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Prevalence of Low Glomerular Filtration Rate in Nondiabetic Americans: Third National Health and Nutrition Examination Survey (NHANES III)

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Abstract. End-stage renal disease is an important and costly health problem. Strategies for its prevention are urgently needed. Knowledge of the population-based prevalence of renal insufficiency in nondiabetic adults would inform such strategies. Black and white nondiabetic adult participants in the Third National Health and Nutrition Examination Survey were analyzed. The analysis was stratified by age, gender, and race, and four clinically applicable methods were used to assess renal function. There were 13,251 complete records for analysis. By the Modification of Diet in Renal Diseases (MDRD) GFR (GFR) prediction Equation 7, 58% (95% confidence interval [CI], 56 to 60%) of the total adult nondiabetic black and white US population had MDRD GFR below 80 ml/min per 1.73m^2, 13% (95% CI, 11 to 14%) below 60 ml/min per 1.73m^2, and 0.26% (95% CI, 0.19 to 0.33%) below 30 ml/min per 1.73m^2. By the Cockcroft-Gault formula, the equivalent figures were 39% (95% CI, 37 to 41%), 14% (95% CI, 12% - 16%), and 0.81% (95% CI, 0.46 to 1.2%), respectively. The findings of an unexpectedly high prevalence of low clearance and the increased prevalence of low clearance with age were consistent across the four clearance estimation methods used and for each race-sex stratum. The absolute magnitude of the prevalence of low clearance was, however, dependent on the clearance method used. Assessed by estimation from serum creatinine, low clearance may be very common, particularly with advancing age. The prognosis (in terms of risk for progression and end-stage renal disease) of low clearance in unreferred populations may differ from that in referred populations and requires further study.

The incidence of end-stage renal disease (ESRD) increases annually in the United States and is projected to continue to increase over the next decade (1). ESRD is associated with increased morbidity (1) and with mortality comparable with that of common malignancies (2). Improving outcomes for patients at risk of ESRD is an important mandate for primary care practitioners, generalists, and nephrologists. There is compelling evidence that BP control and angiotensin-converting enzyme (ACE) inhibitor use reduce the rate of progression of chronic renal insufficiency (CRI) (3–7) and should reduce the number of patients with ESRD. Referral to a nephrologist several months before the initiation of dialysis is associated with lower morbidity on dialysis and improved outcomes (8–11) but is underutilized (12).

Strategies to enhance implementation of these approaches are needed. Guidelines for the appropriate management and referral of patients with CRI have been developed in Canada (13), and they are under development in the US (the Kidney Disease Outcomes Quality Initiative [K/DOQI]) (14). To be feasible and effective, recommendations about suitable strategies must take the prevalence of renal insufficiency into account. The population prevalence for elevated creatinine (>1.5 mg/dl in men; >1.4 mg/dl in women) has been estimated at 8.0% of men and 8.9% of women by Culleton *et al.* (15) in Framingham Heart Study participants. Nissenson *et al.* (16), using data from a large US health maintenance organization, estimated the prevalence of elevated creatinine (>1.2 mg/dl in men; >1.4 mg/dl in women) at 9.3% in men and 5.6% in women and also examined the proportions of patients with more severe elevations in creatinine and with evidence of persistent elevation in creatinine. The Third National Health and Nutritional Examination Survey (NHANES III) provides an opportunity to examine this issue in a large, community-based sample. These data have been previously analyzed by Jones *et al.* (17), who showed that 9.7% of men and 1.8% of women participants had a serum creatinine greater than 1.5 mg/dl. However, the prevalence of different degrees of severity of renal insufficiency, estimated as GFR or creatinine clearance, is not known. We provide estimates of the prevalence of renal insufficiency in adult nondiabetic black and white Americans sampled in NHANES III, using four clinically relevant methods of estimating clearance.

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Materials and Methods

NHANES III Data

Detailed methods of NHANES III are described elsewhere (18,19). It was a national cross-sectional survey conducted between 1988 and 1994 by the National Center for Health Statistics (NCHS) in the US, using multistage, stratified, clustered sampling of the civilian, noninstitutionalized population. Participants underwent a home interview for demographic, social, economic, and medical information as well as a standardized examination and laboratory testing (20).

For this study, we used the following inclusion criteria: race (either white or black to avoid the analytic problems associated with the small numbers of people of other ethnic origins), nondiabetic, aged 20 yr or older, with complete data for the calculation of each of the clearance estimates. Nondiabetic participants were defined as those who answered "no" to the question "Have you ever been told by a doctor that you have diabetes or sugar diabetes?" and whose fasting glucose level was less than 126 mg/dl (7.0 mmol/L) (21). Plasma glucose was measured after a 10- to 16-h fast for morning-examined patients and after a 6-h fast in afternoon-examined patients.

Creatinine was measured by a modified kinetic Jaffé reaction, albumin by bromcresol purple, and urea by a kinetic method (22). Clearance was estimated by the Modification of Diet in Renal Diseases (MDRD) Equation 7 (23) for prediction of GFR, by the Cockcroft-Gault formula for creatinine clearance (24), and by 100/(serum creatinine [mg/dl]) (25). The dimensions of each of these estimates are different (ml/min per 1.73m^2; ml/min; and dl/mg, respectively). For each equation, we chose the same numerical cutpoints—80, 60, and 30—to create four strata from normal/near-normal renal function through to advanced renal insufficiency. We also stratified participants using a set of creatinine cutpoints described by Couchoud *et al.* (26). These were 1.3 mg/dl (115 μmol/L), 1.5 mg/dl (137 μmol/L), and 2.0 mg/dl (177 μmol/L) in men and 1.0 mg/dl (90 μmol/L), 1.2 mg/dl (104 μmol/L), and 1.7 mg/dl (146 μmol/L) in women; equivalent to inulin clearances of 80, 60, and 30 ml/min per 1.73m^2, respectively. History of other medical conditions was determined by self-report. BP was the mean of three measurements at the end of the interview according to standardized BP measurement protocols (27).

Statistical Analyses

Data were extracted from the databases provided by the NCHS using SETS 2.0 (NCHS, Bethesda, MD). The survey data were analyzed using methodology that accounts for the complex sampling design, using analytic methods recommended by the US NCHS. Sample weights were used to calculate prevalence estimates and to account for oversampling and nonresponse to the household interview and physical examination. All analyses were conducted with WesVarPC (28,29) (Fay's replication method), a statistical program appropriate for the analysis of complex sample survey data (30). Fay's replicate weights, provided by the NCHS, were used for variance estimates.

