Moderate Renal Impairment and Risk of Dementia among Older Adults: The Cardiovascular Health Cognition Study

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Abstract. Renal impairment is associated with an increased risk of carotid atherosclerosis and stroke, determinants of cognitive dysfunction and dementia. The purpose of this study was to determine whether moderate renal impairment is associated with incident dementia among community-dwelling older adults. Participants in the Cardiovascular Health Cognition Study without prevalent dementia ($n = 3349$) were included in the analysis. Incident dementia was confirmed through neurologic testing. Renal function at baseline was estimated by the inverse of serum creatinine (1/SCr); moderate renal impairment was defined as SCr $\geq$ 1.3 mg/dl for women and $\geq$ 1.5 mg/dl for men. Cox regression models were used to estimate the association of renal impairment with incident dementia. Because SCr is also a function of muscle mass, the authors determined whether the relationship between SCr and dementia was particularly strong among individuals without severe comorbidity at baseline, as reflected by self-reported general health status. There were 477 incident dementia cases over a median 6 yr follow-up. After adjustment for potential confounders, moderate renal insufficiency was associated with a 37% increased risk of dementia (95% CI = 1.06 to 1.78). Similarly, a 0.5-unit decrement in 1/SCr (equivalent to an increase in SCr from 1.0 to 2.0 mg/dl) was associated with a 26% increased risk (95% CI = 1.02 to 1.60). These associations were present only among the 84% of older adults who reported good–excellent health. Among those in good–excellent health, higher SCr was associated with vascular-type dementia but not Alzheimer-type dementia. Moderate renal impairment, reflected by a higher SCr, is associated with an excess risk of incident dementia among individuals in good–excellent health. Strategies to prevent or delay the onset of dementia in patients with moderate renal impairment are needed.

Recent studies of end-stage renal disease (ESRD) patients treated with dialysis have found exceedingly high rates of clinical dementia (1–3) and cognitive dysfunction compared with the general population (3–6). Factors that may explain these higher rates include an increased risk of clinical stroke (7,8) and carotid atherosclerosis (9–11) among ESRD patients, leading to progressive cognitive impairment (12–14).

Although there are an estimated 7.5 million individuals in the US with moderate renal disease (15) who suffer from similar physiologic abnormalities as those with more severe renal impairment, no studies have focused on the relationship between moderate renal impairment and dementia. The purpose of this study was to determine the association between moderate renal impairment and incident dementia among older community-dwelling adults, using data collected by the Cardiovascular Health Cognition Study (CHCS).

Materials and Methods
Study Population: CHS and CHCS

The design of the Cardiovascular Health Study (CHS) has been described in previous reports (16). Briefly, the study consisted of 5888 individuals aged 65 years and older selected at random from Medicare eligibility lists in four US communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. Eligible subjects were non-institutionalized, not wheelchair-dependent at home, did not require a proxy for consent, and were expected to remain in their local region for at least 3 yr. A total of 5201 subjects were recruited in 1989–1990, and an additional 687 African-American subjects were recruited in 1992–1993. Subjects had cognitive function assessed annually using several instruments, as described previously (17).

