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Albuminuria and Dementia in the Elderly: A Community Study

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Abstract

Background—Dementia is associated with microvascular disease of the retina. In this study we examine if 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 and Participants—2316 participants from the Cardiovascular Health Cognition Study who underwent a brain MRI 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 the odds ratio and 95% confidence intervals of dementia and mild cognitive impairment with doubling of albuminuria as compared to the odds with normal cognition.

Results—283 (12.2%) participants had dementia, 344 (14.9%) had mild cognitive impairment, and 1689 (72.9%) had normal cognition. As compared to participants with normal cognition, a doubling

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of albuminuria was associated with increased odds of dementia (OR 1.22, 95% CI, 1.15, 1.29). Adjustment for prevalent cardiovascular disease and cardiovascular risk factors, lipid levels, C reactive protein, estimated GFR, and apolipoprotein E-4 genotype attenuated this association, but it remained statistically significant (OR 1.12, 95% CI, 1.03, 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 are 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.

Keywords

albuminuria; elderly; dementia; mild cognitive impairment; MRI brain

INTRODUCTION

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

Albuminuria, the excessive excretion of protein in the 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, elevated 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 shows many of the same capillary findings as found in brain specimens of people with dementia and with retinal vascular disease (6). These findings lead us to test the hypothesis that albuminuria is associated on cross section with an increased odds of dementia.

METHODS

Participants for this study were from the Cardiovascular Health Study (CHS), an observational study of cardiovascular risk factors in adults 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 four field centers. 5201 participants were recruited in 1989 – 1990. In 1992–1993, 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 upon study entry.

All participants were examined annually at their clinic sites through 1998–1999 (year 11 of the study) with the Modified Mini-Mental State Examination (3MSE) (8) (Table 1). For individuals who did not come to the clinic, interval cognitive information was obtained using the Telephone Interview for Cognitive Status (TICS) (9). Further information on cognition was obtained from proxies using the Informant Questionnaire for Cognitive Decline in the Elderly (IQ CODE) (10) and from physicians for participants who had died or who were unable to fill out the 3MSE or TICS. Information regarding functional status was obtained using activities

of daily living and instrumental activities of daily living using standardized questionnaires. Presence of dementia was documented during medical records review of all deaths and cardiovascular events.

Participants also had baseline blood testing, cardiac and carotid artery ultrasound testing, ECG, ankle brachial index (ABI) measurement, and completion of a medical history and clinical examination as previously described (7). MRIs of the brain were completed in 1991/94 and again in 1997/99 for participants willing and able to be scanned. Apolipoprotein E-4 (ApoE-4) genotype was determined for participants providing consent for use of DNA.

The Cognition Cohort and Definition of Dementia (Figure 1)

In 1998–1999 the Cardiovascular Health Cognition Study (CHCS) was assembled. It identified subjects with prevalent dementia at the time of a brain MRI scan in 1991–1994, and those who subsequently developed dementia through 1998–1999. Inclusion in the CHCS required completion of a 3MSE at the time of the MRI scan and ApoE-4 genotyping. The cohort consisted of 3608 individuals. Of these individuals, 777 (21.6%) had died by 1998–1999. There were 1741 white and 357 African American women, 1282 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 have scanning [due mainly to refusal, inability to complete MRI, or MRI contraindications] had lower 3MSE scores, were less educated, and had more clinical CVD than those who had scanning (11). The groups did not differ with regard to prevalence of apoE-4 genotype.

The 3608 participants were divided into groups at high and low likelihood of having dementia based on cognitive testing, changes in cognitive score, nursing home admission, being alive or dead, and a history of stroke. If a participant was alive in 1998–1999, high risk was defined as a 3MSE score < 80 at one of the last two clinic visits, a 5-point decline in the 3MSE from the time of the MRI to the time of last visit, a TICS score < 28 and an IQ CODE score > 3.6, having an incident stroke, a medical chart review with dementia as a diagnosis, or currently residing in a nursing home. If a participant had died before 1998–1999, he/she was considered to have had a high likelihood of having had dementia if they had at least one of the following: a 3MSE score < 80 within 2 years of death; a > 5 point decline in the 3MSE from the year of MRI to the year closest to death; a TICS score of < 28 or an IQ CODE score > 3.6 within 2 years of death or a diagnosis of dementia in a medical record or a history of incident stroke. Prior analysis has shown that few cases of dementia are missed using this classification system of high risk versus low risk (12,13).

