JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 67, NO. 9, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.12.034

ORIGINAL INVESTIGATIONS

Subclinical Cardiovascular Disease and Death, Dementia, and Coronary Heart Disease in Patients 80+ Years

Lewis H. Kuller, MD, DrPH,[a] Oscar L. Lopez, MD,[b,c] Rachel H. Mackey, PhD, MPH,[a] Caterina Rosano, MD, MPH,[a] Daniel Edmundowicz, MD,[d] James T. Becker, PhD,[b,c,e] Anne B. Newman, MD, MPH[a]

ABSTRACT

BACKGROUND The successful prevention and treatment of coronary heart disease (CHD) and stroke has resulted in a substantial increase in longevity, with subsequent growth in the population of older people at risk for dementia.

OBJECTIVES The authors evaluated the relationship of coronary and other peripheral atherosclerosis to risk of death, dementia, and CHD in the very elderly. Because the extent of vascular disease differs substantially between men and women, sex- and race-specific analyses were included, with a specific focus on women with low coronary artery calcium (CAC) Agatston scores.

METHODS We evaluated the relationship between measures of subclinical cardiovascular disease (CAC, carotid intimal medial thickness, stenosis, and ankle brachial index) and risk of dementia, CHD, and total mortality in 532 participants of the Cardiovascular Health Study-Cognition Study from 1998/1999 (mean age, 80 years) to 2012/2013 (mean age, 93 years).

RESULTS Thirty-six percent of participants had CAC scores >400. Women and African-Americans had lower CAC scores. Few men had low CAC scores. CAC score and number of coronary calcifications were directly related to age-adjusted total mortality and CHD. The age-specific incidence of dementia was higher than for CHD. Only about 25% of deaths were caused by CHD and 16% by dementia. Approximately 64% of those who died had a prior diagnosis of dementia. White women with low CAC scores had a significantly decreased incidence of dementia.

CONCLUSIONS In subjects 80+ years of age, there is a greater incidence of dementia than of CHD. CAC, as a marker of atherosclerosis, is a determinant of mortality, and risk of CHD and myocardial infarction. White women with low CAC scores had a significantly decreased risk of dementia. A very important unanswered question, especially in the very elderly, is whether prevention of atherosclerosis and its complications is associated with less Alzheimer disease pathology and dementia. (Cardiovascular Health Study [CHS]; NCT00005133) (J Am Coll Cardiol 2016;67:1013-22)

From the [a]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; [b]Department of Neurology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; [c]Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; [d]Department of Medicine, Section of Cardiology, Temple University School of Medicine, Philadelphia, Pennsylvania; and the [e]Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania. This research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, and N01HC85086; and grant U01HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided by R01AG023629 from the National Institute on Aging and, in part, by grants AG20098, AG15928, and AG05133 from the National Institute on Aging. The funding sources did not have any role in the study design; collection, analysis, or interpretation of data; preparation of the manuscript; or decision to submit it for publication. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 29, 2015; revised manuscript received November 24, 2015, accepted December 14, 2015.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ABBREVIATIONS AND ACRONYMS

AA = African American
CAC = coronary artery calcium
CAD = coronary artery disease
CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
HR = hazard ratio
IMT = intimal medial thickness
MCI = mild cognitive impairment
MI = myocardial infarction
MRI = magnetic resonance imaging
PY = person-years

The prevention and treatment of cardiovascular disease (CVD) has been a primary determinant of increased longevity of older individuals. Improved therapies for clinical coronary heart disease (CHD) and reduced risk factor levels have led to older age at first heart attack, and to higher prevalence of clinical and subclinical CHD (1–5). Women have a lower incidence of clinical CHD than men, even at older ages, and less coronary atherosclerosis, as measured by coronary artery calcium (CAC) (4,6,7). Women also have a first heart attack at an older age than men: at about 72 years of age in women and in the mid-60s in men (8). The extent of subclinical coronary atherosclerosis is a very powerful predictor of risk of clinical coronary artery disease (CAD), congestive heart failure, and stroke (6,9–13). A zero CAC Agatston score is associated with very long-term lower risk of CHD and death, even at older ages (14).

The greater longevity has resulted in an increased population of older people at risk for dementia. Most dementia cases in the United States are older than the age of 75 years at the time of diagnosis. Women live longer than men and, therefore, are at increased lifetime risk for Alzheimer disease, especially at 85+ years of age (15–19). The overall incidence rate of all-cause dementia was similar in men and women in the 90+ study (20). The pathology of dementia at this older age included Alzheimer disease pathology, neurodegeneration, and brain vascular disease (21,22). Numerous studies have documented the association between brain and systemic vascular disease, and risk of dementia (23–31). An important unanswered question is whether older subjects who survived to 80+ years of age with minimal cerebral, peripheral, or coronary atherosclerosis have a reduced risk of dementia and brain neuropathology, as compared with most older patients with extensive subclinical vascular disease.