All subjects alive in 1991–1994 were invited to receive a cranial magnetic resonance imaging (MRI) scan to assess for cerebral vascular disease (18). A total of 3660 CHS subjects received cranial MRI imaging during this time; of these, 3608 had measurements of cognitive function available at the time of the MRI scan and are the subject of this analysis (Figure 1). This subgroup of subjects formed the study population of the CHCS (17) and were evaluated for prevalent or new-onset dementia using the methods described below.
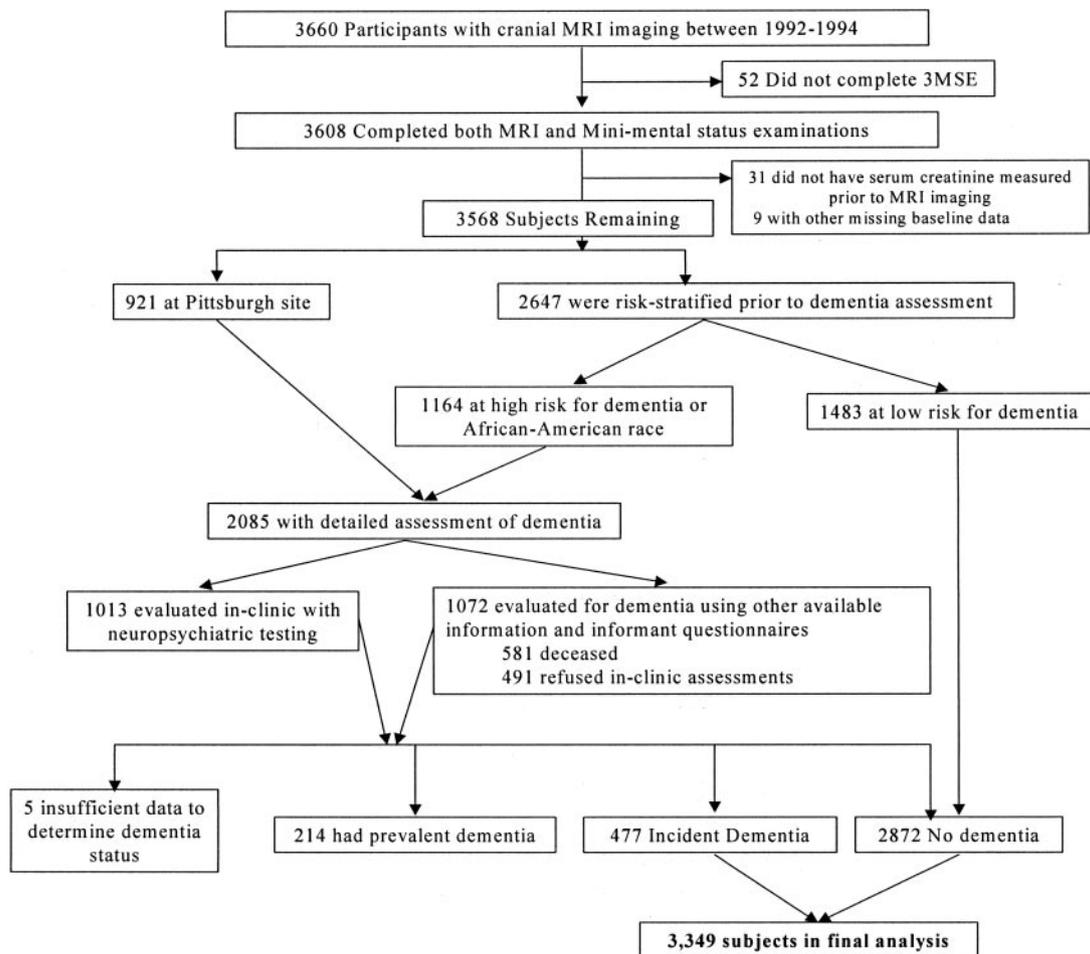
Figure 1. Flow of subjects in the Cardiovascular Health Cognition Study.

Definition of Dementia

Participants were evaluated for dementia in 1998–1999 using a three-stage system as described previously (Figure 1) (17). In the first stage, subjects at 3 study sites were retrospectively defined as high risk for dementia if they had subnormal or declining scores on cognitive testing, had suffered a stroke, were residing in a nursing home, were deceased by the 1998–1999 visit, or were of African-American race. In the second stage, detailed neuropsychological testing was performed in 1998–1999 on all available subjects who were classified as high risk; in addition, all participants at one study site (Pittsburgh, PA) received this testing regardless of dementia risk. The neuropsychological battery included the following tests: the American version of the National Reading test (19), Raven's Colored Progressive Matrices (20), California Verbal Learning Test (21), Rey-Osterreith figure (22), Immediate and Delayed Recall, modified Boston Naming test (23), Verbal Fluency test (24), Block design (modified from the Wechsler Adult Intelligence Scale-revised), Stroop Neuropsychological Screening Test (25), Trail Making, Digit Spans, and the Baddeley & Papagno Divided Attention Task (26). In the third stage of dementia evaluation, those participants who were classified as abnormal on neuropsychological tests were referred for detailed evaluation by a neurologist and psychiatrist.

For subjects who were deceased by 1998–1999 or who were identified as high risk for dementia but unavailable for in-person evaluation, data were collected from other sources to allow for the retrospective diagnosis of dementia. These data included the annual cognitive testing performed during the CHS main study, medical record review, questionnaires sent to participants' personal physicians, and telephone interviews held with the participant or an informant if the participant was deceased.