In three clinic sites (in 1998–1999) all living high risk white participants, and all black participants (because of their small sample size) were neuro-psychologically evaluated for dementia [1,192 (44%) were classified as high risk including minorities; 1,492 (56%) of all whites as low risk]. In one center (Pittsburgh, n = 927), all participants underwent evaluation for dementia, whether or not they were considered at high probability for having dementia. This was done to estimate “misses” among 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) (a list of tests is presented as 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 as to affect the participant's activities of daily living, and on a history of normal intellectual function prior to the cognitive decline. An abnormal domain was present when the 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 using all available data. Mild cognitive impairment was defined as cognitive impairment, especially memory deficit, without dementia (14,15).

Following the decision whether or not dementia was present, the classification of the type of dementia was made before and after review of the brain MRI. There was a high degree of correlation of the classifications of the types of dementia both before and after reviewing MRI scans (14). Classification of dementia type was based on several classification systems (see table 1, in ref 13, for a definitions of each set of criteria). The diagnosis of probable Alzheimer's disease was made following the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease Related Disorders Association (NINDS-ADRDA) classification system (16) and required the participant to show a gradual cognitive decline without history or evidence of another illness that could cause mental impairment. There could be no evidence of a focal CNS lesion based on clinical or radiological examinations. Possible Alzheimer's disease used the same criteria as probable Alzheimer's disease but with evidence of other concomitant diseases that may have caused cognitive decline (e.g., depression, hypothyroidism, head injury, alcoholism, CNS infection, 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 (AADTC) (17), and the National Institute of Neurological Diseases and Stroke Association Internationale pour la Recherche et Enseignement en Neurosciences (NINDS-AIREN) (18) criteria were used primarily for these diagnoses. Classification based on the ADDTC criteria includes more vascular dementia than the NINDS-AIREN criteria since MRI data is relied upon 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 TIA at baseline or upon follow up. Only infarcts ≥ 3 mm were included in analyses (reproducibility was low for lesions less than 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 that they had to be hypointense on T1 images in order to distinguish from diffuse white matter disease. White matter changes were estimated by 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 have shown that a high white matter score is an independent predictor of incident clinical stroke (20). When elements of both Alzheimer's disease and vascular dementia were present the participant was diagnosed as having mixed dementia. For these analyses individuals with mixed dementia were included in the vascular dementia group.

Albuminuria Testing

Of the CHCS participants who were alive in 1996–1997, 2389 had albuminuria testing 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 rate nephelometry using the Array 360 CE Protein Analyzer (Beckman Instruments, Fullerton, CA). Urinary creatinine was measured on a Kodak Ektachem 700 Analyzer. Participants with < 30 mg albumin/g creatinine were defined as normoalbuminuria. Those with levels ≥ 30 mg albumin/g creatinine were defined as having albuminuria.

Statistical Methods

Chi square, t-test, and non-parametric methods were used, as appropriate, to compare baseline parameters between those with and without albuminuria and between those with normal cognition, mild cognitive impairment and dementia. Multinomial logistic regression was used to test the association of a doubling of albuminuria in those with mild cognitive impairment

and dementia compared to those with normal cognition. Models were adjusted for (1) age, sex, race, education; (2) history of coronary heart disease (CHD), stroke, hypertension, diabetes and smoking, serum cholesterol, LDL cholesterol, C-reactive protein (CRP), and eGFR; and (3) ApoE-4 genotype. Cox proportional hazards regression models were constructed to assess the association of albuminuria with incident cases of dementia following urine collection in 1997 through follow up in 1999. Analyses were done using SPSS, version 14.0.

RESULTS

Of the 3608 participants in CHCS, 3229 (89.6%) were alive at the time of albuminuria testing (Figure 1). Of these, 840 participants did not have albuminuria testing, leaving 2389 participants for analysis. Participants who did not have albuminuria testing were older (75.7 ± 5.3 vs 74.4 ± 4.8 years, $p < 0.001$) and more likely to be women (66.3 vs 58.3%, $p < 0.001$) than those who had testing. They were similar in distribution of race and prevalence of hypertension and diabetes.

