Moderate Chronic Kidney Disease and Cognitive Function in Adults 20 to 59 Years of Age: Third National Health and Nutrition Examination Survey (NHANES III)

Susan M. Hailpern,* Michal L. Melamed,*† Hillel W. Cohen,* and Thomas H. Hostetter†

Departments of *Epidemiology and Population Health and †Medicine, Albert Einstein College of Medicine, Bronx, New York

ABSTRACT

Previous studies among elderly suggest an association between chronic kidney disease (CKD) and cognitive impairment. The purpose of this study was to determine whether moderate CKD is associated with cognitive performance among young, healthy, ethnically diverse adults. Three computerized cognitive function tests of visual-motor reaction time (Simple Reaction Time), visual attention (Symbol Digit Substitution), and learning/concentration (Serial Digit Learning) were administered to a random sample of participants, aged 20 to 59 yr, who completed initial interviews and medical examination in the Third National Health and Nutrition Examination Survey (NHANES III). Participants for this study ($n = 4849$) completed at least one cognitive function test. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation. Moderate CKD was defined as estimated GFR (eGFR) 30 to 59 ml/min per 1.73 m^2. Unadjusted, residual-adjusted, and multivariate-adjusted logistic regression models were used. The cohort was 49.0% male and 11.6% black, and median (interquartile range) age was 36 yr (27 to 45) and eGFR was 107.9 ml/min per 1.73 m^2 (95.0 to 125.4). There were 31 (0.8%) prevalent cases of moderate CKD. Models were adjusted for residual effects of age, gender, race, diabetes, and other known potential confounders. In multivariate models, moderate CKD was not significantly associated with reaction time but was significantly associated with poorer learning/concentration (odds ratio 2.41; 95% confidence interval 1.30 to 5.63) and impairment in visual attention (odds ratio 2.74; 95% confidence interval 1.01 to 7.40). In summary, among those in a large nationally representative sample of healthy, ethnically diverse 20- to 59-yr-old adults, moderate CKD, reflected by eGFR 30 to 59 ml/min per 1.73 m^2, was significantly associated with poorer performance in visual attention and learning/concentration.

J Am Soc Nephrol 18: 2205–2213, 2007. doi: 10.1681/ASN.2006101165

High rates of cognitive impairment and dementia have been reported in many but not all studies of patients with ESRD.[1–7] Factors that may contribute to cognitive impairment in those with ESRD include a high prevalence of traditional cardiovascular risk factors that cause subclinical damage and uremia and its associated metabolic disturbances.[8] Increased risk for stroke[9] and carotid atherosclerosis[10,11] among those with ESRD may also predispose them to cognitive impairment.

Many of the same factors that are proposed as contributors to cognitive impairment in patients with ESRD are also observed, although to a lesser degree, in patients with moderate kidney impairment.[12–14] Furthermore, several recent studies have reported an association between both dementia and cognitive impairment and moderate kidney dysfunction.[15–17] For example, Seliger *et al.*[15] found elevated serum creatinine to be associated with in-

Received October 27, 2006. Accepted April 15, 2007.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Susan M. Hailpern, Albert Einstein College of Medicine, 1300 Morris Parkway, Belfer 1006A, Bronx, NY 10461. Phone: 718-430-3740; Fax: 718-430-3747; E-mail: shailper@aecom.yu.edu

creased risk for dementia among elderly individuals. Chronic kidney disease (CKD), defined as an estimated GFR (eGFR) <60 ml/min per 1.73 m^2, was found to be associated with cognitive impairment among the elderly[17] and among menopausal women with coronary artery disease.[16] These studies, however, were conducted in elderly cohorts with comorbid conditions and little ethnic diversity; therefore, they were not completely generalizable to the 7.4 million estimated Americans with moderate CKD (eGFR 30 to 59 ml/min per 1.73 m^2).[18] The goal of this study, therefore, was to examine the association between moderate CKD and cognitive function using cross-sectional data from the Third National Health and Nutrition Examination Survey (NHANES III), a representative sample of the US population. The cognitive function tests were administered to a random half-sample of 20- to 59-yr-olds who completed the initial interview and medical examination.

RESULTS

Among the 4849 individuals who participated in at least one of the NHANES III cognitive tests, 31 (0.8%) had moderate CKD (eGFR 30 to 59 ml/min per 1.73 m^2). This represents approximately 1 million Americans between the ages of 20 and 59 yr. Table 1 presents participant characteristics for those with and without CKD and for the entire sample. Median age of the participants was 36 yr (interquartile range [IQR] 27 to 45). Men constituted 49.0% of the cohort, and 11.6% were black. Compared with those with normal kidney function, those with

Table 1. Characteristics of study participants by eGFR category[a]

