Albuminuria and Dementia in the Elderly: A Community Study

Joshua I. Barzilay, MD,[1,2] Annette L. Fitzpatrick, PhD,[3] Jose Luchsinger, MD, MPH,[4] Sevil Yasar, MD,[5] Charles Bernick, MD,[6] Nancy S. Jenny, PhD,[7] and Lewis H. Kuller, MD, DrPH[8]

Background: Dementia is associated with microvascular disease of the retina. In this study, we examine whether cognitive status (normal cognition, mild cognitive impairment, and dementia) is associated with albuminuria, a microvascular disorder of the kidney.

Study Design: Cross-sectional analysis.

Setting & Participants: 2,316 participants from the Cardiovascular Health Cognition Study who underwent brain magnetic resonance imaging and testing for albuminuria.

Predictor: Doubling of albuminuria.

Outcome: Dementia defined according to neuropsychological and clinical evaluation.

Measurements: Multinomial logistic modeling was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of dementia and mild cognitive impairment with doubling of albuminuria compared with the odds with normal cognition.

Results: 283 participants (12.2%) had dementia, 344 (14.9%) had mild cognitive impairment, and 1,689 (72.9%) had normal cognition. Compared with participants with normal cognition, doubling of albuminuria was associated with increased odds of dementia (OR, 1.22; 95% CI, 1.15 to 1.29). Adjustment for prevalent cardiovascular disease and cardiovascular risk factors, lipid levels, C-reactive protein level, estimated glomerular filtration rate, and apolipoprotein E-4 genotype attenuated this association, but it remained statistically significant (OR, 1.12; 95% CI, 1.03 to 1.22). Mild cognitive impairment was associated with albuminuria on unadjusted analysis, but not with adjustment for other factors.

Limitations: Results are cross-sectional; causality cannot be imputed.

Conclusions: The odds of dementia increased in the presence of albuminuria. These findings suggest a role of shared susceptibility for microvascular disease in the brain and kidney in older adults. *Am J Kidney Dis* 52:216-226. © *2008 by the National Kidney Foundation, Inc.*

INDEX WORDS: Albuminuria; elderly; dementia; mild cognitive impairment; magnetic resonance imaging (MRI) brain.

Editorial, p. 201

Microvascular abnormalities are found in the brains of people who die of dementia (reviewed in[1,2]). In patients with Alzheimer disease, the leading cause of dementia, abnormalities include basement membrane thickening, luminal narrowing, loss of pericytes, and increased permeability. In patients with vascular dementia, the second leading cause of dementia, many of the same findings also are present. Recently, the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS) reported that retinal microvascular findings, eg, arteriovenous nicking, focal arteriolar narrowing, microaneurysms, and exudates, were associated with cognitive decline and dementia.[3,4] All these findings support a role for cerebral microvascular disease in the pathogenesis of dementia.

From [1]Kaiser Permanente of Georgia, Tucker; [2]Division of Endocrinology, Emory University School of Medicine, Atlanta, GA; [3]Department of Epidemiology, University of Washington, Seattle, WA; [4]Department of Medicine and Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY; [5]Division of Geriatric Medicine and Gerontology, Johns Hopkins University, Baltimore, MD; [6]Department of Neurology, University of Nevada School of Medicine, Reno, NV; [7]Department of Pathology, University of Vermont, Burlington, VT; and [8]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.

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Address correspondence to Joshua I. Barzilay, MD, Kaiser Permanente of Georgia, 200 Crescent Center Pkwy, Tucker, GA 30084. E-mail: joshua.barzilay@kp.org

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Albuminuria, the excessive excretion of protein in urine, is a marker of renal microvascular disease. It occurs most often in the presence of hypertension and diabetes mellitus and is associated with increasing age, increased systolic blood pressure, and increased levels of inflammation factors.[5] Many of these factors are present in people with dementia.[2] In addition, pathological examination of kidneys in people with albuminuria showed many of the same capillary findings found in brain specimens of people with dementia and retinal vascular disease.[6] These findings led us to test the hypothesis that albuminuria is associated on cross section with increased odds of dementia.

METHODS

Participants in this study were from the CHS, an observational study of cardiovascular risk factors in adults aged 65 years. Recruitment methods have been published.[7] In brief, a random sample of community-living individuals derived from Medicare eligibility lists were invited to participate at 4 field centers. A total of 5,201 participants were recruited in 1989 to 1990. In 1992 to 1993, the fifth year of the study, 687 African Americans were added to the study in the same manner in 3 of the 4 centers. All participants gave informed consent on study entry.

All participants were examined annually at their clinic sites through 1998 to 1999 (year 11 of the study) by using the Modified Mini–Mental State Examination (3MSE)[8] (Table 1). For individuals who did not come to the clinic, interval cognitive information was obtained by using the Telephone Interview for Cognitive Status (TICS).[9] Additional information about cognition was obtained from proxies using the Informant Questionnaire for Cognitive Decline in the Elderly (IQ CODE)[10] and from physicians for participants who died or were unable to fill out the 3MSE or TICS. Information regarding functional status was obtained by using activities of daily living and instrumental activities of daily living by means of standardized questionnaires. The presence of dementia was documented during medical record review of all deaths and cardiovascular events.