Study Cohort (Figure 1)

There were a total of 356 cases of dementia among the 2389 CHCS participants who had albuminuria testing. The 73 cases of dementia detected prior to the time of brain MRI testing (1991–1994) were excluded from analyses. This left 283 cases of incident dementia occurring during the time period 1992–1999 - 96 detected from the time of MRI testing until prior to 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 time period 344 cases of mild cognitive impairment (MCI) were detected, while 1689 participants retained normal cognition.

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

Baseline Factors

Of the 2389 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 shown in Table 2. As compared to individuals without albuminuria, participants with albuminuria were older, were more likely to be men, to have a history of diabetes, hypertension or both, lower renal function and use ACE inhibitors. They were also more likely to have mild cognitive impairment and dementia.

As compared to subjects without cognitive impairment (Table 3), participants with dementia were older, were more likely to be non-white, had lower attained educational level, and had more diabetes and atherosclerotic vascular disease. They also had higher prevalence of the ApoE-4 genotype, higher systolic blood pressure, lower renal function, and were more likely to use ACE inhibitors. They also had a lower BMI and consumed less alcohol. As compared to participants with dementia, participants with MCI were younger, were more likely to be non-white, to have less evidence of CVD, lower prevalence of apo-E4 genotype, less albuminuria and use more anti-hypertension medications.

Association of Albuminuria with Dementia and MCI

As compared to participants who retained normal cognition (reference value), albuminuria was associated with an increased odds of dementia (Table 4). As a continuous variable, there was

an unadjusted OR 1.22, 95% CI, 1.15, 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 (1.13, 95% CI 1.04, 1.23). When albuminuria was categorically defined, a statistically significant fully-adjusted relationship with dementia was likewise found (OR 1.58, 95% CI, 1.09, 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 mild cognitive impairment 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 1996/97 until 1999 (mean follow up ~2.5 years) were analyzed separately. Among them, 14 participants 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 as compared to the association of albuminuria with normal cognition in unadjusted analysis and with adjustment for demographic factors (RR 1.30, 95% CI 1.08, 1.58). Similar results were obtained when albuminuria was examined categorically (RR 1.96, 95% CI 1.03, 3.74). Owing to small numbers further adjustments were not performed.

With regard to MCI (Table 4), there was a statistically significant association with a doubling of albuminuria as compared to those with normal cognition on unadjusted analysis (OR 1.10, 95% CI 1.04, 1.17). With further adjustments the association of albuminuria with MCI became non-significant (OR 1.04, 95% CI 0.96, 1.13). 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 two main categories – Alzheimer's dementia and vascular dementia. As a continuous variable, doubling of albuminuria was associated with a statistically significant increase in the odds of vascular dementia on adjusted analysis (OR 1.17, 95% CI, 1.12, 1.23) as compared to normal cognition (Table 5). There was a borderline association of albuminuria with Alzheimer's disease (OR 1.10, 95% CI 0.98, 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 elevated white matter score (i.e., ≥ 3) was examined (see Table S4 in the Supplementary Data, with this article at www.ajkd.org for the baseline characteristics of the cohort categorized by white matter score). As seen in Table 6, a doubling of albuminuria was significantly associated with an increased odds ratio of an increased white matter score. When albuminuria was defined categorically similar results were obtained, though adjustment for apo-E4 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 anatomical microvascular similarities found in the brains of people with dementia and in the kidneys of people with albuminuria. Aside from these similarities, functional factors common to both conditions may also explain why these conditions coexist.

For example, people with albuminuria have impaired auto-regulation of glomerular filtration (21) while people with dementia have impaired regulation of cerebrovascular flow (1). Also, albuminuria and dementia may be related to one another 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's dementia was of borderline statistical significance. This suggests that the association of albuminuria with dementia is mainly through vascular mechanisms. While this may be so, studies have shown that microvascular disease exists in Alzheimer's dementia and it is often difficult to accurately differentiate between these two types of dementia. As such our results are broadly applicable to the syndrome of dementia and not specific to dementia type.