Characteristic	eGFR (ml/min per 1.73 m^2)		Total (n = 4849)	P
	≥60 (n = 4818)	<60 (n = 31)		
Age (yr)	36 (27 to 45)	51 (42 to 56)	36 (27 to 45)	<0.001
Male gender	49.4	46.2	49.0	0.82
Black race	11.1	4.3	11.6	<0.001
BMI (kg/m^2)	26.2 (22.9 to 30.3)	28.3 (24.5 to 32.1)	26.2 (22.8 to 30.3)	0.03
Diabetes	4.7	13.9	4.8	0.33
SBP (mmHg)	117 (109 to 126)	134 (119 to 153)	117 (109 to 126)	<0.001
DBP (mmHg)	74 (67 to 81)	82 (77 to 88)	74 (67 to 81)	<0.01
Hypertensive (≥140/90)	13.3	56.3	13.7	<0.01
Current smoker	32.2	31.8	32.1	0.97
Physical activity (active)	81.6	79.9	81.4	0.64
Total METS/mo	50.5 (10.0 to 141.5)	45.0 (10.5 to 111.0)	50.5 (10.0 to 142.0)	0.79
<200% FPL	30.2	25.2	30.5	0.65
≥1 alcoholic drink/wk	40.5	20.4	39.8	0.01
Health status[b]				0.08
excellent	52.9	15.6	52.4	
very good	25.6	43.6	25.5	
good	17.8	18.4	18.2	
fair	3.3	22.4	3.5	
poor	0.4	0	0.4	
History of MI	1.7	0.07	1.7	0.21
History of stroke	0.06	0.04	0.5	0.78
History of CHD	2.2	11.3	2.3	0.31
Education >12 yr	45.9	38.7	45.6	0.57
CRP (mg/dl)	0.21 (0.21 to 0.40)	0.33 (0.21 to 0.77)	0.21 (0.21 to 0.40)	0.01
Serum creatinine (mg/dl)	0.77 (0.67 to 0.87)	1.37 (1.17 to 1.67)	0.77 (0.67 to 0.87)	<0.001
Cholesterol (mg/dl)	194 (169 to 222)	220 (189 to 258)	194 (169 to 223)	<0.001
HDL (mg/dl)	49 (40 to 59)	42 (35 to 55)	49 (40 to 59)	0.02
LDL (mg/dl)[c]	121 (98 to 144)	124 (112 to 152)	121 (97 to 144)	0.31
BUN (mg/dl)	12 (10 to 15)	20 (18 to 28)	12 (10 to 15)	<0.001
Hematocrit (%)	41.5 (38.5 to 44.6)	40.0 (37.9 to 42.3)	41.5 (38.5 to 44.6)	0.12
Microalbuminuria[d]	8.8	38.5	8.4	0.03
eGFR (ml/min per 1.73 m^2)	108.3 (95.6 to 125.4)	55.0 (45.3 to 57.9)	107.9 (95.0 to 125.4)	<0.001

[a]Represents participants in the study sample who had valid test results on at least one of three cognitive tests. Continuous variables are median (interquartile range) with P values calculated by Wilcoxon rank-sum test between the chronic kidney disease (CKD) categories and do not take into account the complex sampling design of the Third National Health and Nutrition Examination Survey (NHANES III). Categorical variables are percentages with P values calculated by χ^2 and take into account the complex sampling design of NHANES III. BMI, body mass index; BUN, blood urea nitrogen; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic BP; eGFR, estimated GFR; FPL, federal poverty level; METS, metabolic equivalents; MI, myocardial infarction; SBP, systolic BP.
[b]P for difference between excellent/good health *versus* fair/poor health between eGFR groups. Proportions may not total 100% because of rounding.
[c]LDL missing on 55% of cohort because of nonadherence to fasting laboratory requirements.
[d]Microalbuminuria defined by gender-specific cut points: ≥17 μg/mg for men and ≥25 μg/mg for women.

moderate CKD were more likely to be older; have higher systolic and diastolic BP; be hypertensive; have higher total serum cholesterol; have higher blood urea nitrogen (BUN), body mass index, C-reactive protein, and albumin-to-creatinine ratio; and have lower HDL. Those with moderate CKD were less likely to be black and consume one or more alcoholic drinks per week. There were no significant differences in comorbid conditions, education, or cardiovascular disease between the eGFR groups (Table 1).

Unadjusted mean cognitive function test scores by eGFR category are presented in Table 2. All three cognitive test scores showed significantly poorer performance (longer reaction time/more errors) for those with moderate CKD.

Moderate Kidney Impairment and Cognitive Function

Scores on each of the three cognitive function variables were not normally distributed. No transformation made it possible to satisfy the normality assumption for linear regression; therefore, cognitive function variables were categorized into quartiles. Logistic regression models were constructed to assess whether eGFR predicted the "abnormal" quartile (defined as the quartile with the longest reaction time) compared with the remaining three quartiles with and without adjustment for other covariates.

Simple Reaction Time Test.

Among the 4721 individuals in this study sample, 27 had moderate CKD. Median age was 36 yr (IQR 27 to 44), 49.2% were male, 11.0% were black, and 2.8% had diabetes. Scores on the Simple Reaction Time Test (SRTT) ranged from 154.0 to 209.1 milliseconds in the shortest reaction time (first) quartile, 209.1 to 228.7 milliseconds in the second quartile, 228.7 to 255.5 milliseconds in the third quartile, and 255.6 to 660.0 milliseconds in the longest reaction time ("abnormal") quartile. There was no statistically significant association between scoring in the longest reaction time ("abnormal") quartile of the SRTT and moderate CKD on unadjusted, residual analysis, or multivariable analysis (Table 3).

Symbol Digit Substitution Test.

Among the 4865 individuals in this study sample, 27 (0.6%) had moderate CKD. Median age was 36 yr (IQR 27 to 44), 49.1% were male, 10.9% were black, and 2.8% had diabetes. Scores on the Symbol Digit Substitution Test (SDST) ranged from 1.38 to 2.29 seconds for the shortest reaction time (first) quartile, 2.30 to 2.66 seconds for the second quartile, 2.67 to 3.15 seconds for the third quartile, and 3.16 to 22.2 seconds for the longest reaction time ("abnormal") quartile. Odds for scoring in the longest reaction time ("abnormal") quartile of the SDST were significantly associated with moderate CKD ($P = 0.01$) in the unadjusted model. Odds ratios (OR) remained statistically significant for poorer performance on SDST in multivariate analysis, although the association was attenuated ($P = 0.05$; Table 4).