SEE PAGE 1023

Few longitudinal studies have evaluated the relationship between CAC and risk of dementia (31). In the Rotterdam Study, common carotid artery intimal medial thickness (IMT), carotid plaque, and peripheral arterial disease were associated with increased risk of dementia greater than 9 years, attenuated with longer follow-up. The extent of calcification in the coronary arteries, aortic arch, extracranial carotid arteries, and intracranial carotid arteries was correlated cross-sectionally with lower cognitive scores (31–33). Calcification in the intracranial and extracranial carotid arteries (but not coronary artery calcification) was a risk factor for incident dementia. In the Age, Gene/Environmental Susceptibility Study (34), dementia increased with age and was significantly related to quartiles of CAC, reduced by adjustment for other risk factors.

The incidence of dementia (1992 to 1998) was higher in participants with prevalent CVD in a previous report from the Cardiovascular Health Study (CHS). The risk of dementia was higher with increased common and internal carotid IMT, and lower ankle-brachial index (35). Participants with higher CAC scores or greater carotid IMT measurements had more CVD events over 5 years of follow-up (36). Higher CAC scores were associated with more brain magnetic resonance imaging (MRI) vascular abnormalities, and with both mild cognitive impairment (MCI) and prevalent dementia, but not after age adjustment (37,38). Black persons had lower CAC than white persons (39).

In this study, we examined the relationship of subclinical CAD and risk of clinical CVD and dementia at 80+ years of age in 532 participants of the CHS Cognition Study (CHS-CS) in Pittsburgh from 1998/1999 to 2014. We specifically tested 2 hypotheses in participants aged 80+ years followed for 10+ years: whether CAC and other measures of subclinical vascular disease predict risk of death and risk of dementia and CHD. We further evaluated whether these associations were similar among men and women.

This report differs from previous CHS publications that included CAC by including predominantly older-age participants 80+ years of age, much longer follow-up, more detailed evaluations of dementia status, and incident (as compared with predominantly prevalent) dementia.

METHODS

The CHS-CS dementia follow-up study was a continuation of the original CHS limited to the Pittsburgh field center of the CHS from 1998/1999 to 2014. In 1992 to 1994, a total of 924 participants had an MRI of the brain. In 1998/1999, 532 of the 924 (58%) participants were included in the Pittsburgh CHS-CS (1998/1999 through 2014) if alive and not demented in 1998/1999, and having either a second MRI and/or a detailed cognitive evaluation in 1998/1999 (40,41). There were 199 deaths and 116 demented before 1998/1999 and, of the 609 participants eligible for the Pittsburgh CHS-CS, 87.5% (n = 532) were included in the study: 449 who had a second MRI and 83 with detailed cognitive evaluation only. The 77 eligible participants not included in the detailed study were followed as part of the CHS, but did

not have repeat MRI or detailed cognitive evaluations after 1998/1999. Also, 14 of the 532 participants refused further evaluations and have been excluded from most of the analysis (Online Figure 1).

The detailed methods for the CHS-CS have been published (41). MRI acquisition and measurements have been described. MRI scanning was completed using a 1.5-T scanner, as previously described (42,43). White matter lesions and ventricular size were determined using a linear scale from 0 to 9 on the basis of a referenced standard.

COGNITIVE AND NEUROLOGICAL EVALUATIONS. All participants had a neuropsychological battery in 1998/1999, which was repeated yearly through 2013. For those participants who could not come in to the clinic for cognitive evaluation, information on cognitive status was obtained at home visits (41) or by telephone, using the Telephone Interview for Cognitive Status. Information on cognition was also obtained from proxies using the Dementia Questionnaire. Symptoms of depression were measured annually with the modified Centers for Epidemiological Studies Depression Scale (41,44). Neurological examinations were done in 1998/1999 and annually from 2002/2003 through 2013.

DIAGNOSTIC PROCEDURE. Diagnosis of dementia was on the basis of a deficit in performance of sufficient severity to affect instrumental activities of daily living in 2 or more cognitive domains, with a history of normal intellectual function before the onset of cognitive abnormalities. A memory deficit was not required for the diagnosis of dementia. Dementia was further classified by type of dementia using standard criteria (41). Participants were classified by adjudicators as having dementia, MCI, or as cognitively normal and then adjudicated to specific type of dementia or MCI on the basis of standard criteria (40,41).

