR (ml/min per 1.73 m^2)					
≥75	8241	122 (1.5%)	1.00 (referent)	1.00 (referent)	1.00 (referent)
60 to 75	4128	63 (1.5%)	1.03 (0.76 to 1.39)	0.91 (0.66 to 1.27)	0.89 (0.64 to 1.24)
<60	497	28 (5.6%)	3.85 (2.55 to 5.82)	3.09 (1.97 to 4.82)	2.41 (1.52 to 3.82)
β (SE)			−0.020 ± 0.006	−0.020 ± 0.006	−0.015 ± 0.006
P value			<0.001	0.001	0.014
Creatinine (mg/dl)					
<1.0	1706	20 (1.2%)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1.0 to 1.2	9344	141 (1.5%)	1.17 (0.73 to 1.86)	1.18 (0.72 to 1.93)	1.18 (0.72 to 1.95)
1.3 to 1.4	1603	29 (1.8%)	1.40 (0.79 to 2.48)	1.29 (0.70 to 2.37)	1.29 (0.70 to 2.37)
≥1.5	213	23 (10.8%)	8.99 (4.91 to 16.47)	7.10 (3.71 to 13.58)	4.28 (2.15 to 8.52)
β (SE)			2.330 ± 0.420	1.964 ± 0.443	1.314 ± 0.426
P value			<0.001	<0.001	0.002
Hematocrit (%)					
<42	1043	20 (1.9%)	1.16 (0.72 to 1.86)	1.03 (0.64 to 1.67)	0.97 (0.59 to 1.58)
42 to 54	11550	188 (1.6%)	1.00 (referent)	1.00 (referent)	1.00 (referent)
≥55	264	4 (1.5%)	0.94 (0.35 to 2.56)	0.96 (0.35 to 2.62)	0.90 (0.33 to 2.46)
β (SE)			−0.001 ± 0.002	−0.001 ± 0.002	−0.001 ± 0.002
P value			0.669	0.779	0.784

[a]Values are for analyses using those variables as continuous measures. *P* values associated with β coefficients are from Wald tests.
[b]Included in model are age, race (black/nonblack), plasma triglycerides, LDL cholesterol, HDL cholesterol, smoking status (yes/no), family history of diabetes (yes/no), serum glucose and uric acid, BMI, and baseline systolic BP.
[c]All variables in [b] plus proteinuria, eGFR, and hematocrit.

and proteinuria with smoking, BP, and serum cholesterol. A significant interaction between proteinuria and smoking was found ($P = 0.013$). The increased risk for ESRD associated with proteinuria was greater among nonsmokers (HR 9.7) than smokers (HR 3.6). Other interactions with proteinuria and interactions with eGFR were NS.

Hematocrit and Risk for ESRD

Approximately 8% of men had a hematocrit <42%, and 2% had a hematocrit >54%; the remainder fell within the normal range. Figure 1C gives the cumulative incidence of ESRD by baseline hematocrit. Baseline hematocrit was not significantly associated with development of ESRD in either univariate or multivariate models. The full model HR for men with hematocrit values <42% was 0.97 (95% CI 0.59 to 1.6) compared with men in the normal hematocrit range (Table 4). Similarly, no association between hematocrit and ESRD was found in analyses using tertiles of hematocrit or when hematocrit was modeled as a continuous variable.

Discussion

In middle-aged men who are at above-average risk for CVD and do not have significant kidney disease, our findings indicate that greater than trace amounts of protein on a casual urine dipstick, present in only a small percentage of men, is an important predictor of the 25-yr incidence of ESRD. The risk for ESRD rose with increasing amounts of proteinuria. Among those with ≥2+ proteinuria at baseline, the 25-yr incidence of ESRD was 18.7%. This risk for ESRD was magnified further when proteinuria was present in those with a baseline eGFR <60 ml/min per 1.73 m^2, increasing the 25-yr incidence of ESRD to 40.9% in men with ≥2+ proteinuria. The strong additive effects of proteinuria and eGFR and the simplicity of these measurements suggest that periodic remeasurement of them along with major CVD risk factors should be considered for identifying individuals who are at risk for ESRD. Although a combined eGFR <60 ml/min per 1.73 m^2 and the presence of proteinuria were strong independent risk factors for developing ESRD over a 25-yr period, the prevalence of these conditions was low (7.2% with proteinuria and/or eGFR <60 ml/min per 1.73 m^2), and many individuals who developed ESRD did not have these risk factors at baseline. This highlights the need to identify other factors that improve the prediction of the development of ESRD. Our results indicate that in addition to age, eGFR, and proteinuria, common CVD risk factors such