Serial Digit Learning Test.

Among the 4676 individuals in this study sample, 30 (0.6%) had moderate CKD. Median age was 36 yr (IQR 27 to 45), 49.3% were male, 10.8% were black, and 4.8% had diabetes. Scores on the Serial Digit Learning Test (SDLT) ranged from zero to one total error committed during the trials for the smallest number of errors (first) quartile, two to three errors committed for the second quartile, five to nine errors committed for the third quartile, and 10 to 16 total errors committed during the trials for the largest number of errors ("abnormal") quartile. OR indicate a significant association of scoring in the

Table 2. Cognitive function test results by eGFR category[a]

Cognitive Test	eGFR (ml/min per 1.73 m^2)		Total	*P*
	≥60	<60		
SRTT (ms)	229.8 (209.8 to 257.7)	237.9 (227.8 to 267.8)	230.1 (210.0 to 255.5)	0.04
SDST (s)	2.66 (2.29 to 3.15)	3.45 (2.95 to 4.39)	2.67 (2.30 to 3.15)	<0.001
SDLT (errors committed)	4 (2 to 9)	8.5 (2.5 to 14)	4 (2 to 9)	0.04

[a]Data are median (IQR); *P* values are calculated by Wilcoxon rank-sum test between the CKD categories and do not take into account the complex sampling design of NHANES III. SDLT, Serial Digit Learning Test; SDST, Symbol Digit Substitution Test; SRTT, Simple Reaction Time Test.

Table 3. eGFR and cognitive function by SRTT[a]

Parameter	Unadjusted OR (95% CI), *P*	Residual Adjusted OR (95% CI), *P*	Full Model OR (95% CI), *P*
eGFR <60 ml/min per 1.73 m^2	0.78 (0.26 to 2.30), 0.62	0.70 (0.26 to 1.93), 0.50	0.64 (0.24 to 1.76), 0.47
Age (yr)	—	1.02 (1.00 to 1.03), 0.01	1.01 (1.00 to 1.03), 0.02
Male gender	—	0.59 (0.45 to 0.79), 0.01	0.64 (0.48 to 0.85), 0.02
Black race	—	1.85 (1.45 to 2.36), 0.01	1.38 (1.07 to 1.78), 0.01
Diabetes	—	—	1.52 (0.89 to 2.62), 0.11
Education (>12 yr)	—	—	0.59 (0.41 to 0.85), 0.02
<200% FPL	—	—	0.86 (0.79 to 0.94), 0.01
Activity (yes)	—	—	0.73 (054 to 0.98), 0.21
CRP	—	—	1.04 (0.84 to 1.28), 0.63

[a]Odds ratios (OR) for scoring in the "abnormal" (fourth) quartile of SRTT (≥255.6 ms) compared with lower three quartiles (154.0 to 255.5 ms).

Table 4. eGFR and cognitive function by SDST[a]

Parameter	Unadjusted OR (95% CI), *P*	Residual Adjusted OR (95% CI), *P*	Full Model OR (95% CI), *P*
eGFR<60 ml/min per 1.73 m^2	4.16 (1.41 to 12.28), 0.01	2.33 (0.84 to 6.46), 0.10	2.74 (1.01 to 7.40), 0.05
Age (yr)	—	1.08 (1.07 to 1.10), 0.01	1.09 (1.09 to 1.12), 0.01
Male gender	—	1.58 (1.18 to 2.16), 0.01	2.06 (1.46 to 2.90), 0.01
Black race	—	3.00 (2.41 to 3.74), 0.01	1.57 (1.59 to 2.64), 0.01
Diabetes	—	—	1.57 (0.99 to 2.51), 0.06
Education (>12 yr)	—	—	0.16 (0.12 to 0.23), 0.01
<200% FPL	—	—	2.39 (1.77 to 3.21), 0.01
Activity (yes)	—	—	0.54 (0.41 to 0.72), 0.01
SBP (mmHg)	—	—	0.99 (0.98 to 1.00), 0.24
Hyperlipidemia	—	—	0.84 (0.63 to 1.15), 0.29

[a]OR for scoring in the "abnormal" (fourth) quartile of the SDST (≥3.16 seconds) compared with lower three quartiles (1.38 to 3.15 seconds).

largest number of errors ("abnormal") quartile of the SDLT with moderate CKD in unadjusted and multivariate models ($P = 0.02$ and 0.04, respectively), although multivariate adjustment attenuated the association (Table 5).

There were no statistically significant interactions of eGFR with any covariate for all models tested.

Sensitivity Analysis

To determine whether the presence of diabetes may have biased the observed association between eGFR and cognitive function, we conducted a sensitivity analysis in a low-risk subset of individual without diabetes. Among the 4512 individuals who did not have diabetes and were in the SRTT study sample, 25 had moderate CKD. There remained no statistically significant association between SRTT and eGFR multivariable analysis, and point estimates remained similar (OR 0.68; 95% confidence interval [CI] 0.24 to 1.92; $P = 0.46$) to that of the full cohort.