Mild cognitive impairment, 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 for the apo-E4 genotype made this association statistically non-significant. This latter finding may be understood in two ways. First, mild cognitive impairment is a heterogeneous disorder, perhaps more strongly associated with Alzheimer's disease than to vascular dementia. Second, it may be that mild cognitive impairment, as an initial phase of cognitive decline, is more strongly related to traditional CVD risk factors that initiate cognitive decline 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 odds ratio of 2.10 (1.04, 4.24) for dementia. In the ARIC study (3), which examined a younger middle aged cohort, the odds ratios varied from 1.91 to 2.60. The somewhat higher association of microvascular eye lesions with dementia as compared to our renal microvascular findings (1.49 [1.02–2.19] for albuminuria > 30 mg/g) may be due to differences in study methods. Also albuminuria is not a pathological diagnosis as compared to the eye studies where direct examination of eye vessels is available.

Limitations of our results should be noted. Our results are cross-sectional. Causality cannot be imputed. The results of the small sub-cohort 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 shows the prevalence of albuminuria to increase from 14.6% at ages 60–69 years to 32.7% at age ≥ 80 years (24). A large pool of older adults is therefore at risk for having or developing dementia in association with albuminuria. Second, our results suggest the possibility that treatments which reduce albuminuria, such as ACE inhibitors / blockers, may have a salutary impact on the development of dementia. The 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, are also associated with increased risk of dementia (26). Last, nephrologists are often 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 has shown that cognitive decline can appear with moderate renal

decline (27). Our study extends these findings to an earlier stage of renal disease, since albuminuria often is present prior to decline in glomerular function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Farkas E, Luiten PGM. Cerebral microvascular pathology in aging and Alzheimer's disease. *Prog Neurobiol* 2001;64:575–611. [PubMed: 11311463]
2. de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. *Stroke* 2002;33:1152–1162. [PubMed: 11935076]
3. Wong TY, Klein R, Sharrett AR, et al. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. *Stroke* 2002;33:1487–1492. [PubMed: 12052979]
4. Baker ML, Larsen EK, Kuller LH, et al. Retinal microvascular signs, cognitive function, and dementia in older persons. The Cardiovascular Health Study. *Stroke*. 2007 May 24;[Epub ahead of print]
5. Barzilay JI, Peterson D, Cushman M, Heckbert SR, Cao JJ, Blaum C, et al. The relationship of cardiovascular risk factors to microalbuminuria in older adults with or without diabetes mellitus or hypertension: The Cardiovascular Health Study. *Am J Kid Dis* 2004;44:25–34. [PubMed: 15211434]
6. Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC. Structural-functional relationships in diabetic nephropathy. *J Clin Invest* 1984;74:1143–1155. [PubMed: 6480821]
7. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;1:263–276. [PubMed: 1669507]
8. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry* 1987;48:314–318. [PubMed: 3611032]
9. Brandt J, Spencer M, Folstein M. The Telephone Interview for Cognitive Status. *Neuropsychiat Neuropsychol Behav Neurol* 1988;1:111–117.
10. Jorm AF, Korten AE. Assessment of cognitive decline in the elderly by informant interview. *Br J Psychiatry* 1988;152:209–213. [PubMed: 3167337]
11. Kuller LH, Shemanski L, Manolio T, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke* 1998;29:388–398. [PubMed: 9472879]
12. Fitzpatrick AL, Kuller LH, Ives DG, et al. Incidence and prevalence of dementia in the Cardiovascular Health Study. *J Am Geriatr Soc* 2004;52:195–204. [PubMed: 14728627]
13. Lopez OL, Kuller LH, Becker JT, et al. Classification of vascular dementia in the Cardiovascular Health Study Cognition Study. *Neurology* 2005;64:1539–1547. [PubMed: 15883314]
14. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the Cardiovascular Health Cognition Study. *Neuroepidemiol* 2003;22:1–12.
15. Lopez OL, Jagust WJ, DeKosky ST, Becker JT, Fitzpatrick A, Dulberg C, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Cognition Study. *Arch Neurol* 2003;60:1385–1389. [PubMed: 14568808]
16. McKhann G, Drachman DA, Folstein MF, et al. NINCDS-ADRDA. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–944. [PubMed: 6610841]
17. Chui HC, Victoroff JI, Margolin D, et al. ADDTC. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology* 1992;42:473–480. [PubMed: 1549205]

18. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250–260. [PubMed: 8094895]
19. Bryan RN, Manolio TA, Schertz LD, Jungreis C, Poirier VC, Elster AD, Kronmal RA. A method of using MR to evaluate the effects of cardiovascular disease on the brain: the Cardiovascular Health Study. *Am J Neuroradiol* 1994;15:1625–1633. [PubMed: 7847205]
20. Kuller LH, Longstreth WT Jr, Arnold AM, Bernick C, Bryan RN, Beauchamp NJ Jr. White matter hyperintensity on cranial magnetic resonance imaging. A predictor of stroke. *Stroke* 2004;35:1821–1825. [PubMed: 15178824]
21. Christensen PK, Hommel EE, Clausen P, Feldt-Rasmussen B, Parvin HH. Impaired autoregulation of the glomerular filtration rate in patients with nephropathies. *Kid Int* 1999;56:1517–1523.
22. Zhu X, Lee HG, Perry G, Smith MA. Alzheimer disease, the two-hit hypothesis: an update. *Biochim Biophys Acta* 2007;1772:494–502. [PubMed: 17142016]
23. Ha H, Kim KH. Pathogenesis of diabetic nephropathy: the role of oxidative stress and protein kinase C. *Diabetes Res Clin Pract* 1999;45:147–151. [PubMed: 10588367]
24. Garg AX, Kiberd BA, Clark WF, Haynes B, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening: Results from NHANES III. *Kidney Int* 2002;61:2165–2175. [PubMed: 12028457]
25. Teo K, Yusuf S, Sleight P, Anderson C, Mookadam F, Ramos B, et al. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET / TRANSCEND) trials. *Am Heart J* 2004;148:52–61. [PubMed: 15215792]
26. Allen KV, Frier BM, Strachan MW. The relationship between type 2 diabetes and cognitive dysfunction: longitudinal studies and their methodological limitations. *Eur J Pharmacol* 2004;490:169–175. [PubMed: 15094083]
27. Seliger SL, Siscovick DS, Stehman-Breen CO, et al. Moderate renal impairment and risk of dementia among older adults: The Cardiovascular Health Cognition Study. *J Am Soc Nephrol* 2004;15:1904–1911. [PubMed: 15213280]

Figure 1.
Time line of the Cardiovascular Health Cognition Study.

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

Modified Mini-Mental State Examination – At baseline examination participants completed the Mini-Mental State Examination (MMSE). Thereafter, the MMSE was replaced by the Modified Mini-Mental State Examination (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. MMSE and 3MSE are strongly related to age and attained education.

Telephone Interview for Cognitive Status – The TICS is a brief, standardized test of cognitive functioning developed for use in situations where in-person cognitive screening is impractical or inefficient (e.g., large-scale population screening, epidemiological surveys, or with patients who are unable to appear in person for clinical follow-up). The test is standardized and validated for use with English-speaking adults, ages 60–98 years. Research has demonstrated 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 Mini-Mental State Examination (MMSE). The TICS Total score provides a measure of global cognitive functioning and can be used to monitor changes in cognitive functioning over time.

Informant Questionnaire for Cognitive Decline in the Elderly - The IQCODE is a short questionnaire designed to assess cognitive decline 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 decline. It performs as well as other tests of cognitive screening tests and correlates well with other cognitive tests. It predicts dementia. It is unaffected by attained education level.

SCREENING TESTS OF FUNCTIONAL STATUS

Activities of Daily Living – functions performed during daily living, such as self-care (feeding oneself, bathing, dressing, 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.

Table 2

Selected characteristics of participants in the Cardiovascular Health Cognition Study cohort categorized by presence or absence of albuminuria (≥ 30 mg albumin / gram creatinine).