Participants also underwent baseline blood testing, cardiac and carotid artery ultrasound testing, electrocardiography, ankle-brachial index measurement, and completion of medical history and clinical examination, as previously described.[7] Magnetic resonance imaging (MRI) of the brain was completed in 1991 to 1994 and again in 1997 to 1999 for participants willing and able to undergo scanning. Apolipoprotein E-4 (ApoE-4) genotype was determined for participants providing consent for use of DNA. ApoE-4 is a genotype heterozygote or homozygote for at least one copy of ApoE-4.

The Cognition Cohort and Definition of Dementia

In 1998 to 1999, the Cardiovascular Health Cognition Study (CHCS) was assembled. It identified subjects with prevalent dementia at the time of brain MRI in 1991 to 1994 and those who subsequently developed dementia through 1998 to 1999. Inclusion in the CHCS required completion of a 3MSE at the time of MRI and ApoE-4 genotyping. The cohort consisted of 3,608 individuals (Fig 1). Of these

Table 1. Tests Used to Determine Cognitive and Functional Status at Baseline and During Follow-up in the Cardiovascular Health Cognition Study

Screening Tests of Cognition
3MSE: At baseline examination, participants completed the MMSE. Thereafter, the MMSE was replaced by the 3MSE. The 3MSE samples a wider range of cognitive abilities than the MMSE and enhances the reliability and validity of the scores. Components of the MMSE include short-term and delayed recall and temporal and spatial orientation. The MMSE and 3MSE are strongly related to age and attained education.
TCIS: The TICS is a brief standardized test of cognitive functioning developed for use in situations in which in-person cognitive screening is impractical or inefficient (eg, large-scale population screening, epidemiological surveys, or patients who are unable to appear in person for clinical follow-up). The test is standardized and validated for use with English-speaking adults aged 60 to 98 years. Research showed that psychological data obtained over the telephone are as reliable and valid as those obtained through face-to-face interaction. The TICS correlates highly with the MMSE. The TICS total score provides a measure of global cognitive functioning and can be used to monitor changes in cognitive functioning over time.
IQ CODE: The IQ CODE is a short questionnaire designed to assess cognitive decrease and dementia in elderly people. The questionnaire is filled out by a relative or friend who has known the elderly person for 10 years or more. It has high reliability and measures a single general factor of cognitive decrease. It performs as well as other tests of cognitive screening and correlates well with other cognitive test results. It predicts dementia. It is unaffected by attained education level.
Screening Tests of Functional Status
Activities of Daily Living: This test measures functions performed during daily living, such as self-care (feeding oneself, bathing, dressing, and grooming), work, homemaking, and leisure.
Instrumental Activities of Daily Living: These activities are not necessary for fundamental functioning, but enable the individual to live independently within a community. They are light housework, preparing meals, taking medications, shopping for groceries or clothes, using the telephone, and managing money.

Abbreviations: MMSE, Mini–Mental State Examination; 3MSE, Modified Mini–Mental State Examination; TCIS, Telephone Interview for Cognitive Status; IQ CODE, Informant Questionnaire for Cognitive Decline in the Elderly.

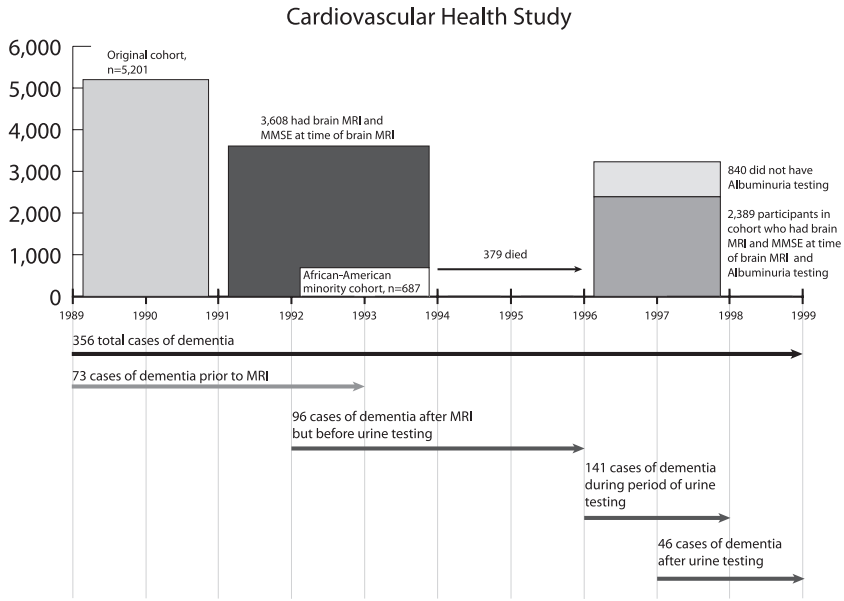

Figure 1. Time line of the Cardiovascular Health Cognition Study. Abbreviations: MRI, magnetic resonance imaging; MMSE, Mini–Mental State Examination.

individuals, 777 (21.6%) had died by 1998 to 1999. There were 1,741 white and 357 African American women, 1,282 white and 212 African American men, and 16 of other races; 62% of white and 62% of African American subjects completed the MRI examination. Participants who did not undergo scanning (mainly because of refusal, inability to complete MRI, or MRI contraindications) had lower 3MSE scores, were less educated, and had more clinical cardiovascular disease than those who underwent scanning.[11] Groups did not differ with regard to prevalence of ApoE-4 genotype.