Results

Of 17,030 NHANES III participants aged ≥20 yr who completed the interview and the examination, 558 were excluded on the basis of ethnic status and 2856 because of diabetes mellitus or incomplete diabetes assessment, leaving 13,616 eligible records. Of these, 365 were incomplete for one or more items required for the calculation of the four different clearance estimates (missing data), leaving 13,251 participants for analysis. Eligible participants with complete and incomplete data are compared in Table 1. Further biochemicaldata for analyzed cases are shown in Table 2. Figures 1 to 4 show the prevalence of levels of renal function by MDRD GFR, Cockcroft-Gault creatinine clearance, Couchoud cutpoints, and

Table 1. NHANES III participants who met inclusion criteria. Comparison of those selected for analysis with those excluded on the basis of missing biochemical data for clearance calculations[a]

Parameter	Excluded	Included	*P*
n	365	13,251	
Age			
20 to 39 yr	53.6% (4.3)	48.4% (1.0)	0.2
40 to 59 yr	20.0% (3.1)	31.9% (0.5)	<0.01
60 to 79 yr	21.1% (2.1)	17.1% (0.7)	0.08
≥80 yr	5.4% (1.5)	2.6% (0.8)	0.03
Gender (women)	49.9% (4.2)	51.9% (0.4)	0.6
Race (black)	19.1% (2.0)	11.0% (0.2)	<0.001
Past medical history			
hypertension	22.8% (3.2)	21.9% (0.7)	0.7
myocardial infarction	6.6% (1.3)	2.7% (0.3)	0.005
stroke	1.2% (0.6)	1.4% (0.2)	0.80
congestive heart failure	3.1% (1.0)	1.5% (0.1)	0.15
smoking (ever)	52.6% (3.3)	54.7% (0.8)	0.53
kidney stones	6.8% (2.7)	5.4% (0.4)	0.65
Systolic BP (mmHg)	122 (1.2)	121 (0.4)	0.33
Diastolic BP (mmHg)	73 (0.9)	74 (0.2)	0.46

[a] Data are mean (standard error [SE]) for continuous variables and proportions (SE) for discrete variables. Missing data: all variables had 98.6% or more complete information. *P* values for proportions were assessed by χ^2 test, and for continuous variables with *t* test for independent samples.

Table 2. Further characteristics of the 13,251 NHANES III nondiabetic adult participants included in the analysis[a]

Parameter	Conventional Units	SI Units
Body wt		75 (0.3) kg
Height	169 (0.2) cm	1.69 (0.002) m
Body surface area[b]		1.85 (0.004) m^2
Body mass index[c]		26.3 (0.08) kg/m^2
MDRD GFR[d]	77 (0.4) ml/min per 1.73m^2	0.74 (0.004) ml/s per m^2
Cockcroft-Gault creatinine clearance[e]	89 (0.9) ml/min	1.48 (0.02) ml/s
Serum creatinine	1.07 (0.002) mg/dl	94.5 (0.2) mmol/L
Serum urea	14.0 (0.08) mg/dl	5.0 (0.03) mmol/L
Serum cholesterol	203 (0.8) mg/dl	5.26 (0.02) mmol/L
Serum albumin	4.20 (0.01) g/dl	42.0 (0.1) g/L
Glycated hemoglobin		5.2 (0.01)%

[a] Data are mean (SE). Missing data: all variables had 99.4% or more complete information.
[b] Body surface area (m^2) = 0.20247 × [height (m)]$^{0.725}$ × [weight (kg)]$^{0.425}$ (58).
[c] Body mass index = [weight (kg)]/[height (m)]^2.
[d] MDRD GFR (ml/min per 1.73 m^2) = 170 × [serum creatinine (mg/dl)]$^{-0.999}$ × [age]$^{-0.176}$ × [0.762 if patient is female] × [1.180 if patient is black] × [serum urea nitrogen (mg/dl)]$^{-0.170}$ × [serum albumin (g/dL)]$^{0.318}$.
[e] Cockcroft-Gault creatinine clearance = ([140 − age] × [weight (kg)])/(72 × [serum creatinine (mg/dl)]) × [0.85 if female].

100/(serum creatinine [mg/dl]), respectively. For each age-gender stratum, the number of participants in each decade, and the proportion of those participants whose clearance level fell into each of the different categories is enumerated and illustrated. For the sake of brevity, 95% confidence intervals (CI) are shown for MDRD GFR only (Table 3).

By MDRD GFR, 58% (95% CI, 56 to 60%) of adult nondiabetic (black or white) Americans had a GFR below 80 ml/min per 1.73m^2, 13% (95% CI, 11 to 14%) below 60 ml/min per 1.73m^2, and 0.26% (95% CI, 0.19 to 0.33%) below 30 ml/min per 1.73m^2. Preserved MDRD GFR was more common in older black participants compared with white counterparts. In whites, MDRD GFR was below 80 ml/min per 1.73m^2 in more than 80% of participants over the age of 40 yr, and below 60 ml/min per 1.73m^2 in more than 40% of participants over the age of 60 yr. In blacks, MDRD GFR was below 80 ml/min per 1.73m^2 in more than 50% of participants over the age of 40 yr and below 60 ml/min per 1.73m^2 in more than 30% of participants over the age of 60 yr. Women tended to have lower MDRD GFR than men, and this effect was most marked in white participants.

The analysis using the Cockcroft-Gault formula produced similar results. However, compared with the corresponding MDRD GFR results, fewer 30- to 60-yr-olds were estimated to have clearance below 80 ml/min, and more participants beyond the age of 60 y were estimated to have a clearance less then 60 ml/min. By the Cockcroft-Gault formula, 39% (95% CI, 37 to 41%) of adult nondiabetic (black or white) Americans had a clearance below 80 ml/min, 14% (95% CI, 12 to 16%) below 60 ml/min, and 0.81% (95% CI, 0.46 to 1.2%) below 30 ml/min.

Compared with the clearance formulae, the Couchoud cut-points (Figure 3) identified fewer people as having low GFR in all race-gender-age categories. As with the MDRD GFR and Cockcroft-Gault estimates, the proportion of participants in each stratum of low GFR increased with advancing age. Using reciprocal of serum creatinine–produced estimates in which the proportion of women with low clearance was consistently lower than the equivalent proportion for men.

We examined the agreement between the validated prediction equations in categorizing individual participants. The proportion of people in a given MDRD GFR category, who would be categorized into the same numerical category by Cockcroft-Gault creatinine clearance, varied between 35 and 95% and was dependent on level of GFR (Table 4). Higher levels of agreement were noted for both black and white participants at the extremes of each scale (*e.g.*, for white participants, 95% of those with MDRD GFR <30 ml/min per 1.73m^2 were also found to have Cockcroft-Gault creatinine clearance <30 ml/min; 80% of white participants with MDRD GFR >80 ml/min per 1.73m^2 had Cockcroft-Gault creatinine clearance in the same range). More differences were noted in the assignment into the 30 to 59 ml/min per 1.73m^2 and 60 to 80 ml/min per 1.73m^2 groups, but in general, the recategorization was into an adjacent group, with the exception of 16 participants with MDRD GFR in the 60 to 79 ml/min per 1.73m^2 category who were found to have Cockcroft-Gault clearances less than 30 ml/min.

Discussion

On the basis of the NHANES III survey conducted between 1988 and 1994, we have described clearance levels for adult nondiabetic black and white Americans. The results obtained are broadly similar for both the MDRD equation and the Cockcroft-Gault formula; large proportions of people in middle age and beyond had low GFR by these estimates. The proportion of participants in each stratum of low GFR increased with advancing age, independent of the method of assessment of GFR.