The classification of dementia was completed by a committee of neurologists and psychiatrists from all four clinical centers. The clinical definition of dementia used was a progressive or static cognitive deficit of sufficient severity to affect the subjects' activities of daily living and history of normal intellectual function before the onset of cognitive abnormalities. Participants were also required to have impairments in two cognitive domains of which memory may have been one (17). This definition correlates very closely to criteria used in the DSM-IV (27). The adjudicators were unaware of subjects' baseline creatinine measurements. Dementia was characterized as prevalent at the time of MRI imaging or as incident (occurring subsequent to this imaging); for incident cases, an estimated year of onset was determined. Type of dementia was classified using standardized criteria and up to two MRI scans available for each participant. For the purposes of the present analysis, we considered two mutually exclusive subtypes of dementia as secondary outcomes: (*1*) "pure" Alzheimer-type dementia (AD)—probable or possible AD (28) without concurrent vascular dementia; (*2*) vascular dementia (VaD)—probable or

possible VaD (29) alone or with concurrent Alzheimer-type dementia.

Predictor Variables

The purpose of the primary analysis was to determine the association between renal function at the time of MRI imaging (baseline) and risk of subsequent dementia. The primary predictor of interest was the inverse of serum creatinine (1/SCr). The decision to use 1/SCr as a measure of renal function rather than serum SCr or a formula-derived estimate of GFR was motivated by several factors. First, SCr is inversely related to GFR, such that a 1 mg/dl increment in SCr does not correspond to a consistent decrement in GFR. Second, the distribution of SCr values is highly skewed in the CHS cohort (30). Third, formula-derived estimates of renal function, such as those proposed by Cockroft and Gault (31) and by Levey *et al.* (37), have not been validated in the elderly population. Fourth, the use of ratios, such as the Cockroft-Gault formula, as predictor variables in multivariate regression models introduces a number of statistical difficulties; the variables which are used to predict GFR (*e.g.*, age, body weight) cannot also be included in the model as adjustment covariates, because this would be equivalent to adjusting for these variables twice.

In a secondary analysis, we used gender-specific cutoff values ($\geq$1.3 mg/dl in women, $\geq$1.5 mg/dl in men) to characterize moderate renal impairment. These threshold criteria have been shown to have high sensitivity and specificity in identifying older individuals with a true GFR < 60 cc/min (33). SCr was measured at years 2 and 5 in CHS; this analysis used measurements at the study visit closest to and preceding the MRI imaging.

Statistical Analyses

Baseline covariate values were compared between those with and without elevated SCr using the *t* test (for continuous variables) or the χ^2 test (for categorical variables). The Cox proportional hazards model for censored survival data were used to determine the association between renal function and incident dementia, after adjustment for other risk factors. We a priori included two sets of adjustment variables: (*1*) those characteristics that are known to influence SCr independently of renal function: age, gender, race, and body weight; (*2*) variables that might plausibly be independently associated with dementia or confound the relationship between renal function and dementia: educational achievement, prevalent coronary heart disease (CHD), hypertension, diabetes, smoking history, and apoE genotype. CHD was defined as the presence of one or more of the following conditions at the time of cranial MRI imaging: myocardial infarction, angina pectoris, coronary angioplasty, or coronary artery bypass surgery. Diabetes was defined by a fasting glucose of >126 mg/dl or use of insulin or hypoglycemic medications. Hypertension was defined as a systolic BP > 140 mmHg, diastolic BP > 90 mmHg, or use of antihypertensive medications. ApoE genotype was determined in the Core Molecular Genetics facility by methods described previously (34). Since carotid atherosclerosis and clinical stroke may mediate the association between impaired renal function and dementia, we did not adjust for these co-morbidities in the primary model, but rather we assessed in an exploratory analysis whether additional adjustment for carotid artery disease variables (intima-media thickness of internal and common carotid arteries (35) and maximum degree of carotid artery stenosis) and clinical stroke events (36) changed the estimates of dementia risk associated with high creatinine.