The 3,608 participants were divided into groups at high and low likelihood of having dementia based on cognitive testing, changes in cognitive scores, nursing home admission, alive or dead status, and history of stroke. If a participant was alive in 1998 to 1999, high risk was defined as 3MSE score less than 80 at 1 of the last 2 clinic visits, a 5-point decrease in 3MSE score from the time of MRI to the time of last visit, TICS score less than 28, IQ CODE score greater than 3.6, having an incident stroke, medical chart review with dementia as a diagnosis, or currently residing in a nursing home. If a participant died before 1998 to 1999, he or she was considered to have a high likelihood of having had dementia if they had at least 1 of the following: 3MSE score less than 80 within 2 years of death, greater than 5-point decrease in 3MSE score from the year of MRI to the year closest to death, TICS score less than 28 or IQ CODE score greater than 3.6 within 2 years of death, or diagnosis of dementia in a medical record or history of incident stroke. Prior analysis showed that few cases of dementia are missed by using this classification system of high versus low risk.[12,13]

In 3 clinic sites (in 1998 to 1999), all living high-risk white participants and all African American participants (because of their small sample size) were neuropsychologically evaluated for dementia (1,192 [44%] were classified as high risk, including minorities; 1,492 [56%] of all whites, as low risk). In 1 center (Pittsburgh, PA; n = 927), all participants underwent evaluation for dementia regardless of whether they were considered at high probability for having dementia. This was done to estimate "misses" in low-risk participants at the other 3 centers. Neuropsychological evaluation consisted of tests of intelligence, memory, immediate and delayed recall, language, visual perception and construction, and executive functioning (tests are listed in Table S1, which is provided as supplementary material available with this article at www.ajkd.org). Results were classified as normal or abnormal.[13]

The diagnosis of dementia was based on a deficit in performance in 2 or more cognitive domains that were of sufficient severity to affect the participant's activities of daily living and a history of normal intellectual function before the cognitive decrease. An abnormal domain was present when results of at least 2 tests of the same domain were abnormal. A memory deficit was not required for the diagnosis of dementia. Diagnosis was made by an adjudication committee of neurologists with expertise in dementia. Year of onset for dementia was determined by using all available data. Mild cognitive impairment (MCI) was defined as cognitive impairment, especially memory deficit, without dementia.[14,15]

After the decision of whether dementia was present, classification of the type of dementia was made before and after review of brain MRI results. There was a high degree of correlation of classifications of type of dementia both before and after reviewing MRI scans.[14] Classification of dementia type was based on several classification systems (see Table 1 in[13] for definitions of each set of criteria). The diagnosis of probable Alzheimer disease was made following the National Institute of Neurological and Communicative Diseases and Stroke (NINDS)/Alzheimer's Disease Related Disorders Association clas-

sification system[16] and required the participant to show a gradual cognitive decrease without history or evidence of another illness that could cause mental impairment. There could be no evidence of a focal central nervous system lesion based on clinical or radiological examinations. Possible Alzheimer disease used the same criteria as probable Alzheimer disease, but with evidence of other concomitant diseases that may have caused cognitive decrease (eg, depression, hypothyroidism, head injury, alcoholism, central nervous system infection, and cerebrovascular disease). Vascular dementia was diagnosed based on clinical and/or radiological evidence of cerebral infarctions contributing to dementia. The State of California Alzheimer's Disease Diagnostic and Treatment Centers[17] and the NINDS Association Internationale pour la Recherche et Enseignement en Neurosciences[18] criteria primarily were used for these diagnoses. Classification based on Alzheimer's Disease Diagnostic and Treatment Centers criteria includes more vascular dementia than the NINDS-Association Internationale pour la Recherche et Enseignement en Neurosciences criteria because MRI data are relied on more heavily. MRI infarcts were defined as an area of abnormal signal in a vascular distribution that lacked a mass effect.[19] An infarct was considered "silent" if there was no history of stroke or transient ischemic attack at baseline or on follow-up. Only infarcts of 3 mm or greater were included in analyses (reproducibility was low for lesions < 3 mm). Infarcts of the cortical gray and deep nuclear regions had to be brighter than on spin density and T2-weighted images than normal gray matter. Infarcts in white matter were similarly defined, except they had to be hypointense on T1 images to distinguish from diffuse white matter disease. White matter changes were estimated by using the total extent of periventricular and subcortical white matter signal abnormality on spin-weighted images, graded from none/barely present (0 or 1) to almost all white matter involved (grade 9). Prior CHS analyses showed that a high white matter score was an independent predictor of incident clinical stroke.[20] When elements of both Alzheimer disease and vascular dementia were present, the diagnosis of mixed dementia was made. For these analyses, individuals with mixed dementia were included in the vascular dementia group.