We have provided age-, gender-, and race-specific estimates

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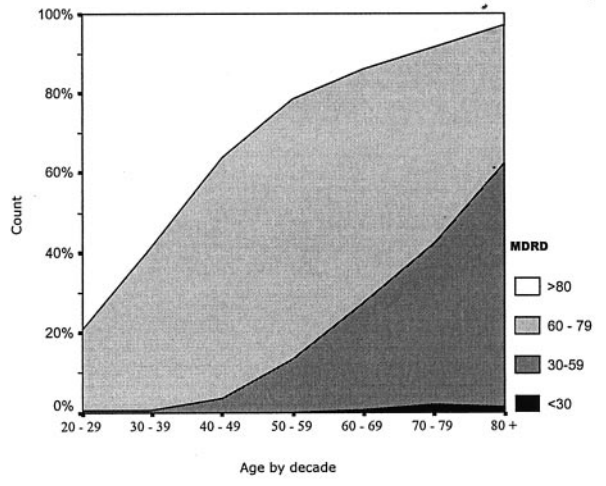

N	970	823	708	490	657	470	404	Total 4522
≥ 80	79.1%	58.8%	36.3%	21.6%	14.1%	8.4%	3.1%	45.6%
60-79	20.4%	40.7%	60.0%	64.9%	58.7%	49.2%	34.8%	45.2%
30-59	0.5%	0.6%	3.7%	13.4%	26.7%	40.5%	60.8%	9.0%
< 30	0%	0%	0%	<0.1%	0.6%	1.9%	1.4%	0.2%

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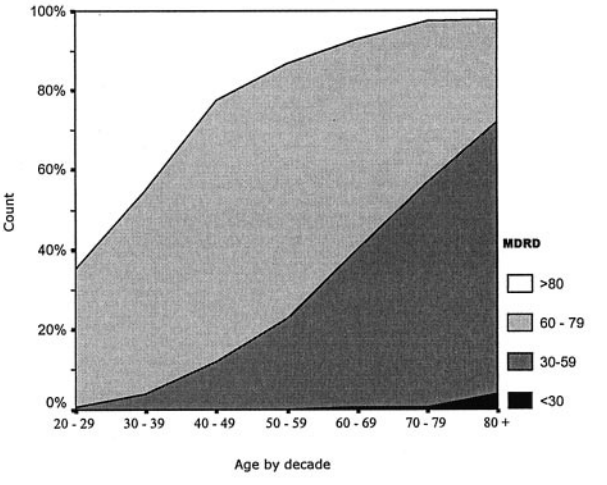

1028	999	724	568	616	539	435	Total 4909
64.8%	45.3%	22.6%	13.2%	7.2%	2.8%	2.2%	32%
34.6%	50.9%	65.3%	63.9%	52.8%	40.3%	25.7%	50.2%
0.7%	3.8%	12.2%	22.9%	39.2%	56.2%	68.2%	17.5%
0%	<0.1%	0%	0%	0.8%	0.8%	3.9%	0.3%

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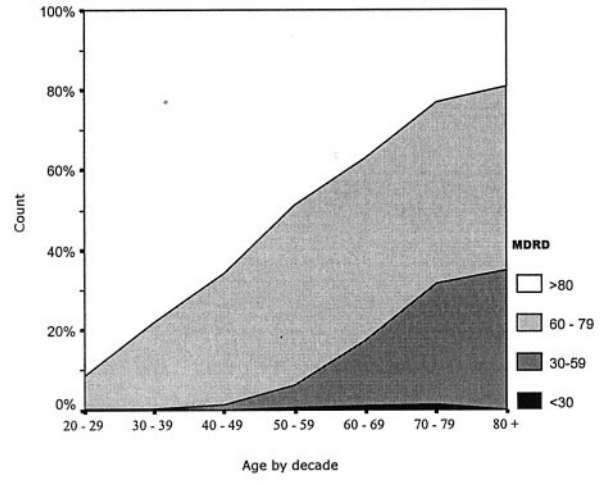

N	455	435	314	162	209	128	32	Total 1735
≥ 80	91.7%	78.2%	65.9%	48.9%	37.2%	23.1%	19.3%	70.9%
60-79	7.9%	21.3%	32.7%	45.1%	45.7%	45.4%	45.7%	25.0%
30-59	0.5%	0.2%	1.4%	5.4%	16.2%	30.3%	35.0%	3.9%
< 30	0%	0.3%	0%	0.7%	0.9%	1.3%	0%	0.3%

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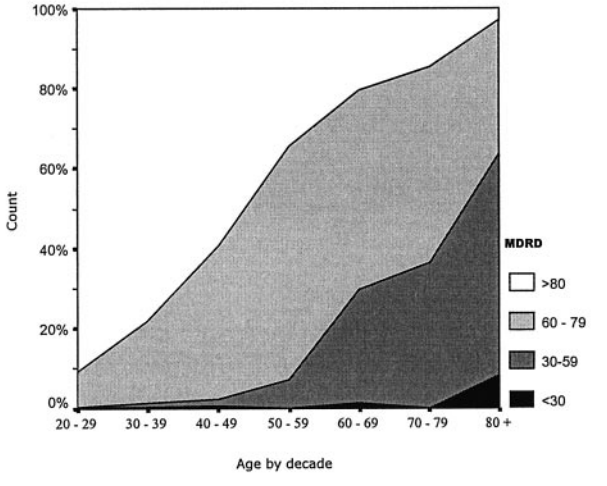

584	570	392	202	188	104	45	Total 2085
90.9%	78.1%	59.3%	34.6%	20.6%	14.6%	2.9%	65.7%
8.9%	20.6%	38.5%	58.3%	49.7%	48.8%	33.8%	27.9%
0.1%	0.9%	1.8%	7.2%	28.4%	36.6%	55.1%	5.9%
0.1%	0.4%	0.5%	0%	1.4%	0%	8.3%	0.5%

Figure 1. Nondiabetic adults in NHANES III. Weighted distribution of level of predicted GFR (MDRD categories) in ml/min per 1.73 m^2 by age (in decades) and stratified by race and gender.

of the prevalence of low clearance for four different methods of clearance prediction. The large sample size compared with the Framingham study (15) has allowed us to provide prevalence estimates for different degrees of renal insufficiency; we used three different cutpoints, representing decreasing clearance, for each measure of renal function. We also used three different validated methods of estimating GFR and documented the differences between results expected with each of these methods and for non–gender-specific creatinine cutpoints. We studied nondiabetic participants, as we sought to produce estimates