	ALB-	ALB+	TOTAL	
Characteristic	N=1871	N=445	N=2316	p
Age				<.001
Under 75	664 (35.5)	130 (29.2)	794 (34.3)	
76–80	733 (39.2)	150 (33.7)	883 (38.1)	
80 or older	474 (25.3)	165 (37.1)	639 (27.6)	
Sex				<.001
Women	1129 (60.3)	227 (51.0)	1356 (58.5)	
Men	742 (39.7)	218 (49.0)	960 (41.5)	
Race				.3
White	1585 (84.7)	372 (83.6)	1957 (84.5)	
Non-White	286 (15.3)	73 (16.4)	359 (15.5)	
History of Diabetes *				<.001
Normal	1494 (82.0)	266 (62.1)	1760 (78.2)	
Impaired Fasting	114 (6.3)	34 (7.9)	148 (6.6)	
Glucose Diabetes	215 (11.8)	128 (29.9)	343 (15.2)	
History of Hypertension *				<.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)	1156 (50.1)	
Hypertension without Diabetes *	705 (38.2)	210 (48.2)	915 (40.1)	<.001
ACE inhibitor use (%)	12.7	22.2	14.6	<.001
Mean creatinine (SD) * mg/dL	0.97 (0.22)	1.10 (0.37)	0.99 (0.26)	<.001
Mean eGFR (SD) *	80.3 (21.3)	72.4 (25.9)	78.8 (22.5)	<.001
Cognition Status				<.001
Normal	1407 (75.2)	282 (63.4)	1689 (72.9)	
MCI	267 (14.3)	77 (17.3)	344 (14.9)	
Dementia	197 (10.5)	86 (19.3)	283 (12.2)	

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; MCI, mild cognitive impairment.

* n's do not add up to 2316 due to missing data of specific characteristic.

eGFR – estimated GFR (ml/min/m²) based on the Modification of Diet in Renal Disease (MDRD) Study equation.

To convert creatinine in mg/dL to umol/L multiply by 88.4; GFR in mL/min/1.73m² to mL/s/1.73m², multiply by 0.01667.

Table 3

Selected characteristics of participants in the Cardiovascular Health Cognition Study cohort categorized by cognitive status. All values are from the baseline examination performed in 1989–1991.

Characteristic	Dementia	MCI	No Cognitive Impairment	P
(N)	283	344	1689	
Age				
Under 75	41 (14.5)	100 (29.1)	653 (38.7)	<.001
76–80 years	102 (36.0)	119 (34.6)	662 (39.2)	
Over 75 years	140 (49.5)	125 (26.3)	374 (22.1)	
Sex				
Women	167 (59.0)	190 (55.2)	999 (59.1)	.4
Men	116 (41.0)	154 (44.8)	690 (40.9)	
Race				
White	228 (80.6)	208 (60.5)	1521 (90.1)	<.001
Non-White	55 (19.4)	136 (39.5)	168 (9.9)	
Education				
LT HS	96 (33.9)	118 (34.3)	308 (18.3)	<.001
High school grad	71 (25.1)	108 (31.4)	492 (29.2)	
Some college	55 (19.4)	63 (18.3)	446 (26.5)	
College grad	61 (21.6)	55 (16.0)	439 (26.1)	
Smoking Status				
Never	136 (48.7)	141 (41.8)	821 (49.5)	.1
Former	126 (45.2)	166 (49.3)	725 (43.7)	
Current	17 (6.1)	30 (8.9)	114 (6.9)	
Alcohol Use*				
None	195 (69.1)	215 (62.9)	871 (51.8)	<.001
1–3 drinks/week	62 (22.0)	88 (25.7)	531 (31.6)	
4 or more drinks/week	25 (8.9)	39 (11.4)	279 (16.6)	
Body Mass Index*				
< 25	138 (50.4)	136 (39.9)	573 (34.2)	<.001
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)	.2
Diabetes	53 (19.6)	61 (18.7)	229 (13.9)	.009
CHD	86 (30.4)	80 (23.3)	373 (22.1)	.009
Stroke	37 (13.1)	26 (7.6)	73 (4.3)	<.001
TIA	17 (6.0)	14 (4.1)	49 (2.9)	.02
CHF	36 (12.7)	44 (12.8)	102 (6.0)	<.001
ABI				
> 1.0	197 (72.2)	258 (78.7)	1395 (85.0)	<.001
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	81 (33.5)	84 (26.8)	332 (21.3)	<.001
Body Mass Index (mean/SD)	25.7 (4.7)	26.6 (4.7)	26.9 (4.4)	<.001
IMT-Common (mean/SD)	1.11 (0.23)	1.09 (0.21)	1.04 (0.21)	<.001
IMT – Internal (mean/SD)	1.57 (0.65)	1.40 (0.55)	1.36 (0.51)	<.001
Systolic BP (mean/SD)	139.7 (22.5)	137.5 (21.5)	135.4 (20.5)	.01
Diastolic BP (mean/SD)	69.3 (12.5)	70.1 (10.7)	69.7 (10.9)	.7
ACE inhibitor use (%)	18.4	18.6	13.1	.005
Any antihypertension medication use (%)	57.6	66.0	55.8	.002
Creatinine (mean/SD) mg/dL	1.04 (0.32)	1.02 (0.29)	0.98 (0.24)	<.001
Cholesterol (mean/SD) mg/dL	201.8 (43.4)	202.4 (40.8)	200.4 (38.6)	.7
LDL (mean/SD) mg/dL	129.3 (39.3)	128.7 (35.7)	127.3 (31.6)	.6
HDL (mean/SD) mg/dL	53.1 (15.1)	54.0 (15.0)	53.3 (14.1)	.7
Fasting glucose (mean/SD) mg/dL	108.3 (36.3)	109.5 (36.5)	104.8 (28.4)	.02
Insulin (mean/SD)	12.7 (11.9)	15.9 (34.9)	13.0 (18.1)	.07
CRP (mean/SD) mg/L	4.2 (5.0)	5.4 (8.7)	4.7 (8.2)	.2
eGFR (mean/SD) mL/min/1.73m ²	74.9 (24.4)	78.5 (23.3)	79.6 (21.9)	<.001
Albuminuria (mean/SD) mg/g creatinine	105.6 (592.2)	83.0 (365.1)	50.9 (260.9)	.02