Albuminuria Testing

Of CHCS participants alive in 1996 to 1997, a total of 2,389 had albuminuria tested on a random morning urine sample. Albuminuria testing was not done at the time of entry into the main CHS study. Urinary albumin was measured by means of rate nephelometry using the Array 360 CE Protein Analyzer (Beckman Instruments, Fullerton, CA). Urinary creatinine was measured on a Kodak Ektachem 700 Analyzer (Kodak, Rochester, NY). Participants with less than 30 mg of albumin/g creatinine were defined as having normoalbuminuria. Those with 30 mg of albumin/g creatinine or greater were defined as having albuminuria.

Statistical Methods

The χ^2, *t*-test, and nonparametric methods were used, as appropriate, to compare baseline parameters between those with and without albuminuria and among those with normal cognition, MCI, and dementia. Multinomial logistic regression was used to test the association of doubling of albuminuria in those with mild cognitive impairment and dementia compared with those with normal cognition. Models were adjusted for: (1) age, sex, race, and education; (2) history of coronary heart disease, stroke, hypertension, diabetes, and smoking; serum cholesterol, low-density lipoprotein cholesterol, and C-reactive protein levels; and estimated glomerular filtration rate; and (3) ApoE-4 genotype. Cox proportional hazards regression models were constructed to assess the association of albuminuria with incident cases of dementia after urine collection in 1997 through follow-up in 1999. Analyses were performed using SPSS, version 14.0 (SPSS Inc, Chicago, IL).

RESULTS

Of 3,608 participants in the CHCS, 3,229 (89.6%) were alive at the time of albuminuria testing (Fig 1). Of these, 840 participants did not undergo albuminuria testing, leaving 2,389 participants for analysis. Participants who did not undergo albuminuria testing were older (75.7 ± 5.3 versus 74.4 ± 4.8 years; $P < 0.001$) and more likely to be women (66.3% versus 58.3%; $P < 0.001$) than those who underwent testing. They were similar in distribution of race and prevalences of hypertension and diabetes.

Study Cohort

There were 356 cases of dementia in the 2,389 CHCS participants who underwent albuminuria testing (Fig 1). The 73 cases of dementia detected before the time of brain MRI (1991 to 1994) were excluded from analyses. This left 283 cases of incident dementia occurring during 1992 to 1999; a total of 96 detected from the time of MRI until before albuminuria testing (1992 through 1995), 141 in 1996 and 1997 at the time of albuminuria testing, and 46 in 1997 through 1999 after albuminuria testing. During this same period, 344 cases of MCI were detected, whereas 1,689 participants retained normal cognition.

Of the 73 prevalent cases of dementia removed from analysis, 18 (24.7%) had albuminuria on subsequent testing in 1996 to 1997. Of 840 participants who did not undergo albuminuria testing, 161 (19.5%) had incident dementia and 165 (20.0%) had MCI. Of 379 who died, 36 (9.5%) had incident dementia when assessed before death, and 68 (17.9%) had MCI.

Table 2. Selected Characteristics of Participants in the Cardiovascular Health Cognition Study Cohort Categorized by the Presence of Albuminuria

Characteristic	No Albuminuria (n = 1,871)	Albuminuria (n = 445)	Total (n = 2,316)	*P*
Age (y)				<0.001
<75	664 (35.5)	130 (29.2)	794 (34.3)	
76-80	733 (39.2)	150 (33.7)	883 (38.1)	
≥80	474 (25.3)	165 (37.1)	639 (27.6)	
Sex				<0.001
Women	1,129 (60.3)	227 (51.0)	1,356 (58.5)	
Men	742 (39.7)	218 (49.0)	960 (41.5)	
Race				0.3
White	1,585 (84.7)	372 (83.6)	1,957 (84.5)	
Nonwhite	286 (15.3)	73 (16.4)	359 (15.5)	
History of diabetes*				<0.001
Normal	1,494 (82.0)	266 (62.1)	1,760 (78.2)	
Impaired fasting glucose	114 (6.3)	34 (7.9)	148 (6.6)	
Diabetes	215 (11.8)	128 (29.9)	343 (15.2)	
History of hypertension*				<0.001
Normal	777 (41.7)	98 (22.1)	875 (37.9)	
Borderline	236 (12.7)	41 (9.2)	277 (12.0)	
Hypertension	851 (45.7)	305 (68.7)	1,156 (50.1)	
Hypertension without diabetes*	705 (38.2)	210 (48.2)	915 (40.1)	<0.001
ACE-inhibitor use (%)	12.7	22.2	14.6	<0.001
Mean creatinine (mg/dL)	0.97 ± 0.22	1.10 ± 0.37	0.99 ± 0.26	<0.001
Mean eGFR (mL/min/1.73 m^2)	80.3 ± 21.3	72.4 ± 25.9	78.8 ± 22.5	<0.001
Cognition status				<0.001
Normal	1,407 (75.2)	282 (63.4)	1,689 (72.9)	
Mild cognitive impairment	267 (14.3)	77 (17.3)	344 (14.9)	
Dementia	197 (10.5)	86 (19.3)	283 (12.2)	

Note: Values expressed as number (percent) or mean ± SD. Albuminuria defined as 30 mg albumin/g creatinine or greater. eGFR based on the Modification of Diet in Renal Disease Study equation. To convert creatinine in mg/dL to μmol/L, multiply by 88.4; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

Abbreviations: ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate.