Among the 4481 individuals who did not have diabetes and were in the SDST study sample, 25 had an eGFR <60 ml/min per 1.73 m^2. The association between moderate CKD and cognition was slightly attenuated from that of the full cohort (OR 2.59; 95% CI 0.94 to 7.18) and of borderline significance in a multivariate model ($P = 0.06$).

Among the 4373 individuals who did not have diabetes and were in the SDLT study sample, 25 had CKD. Although the association between eGFR remained in the same positive direction, with the smaller number of outcome event and commensurate lower statistical power, it was attenuated from that of the full cohort and was no longer statistically significant (OR 1.64; 95% CI 0.56 to 4.81; $P = 0.36$).

Although microalbuminuria (dichotomized at gender-specific cut points) was significantly associated with SDST in an unadjusted model (OR 1.65; 95% CI 1.20 to 2.26), the association did not reach statistical significance in an adjusted model (OR 1.18; 95% CI 0.83 to 1.71). No other statistically significant associations were found between SRTT or SDLT and microalbuminuria in unadjusted or adjusted models.

DISCUSSION

In a random sample of NHANES III participants who were aged 20 to 59 yr and were administered three computerized tests to evaluate cognitive functioning, moderate CKD, as reflected by eGFR 30 to 59 ml/min per 1.73 m^2, was associated with poor cognitive function in two of the three tests: SDST and SDLT. Furthermore, these associations were independent of the residual effects of age, race, gender, diabetes, and other factors that are known to confound the association between CKD and cognitive function.

Previous studies of cognitive impairment and kidney disease reported similar results.[1,5,8,15–17] However, because many cohorts in previous studies were elderly, had ESRD, and lacked ethnic diversity, any direct comparison should be made with caution.

Similar to the null findings reported here on the SRTT, the

Table 5. eGFR and cognitive function by SDLT[a]

Parameter	Unadjusted OR (95% CI), *P*	Residual Adjusted OR (95% CI), *P*	Full Model OR (95% CI), *P*
eGFR<60 ml/min per 1.73 m^2	3.61 (1.22 to 10.65), 0.02	2.73 (0.95 to 7.83), 0.06	2.41 (1.30 to 5.63), 0.04
Age (yr)	—	1.04 (1.03 to 1.05), 0.01	1.04 (1.03 to 1.06), 0.01
Male gender	—	1.10 (0.85 to 1.44), 0.46	1.26 (0.94 to 1.68), 0.12
Black race	—	2.44 (2.00 to 2.99), 0.01	1.68 (1.35 to 2.07), 0.01
Diabetes	—	—	1.54 (1.01 to 2.36), 0.08
Education (>12 yr)	—	—	0.25 (0.20 to 0.33), 0.01
Activity (yes)	—	—	0.58 (0.44 to 0.77), 0.01
CRP	—	—	1.19 (1.03 to 1.38), 0.02
<200% FPL	—	—	2.03 (1.03 to 2.64), 0.01

[a]OR for scoring in the "abnormal" (fourth) quartile of the SDLT (≥10 errors committed) compared with lower three quartiles (zero to nine errors committed).

National Cooperative Dialysis Study (NCDS) also reported no significant differences on the Choice Reaction Time test (a measure of psychomotor speed). The NCDS randomly assigned hemodialysis patients to either a low or high BUN target level with either long or short dialysis time. Cognitive function was examined as part of the study. No differences in reaction time between those with high or low BUN levels were found, although electroencephalogram abnormalities were noted in the high BUN group.[19]

Also similar to findings reported here, Seliger *et al.*[15] found moderate kidney insufficiency, defined as an elevated serum creatinine, to be associated with a 37% increased risk for dementia among community-dwelling individuals who were 65 yr and older and participating in the Cardiovascular Health Cognition Study. In the same study, kidney function analyzed as a continuous variable was associated with a 26% increased risk for dementia.

In a cross-sectional study of primarily white postmenopausal women who had established coronary artery disease and participated in the Heart Estrogen/Progestin Study, Kurella *et al.*[16] found low eGFR significantly associated with impaired global cognitive function, executive function, language, and memory. The association was independent of residual effects of age and race and other confounding variables.

Also consistent with results reported here, Kurella *et al.*[17] showed that an eGFR <60 ml/min per 1.73 m^2 was associated with cognitive impairment in a cohort of Medicare-eligible individuals who participated in the Health, Aging and Body Composition Study. The risk for cognitive impairment was greater for those with lower eGFR.

Biologic mechanisms for the observed association between moderate kidney impairment and cognitive function cannot be determined by this study and are likely multifactorial. Traditional vascular risk factors that are associated with cognitive impairment in the general population, such as age, hypertension, diabetes, and dyslipidemia,[20–22] are often more prevalent among those with CKD. These risk factors for stroke may account for decreased cognitive function through subclinical damage to the central nervous system (CNS). Results presented here, however, suggest that cognitive impairment was independent of these factors in an otherwise healthy adult population.