To convert creatinine in mg/dL to umol/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 uU/mL to pmol/L, multiply by 7.175; eGFR in mL/min/1.73m² to mL/s/1.73m², multiply by 0.01667.

Abbreviations: MCI, mild cognitive impairment; CHD, coronary heart disease; TIA, transient ischemic attack; CHF, congestive heart failure; ABI, ankle brachial index measurement; BP, blood pressure; ACE inhibitor, angiotensin-converting enzyme inhibitor; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

Table 4

Unadjusted and adjusted cross sectional association between albuminuria and the odds of dementia and mild cognitive impairment using multinomial logistic regression. Albuminuria is shown as a continuous variable (log transformed base 2 continuous measure, mg/g creatinine) and as a categorical variable: (albuminuria ≥ 30 mg/g) compared to normal albuminuria (< 30 mg/g) as the reference). Odds ratios (OR), 95% confidence intervals (95% CI) and p-values for each model are shown. Reference category of the multinomial logistic regression is normal cognition.

	Cases/Controls	Unadjusted OR (95% CI)		P	Adjusted for Demographic Factors ¹ OR (95% CI)		P	Adjusted for CVD & Lipid Risk Factors ² OR (95% CI)		P	Adjusted for ApoE ³ OR (95% CI)		P
Albuminuria (Log base 2)	Incident Dementia	283/1689	1.22 (1.15–1.29)	<.001	1.16 (1.08–1.23)		<.001	1.14 (1.06–1.24)		.001	1.13 (1.04–1.23)		.03
	Mild Cognitive Impairment	344/1689	1.10 (1.04–1.17)	.001	1.06 (0.99–1.13)		.08	1.05 (0.98–1.14)		.2	1.04 (0.96–1.13)		.3
Albuminuria < 30 mg/g	Incident Dementia	197/1407	1.00 (reference)		1.00 (reference)			1.00 (reference)			1.00 (reference)		
		86/282	2.18 (1.64–2.89)	<.001	1.77 (1.31–2.40)		<.001	1.64 (1.15–2.32)		.006	1.58 (1.09–2.30)		.02
≥ 30 mg/g	Mild Cognitive Impairment	267/1407	1.00 (reference)		1.00 (reference)			1.00 (reference)			1.00 (reference)		
		77/282	1.44 (1.08–1.91)	.01	1.24 (0.92–1.69)		.2	1.13 (0.80–1.60)		.50	1.07 (0.74–1.54)		.7

¹Model adjusted for demographics: age, sex, race (white/non-white), years of education.