*Numbers do not add up to 2,316 because of missing data for specific characteristic.

Baseline Factors

Of 2,389 CHCS participants with albuminuria testing, 445 (18.6%) had albuminuria. The distribution of participant baseline characteristics by albuminuria status (presence of albumin excretion ≥ 30 mg/g creatinine) is listed in Table 2. Compared with individuals without albuminuria, participants with albuminuria were older and were more likely to be men; have a history of diabetes, hypertension, or both; have lower renal function; and use angiotensin-converting enzyme inhibitors. They also were more likely to have MCI and dementia.

Compared with subjects without cognitive impairment (Table 3), participants with dementia were older, were more likely to be nonwhite, had lower attained educational level, and had more diabetes and atherosclerotic vascular disease. They also had a greater prevalence of the ApoE-4 genotype, greater systolic blood pressure, lower renal function, and were more likely to use angiotensin-converting enzyme inhibitors. They also had a lower body mass index and consumed less alcohol. Compared with participants with dementia, participants with MCI were younger and were more likely to be nonwhite; have less evidence of cardiovascular disease, lower prevalence of Apo-E4 genotype, and less albuminuria; and use more antihypertension medications.

Association of Albuminuria With Dementia and MCI

Compared with participants who retained normal cognition (reference value), albuminuria was

Table 3. Selected Characteristics of Participants in the Cardiovascular Health Cognition Study Cohort Categorized by Cognitive Status

Characteristic	Dementia (n = 283)	Mild Cognitive Impairment (n = 344)	No Cognitive Impairment (n = 1,689)	*P*
Age (y)				<0.001
<75	41 (14.5)	100 (29.1)	653 (38.7)	
76-80	102 (36.0)	119 (34.6)	662 (39.2)	
>75	140 (49.5)	125 (26.3)	374 (22.1)	
Sex				0.4
Women	167 (59.0)	190 (55.2)	999 (59.1)	
Men	116 (41.0)	154 (44.8)	690 (40.9)	
Race				<0.001
White	228 (80.6)	208 (60.5)	1,521 (90.1)	
Nonwhite	55 (19.4)	136 (39.5)	168 (9.9)	
Education				<0.001
< high school	96 (33.9)	118 (34.3)	308 (18.3)	
High school graduate	71 (25.1)	108 (31.4)	492 (29.2)	
Some college	55 (19.4)	63 (18.3)	446 (26.5)	
College graduate	61 (21.6)	55 (16.0)	439 (26.1)	
Smoking status				0.1
Never	136 (48.7)	141 (41.8)	821 (49.5)	
Former	126 (45.2)	166 (49.3)	725 (43.7)	
Current	17 (6.1)	30 (8.9)	114 (6.9)	
Alcohol use (drinks/wk)				<0.001
0	195 (69.1)	215 (62.9)	871 (51.8)	
1-3	62 (22.0)	88 (25.7)	531 (31.6)	
≥4	25 (8.9)	39 (11.4)	279 (16.6)	
Body mass index (kg/m^2)				<0.001
<25	138 (50.4)	136 (39.9)	573 (34.2)	
25-29.9	92 (33.6)	144 (42.4)	761 (45.4)	
≥30	44 (16.1)	61 (17.9)	342 (20.4)	
Hypertension	137 (48.6)	188 (54.8)	831 (49.4)	0.2
Diabetes	53 (19.6)	61 (18.7)	229 (13.9)	0.009
Coronary heart disease	86 (30.4)	80 (23.3)	373 (22.1)	0.009
Stroke	37 (13.1)	26 (7.6)	73 (4.3)	<0.001
Transient ischemic attack	17 (6.0)	14 (4.1)	49 (2.9)	0.02
Congestive heart failure	36 (12.7)	44 (12.8)	102 (6.0)	<0.001
Ankle-brachial index				<0.001
>1.0	197 (72.2)	258 (78.7)	1,395 (85.0)	
1.0-0.9	29 (10.6)	35 (10.7)	133 (8.9)	
<0.9	47 (17.2)	35 (10.7)	114 (6.9)	
ApoE-4 genotype	81 (33.5)	84 (26.8)	332 (21.3)	<0.001
Body mass index (kg/m^2)	25.7 ± 4.7	26.6 ± 4.7	26.9 ± 4.4	<0.001
IMT-common (mm)	1.11 ± 0.23	1.09 ± 0.21	1.04 ± 0.21	<0.001
IMT-internal (mm)	1.57 ± 0.65	1.40 ± 0.55	1.36 ± 0.51	<0.001
Systolic blood pressure (mm Hg)	139.7 ± 22.5	137.5 ± 21.5	135.4 ± 20.5	0.01
Diastolic blood pressure (mm Hg)	69.3 ± 12.5	70.1 ± 10.7	69.7 ± 10.9	0.7
ACE inhibitor use (%)	18.4	18.6	13.1	0.005
Any antihypertensive use (%)	57.6	66.0	55.8	0.002
Creatinine (mg/dL)	1.04 ± 0.32	1.02 ± 0.29	0.98 ± 0.24	<0.001
Cholesterol (mg/dL)	201.8 ± 43.4	202.4 ± 40.8	200.4 ± 38.6	0.7
LDL cholesterol (mg/dL)	129.3 ± 39.3	128.7 ± 35.7	127.3 ± 31.6	0.6
HDL cholesterol (mg/dL)	53.1 ± 15.1	54.0 ± 15.0	53.3 ± 14.1	0.7
Fasting glucose (mg/dL)	108.3 ± 36.3	109.5 ± 36.5	104.8 ± 28.4	0.02
Insulin (μU/mL)	12.7 ± 11.9	15.9 ± 34.9	13.0 ± 18.1	0.07
C-Reactive protein(mg/L)	4.2 ± 5.0	5.4 ± 8.7	4.7 ± 8.2	0.2
eGFR (mL/min/1.73 m^2)	74.9 ± 24.4	78.5 ± 23.3	79.6 ± 21.9	<0.001
Albuminuria (mg/g creatinine)	105.6 ± 592.2	83.0 ± 365.1	50.9 ± 260.9	0.02