Because SCr is influenced by both creatinine production (which is mostly dependent on muscle mass) and GFR, the effect of SCr on dementia risk may differ among those with low muscle mass or malnutrition due to severe co-morbidity. We therefore examined the association of SCr and dementia stratified by a measure of co-morbidity—self-assessed general health status, rated poor to excellent. We dichotomized this measurement of self-assessed general health status into two categories: poor–fair and good–excellent. Self-assessed health status measured at the time of the subject's SCr was used for this analysis.

Patients were considered at risk for dementia from the start of the study (*i.e.*, the date of their MRI imaging) and were censored at death or end of the study period (June 30, 1999). Formal and graphical techniques were used to confirm the presence of proportional hazards and to identify potential outliers. We hypothesized that all continuous covariates would be linearly related to the outcome of interest; however, exploratory residual analyses were performed to investigate the correct functional form of all continuous covariates.

For analysis of the secondary outcome vascular-type dementia, we excluded those subjects who developed pure Alzheimer-type dementia or mild cognitive impairment (MCI), and we excluded subjects with MCI or vascular-type dementia from the analysis of Alzheimer-type dementia.

Results

The CHCS comprised 3608 subjects; of these, 31 did not have a SCr measurement before MRI imaging and 9 had other missing baseline data – these were excluded from further analysis. The number of participants receiving each type of evaluation for dementia at each stage of the study is shown in Figure 1. Among the 3568 participants with non-missing SCr values, 5 had insufficient data to assess dementia and 214 were adjudicated to have prevalent dementia at the time of MRI imaging, resulting in 3349 subjects for whom risk of incident dementia could be assessed. The characteristics of these subjects at the start of the Cognition Study are shown in Table 1. Compared with the 3019 individuals with non-elevated creatinine levels, the 330 (9.9%) subjects with an elevated creatinine above gender-specific threshold values for moderate renal insufficiency were somewhat older (76.9 *versus* 74.6 yr) and were more likely to be male and to have prevalent coronary heart disease, hypertension, and poor–fair health. Values of SCr ranged from 0.5 to 3.3 mg/dl among women and from 0.7 to 3.4 mg/dl among males.

Incident Dementia

A total of 477 incident dementia cases occurred over 18,125 person-years of observation (median follow-up = 6.0 yr), resulting in an incidence density of 26.3/1000 person-years. The proportion of dementia cases and types of dementia evaluations among those with and without elevated SCr levels is shown in Table 2. Among those participants who received detailed evaluations for dementia, those with elevated SCr were less likely to receive an in-center evaluation compared with those without elevated SCr (36.5% *versus* 54.5%), primarily due to an excess in early mortality before the 1998 to 1999 in-center evaluation.

The associations between measures of renal function and incident dementia are shown in Table 2. In the entire cohort, a 0.5-unit decrease in 1/SCr (equivalent to an increase in SCr from 1.0 to 2.0) was associated with a 26% increased risk of

Table 1. Characteristics of study population at baseline, by serum creatinine level

	Non-Elevated Creatinine (*n* = 3019)	Elevated Creatinine[a] (*n* = 330)	*P*
	N (%) or mean (SD)		
Age (yr)	74.6 (4.8)	76.9 (5.4)	<.001
Gender			
male	1185 (39%)	191 (58%)	<.001
female	1834 (61%)	139 (42%)	
Race			
white	2596 (86%)	261 (79%)	.001
non-white	423 (14%)	69 (21%)	
Education (yr)	12.7 (2.9)	12.5 (3.1)	.2
Body mass index (kg/m^2)	26.6 (4.5)	27.0 (4.4)	.1
Coronary heart disease	561 (19%)	103 (31%)	<.001
Diabetes	406 (13.5%)	52 (15.8%)	.2
Hypertension	1665 (55%)	249 (75%)	<.001
ApoE-4 allele[b]	678 (22.5%)	58 (17.6%)	.03
Smoker			
never	1367 (45%)	126 (38%)	.008
former	1368 (45%)	179 (54%)	
current	284 (9%)	25 (8%)	
Self-reported health			
fair–poor	459 (15.2%)	80 (24.2%)	<.001
good–excellent	2557 (84.8%)	250 (76%)	
Clinic site			
Pittsburgh[c]	775 (25.7%)	98 (29.7%)	.11
other sites	2244 (74.3%)	232 (70.3%)	

[a] Serum creatinine ≥1.3 mg/dl for females and ≥1.5 mg/dl for males.
[b] Homozygous or heterozygous for apoE-4 allele.
[c] All participants from the Pittsburgh site received detailed evaluations for dementia regardless of their risk category.