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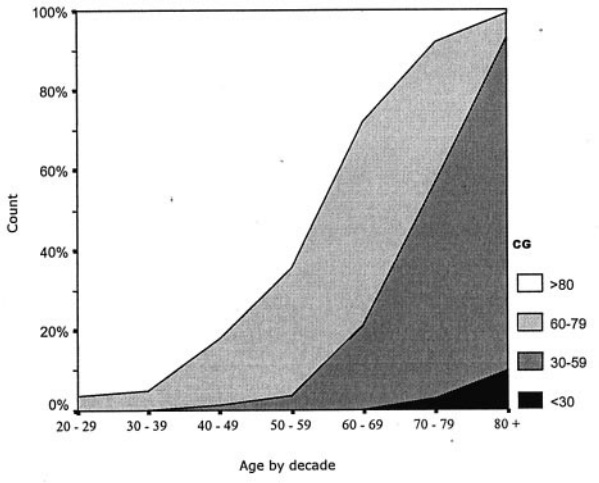

N	970	823	708	490	657	470	404	Total 4522
≥ 80	96.5%	95.3%	82.2%	64.6%	27.9%	8.2%	1.0%	75.1%
60-79	3.5%	4.8%	16.3%	31.8%	50.7%	34.8%	6.0%	16.7%
30-59	0%	0%	1.4%	3.6%	21.3%	54.1%	83.1%	7.8%
< 30	0%	0%	0%	0%	0%	2.8%	9.9%	0.4%

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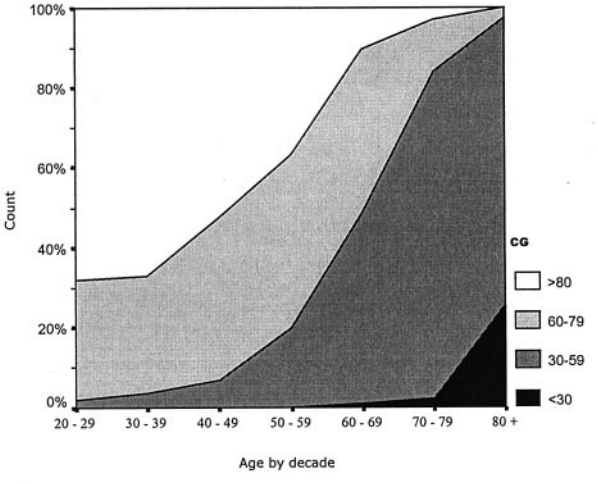

1028	999	724	568	616	539	435	Total 4909
67.9%	67.1%	52.3%	36.9%	10.4%	3.0%	0%	46.8%
30.1%	29.4%	40.7%	43.2%	41.0%	12.9%	2.6%	32.5%
1.9%	3.5%	7.0%	20.0%	47.5%	81.8%	71.9%	19.5%
0%	<0.1%	0%	<0.1%	1.1%	2.4%	25.5%	1.2%

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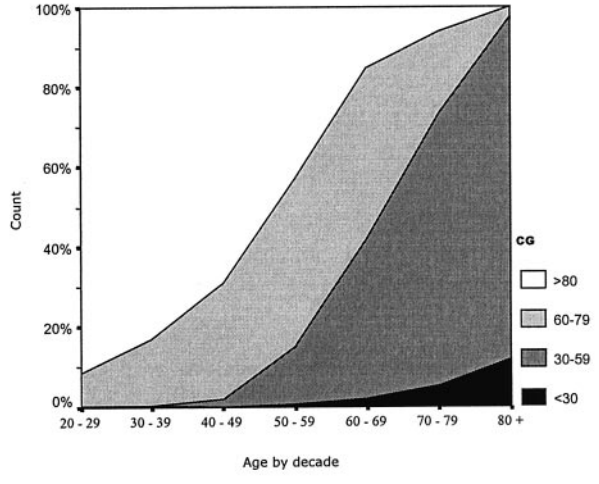

N	455	435	314	162	209	128	32	Total 1735
≥ 80	91.6%	83.2%	69.2%	42.9%	15.3%	6.1%	0%	69.8%
60-79	8.2%	16.4%	28.8%	42.2%	42.9%	20.6%	2.7%	20.9%
30-59	0.2%	0.2%	2.1%	14.2%	39.9%	68.0%	85.6%	8.7%
< 30	<0.1%	0.3%	<0.1%	0.7%	1.9%	5.2%	11.7%	0.6%

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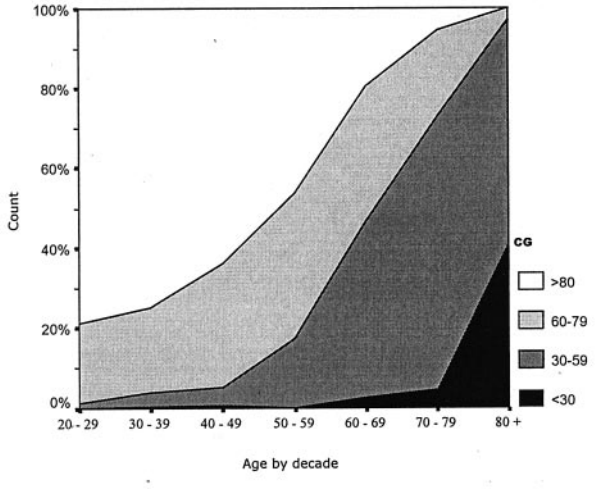
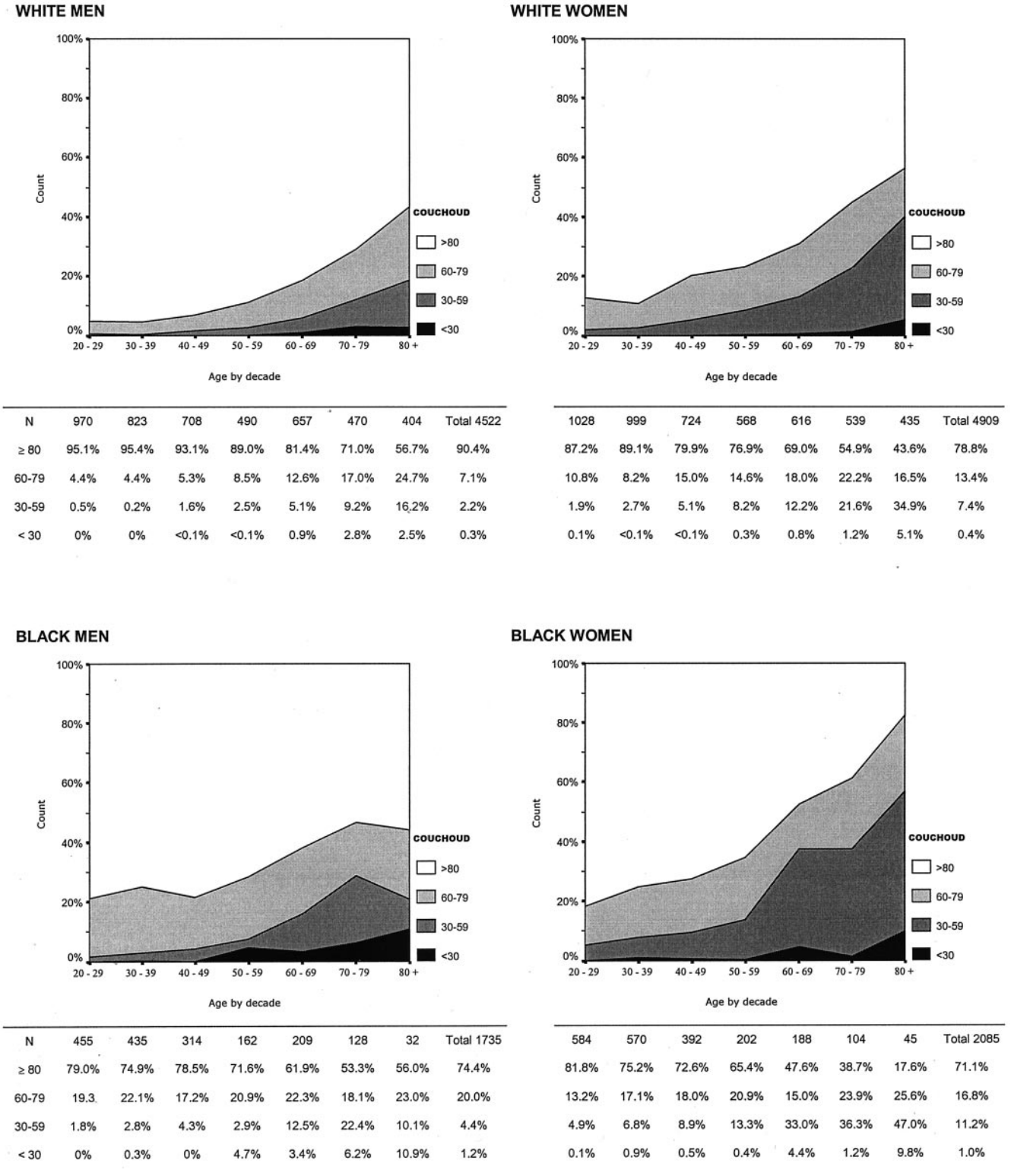