Another explanation for the association between kidney and cognitive dysfunction is the accumulation of solutes. This explanation would suggest a potentially reversible cause, making this explanation tantalizing. A recent small study of patients who were on nocturnal hemodialysis revealed improvements in cognitive function after initiation of nocturnal dialysis, suggesting a reversible cause to the impaired cognitive function.[23] Other studies suggested that elevated plasma homocysteine levels may also be a potential vascular risk factor for dementia and cardiovascular disease in the general population.[24–27] Elevated homocysteine is present in 85% of dialysis patients[8] and also common among those with moderate CKD.[28] Increased oxidative stress and cognitive impairment have been seen in the general population[26] and are also associated with CKD.[28]

This study has a number of limitations. Because only three cognitive function tests were administered as part of NHANES III, this study cannot provide a comprehensive cognitive assessment of moderate kidney impairment and cognitive function across the full range of cognitive function. One of the three cognitive tests in this study (SRTT) did not have consistent results with the other two tests. However, the null findings were consistent with those of other investigators, suggesting that the difference with the other tests may be related to the distinct cognitive domain assessed by the SRTT that might not be related to kidney impairment. Direct comparison with other tests of cognitive function is also not possible. Another limitation is that there was an overall test nonresponse rate of 9%. Nonresponse rates increased with age, decreased with educational level, were higher for men, and were lower for non-Hispanic white individual than other ethnic groups.[29] Although it is impossible to determine whether eGFR status had any influence on nonresponse, it is possible that nonresponse rates may have introduced some bias into the study.

Most known correlates of kidney impairment were adjusted for in these analyses. However, other confounders, such as vascular disease, which we could not adjust for in these analyses, might also explain these results. Plasma homocysteine was measured on a small subset of the NHANES III cohort during the second laboratory examination and therefore not suitable for inclusion in this analysis. In addition, parathyroid hormone levels, often elevated in those with CKD, were not measured in NHANES III and could not be adjusted for in these analyses. Furthermore, although this study found an association between cognitive function and moderate CKD, the cross-sectional nature of the study makes it impossible to suggest any inferences as to the cause of the observed findings.

There was a relatively small number (0.8%) with CKD in this younger, relatively healthy sample, which limited the ability to perform subgroup analyses. The small number of individuals with moderate CKD made it impossible to stratify by National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI)-defined eGFR categories to assess whether there was a threshold effect. Also, caution should be taken when assuming a relationship between moderate CKD and cognition because of the low prevalence of CKD. Nonetheless, even with the low prevalence of CKD, the statistical significance at an α of 0.05 was observed.

Despite the limitations, our study has several strengths. They include the large, nationally representative, educationally and ethnically diverse sample of healthy 20- to 59-yr-olds. The extensive laboratory data and extensive medical history data collected using standardized methods of NHANES III allowed us to adjust for potential confounders.

CONCLUSION

Moderate CKD, as reflected by an eGFR 30 to 59 ml/min per 1.73 m^2, was significantly associated with poorer performance in visual attention, learning, and concentration in a large, nationally representative sample of healthy, ethnically diverse 20- to 59-yr-olds. These findings provide an important extension to the existing literature on older adults with CKD, and adults with ESRD and may provide important insights into the early development of cognitive impairment that predate comorbid conditions that are prevalent in the elderly and those with more advanced kidney disease.

CONCISE METHODS

Participants

NHANES III was conducted at 89 survey locations between 1988 and 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. This national survey of the civilian, noninstitutionalized US population aged 2 mo and older used a complex, stratified, multistage probability design with oversampling among individuals who were ≥60 yr of age, non-Hispanic black, and Mexican American to enhance the precision among these groups. The survey was designed to obtain nationally representative information on the health and nutritional status of the US population by means of interview and physical examination.[30,31] CNS (cognitive) function evaluation was administered to a random half-sample of NHANES III examinees who were aged 20 to 59 yr and participated in the mobile component of the NHANES III examination ($n = 5662$). Cognitive tests were systematically administered to those with odd-numbered survey identification numbers. Cognitive testing was not administered to those who could not speak English or Spanish or to those who were legally blind.[29]

Cognitive Function Testing and Definition of Outcomes

Three computerized tests were administered to evaluate cognitive functioning. The tests were components of the *Neurobehavioral Evaluation System 2*, a system of neurobehavioral tests that were developed by Baker and Letz[32,33] and are used in epidemiologic studies. Trained technicians administered all cognitive tests using a standardized protocol in both English and Spanish. Each test was preceded by a practice phase.

The SRTT is a measure of visual-motor speed, or response time, measured in milliseconds. Participants were instructed to press a button as quickly as possible when a solid square appeared in the center of a blank computer screen. A total of 50 trials were administered. The SRTT was scored as the average reaction time, excluding the first 10 trials. NHANES III has determined a reaction time ≥750 or ≤50 milliseconds to be invalid. Furthermore, individuals with mean scores representing <20 trials are considered invalid by NHANES III.[29,34]

The SDST is a test of coding ability and visual attention. A set of nine symbols is matched to the digits one through nine. The participant is shown a series of symbols and must match the symbol with the correct corresponding digit as quickly as possible. A total of four trials were conducted with a different pairing of digits and symbols. The SDST was scored as the average total time, in seconds (s), for completion of the four trials.[29,32–34]

The SDLT is a test of learning recall and concentration. Participants were presented with a series of digits displayed on a computer screen, one at a time, for 6 seconds, with a 6-second interval between digits. Once all digits were displayed, participants were required to enter the entire sequence on the keyboard in the order in which they were presented. Testing stopped when participants responded correctly on two consecutive trials or after a total of eight trials. The SDLT was scored as the sum of the errors committed during the trials.[29,32–34]