dementia (hazard ratio [HR] = 1.26; 95% Confidence Interval [CI], 1.02 to 1.54), after adjusting for age, gender, race, weight, educational achievement, CHD, diabetes, hypertension, smoking, and apoE genotype. This HR can be interpreted as a 26% increased dementia risk for an individual with a creatinine of 2.0 mg/dl compared with an individual with a creatinine of 1.0 mg/dl and the same demographic and clinical characteristics. When considered as a dichotomous variable, moderate renal insufficiency, as reflected by an elevated SCr, was associated with a 37% increased risk of dementia (HR = 1.37; 95% CI = 1.06 to 1.78), after adjustment for other covariates. The association between renal function and dementia was similar in a model with a reduced set of covariates (age, race, weight, and gender) without further adjustment for co-morbidity or genotype (1/SCr: per 0.5-unit decrement, HR = 1.24; elevated SCr above gender-specific threshold: HR = 1.37)

In exploratory analyses, further adjustment for measures of carotid atherosclerosis (intima-media thickness and degree of stenosis) did not meaningfully change the HR estimates for 1/SCr (0.5-unit decrement: HR = 1.26) or elevated SCr (HR = 1.33). The association between renal function and dementia was also similar after exclusion of 370 subjects (116 dementia cases) who had a clinical stroke preceding the onset of dementia or the end of follow-up (1/SCr, per 0.5-unit decrement: HR = 1.34; elevated SCr: HR = 1.42).

The associations between the measures of renal function and incident dementia were found to differ among the 539 (16.1%) subjects who described themselves as being in poor or fair general health at baseline compared with the 2807 (83.9%) subjects in self-assessed good–excellent health. Therefore, separate Cox regression models were developed for each subgroup (Table 2). Among subjects in poor–fair health, there was no association between either 1/SCr (per 0.5-unit decrement: HR = 0.79; 95% CI = 0.50 to 1.23) or an elevated *versus* non-elevated creatinine (HR = 0.75; 95% CI = 0.43 to 1.31) and incident dementia; the estimated HR suggested a non-significant trend of increased risk with *lower* levels of SCr. Among subjects with good–excellent health status, there were significant associations with incident dementia for 1/SCr (per 0.5-unit decrement: HR = 1.41; 95% CI = 1.12 to 1.79) and an elevated creatinine (HR = 1.62; 95% CI = 1.21 to 2.18). The *P*-value for the interaction term for self-assessed general health status and elevated creatinine was significant (*P* = 0.02) and suggested a trend toward significance for health status and 1/SCr (*P* = 0.10). When estimated GFR from the Levey formula (37) was used as a measure of renal function, there was still a significant interaction with self-reported health status (*P* = 0.01).

Vascular-Type Dementia

There were 211 cases of incident vascular-type dementia (VaD, with or without concurrent Alzheimer-type dementia), with an incidence density of 15/1,000 person-years. After adjustment for age, gender, race, body weight, and co-morbidities, there was no significant association between 1/SCr and incident VaD (per 0.5-unit decrement: HR = 1.29; 95% CI = 0.93 to 1.79), although exploratory analysis suggested that a quadratic function for 1/SCr best characterized the risk of VaD, with an increased risk at both low and high creatinine (data not shown). When considered as a dichotomous variable, an elevated SCr was associated with a 58% increased risk of VaD (HR = 1.58; 95% CI = 1.10 to 2.26). Additional adjustment for measures of carotid atherosclerosis did not materially change the associations between dementia and either an elevated SCr (HR = 1.48) or 1/SCr (per 0.5-unit decrement, HR = 1.26).

Among subjects in good–excellent self-reported health, both 1/SCr (per 0.5-unit decrement: HR = 1.64; 95% CI = 1.11 to 2.42) and an elevated *versus* non-elevated creatinine (HR = 1.94; 95% CI = 1.28 to 2.93) were associated with incident VaD, indicating a higher risk with higher SCr levels. In contrast, among subjects in poor or fair health, there was no association between risk of VaD and either 1/SCr (per 0.5-unit decrement: HR = 0.63; 95% CI = 0.34 to 1.19) or elevated creatinine as a dichotomous variable (HR = 0.80; 95% CI = 0.38 to 1.69).