584	570	392	202	188	104	45	Total 2085
78.8%	75.0%	63.8%	46.2%	19.5%	5.5%	0%	62.8%
19.9%	21.1%	31.0%	36.6%	34.0%	21.7%	2.9%	24.8%
1.3%	3.6%	4.7%	17.2%	44.0%	68.3%	56.8%	11.0%
0%	0.4%	0.5%	0%	2.6%	4.6%	40.3%	1.3%

Figure 2. Nondiabetic adults in NHANES III. Weighted distribution of level of creatinine clearance (Cockcroft-Gault [CG] categories) in ml/min by age (in decades) and stratified by race and gender.

that could be generalized to other populations in whom the prevalence of diabetes might differ from that observed in the United States, and to inform the management of nondiabetic renal disease. The large number of black participants allows the determination of more precise estimates for black Americans than was possible with the Framingham data (15). Reporting black and white participants separately also facilitates generalization to populations of predominantly black and white individuals.

The large proportion of NHANES III participants with a low



N	970	823	708	490	657	470	404	Total 4522
≥ 80	95.1%	95.4%	93.1%	89.0%	81.4%	71.0%	56.7%	90.4%
60-79	4.4%	4.4%	5.3%	8.5%	12.6%	17.0%	24.7%	7.1%
30-59	0.5%	0.2%	1.6%	2.5%	5.1%	9.2%	16.2%	2.2%
< 30	0%	0%	<0.1%	<0.1%	0.9%	2.8%	2.5%	0.3%

1028	999	724	568	616	539	435	Total 4909
87.2%	89.1%	79.9%	76.9%	69.0%	54.9%	43.6%	78.8%
10.8%	8.2%	15.0%	14.6%	18.0%	22.2%	16.5%	13.4%
1.9%	2.7%	5.1%	8.2%	12.2%	21.6%	34.9%	7.4%
0.1%	<0.1%	<0.1%	0.3%	0.8%	1.2%	5.1%	0.4%

N	455	435	314	162	209	128	32	Total 1735
≥ 80	79.0%	74.9%	78.5%	71.6%	61.9%	53.3%	56.0%	74.4%
60-79	19.3	22.1%	17.2%	20.9%	22.3%	18.1%	23.0%	20.0%
30-59	1.8%	2.8%	4.3%	2.9%	12.5%	22.4%	10.1%	4.4%
< 30	0%	0.3%	0%	4.7%	3.4%	6.2%	10.9%	1.2%

584	570	392	202	188	104	45	Total 2085
81.8%	75.2%	72.6%	65.4%	47.6%	38.7%	17.6%	71.1%
13.2%	17.1%	18.0%	20.9%	15.0%	23.9%	25.6%	16.8%
4.9%	6.8%	8.9%	13.3%	33.0%	36.3%	47.0%	11.2%
0.1%	0.9%	0.5%	0.4%	4.4%	1.2%	9.8%	1.0%

Figure 3. Nondiabetic adults in NHANES III. Weighted distribution of level of predicted GFR (Couchoud categories) in ml/min per 1.73 m^2 by age (in decades) and stratified by race and gender. For (L/creatinine) $\times 100$, the cutpoint of 80 ml/min corresponds to serum creatinine of 1.25 mg/dl; 60 ml/min to 1.67 mg/dl; and 30 ml/min to 3.33 mg/dl.

GFR was an unexpected finding. The Boston Longitudinal Study of Aging documented mean creatinine clearance (by 24-h urine) of 97 ml/min in healthy octogenarians (31,32) and a decline in clearance of 0.75 ml/min per yr; these data are widely cited as representing normal healthy aging (33,34). This rate of decline in renal function was similar to that observed

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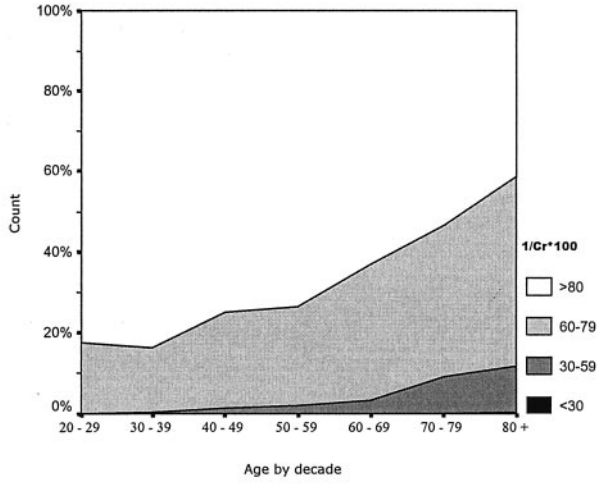
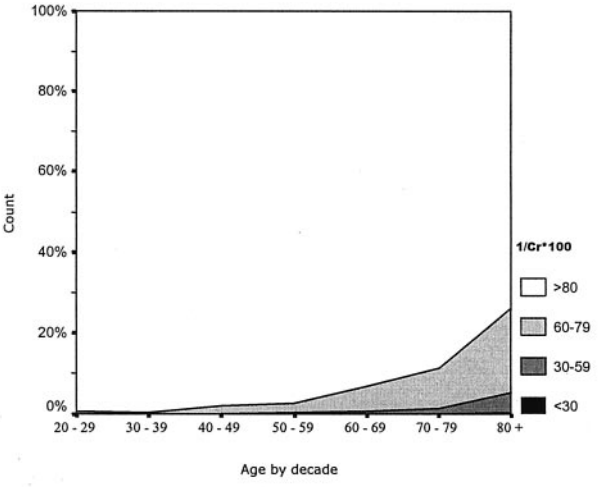