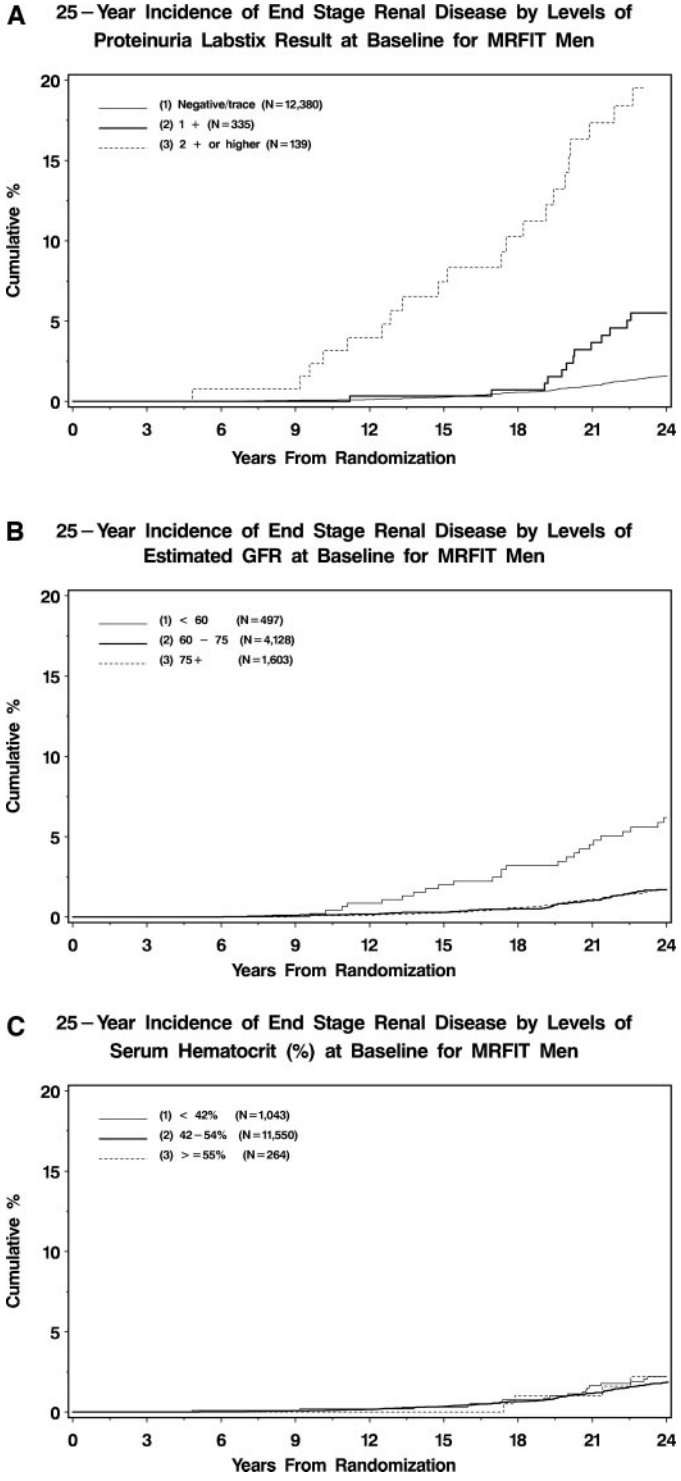

Figure 1. (A) Twenty-five-year incidence of ESRD by levels of proteinuria Labstix result at baseline for men in the Multiple Risk Factor Intervention Trial (MRFIT). (B) Twenty-five-year incidence of ESRD by levels of estimated GFR at baseline for men in the MRFIT. (C) Twenty-five-year incidence of ESRD by levels of serum hematocrit (%) at baseline for men in the MRFIT.

as elevated cholesterol and BP, smoking, diabetes, and race are major risk factors for ESRD. These observations extend those of earlier work on the screened cohort for MRFIT, for which similar risk factors were identified. A limitation of our earlier work that is addressed in this article is that the men who were screened and not randomly assigned did not have baseline creatinine and proteinuria measurements (7,11,13). Importantly, the major risk factors for CVD and renal disease are modifiable. Finally, in the MRFIT cohort, hematocrit at baseline had no significant association with subsequent risk for ESRD.