Table 2. Methods of evaluation for dementia, by serum creatinine level[a]

	Non-Elevated Creatinine		Elevated Creatinine[b]	
	Total with Detailed Dementia Evaluation (*n* = 1652)	Incident Dementia Cases (*n* = 407)	Total with Detailed Dementia Evaluation (*n* = 214)	Incident Dementia Cases (*n* = 70)
In-center evaluation with neuropsychiatric testing	901 (54.5%)	181	78 (36.5%)	24
Non-center evaluation—deceased	365 (22.1%)	121	93 (43.5%)	34
Non-center evaluation—refused in-center visit	386 (23.4%)	105	43 (20%)	12

[a] Subjects screened as low-risk for dementia are not included in the calculations of frequencies and percentages.
[b] Serum creatinine ≥1.3 mg/dl for females and ≥1.5 mg/dl for males.

Table 3. Association between renal function and incident dementia: Adjusted[c] Hazard Ratio (95% CI)

Measurement of Renal Function	All Subtype Dementia (477 cases)	Vascular-Type Dementia[a] (211 cases)	Pure Alzheimer-Type Dementia[b] (244 cases)
1/SCr (0.5-unit decrement)			
total cohort	1.26 (1.02 to 1.54)	1.29 (0.93 to 1.79)	1.22 (0.89 to 1.69)
good–excellent self-reported health	1.41 (1.12 to 1.79)	1.64 (1.11 to 2.42)	1.26 (0.90 to 1.78)
fair or poor self-reported health	0.79 (0.50 to 1.23)	0.63 (0.34 to 1.19)	0.99 (0.52 to 1.88)
Elevated serum creatinine[d]			
total cohort	1.37 (1.06 to 1.78)	1.58 (1.10 to 2.26)	1.09 (0.72 to 1.65)
good–excellent self-reported health	1.62 (1.21 to 2.18)	1.94 (1.28 to 2.93)	1.28 (0.81 to 2.03)
fair or poor self-reported health	0.75 (0.43 to 1.31)	0.80 (0.38 to 1.69)	0.61 (0.23 to 1.59)

[a] Possible or probable vascular-type dementia (29), alone or with superimposed Alzheimer-type dementia. Subjects who developed pure Alzheimer-type dementia or minimal cognitive impairment were excluded from this analysis.
[b] Possible or probable Alzheimer-type dementia (28) without superimposed vascular-type dementia. Subjects who developed vascular-type dementia or minimal cognitive impairment were excluded from this analysis.
[c] Adjusted for age, gender, race, body weight (quadratic term), educational achievement, prevalent coronary heart disease, diabetes, hypertension, smoking status, and apoE genotype.
[d] Creatinine ≥1.3 mg/dl if female or ≥1.5 mg/dl if male.

Alzheimer-Type Dementia

There were 244 cases of incident pure Alzheimer-type dementia (*i.e.*, without evidence for a vascular etiology), with an incident density of 17.1/1000 person-years. Among the total at-risk cohort, neither 1/SCr as a continuous variable (per 0.5-unit decrement: HR = 1.22; 95% CI = 0.89 to 1.69) nor an elevated creatinine as a dichotomous variable (HR = 1.09; 95% CI = 0.72 to 1.65) were significantly associated with risk of pure AD (Table 2). There were no significant associations between measures of renal function and AD within subgroups defined by self-reported health (Table 2), nor were there any significant interactions between renal function measures and self-reported health (data not shown).

Discussion

In a population of community-dwelling older adults free of dementia at baseline, moderate renal impairment reflected by an elevated SCr was associated with a higher risk of incident dementia among those subjects in good–excellent baseline health. This increased risk persisted after adjusting for factors that might confound the association between renal insuffi-

ciency and dementia, including diabetes, hypertension, apoE genotype, and race. Although the risk of dementia has not been studied previously in individuals with mild-moderate renal insufficiency, a few studies have suggested an increased risk associated with end-stage renal failure requiring dialysis. Murray *et al.* (1) reported a 5% annual incidence rate of dementia among elderly individuals on dialysis, using billing records to identify incident cases. In a population of Japanese hemodialysis patients assessed for dementia over 4 yr, Fukunishi *et al.* (2) reported an incidence rate of 2.5%, which was more than double the rate reported in the Japanese general population (38). The rates of general cognitive dysfunction also appear to be elevated in ESRD, with one study reporting a 30% prevalence of at least mild dysfunction (4). Although these studies suggest a high rate of dementia and cognitive dysfunction in end-stage renal failure, it is unclear whether this increased rate is attributable to renal failure itself, the effects of hemodialysis treatment, or differences in demographic factors and co-morbid conditions between the renal failure and general populations.