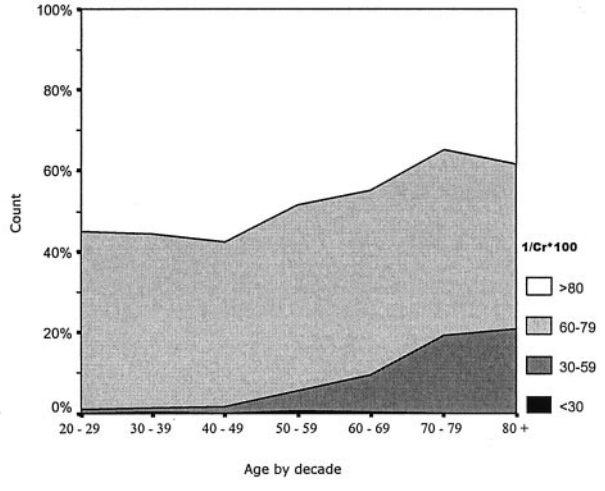
N	970	823	708	490	657	470	404	Total 4522
≥ 80	82.5%	83.6%	75.0%	73.7%	63.2%	53.4%	41.5%	75.6%
60-79	17.5%	16.2%	23.8%	24.5%	33.6%	37.6%	46.9%	22.7%
30-59	<0.1%	0.2%	1.2%	1.8%	3.2%	9.1%	11.3%	1.6%
< 30	0%	0%	0%	0%	0%	0%	0.4%	<0.1%

WHITE WOMEN



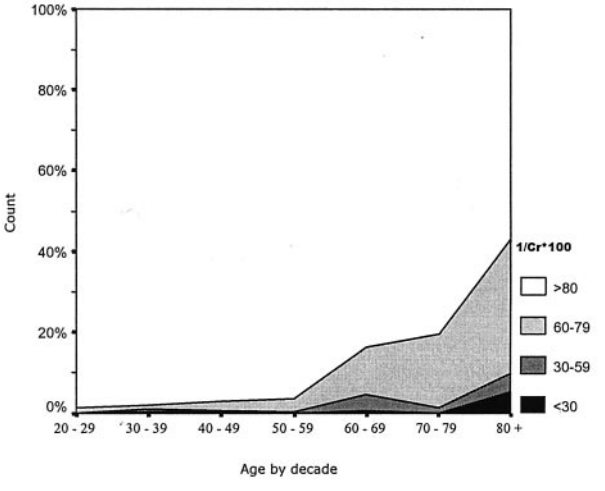
1028	999	724	568	616	539	435	Total 4909
99.4%	99.6%	98.0%	97.5%	93.1%	88.7%	73.8%	96.5%
0.5%	0.4%	2.0%	2.2%	6.1%	10.1%	21.1%	3.1%
0.1%	<0.1%	0%	0.3%	0.8%	1.2%	4.8%	0.4%
0%	<0.1%	0%	0%	0%	0%	0.3%	<0.1%

BLACK MEN



N	455	435	314	162	209	128	32	Total 1735
≥ 80	54.9%	55.8%	57.8%	48.6%	44.8%	34.7%	38.4%	53.3%
60-79	44.2	42.9%	40.6%	45.9%	45.6%	46.1%	40.7%	43.4%
30-59	0.9%	1.1%	1.6%	4.9%	9.1%	19.2%	20.9%	3.1%
< 30	0%	0.3%	0%	0.7%	0.5%	0%	0%	0.2%

BLACK WOMEN



584	570	392	202	188	104	45	Total 2085
98.9%	98.1%	96.9%	96.4%	83.6%	80.4%	56.9%	95.4%
1.0%	1.1%	2.6%	3.2%	12.0%	18.4%	33.3%	3.7%
0.1%	0.5%	0%	0.4%	3.6%	1.2%	4.7%	0.6%
0%	0.4%	0.5%	0%	0.8%	0%	5.1%	0.4%

Figure 4. Nondiabetic adults in NHANES III. Weighted distribution of level of predicted GFR (reciprocal of creatinine categories) in dl/mg by age (in decades) and stratified by race and gender. For (L/creatinine) × 100, the cutpoint of 80 ml/min corresponds to serum creatinine of 1.25 mg/dl; 60 ml/min to 1.67 mg/dl; and 30 ml/min to 3.33 mg/dl.

with each year of life in the NHANES III cross-sectional data (MDRD GFR, 0.6 ml/min per 1.73m^2 per yr; Cockcroft-Gault creatinine clearance, 1 ml/min per yr [data not shown]). The analysis of the predominantly white Framingham population by Culleton *et al.* (15), which included diabetic participants, suggested that overall 8.9% of men and 8.0% of women had

Table 3. Nondiabetic adults in NHANES III 95% confidence intervals (CI) for weighted distribution of level of GFR[a]

GFR Category (ml/min per 1.73m2)	20 to 29 yr	30 to 39 yr	40 to 49 yr	50 to 59 yr	60 to 69 yr	70 to 79 yr	≥80 yr	Total
≥80								
white male	75 to 83	54 to 63	31 to 42	18 to 25	11 to 17	6.2 to 11	1.4 to 4.7	43 to 48
white female	61 to 69	41 to 49	19 to 26	9.3 to 17	4.7 to 9.7	1.6 to 4.0	0.7 to 3.7	30 to 34
black male	89 to 94	74 to 82	60 to 72	42 to 56	30 to 44	13 to 33	3.8 to 35	69 to 73
black female	88 to 94	74 to 82	54 to 65	27 to 42	14 to 27	7.6 to 22	0 to 8.0	63 to 68
60 to 79								
white male	17 to 24	36 to 45	55 to 65	61 to 69	55 to 62	44 to 54	28 to 42	43 to 47
white female	30 to 39	46 to 55	61 to 69	59 to 69	49 to 57	35 to 45	21 to 30	48 to 52
black male	5.4 to 10	17 to 25	26 to 39	38 to 52	38 to 54	36 to 54	29 to 63	23 to 27
black female	6.0 to 11	17 to 24	34 to 43	51 to 65	40 to 60	38 to 60	20 to 48	26 to 30
30 to 59								
white male	0 to 1.2	0 to 1.4	2.0 to 5.4	9.2 to 18	23 to 30	35 to 46	54 to 68	8 to 10
white female	0.1 to 1.3	2.3 to 5.3	8.7 to 16	19 to 27	35 to 44	51 to 61	64 to 72	15 to 20
black male	0 to 1.1	0 to 0.7	0.3 to 2.5	2.9 to 8.0	11 to 22	20 to 41	21 to 49	3.2 to 4.6
black female	0 to 0.2	0.1 to 1.8	0.6 to 2.9	3.1 to 11	20 to 36	26 to 48	43 to 68	4.8 to 7.0
<30								
white male	0 to 0	0 to 0	0 to 0	0 to 0.1	0 to 1.3	0.2 to 3.5	0.5 to 2.2	0.1 to 0.3
white female	0 to 0	0 to 0.1	0 to 0	0 to 0	0.1 to 1.5	0 to 1.6	2.0 to 5.7	0.1 to 0.5
black male	0 to 0	0 to 0.7	0 to 0	0 to 1.9	0 to 2.5	0 to 3.3	0 to 0	0 to 0.5
black female	0 to 0.4	0 to 1.0	0 to 1.4	0 to 0	0.1 to 2.7	0 to 0	1.9 to 15	0.2 to 0.8