Estimation of Kidney Function

GFR, an estimate of kidney function was estimated (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula, which is based on baseline age, gender, race, and serum creatinine concentration.[35] Serum creatinine measurements were calibrated to the Cleveland Clinic laboratory by subtracting 0.23 mg/dl.[36] eGFR was dichotomized using a threshold value of 30 to 59 ml/min per 1.73 m^2 to define moderate CKD. This threshold was chosen on the basis of current National Kidney Foundation guidelines defining CKD.[37] Microalbuminuria was defined by gender-specific cut points using ≥17 μg/mg for men and ≥25 μg/mg for women.[37]

Covariates

Variables that were known or hypothesized to be associated with cognitive function, CKD, or both were chosen from the NHANES III data files. Demographic variables including age, gender, and self-reported race (coded as non-Hispanic black [black] *versus* others), educational level (>12 yr), medication use (use of blood glucose regulators, antidepressants, lipid-lowering medication, antihypertensive medication, or drugs that effect the CNS), smoking status (current or nonsmoker), ethanol use (one or more drinks per week), and self-reported current health status (excellent, very good, good, fair, and poor) were ascertained by in-person questionnaire. Physical activity was categorized as having any leisure-time activity during the past month as well as the self-reported total metabolic equivalents expended during the past month. History of myocardial infarction, stroke, and all cardiovascular disease (myocardial infarction, stroke, and/or congestive heart failure) was ascertained by self-report. Socioeconomic status was dichotomized at <200% federal poverty level ("poor or near poor") using methods similar to those described by Martins *et al.*[38]

Physical measures including systolic and diastolic BP, height, and weight were obtained during physical examination. Body mass index was calculated as kg/m^2. Participants were considered hypertensive when they reported having been told by a doctor that they had high BP, reported taking antihypertensive medication, or had an average BP ≥140/90 mmHg. Diabetes was defined as a fasting plasma glucose >126 mg/dl, a self-report of diabetes, or self-report the use of blood glucose regulators. Hyperlipidemia was defined as a total cholesterol ≥240 mg/dl or self-report of taking lipid-lowering medication. Laboratory measures including serum creatinine (mg/dl), total cholesterol (mg/dl), HDL (mg/dl), BUN (mg/dl), hematocrit (%), urinary

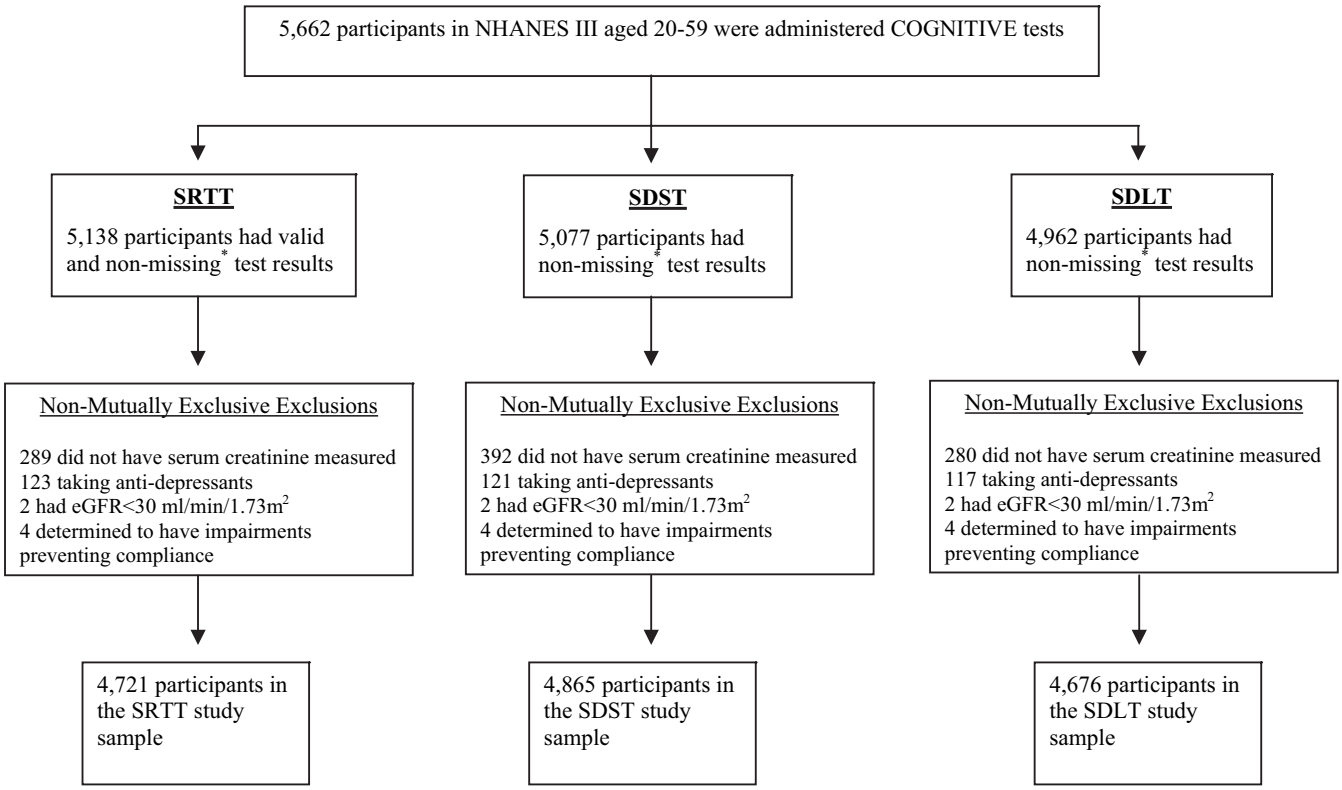

Figure 1. Schema of study sample for the Simple Reaction Time Test (SRTT), the Symbol Digit Substitution Test (SDST), and the Serial Digit Learning Test (SDLT). *Any SRTT was determined by the Third National Health and Nutrition Examination Survey (NHANES III) to be invalid when it had a reaction time ≥750 or ≤50 milliseconds. Individuals with mean SRTT scores representing <20 trials were also considered invalid by NHANES III. Missing test scores are due to nonresponse and vary by cognitive test.

albumin (μg/min), and urinary creatinine (mg/d) were obtained during laboratory examination.