There are several biologically plausible mechanisms through which impairment of renal function could result in an increased

risk of dementia. One factor may be elevated homocysteine, which is common even in moderate renal insufficiency (39) and was strongly associated with incident dementia in an analysis from the Framingham Study (40). Anemia is another common consequence of renal insufficiency, which has been associated with poor cognitive function (41) and clinical dementia (1) in patients with end-stage renal failure. Another potential mediating factor is increased oxidative stress, which is associated with renal impairment and which has also been implicated in the pathogenesis of dementia (42,43). For example, levels of the antioxidant enzyme paraoxonase are decreased in moderate renal insufficiency, (44) and lower levels of this enzyme are associated with an increased prevalence of both vascular-type and Alzheimer-type dementia (45).

Renal insufficiency is also associated with an increased risk of cerebrovascular disease, as manifested by an increased risk of clinical stroke (46–48) and a greater severity of subclinical carotid atherosclerosis (49,50). Results from laboratory and epidemiologic studies suggest that atherosclerotic carotid artery disease has an important role in the pathophysiology of dementia, not only for dementia traditionally recognized as "vascular-type," but also for Alzheimer-type dementia and for cognitive impairment in general (12,14,51,52,53). Therefore, the association between renal insufficiency and dementia could be mediated through an excess risk of stroke and carotid artery atherosclerosis. This hypothesis is supported somewhat by our finding of a significant association with vascular-type dementia (*i.e.*, dementia associated with probable or possible vascular etiology) but no significant association with pure Alzheimer-type dementia (*i.e.*, dementia without any evidence of possible vascular etiology). On the other hand, additional adjustment for measures of carotid atherosclerosis and clinical stroke did not change the association between high SCr and risk of all-cause or vascular-type dementia, suggesting that factors other than cerebrovascular disease mediate this association.

The association between measures of renal function and dementia varied considerably among subgroups characterized by self-assessed health status. Among subjects who described themselves in good–excellent health, higher creatinine was associated with a higher risk of dementia. In contrast, among those subjects with self-described poor–fair health, there was little evidence of an association of higher creatinine with incidence of dementia. This interaction may be explained by the influence on SCr levels by creatinine production, which is determined by relative muscle mass. Among patients with poor–fair general health, a low SCr is unlikely to represent supranormal renal function, but it is more likely a manifestation of low muscle mass due to subclinical dementia itself or due to severe co-morbid illness, which is strongly associated with dementia.

This study has a number of limitations. Cases of incident dementia were identified retrospectively. In 33% of these cases, subjects were already deceased by 1998–1999; therefore, the diagnosis was made without direct detailed neuropsychiatric testing. Although all available medical information was used to adjudicate these cases, including results of annual cognitive testing and the use of informant questionnaires, it is possible that the classification of deceased patients as demented or non-demented was not as accurate as among those patients alive in 1998–1999. Since patients with renal insufficiency were more likely to suffer early mortality, a selective misclassification of dementia status could have biased the results of the present analysis. Other bias from unmeasured or residual confounding cannot be excluded.

Strengths of this study include the large cohort size and high frequency of incident dementia, which provided sufficient power to detect moderate associations between renal impairment and dementia. Extensive data on comorbid conditions collected during the CHS allowed for adjustment for important potential confounders, such as diabetes, hypertension, and apoE genotype. In addition, cranial MRI imaging and extensive medical record review allowed for the differentiation of incident vascular-type dementia from Alzheimer-type dementia.

In conclusion, we observed a higher risk of incident dementia, especially vascular-type dementia, associated with moderate renal impairment as reflected by an elevated SCr in a population of community-dwelling older adults. These findings suggest the presence of moderate renal impairment in older adults may identify an at-risk group for vascular-type dementia. The development and evaluation of strategies to delay or prevent the onset of dementia in this clinical population should be targeted in future research.

Acknowledgments

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