[a] All values are % within race-gender-age stratum. GFR is categorized according to the MDRD equation and stratified by age (in decades), race, and gender. Point estimates for this analysis are shown in Figure 1.

abnormal renal function (defined by creatinine exceeding the 95th percentile for a healthy subset). Jones *et al.* (17) noted prevalence of serum creatinine above 1.5 mg/dl in 9.0% of white men and 1.9% of white women (diabetics and nondiabetics were not reported separately). Nissenson *et al.* (16) estimated the prevalence of gender-specific increases in creatinine (>1.2 mg/dl in women; >1.4 mg/dl in men) using all diabetic and nondiabetic health maintenance organization patients whose creatinine had been measured as the denominator. Acknowledging that this methodology likely leads to overestimation of prevalence, they reported that 9.3% of men and 5.6% of women had at least one creatinine value above these cutpoints in the period studied. In contrast, in the nondiabetic population that we studied, 54% of white men and 68% of white women were estimated to have GFR below 80 ml/min per 1.73m^2 by the MDRD formula; 25% and 53%, respectively, to have creatinine clearances below 80 ml/min by the Cockcroft-Gault formula. Our results in terms of serum creatinine values are, however, in keeping with previous estimates; for example, we found that creatinine above 1.25 mg/dl occurred in 23% of white men and 3.1% of white women, above 1.67 mg/dl in 1.6% and 0.4%, respectively (Figure 4).

We did not anticipate the finding of such large proportions of the nondiabetic population having clearance estimates below 80 ml/min or ml/min per 1.73m^2, and we sought alternative explanations for these results. We consider three potential explanations. First, the prediction equations may not perform well in the general population. The MDRD formula was derived in patients with CRI (23), and the Cockcroft-Gault formula in hospitalized white men (24); both have been validated in CRI (23) and in hypertensive African Americans (25,35) but not in community-based samples. However, by categorizing the data so that all patients with normal or near-normal clearance are counted in the >80 ml/min (or ml/min per 1.73m^2) stratum, any effect of lack of precision of clearance estimates at the higher (normal) end of the range (underrepresented in validation studies) is minimized. The association we observed between age and clearance may be an artifact arising from the age term, which occurs in both the Cockcroft-Gault and MDRD formulae, a problem sometimes referred to as mathematical coupling. To examine this issue, we performed the additional analyses on the basis of the Couchoud cutpoints (which are gender- but not age-specific) and on reciprocal creatinine (without adjustment for age or gender). As expected, age effects are less prominent in these analyses, but still occur. Comparison of the results using Couchoud cutpoints (Figure 3) with those using reciprocal creatinine cutpoints (Figure 4) confirms that use of creatinine-based cutpoints that are not gender-specific will consistently underestimate renal insufficiency in women, and, if applied, they would lead to substantial underrecognition of low GFR in women. Failure to take gender into account when interpreting serum creatinine may account for the increased risk of late initiation of dialysis in women (36). We believe that using the Couchoud cutpoints might result in overestimation of GFR in older people. Reduction of creatinine production with advancing age is well documented (37); therefore, cutpoints in serum creatinine that disregard age are inherently biologically implausible. Cou-

Table 4. Relationship between MDRD GFR and Cockcroft-Gault (CG) creatinine clearance in white and black participants[a]

MDRD GFR (ml/min per 1.73 m^2)	CG CrCl (ml/min)							
	White Participants				Black Participants			
	<30	30 to 59	60 to 79	≥80	<30	0 to 59	60 to 79	≥80
<30								
n	**31**	6			**14**	1		
% within MDRD GFR category	**74**	26			**95**	5.1		
% within CG CrCl category	**23**	0.5			**37**	0.2		
30 to 59								
n	140	**1082**	319	112	27	**174**	29	13
% within MDRD GFR category	4.4	**56**	27	13	11	**69**	14	6.7
% within CG CrCl category	74	**54**	15	2.9	53	**35**	2.9	0.5
60 to 79								
n	11	790	**1440**	1761	5	237	**403**	433
% within MDRD GFR category	<0.1	13	**35**	53	0.4	18	**38**	44
% within CG CrCl category	2.9	43	**67**	42	10	49	**44**	18
≥80								
n		56	452	**3231**		79	477	**1928**
% within MDRD GFR category		0.9	12	**87**		2.5	18	**80**
% within CG CrCl category		2.5	18	**56**		17	54	**82**

[a] The number of participants and the percentages that would be classified into the same clearance category by both estimating equations are shown in bold. Numbers and percentages for noncongruent results (*i.e.*, participants who would be categorized differently by the two formulae) are also shown. *n* represents the actual number of participants in each cell (*i.e.*, unweighted data), whereas percentages are derived from weighted analyses. MDRD GFR estimated according to MDRD Equation 7. CG CrCl Cockcroft-Gault creatinine clearance.

choud *et al.* (26) reported that they had validated their cutpoints in age-specific subgroups, but data were not provided, and it is unlikely that this study had sufficient power to examine this question. In summary, though there is no direct evidence of validity of the formulae in community-based samples, they are not known to be consistently biased (summarized in reference 25), and they represent the best available option for the estimation of clearance in large studies.

The second possible explanation for our findings involves interlaboratory variation. Creatinine measurements from different laboratories, even using the same technique, may differ systematically by as much as 0.1 to 0.2 mg/dl (38–40). A difference of this magnitude between the laboratory used in the validation of the MDRD and Cockcroft-Gault equations and that used in NHANES III would have a large effect on these results. Using measured creatinine, 58% of the total adult nondiabetic black and white US population had MDRD GFR below 80 ml/min per 1.73m^2, 13% below 60 ml/min per 1.73m^2, and 0.26% below 30 ml/min per 1.73m^2. These results were derived from analyses performed according to the analytic guidelines recommended by the NCHS for NHANES III. However, if NHANES III–measured creatinine were systematically as much as 0.2 mg/dl (17.7 μmol/L) higher than MDRD-measured creatinine, these proportions would decrease to 21%, 4%, and 0.17%, respectively. The effect of this correction is most marked in terms of altering the classification of patients at the 80–ml/min per 1.73m^2 cutpoint. However, even with a correction of this magnitude, the proportion of the population with clearance below 80 ml/min per 1.73m^2 is still unexpectedly high. Furthermore, if the results presented here are biased (compared with the laboratory used in MDRD validation) by interlaboratory variation, one might anticipate that creatinine results similar to those from the NHANES III reference laboratory would be obtained by at least some clinical laboratories. Results from such laboratories would, if translated into clearances, result in the identification of large proportions of patients with low clearances. Though the importance of issues of measurement methodology and calibration in research studies has been recognized (40), the importance of these factors in the identification of low GFR in community practice has not previously been emphasized. We suggest that recommending that laboratories report a calculated clearance estimate with each creatinine measurement (41) is premature until further study has examined the implications of widespread introduction of this practice.