Note: Values expressed as number (percent) or mean ± SD. All values are from the baseline examination performed in 1989 to 1991. To convert creatinine in mg/dL to μmol/L, multiply by 88.4; serum cholesterol, LDL cholesterol, and HDL cholesterol in mg/dL to mmol/L, multiply by 0.02586; glucose in mg/dL to mmol/L, multiply by 0.05551; insulin in μU/mL to pmol/L, multiply by 7.175; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

Abbreviations: IMT, intimal medial thickness; ApoE-4, apolipoprotein E-4; ACE, angiotensin-converting enzyme; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.

Table 4. Unadjusted and Adjusted Cross-sectional Association Between Albuminuria and Odds of Dementia and Mild Cognitive Impairment Using Multinomial Logistic Regression

		OR (95% CI)							
	Cases/ Controls	Unadjusted	*P*	Adjusted for Demographic Factors*	*P*	Further Adjusted for CVD & Lipid Risk Factors†	*P*	Further Adjusted for ApoE-4‡	*P*
Albuminuria (log base 2) examined as a continuous variable§									
Incident dementia	283/1,689	1.22 (1.15-1.29)	<0.001	1.16 (1.08-1.23)	<0.001	1.14 (1.06-1.24)	0.001	1.13 (1.04-1.23)	0.03
Mild cognitive impairment	344/1,689	1.10 (1.04-1.17)	0.001	1.06 (0.99-1.13)	0.08	1.05 (0.98-1.14)	0.2	1.04 (0.96-1.13)	0.3
Albuminuria examined as a categorical variable‖									
Incident dementia			<0.001		<0.001		0.006		0.02
<30 mg/g	197/1,407	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥30 mg/g	86/282	2.18 (1.64-2.89)		1.77 (1.31-2.40)		1.64 (1.15-2.32)		1.58 (1.09-2.30)	
Mild cognitive impairment			0.01		0.2		0.5		0.7
<30 mg/g	267/1,407	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥30 mg/g	77/282	1.44 (1.08-1.91)		1.24 (0.92-1.69)		1.13 (0.80-1.60)		1.07 (0.74-1.54)	

Abbreviations: OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease; ApoE-4, apolipoprotein E-4.

*Model adjusted for demographics: age, sex, race (white/nonwhite), and years of education.

†Model includes demographics plus the presence of coronary heart disease, stroke, hypertension, diabetes, smoking history, serum cholesterol level, low-density lipoprotein cholesterol level, C-reactive protein level, and estimated glomerular filtration rate.

‡Model includes demographics, CVD and lipid risk factors, plus ApoE-4 phenotype.

§Log base 2-transformed continuous measure of albuminuria in milligrams/gram of creatinine.

‖Albumin level categorized as albuminuria for >30 mg/g of creatinine and normoalbuminuria (reference) for <30 mg/g creatinine.

associated with increased odds of dementia (Table 4). As a continuous variable, there was an unadjusted odds ratio (OR) of 1.22 (95% confidence interval [CI], 1.15 to 1.29) of dementia with every doubling of albuminuria. Adjustment for demographic and cardiovascular disease and risk factors and for the ApoE-4 genotype attenuated this association, but it remained statistically significant (OR, 1.13; 95% CI, 1.04 to 1.23). When albuminuria was categorically defined, a statistically significant fully adjusted relationship with dementia likewise was found (OR, 1.58; 95% CI, 1.09 to 2.30). When these analyses were repeated in participants without diabetes or without hypertension, similar results were obtained, although the association of albuminuria with dementia and MCI was strongest in those without hypertension (Table S2, provided as supplementary material available with this article at www.ajkd.org).

To further gauge the association of albuminuria with dementia, the 46 cases of dementia in the cohort that occurred from the time of urine collection in 1996 to 1997 until 1999 (mean follow-up, approximately 2.5 years) were analyzed separately. Of these patients, 14 had albuminuria. Cox proportional hazards models (Table S3, provided as supplementary material available with this article at www.ajkd.org) showed a statistically significant association of albuminuria (as a continuous variable) with the presence of dementia compared with the association of albuminuria with normal cognition in unadjusted analysis and with adjustment for demographic factors (relative risk, 1.30; 95% CI, 1.08 to 1.58). Similar results were obtained when albuminuria was examined categorically (relative risk, 1.96; 95% CI, 1.03 to 3.74). Owing to small numbers, further adjustments were not performed.