The National Kidney Foundation (NKF) adopted a new classification scheme for CKD, such that either individuals with an eGFR <60 ml/min per 1.73 m^2 or those with proteinuria were defined as having CKD (23). This definition was based on evidence demonstrating that these categories identify individuals who are at high risk for loss of kidney function and development of CVD. These categories had never previously been validated for the development of ESRD. Results from our study demonstrate that utilization of NKF definitions of CKD identifies a group of individuals with a significantly greater relative risk for developing ESRD compared with those who are not classified as having CKD.

Other studies have demonstrated that proteinuria is associated with either worsening renal function or ESRD. These studies typically have used highly selective cohorts such as those with established kidney disease or diabetes (2,4–6,24,25). In addition, many of these studies have used a combination of end points, which have included surrogate markers of ESRD such as doubling of serum creatinine or change in GFR (2,4–6,24). Finally, the majority of these studies recruited individuals with significant amounts of proteinuria (typically >1 g/d) and compared greater quantities of protein excretion with lesser quantities of protein excretion. Few studies included individuals with no proteinuria at baseline (3,6).

Only two large cohort studies with long duration of follow-up have demonstrated that proteinuria is a risk factor for ESRD. Tozawa *et al.* (12) demonstrated that baseline proteinuria of $\geq 1+$ was associated with a relative risk for the development of ESRD of 11.29 in men and 12.5 in women. Iseki *et al.* (26) demonstrated in an unselected Japanese population that proteinuria was the strongest predictor of ESRD after 18 yr of follow up. In that population, the 18 yr incidence of ESRD was 0.2% negative/trace, 1.4% 1+, and 9.2% for those with $>2+$ proteinuria. These rates are similar to the 18-yr incidence of ESRD in the MRFIT cohort. The rapid increase in the MRFIT men in the incidence of ESRD from 9.2% at 18 yr to 18.7% at 25 yr highlights the exponential increase in the incidence of ESRD with age. A limitation that is common to previously reported studies that used registry data to identify individuals who developed ESRD is that none had an estimate of kidney function at baseline (*i.e.*, serum creatinine). Consequently, unlike the MRFIT randomized cohort, which measured creatinine and excluded men with levels ≥ 2 mg/dl, it is likely that their estimate of risk that was attributed to proteinuria is greater as a result of confounding by established kidney disease.

It remains unclear whether proteinuria is a marker of more advanced kidney disease or a risk factor for the progression of kidney disease. Studies in animal models of kidney disease have suggested that proteinuria is an independent risk factor for progression of kidney disease (27). Proteinuria also has been

Table 5. Bivariate relationship of eGFR and proteinuria and 25-yr ESRD in men in MRFIT[a]

GFR (ml/min per 1.73 m^2)	Protein in Urine from Labstix		
	Negative/Trace	1+	2+ or Higher
<60			
ESRD (*n* [%])	457 (3.94)	17 (5.88)	22 (40.91)
HR (95% CI)[a]	2.36 (1.38 to 4.01)	3.07 (0.41 to 22.99)	32.87 (15.20 to 71.10)
60 to 75			
ESRD (*n* [%])	3984 (1.28)	105 (5.71)	34 (17.65)
HR (95% CI)[a]	0.84 (0.59 to 1.21)	2.80 (1.18 to 6.61)	12.93 (5.52 to 30.26)
≥75			
ESRD (*n* [%])	7939 (1.31)	213 (3.29)	83 (13.25)
HR (95% CI)[a]	1.00 (reference)	1.92 (0.82 to 4.51)	11.42 (5.99 to 21.77)

[a]From Cox regression model including indicator variables for categories of GFR and proteinuria and covariates listed in footnote [b] of Table 4.

shown to be the most significant risk factor for ESRD among those with established nondiabetic kidney disease in a pooled analysis of randomized, controlled trials that compared antihypertensive drugs (28). In addition, there was a significant interaction between baseline proteinuria levels and the treatment effect by angiotensin-converting enzyme inhibitors in that those who obtained the greatest benefit from angiotensin-converting enzyme inhibitor therapy were those with the greatest quantity of proteinuria at baseline. Recent results from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study have confirmed that the greater the decrease in albuminuria in patients with diabetes during the first 6 mo of therapy with the angiotensin receptor blocker losartan, the greater the prevention of progression of CKD (29).