A third possibility is that limitations of study design have led to biased estimation of clearance. The predictions of clearance reported here are based on single random creatinine measurements without reference to hydration status or diet. We are not aware of any studies of test-retest reliability or day-to-day variation in serum creatinine, but relative stability at a sample level over years has been documented (42), and acute renal failure is a rare event (43). Though the degree of chronicity of low GFR cannot be ascertained with certainty for an individual sampled in NHANES III, it seems unlikely that large numbers of participants would have had significant creatinine elevations (above their baseline) on the day of their evaluation. Sampling was performed during the daytime, when GFR is highest (44).

Sampling of noninstitutionalized individuals only, as in NHANES III, would be more likely to exclude people with higher morbidity and bias results toward higher estimates of clearance. We used fasting glucose to exclude people with undiagnosed diabetes. For half the cohort, this was measured in the afternoon. Some people with undiagnosed diabetes, who would likely have been detected had they been studied in the morning are missed when glucose is measured in this way (1.4%) (45). However, this could not have resulted in a large bias. Albumin in NHANES III was measured by the bromcresol purple (BCP) method, whereas albumin was measured by bromcresol green (BCG) in the MDRD derivation and validation. In the general population, BCG results tend to be somewhat lower than BCP, whereas BCP results tend to be lower in uremic patients (summarized in reference 46). Though this might have resulted in some bias, the absolute magnitude of this effect is of the order of a few ml/min per $1.73m^2$ only and applies to the MDRD results only, because albumin is not included in the Cockcroft-Gault formula. Finally, some of the participants in the lowest clearance categories for each measurement method (GFR $<$ 30 ml/min or $<$ 30 ml/min per $1.73m^2$) would presumably have been receiving renal replacement therapy. This information was not captured in the dataset. However, in comparison with the point-prevalence rate of 697 per million population for ESRD reported by the United States Renal Data System (USRDS) for 1990 (the mid-year of the NHANES III study) (47), we observed prevalences in the range of 2000 to 3000 per million population (Figure 1) in the lowest clearance categories. This suggests that people with ESRD are likely to represent a substantial minority of those in the lowest categories of clearance studies based on these data.

The cross-sectional design implies that the relationship between renal function and age must be interpreted with caution. For this reason, we have reported the relationship between GFR and age as observed prevalences by decade, rather than attempting an explanatory regression analysis.

The findings of consistently higher prevalence of low GFR (by MDRD formula) in white compared with black participants is intriguing. The formula upwardly adjusts clearance estimates on the basis of black race; therefore, it may simply reflect a numerical artifact (the difference is not seen in clearance by Cockcroft-Gault formula). However, since the MDRD formula has been adequately validated in black people (25), the finding may represent a true difference. If this is the case, then given the excess prevalence of ESRD in black Americans (47), it is possible that reduced GFR of any level in a black person carries a substantially worse prognosis than the equivalent for a white person.

With these caveats, we believe that our results have important implications for our understanding of renal disease and for the organization of renal services. The difference in order of magnitude between the prevalence of low GFR and the prevalence of ESRD (*e.g.*, for white males in their 60s, 0.2% have ESRD (1), 0.6% have MDRD GFR below 30 ml/min per $1.73m^2$, but 27% have GFR between 30 and 59 ml/min per $1.73m^2$) prompts the hypothesis that not all low GFR carries the same prognosis. This may be particularly important in the evaluation of older people. Though the Boston Longitudinal Study of Aging documented a clearance of 97 ml/min in healthy octogenarians (31,32), these participants were highly selected (self-recruited middle-aged white men, generally of middle and upper socioeconomic status, without major diseases) and for this reason may not be representative of either normal aging or normal healthy aging. We have shown that low GFR may be very common in older age. Data for older people from other studies are consistent with our findings (15,37,48,49). We postulate that low GFR in some older people may not be associated with the same risks for progression that might coexist with the equivalent GFR in a younger person. This might be because the range of pathologic diagnoses is different in older people or because loss of GFR due to senescence (50) carries a better prognosis than that of other pathologic entities or because the metabolic load on the impaired kidney is also reduced with increasing years (51,52), which might ameliorate the pathologic processes (53,54) associated with single-nephron hyperfiltration in remnant kidneys. In addition, the risk of ESRD will be less than in a younger person, because of the shorter expected period of subsequent life and the competing risks of other diseases.

GFR in the 30- to 80-ml/min range in older people is often accompanied by a serum creatinine within the laboratory normal range (37,41) and may go unrecognized, uninvestigated, and unreferred (41). Only a minority of patients with an elevated creatinine are referred to nephrologists (55,56). We postulate that referred populations are selected for more progressive disease, more advanced disease, and perhaps also on the basis of fewer competing risks (56) compared with those not referred. Referral to a nephrologist is needed when a specifically treatable etiology is possible, when CRI is progressive, or when therapeutic goals cannot be met. Patients with very low GFR (perhaps below 30 ml/min; references 13,57) should also be referred because of the possibility of dialysis treatment and the probable benefits of predialysis nephrologic care (8–11). Strategies to enhance referral in these circumstances warrant immediate attention. However, it seems that low GFR in the range of 30 to 80 ml/min per $1.73m^2$ may be much more common in the population than one would anticipate from previous studies of healthy aging. It may not be valid to generalize findings from studies in referred populations to these unreferred patients. We believe that further community-based research is needed into the prevalence of risk factors for progression of disease, the rate of progression of disease, and optimal methods of identifiying those at risk for progression to ESRD.

In summary, we believe that this work has two major implications. First, widespread implementation of predicted clearance in laboratory reports has the potential to increase identification of low GFR by primary physicians and potential referral to nephrologists by orders of magnitude. Further study is required to determine the characteristics of unreferred patients with low GFR, and the optimal further assessment of such patients is not known. For these reasons, we believe that laboratory-generated clearance reports cannot be recommended without further study. Second, low clearance may be

much more prevalent than previously suspected and may not always reflect high risk of progression to ESRD. Optimal diagnostic and management strategies may differ for unreferred people with low clearance compared with those currently referred at similar clearance levels. Research into the identification of currently unreferred people who are at high risk for progression to ESRD is urgently needed.

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