With regard to MCI (Table 4), there was a statistically significant association with doubling of albuminuria compared with those with normal cognition on unadjusted analysis (OR, 1.10; 95% CI, 1.04 to 1.17). With further adjustments, the association of albuminuria with MCI became nonsignificant (OR, 1.04; 95% CI, 0.96 to 1.13).

Table 5. Unadjusted and Adjusted Cross-sectional Association Between Albuminuria and Odds of Alzheimer Disease and Vascular Dementia Using Multinomial Logistic Regression

		OR (95% CI)							
	Cases/ Controls	Unadjusted	*P*	Adjusted for Demographic Factors*	*P*	Further Adjusted for CVD & Lipid Risk Factors†	*P*	Further Adjusted for ApoE-4‡	*P*
Albuminuria (log base 2) examined as a continous variable§									
Alzheimer disease	152/1,689	1.13 (1.04-1.23)	0.004	1.05 (0.96-1.16)	0.3	1.08 (0.98-1.20)	0.1	1.10 (0.98-1.22)	0.1
Vascular dementia	120/1,689	1.30 (1.20-1.41)	0.001	1.24 (1.13-1.35)	<0.001	1.22 (1.10-1.36)	<0.001	1.17 (1.12-1.23)	0.01
Albuminuria examined as a categorical variable‖									
Alzheimer disease			0.03		0.3		0.2		0.1
<30 mg/g	116/1,407	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥30 mg/g	36/282	1.55 (1.04-2.30)		1.27 (0.84-1.93)		1.40 (0.88-2.24)		1.45 (0.89-2.37)	
Vascular dementia			<0.001		<0.001		0.003		0.02
<30 mg/g	76/1,407	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥30 mg/g	44/282	2.89 (1.95-4.28)		2.32 (1.54-3.50)		2.09 (1.28-3.40)		1.86 (1.09-3.15)	

Note: Cases of dementia not related to Alzheimer disease or vascular dementia are not included in analysis.

Abbreviations: OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease; ApoE-4, apolipoprotein E-4.

*Model adjusted for demographics: age, sex, race (white/nonwhite), and years of education.

†Model includes demographics plus the presence of coronary heart disease, stroke, hypertension, diabetes, smoking history, serum cholesterol level, low-density lipoprotein cholesterol level, C-reactive protein level, and estimated glomerular filtration rate.

‡Model includes demographics, CVD and lipid risk factors, plus ApoE-4 phenotype.

§Log base 2-transformed continuous measure of albuminuria in milligrams/gram of creatinine.

‖Albumin level categorized as albuminuria for >30 mg/g of creatinine and normoalbuminuria (reference) for <30 mg/g creatinine.

Similar findings were obtained when albuminuria was examined as a categorical variable.

Association of Albuminuria With Dementia Type

To further examine the association of dementia with albuminuria, dementia was divided into its 2 main categories: Alzheimer dementia and vascular dementia. As a continuous variable, doubling of albuminuria was associated with a statistically significant increase in odds of vascular dementia on adjusted analysis (OR, 1.17; 95% CI, 1.12 to 1.23) compared with normal cognition (Table 5). There was a borderline association of albuminuria with Alzheimer disease (OR, 1.10; 95% CI, 0.98 to 1.22). When these analyses were repeated with albuminuria as a categorical variable, similar results were obtained. As an example of the association of albuminuria with an MRI factor used to define dementia, the odds of having an increased white matter score (ie, ≥3) was examined (see Table S4 in the Supplementary Data with this article at www.ajkd.org for baseline characteristics of the cohort categorized by white matter score). As listed in Table 6, doubling of albuminuria was associated significantly with an increased OR of increased white matter score. When albuminuria was defined categorically, similar results were obtained, although adjustment for ApoE-4 genotype attenuated the significance of this association.

DISCUSSION

In this study of older adults, a statistically significant cross-sectional association between increasing albuminuria and dementia was found. This association remained significant after adjustment for factors that associate with dementia, such as hypertension, diabetes, and prevalent cardiovascular disease. The association of albuminuria and dementia may be explained by the many anatomic microvascular similarities found in brains of people with dementia and kidneys of people with albuminuria. Aside from these simi-

Table 6. Unadjusted and Adjusted Cross-sectional Association Between Albuminuria and White Matter Disease (≥grade 3) as Measured in 1992 to 1993 by Brain Magnetic Resonance Imaging Using Multivariate Logistic Regression

		OR (95% CI)							
	Cases/ Controls	Unadjusted	*P*	Adjusted for Demographic Factors*	*P*	Further Adjusted for CVD & Lipid Risk Factors†	*P*	Further Adjusted for ApoE-4‡	*P*
Albuminuria (log base 2)	715/1,582	1.12 (1.07-1.17)	<0.001	1.09 (1.04-1.14)	0.001	1.07 (1.01-1.13)	0.02	1.06 (1.00-1.13)	0.04
Albuminuria (mg/g)			<0.001		0.003		0.04		0.08
<30	542/1,312	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥30	173/270	1.55 (1.25-1.92)		1.40 (1.12-1.75)		1.30 (1.01-1.68)		1.26 (0.97-1.64)	

Note: Albuminuria shown as continuous variable (log transformed base 2 continuous measure in milligrams/gram of creatinine) and categorical variable (albuminuria [albumin ≥ 30 mg/g] compared with normoalbuminuria [albumin < 30 mg/g]) as the reference).