Similar to the literature for proteinuria and ESRD, previous studies have demonstrated that serum creatinine is a risk factor for the progression of kidney disease in individuals with previously identified kidney disease. Our results extend these findings to men who are at high risk for CVD but do not have significant kidney disease and to using eGFR as a measure of kidney function. Increased risk was concentrated mainly in men with eGFR values <60 ml/min per 1.73 m^2. The association between eGFR and ESRD is likely the result of unidentified kidney disease in those with lower levels of eGFR, especially in those also with proteinuria. Using an eGFR of <60 ml/min per 1.73 m^2 or ≥1+ proteinuria as the criteria for CKD, 7.2% of the original MRFIT cohort was identified as having CKD at baseline. These individuals had a significantly greater risk for developing ESRD compared with those with an eGFR >60 ml/min per 1.73 m^2 and no proteinuria at baseline

Finally, our results demonstrate no significant association between hematocrit and the 25-yr incidence of ESRD. This contradicts other studies that have demonstrated that lower levels of hemoglobin more likely are associated with faster progression of kidney disease (30). There are important differences between our study cohort and those previously studied. The first is that individuals in the MRFIT study did not have significantly identified kidney disease, whereas most previous reports that demonstrated the inverse association between hemoglobin and progression of kidney disease have studied individuals with established CKD. Individuals with advanced kidney disease are likely to have lower hemoglobin levels as a result of a reduction in erythropoietin production by the kidneys. Consequently, it remains unknown whether the association between lower hemoglobin and greater progression of kidney disease is causative or the result of residual confounding in that those with the most advanced kidney disease are likely to have the lowest hemoglobin concentrations and have the greatest rate of kidney disease progression. By studying individuals without significantly identified kidney disease at baseline, we are able to minimize severity of baseline kidney function as a potential confounder. However, a possible limitation of our analysis of hematocrit and ESRD risk is that few individuals in our cohort had anemia at baseline as defined by the World Health Organization (31). It may be that hematocrit did not range sufficiently to detect an association with ESRD. This limitation seems unlikely given the prolonged duration of follow-up, which should magnify even small differences between groups in baseline hematocrit.

The advantages of our study are its large sample size, the long duration of follow-up, the use of individuals without previously defined kidney disease, the relatively large number of end-stage kidney disease events, and the ability to adjust for baseline renal function. However, there are limitations of our investigation. Only men were included in the MRFIT study. Second, the association between dipstick proteinuria and ESRD was based on a casual urine specimen. Numerous factors such as fever, exercise, body position, and urine concentration are known to influence the results of random dipstick proteinuria assessments. In the Framingham cohort, only 21% of men were persistently positive for urinary albumin excretion between the first and second visits (24). Transient proteinuria, irrespective of cause, could have led to some misclassification of the amount of proteinuria present at baseline, with the majority of misclassification having been false-positive results. Such misclassifications and, more generally, use of single measurements of pro-

teinuria and creatinine would have the effect of biasing our results toward the null.

Third, all our analyses censored individuals who died for causes unrelated to kidney disease. This competing risk for death from other causes also likely reduced the association between risk factors and the development of ESRD. Numerous previous studies have demonstrated that in addition to being a risk factor for renal events, proteinuria and kidney function are risk factors for the development of CVD and death (32–35). As therapies for CVD evolve, an increasing number of individuals will survive to develop ESRD.

Finally, because we used a registry and US death record to identify individuals who developed ESRD, it is possible that we missed individuals with ESRD as a result of undercoding of death caused by kidney disease on death certificates, as result of MRFIT participants' leaving the United States before achieving the end point, or because ESRD events were missed by the USRDS. Again, such misclassifications would have biased our results toward the null and weaken our associations.

The incidence, prevalence, and cost of ESRD disease are increasing rapidly in the United States. Identification of individuals who are at increased risk for developing ESRD and intervening on modifiable risk factors to prevent ESRD should be an important public health priority. In the MRFIT cohort, the presence of proteinuria on a casual dipstick screening and/or an eGFR value <60 ml/min per 1.73 m^2 measured at baseline was a strong predictor of long-term development of ESRD, validating the definitions proposed by the NKF. Age, race, BP, lipids, and smoking also were important risk factors. Despite that eGFR and proteinuria were strong risk factors for ESRD, prevalence at screening was low and many men who developed ESRD did not have proteinuria or low eGFR at baseline. This highlights the importance of emphasizing intervention on more common major risk factors such as elevated BP and lipids and cigarette smoking in preventing ESRD and of further research to develop improved methods to predict ESRD. Finally, it remains unknown whether intervention for proteinuria or early identification of those with CKD is effective in reducing the risk for ESRD.

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