Study Sample

Individuals were excluded from this study when they reported taking antidepressants, when the examining physician found evidence of disabling impairment that prevented them from complying with the examination, when they had invalid (SRTT) or missing (because of nonresponse) test results, when they had an eGFR <30 ml/min per 1.73 m^2, or when they were missing values for serum creatinine. A total of 5662 individuals were administered cognitive function tests. Of these, 5308 had serum creatinine values (93.7%). Cognitive function test scores for individuals with missing serum creatinine values did not differ significantly from those who were included in the study sample. Similarly, serum creatinine and eGFR did not significantly differ between those with complete data and those with invalid or missing test results (data not shown). Nonresponse rates varied by test; therefore, the number who completed each test is not uniform.[29] After the exclusions described, the study sample for the SRTT consisted of 4721 participants, the study sample for the SDST consisted of 4965 participant, and the study sample for the SDLT consisted of 4956 participant (Figure 1).

Statistical Analyses

A cross-sectional analysis was performed to examine the association between moderate CKD and cognitive function. Bivariate associations with dichotomized eGFR and those who participated in any of the cognitive function examinations were assessed with Wilcoxon rank-sum tests and χ^2 for continuous and categorical variables, respectively. Median (IQR) was reported for continuous variables. Proportions were reported for categorical variables.

Each cognitive function test was modeled individually. Model-building strategy followed that of previous studies that examined the association of eGFR and cognitive function.[16,17] *A priori*, it was decided that linear regression would be used to model cognitive function and eGFR. However, should a cognitive function variable not be normally distributed, then transformations of the variable would be attempted to satisfy the normality assumption. If transformations could not satisfy the normality assumption, then the results would be categorized into quartiles, because there were no established cut points for these tests.[16] The "abnormal" quartile is defined as the quartile with the longest reaction time (SRTT and SDST) or the quartile with the largest number of errors (SDLT). Logistic regression was used to compare the "abnormal" quartile with the remaining three quartiles. Because of the known association between diabetes and cognitive impairment,[39] it was decided, *a priori*, to include diabetes in all multivariable models.

Initial unadjusted models included the cognitive test as the dependent variable and eGFR. Next, models were adjusted for the residual effects of variables in the MDRD formula (age, gender, and race).[16,17] Finally, best-fit, or parsimonious, multivariable models were fit using a $P < 0.05$ as criterion for inclusion. Covariates that were considered for inclusion included all those previously mentioned. In addition, any variable that was found to change the β coefficient of eGFR $\geq$10% was included in the model. Interaction product terms with eGFR and each covariate were created and separately tested in the multivariable model including the main effects terms. Sensitivity analysis was performed in a lower risk subset by excluding those with diabetes.

All statistical analyses were performed using Stata SE 9.2 (Stata Corp, College Station, TX). All analyses for proportions and regression analyses incorporated the cognitive function sample weights to accommodate the complex sample survey design. For all analyses, P values are two-tailed with an $\alpha$of 0.05 considered for statistical significance.

ACKNOWLEDGMENTS

A poster based on these data was presented at the 2007 National Kidney Foundation Spring Clinical Meeting; April 10 to 14, 2007; Orlando, FL.

DISCLOSURES

T.H. has served as a consultant to Wyeth Pharmaceuticals once in the past 5 yr.