²Model includes demographics plus presence of CHD, stroke, hypertension, diabetes, smoking history, serum cholesterol, LDL cholesterol, C-reactive protein, and eGFR.

³Model includes demographics, CVD and lipid risk factors, plus ApoE-4 phenotype.

Table 5

Unadjusted and adjusted cross sectional association between albuminuria and the odds of Alzheimer's disease and vascular dementia using multinomial logistic regression. Albuminuria is shown as a continuous variable (log transformed base 2 continuous measure, mg/g creatinine) and as a categorical variable: (albuminuria [≥ 30 mg/g] compared to normoalbuminuria [< 30 mg/g]) as the reference). Odds ratios (OR), 95% confidence intervals (95% CI) and p-values for each model are shown. Reference category of the multinomial logistic regression is normal cognition. Cases of dementia not related to Alzheimer's disease or vascular dementia are not included in analysis.

	Cases/Controls	Unadjusted OR (95% CI)	p	Adjusted for Demographic Factors ¹ OR (95% CI)	p	Adjusted for CVD & Lipid Risk Factors ² OR (95% CI)	p	Adjusted for ApoE ³ OR (95% CI)	p
Albuminuria (Log base 2)	152/1689	1.13 (1.04–1.23)	.004	1.05 (0.96–1.16)	.3	1.08 (0.98–1.20)	.1	1.10 (0.98–1.22)	.1
Vascular Dementia	120/1689	1.30 (1.20–1.41)	.001	1.24 (1.13–1.35)	<.001	1.22 (1.10–1.36)	<.001	1.17 (1.12–1.23)	.01
Alzheimer's disease	116/1407 36/282	1.00 (reference) 1.55 (1.04–2.30)	.03	1.00 (reference) 1.27 (0.84–1.93)	.3	1.00 (reference) 1.40 (0.88–2.24)	.2	1.00 (reference) 1.45 (0.89–2.37)	.1
Alzheimer's disease	76/1407 44/282	1.00 (reference) 2.89 (1.95–4.28)	<.001	1.00 (reference) 2.32 (1.54–3.50)	<.001	1.00 (reference) 2.09 (1.28–3.40)	.003	1.00 (reference) 1.86 (1.09–3.15)	.02

¹Model adjusted for demographics: age, sex, race (white/non-white), years of education.

²Model includes demographics plus presence of CHD, hypertension, diabetes and serum glucose, smoking history, serum cholesterol, LDL cholesterol, C-reactive protein, and eGFR.

³Model includes demographics, CVD and lipid risk factors, plus ApoE-4 genotype.

Unadjusted and adjusted cross sectional association between albuminuria and white matter disease (grade 3 or higher) measured in the 1992–1993 brain MRI using multivariate logistic regression. Albuminuria is shown as a continuous variable (log transformed base 2 continuous measure, mg/g creatinine) and as a categorical variable: (albuminuria ≥ 30 mg/g) compared to normoalbuminuria [< 30 mg/g]) as the reference). Odds ratios (OR), 95% confidence intervals (95% CI) and p-values for each model are shown.

Cases/Controls **Unadjusted OR (95% CI)** **p** **Adjusted for Demographic Factors¹ OR (95% CI)** **p** **Adjusted for CVD & Lipid Risk Factors² OR (95% CI)** **p** **Adjusted for ApoE³ OR (95% CI)** **p**

Albuminuria (Log base 2)	715/1582	1.12 (1.07–1.17)	<.001	1.09 (1.04–1.14)	.001	1.07 (1.01–1.13)	.02	1.06 (1.00–1.13)	.04
Albuminuria < 30 mg/g	542/1312	1.0 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Albuminuria ≥ 30 mg/g	173/270	1.55 (1.25–1.92)	<.001	1.40 (1.12–1.75)	.003	1.30 (1.01–1.68)	.04	1.26 (0.97–1.64)	.08

¹Model adjusted for demographics: age, sex, race (white/non-white), years of education.

²Model includes demographics plus presence of CHD, stroke, hypertension, diabetes and serum glucose, smoking history, serum cholesterol, LDL cholesterol, C-reactive protein, and eGFR.

³Model includes demographics, CVD and lipid risk factors, plus ApoE-4 phenotype.