Abbreviations: OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease; ApoE-4, apolipoprotein E-4.

*Model adjusted for demographics: age, sex, race (white/nonwhite), and years of education.

†Model includes demographics plus the presence of coronary heart disease, stroke, hypertension, diabetes, smoking history, serum cholesterol level, low-density lipoprotein cholesterol level, C-reactive protein level, and estimated glomerular filtration rate.

‡Model includes demographics, CVD and lipid risk factors, plus ApoE-4 phenotype.

larities, functional factors common to both conditions also may explain why these conditions coexist. For example, people with albuminuria have impaired autoregulation of glomerular filtration,[21] whereas people with dementia have impaired regulation of cerebrovascular flow.[1] Also, albuminuria and dementia may be related through factors not measured in this study, such as increased levels of oxidative stress.[22,23]

When the association of albuminuria with dementia was categorized by dementia type, the strongest association was with vascular dementia. The association with Alzheimer dementia was of borderline statistical significance. This suggests that the association of albuminuria with dementia is mainly through vascular mechanisms. Although this may be so, studies showed that microvascular disease exists in patients with Alzheimer dementia, and it often is difficult to accurately differentiate between these 2 types of dementia. As such, our results are broadly applicable to the syndrome of dementia and not specific to dementia type.

MCI, a transitional phase between normal cognitive function and dementia,[15] was associated with increasing albuminuria on unadjusted analysis and with adjustment for demographic factors. Further adjustment for cardiovascular disease, cardiovascular risk factors, and the ApoE-4 genotype made this association statistically nonsignificant. This latter finding may be understood in 2 ways. First, MCI is a heterogeneous disorder, perhaps more strongly associated with Alzheimer disease than vascular dementia. Second, it may be that MCI, as an initial phase of cognitive decrease, is more strongly related to traditional cardiovascular disease risk factors that initiate cognitive decrease and less so to factors that appear later on.

To our knowledge, there are no other studies of the association of albuminuria with dementia. In the prior CHS study, which examined the association of microvascular retinal disease with dementia,[4] participants with retinopathy had an OR of 2.10 (95% CI, 1.04 to 4.24) for dementia. In the ARIC Study,[3] which examined a younger middle-aged cohort, ORs varied from 1.91 to 2.60. The somewhat greater association of microvascular eye lesions with dementia compared with our renal microvascular findings (OR, 1.49; 95% CI, 1.02 to 2.19 for albuminuria with albumin > 30 mg/g) may be caused by differences in study methods. Also, albuminuria is not a pathological diagnosis compared with the eye studies,

in which direct examination of eye vessels is available.

Limitations of our results should be noted. Our results are cross-sectional. Causality cannot be imputed. Results of the small subcohort that was examined prospectively are consistent with our cross-sectional analyses. Second, our inability to establish when albuminuria had its onset makes it impossible to establish a temporal association of albuminuria with dementia onset. Owing to this uncertainty, we included cases of dementia that occurred both before and after the period of urine testing. Last, the CHCS examined a healthy subpopulation of the CHS. As such, our results may be conservative estimates.

What are the implications of our findings? First, they suggest that albuminuria increases the likelihood that dementia is present or will develop. Analysis of the Third National Health and Nutrition Examination Survey (NHANES) showed the prevalence of albuminuria to increase from 14.6% at age 60 to 69 years to 32.7% at 80 years and older.[24] A large pool of older adults therefore is at risk of having or developing dementia in association with albuminuria. Second, our results suggest the possibility that treatments that decrease albuminuria, such as angiotensin-converting enzyme inhibitors/blockers, may have a salutary impact on the development of dementia. Results of several prospective studies will test this hypothesis.[25] Third, the association of albuminuria with dementia may help explain in part why conditions associated with albuminuria, such as diabetes mellitus, also are associated with increased risk of dementia.[26] Last, nephrologists often are called upon to manage patients with albuminuria. To date, the focus of dementia evaluation and management for the nephrology community has been in dialysis patients. Recent work from the CHCS showed that cognitive decrease can appear with moderate renal decrease.[27] Our study extends these findings to an earlier stage of renal disease because albuminuria often is present before the decrease in glomerular function.

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SUPPLEMENTARY MATERIALS

Table S1: Neuropsychological tests performed in Cardiovascular Health Cognition Study participants deemed at high risk of having dementia.

Table S2: Unadjusted and adjusted cross-sectional association between albuminuria and the odds of dementia and mild cognitive impairment using multinomial logistic regression.

Table S3: Unadjusted and adjusted prospective association between doubling of albuminuria and risk of incident dementia using Cox proportional hazards regression.

Table S4: Selected characteristics of participants in the Cardiovascular Health Cognition Study cohort categorized by level of white matter disease measured by brain magnetic resonance imaging in 1992 to 1993.

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2007.12.044) is available at www.ajkd.org.

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