REFERENCES

1. Sehgal AR, Grey SF, DeOreo PB, Whitehouse PJ: Prevalence, recognition, and implications of mental impairment among hemodialysis patients. *Am J Kidney Dis* 30: 41–49, 1997
2. Souheaver GT, Ryan JJ, DeWolfe AS: Neuropsychological patterns in uremia. *J Clin Psychol* 38: 490–496, 1982
3. Hart RP, Pederson JA, Czerwinski AW, Adams RL: Chronic renal failure, dialysis, and neuropsychological function. *J Clin Neuropsychol* 5: 301–312, 1983
4. Wolcott DL, Wellisch DK, Marsh JT, Schaeffer J, Landsverk J, Nissenson AR: Relationship of dialysis modality and other factors to cognitive function in chronic dialysis patients. *Am J Kidney Dis* 12: 275–284, 1988
5. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, Smith GE, Hochhalter AK, Collins AJ, Kane RL: Cognitive impairment in hemodialysis patients is common. *Neurology* 67: 216–223, 2006
6. Umans JG, Pliskin NH: Attention and mental processing speed in hemodialysis patients. *Am J Kidney Dis* 32: 749–751, 1998
7. Pliskin NH, Yurk HM, Ho LT, Umans JG: Neurocognitive function in chronic hemodialysis patients. *Kidney Int* 49: 1435–1440, 1996
8. Pereira AA, Weiner DE, Scott T, Sarnak MJ: Cognitive function in dialysis patients. *Am J Kidney Dis* 45: 448–462, 2005
9. Seliger SL, Gillen DL, Longstreth WT Jr, Kestenbaum B, Stehman-Breen CO: Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int* 64: 603–609, 2003
10. Kennedy R, Case C, Fathi R, Johnson D, Isbel N, Marwick TH: Does renal failure cause an atherosclerotic milieu in patients with end-stage renal disease? *Am J Med* 110: 198–204, 2001
11. Zoungas S, Ristevski S, Lightfoot P, Liang YL, Branley P, Shiel LM, Kerr P, Atkins R, McNeil JJ, McGrath BP: Carotid artery intima-medial thickness is increased in chronic renal failure. *Clin Exp Pharmacol Physiol* 27: 639–641, 2000
12. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM: Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 107: 87–92, 2003
13. Desmond DW, Moroney JT, Sano M, Stern Y: Incidence of dementia after ischemic stroke: Results of a longitudinal study. *Stroke* 33: 2254–2260, 2002
14. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W: Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: The ARIC Study. *Kidney Int* 64: 610–615, 2003
15. Seliger SL, Siscovick DS, Stehman-Breen CO, Gillen DL, Fitzpatrick A, Bleyer A, Kuller LH: Moderate renal impairment and risk of dementia among older adults: The Cardiovascular Health Cognition Study. *J Am Soc Nephrol* 15: 1904–1911, 2004
16. Kurella M, Yaffe K, Shlipak MG, Wenger NK, Chertow GM: Chronic kidney disease and cognitive impairment in menopausal women. *Am J Kidney Dis* 45: 66–76, 2005
17. Kurella M, Chertow GM, Fried LF, Cummings SR, Harris T, Simonsick E, Satterfield S, Ayonayon H, Yaffe K: Chronic kidney disease and cognitive impairment in the elderly: The health, aging, and body composition study. *J Am Soc Nephrol* 16: 2127–2133, 2005
18. Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, Hostetter TH: Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. *J Am Soc Nephrol* 16: 180–188, 2005
19. Teschan PE, Bourne JR, Reed RB, Ward JW: Electrophysiological and neurobehavioral responses to therapy: The National Cooperative Dialysis Study. *Kidney Int Suppl* 13: S58 –S65, 1983
20. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR; Atherosclerosis Risk in Communities (ARIC) Study Investigators: Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology* 56: 42–48, 2001
21. Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM, Cummings SR: Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 160: 174–180, 2000
22. Moroney JT, Tang MX, Berglund L, Small S, Merchant C, Bell K, Stern Y, Mayeux R: Low-density lipoprotein cholesterol and the risk of dementia with stroke. *JAMA* 282: 254–260, 1999
23. Jassal SV, Devins GM, Chan CT, Bozanovic R, Rourke S: Improvements in cognition in patients converting from thrice weekly hemodialysis to nocturnal hemodialysis: A longitudinal pilot study. *Kidney Int* 70: 956–962, 2006
24. Lindsberg PJ, Grau AJ: Inflammation and infections as risk factors for ischemic stroke. *Stroke* 34: 2518–2532, 2003
25. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA: Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 346: 476–483, 2002
26. Berr C: Oxidative stress and cognitive impairment in the elderly. *J Nutr Health Aging* 6: 261–266, 2002
27. Parsons DS, Reaveley DA, Pavitt DV, Brown EA: Relationship of renal function to homocysteine and lipoprotein(a) levels: The frequency of the combination of both risk factors in chronic renal impairment. *Am J Kidney Dis* 40: 916–923, 2002
28. Deschamps V, Barberger-Gateau P, Peuchant E, Orgogozo JM: Nutritional factors in cerebral aging and dementia: Epidemiological arguments for a role of oxidative stress. *Neuroepidemiology* 7–15, 1920
29. Krieg EF Jr, Chrislip DW, Letz RE, Otto DA, Crespo CJ, Brightwell WS, Ehrenberg RL: Neurobehavioral test performance in the third National

Health and Nutrition Examination Survey. *Neurotoxicol Teratol* 23: 569–589, 2001
30. Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–1994. Series 1: Programs and Collection Procedures. *Vital Health Stat* 1: 1–407, 1992
31. Ezzati TM, Massey JT, Waksberg J, Chu A, Maurer KR: Sample design: Third National Health and Nutrition Examination Survey, 1988–1994. *Vital Health Stat* 2: 1–35, 1992
32. Baker EL, Letz RE, Fidler AT, Shalat S, Plantamura D, Lyndon M: A computer-based neurobehavioral evaluation system for occupational and environmental epidemiology: Methodology and validation studies. *Neurobehav Toxicol Teratol* 7: 369–377, 1985
33. Letz R: *The Neurobehavioral Evaluation System 2 User's Manual*, Winchester, Neurobehavioral Systems, 1990
34. National Center for Health Statistics: *NHANES III Examination Data File Documentation* [Cat. No. 76200], Centers for Disease Control and Prevention, Hyattsville, MD, 1996
35. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration: Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 145: 247–254, 2006
36. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, Levey AS: Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 39: 920–929, 2002
37. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation: National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann Intern Med* 139: 137–147, 2003
38. Martins D, Tareen N, Zadshir A, Pan D, Vargas R, Nissenson A, Norris K: The association of poverty with the prevalence of albuminuria: Data from the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* 47: 965–971, 2006
39. Convit A: Links between cognitive impairment in insulin resistance: An explanatory model. *Neurobiol Aging* 26[Suppl 1]: 31–35, 2005