Prevalent CHD was determined at entry into the CHS. Methods of evaluating the prevalent CHD diagnosis have been published (35,37). Incident events occurring after the baseline were evaluated every 6 months, by telephone call or clinic visit, followed by review of medical records and informant interviews, and adjudicated by a committee through 2014 (35,37). The definition of CHD included myocardial infarction (MI), angina pectoris, angioplasty, coronary artery bypass graft, silent MI, and death caused by CHD (45,46).

CAC was measured in May 1998 to June 2000 by electron beam tomography scanning. Quantification of CAC was measured in 434 of 532 (82%) participants in the CHS-CS (35,37). Ultrasound measures of the carotid arteries were obtained using a Toshiba SSA

TABLE 1 Relationship of Risk Factors in 1998/1999 and CAC Agatston Scores in the CHS-CS (n = 311 Free of CVD in 1998/1999)*

	CAC Agatston Score				
	≤10	11–100	101–400	>400	Age-Adjusted p Value
Median age, yrs	75	77	76	78	<0.0001
Race and sex					
White women	25 (16)	33 (21)	44 (28)	55 (35)	
Black women	18 (40)	10 (22)	12 (27)	5 (11)	
White men	5 (6)	12 (16)	18 (23)	42 (55)	
Black men	10 (34)	5 (17)	5 (17)	9 (32)	<0.0001
Smoking					
Never	25 (45)	27 (44)	42 (55)	41 (38)	
Past	24 (44)	31 (51)	27 (36)	56 (52)	
Current	6 (11)	3 (5)	7 (9)	10 (9)	0.291
Hypertension					
No	35 (61)	34 (57)	41 (54)	62 (57)	
Yes	22 (39)	26 (43)	35 (46)	47 (43)	0.863
SBP, mm Hg					
≤120	22 (39)	21 (35)	21 (28)	41 (38)	
121–140	22 (39)	25 (42)	32 (43)	38 (35)	
>140	12 (21)	14 (23)	21 (28)	30 (28)	0.780
DBP, mm Hg					
≤65	19 (34)	27 (45)	23 (31)	52 (48)	
66–74	24 (43)	20 (33)	27 (36)	36 (33)	
≥74	13 (23)	13 (22)	24 (32)	21 (19)	0.208
HDL-C, mg/dl					
≤45	13 (26)	7 (13)	19 (28)	34 (35)	
46–56	13 (26)	23 (42)	27 (39)	28 (29)	
>56	24 (48)	25 (45)	23 (33)	35 (36)	0.059
LDL-C, mg/dl					
≤112	20 (40)	21 (38)	28 (41)	33 (35)	
113–133	15 (30)	19 (35)	17 (25)	30 (32)	
>133	15 (30)	15 (27)	23 (34)	32 (34)	0.909
Triglycerides, mg/dl					
≤93	2 (42)	24 (44)	20 (29)	33 (34)	
94–140	16 (32)	23 (42)	22 (32)	36 (37)	
>140	13 (26)	8 (15)	27 (39)	28 (29)	0.116
Diabetes					
No	49 (88)	53 (88)	67 (91)	100 (92)	
Yes	7 (13)	7 (12)	7 (9)	9 (8)	0.810
Wall maximum-common, mm					
≤0.95	24 (45)	20 (33)	20 (26)	23 (22)	
0.96–1.06	13 (25)	15 (25)	19 (25)	23 (22)	
1.07–1.24	11 (21)	16 (27)	22 (29)	28 (27)	
>1.24	5 (9)	9 (15)	15 (20)	30 (29)	0.074
Wall maximum-internal, mm					
≤1.01	26 (49)	20 (34)	21 (28)	17 (17)	
1.02–1.45	15 (28)	17 (29)	18 (24)	19 (18)	
1.46–2.15	10 (19)	12 (20)	17 (23)	30 (29)	
>2.15	2 (4)	10 (17)	18 (24)	37 (36)	<0.0001
ABI					
<0.9	4 (7)	11 (18)	15 (20)	25 (24)	
≥0.9	51 (93)	49 (82)	60 (80)	78 (76)	0.075

Values are n (%) unless otherwise indicated. *Comparison of level of risk factor and CAC Agatston score.

ABI = ankle brachial index; CAC = coronary artery calcium; CHS-CS = Cardiovascular Health Study Cognition Study; CVD = cardiovascular disease; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

TABLE 2 Causes of Death by Dementia Status to 2015 in the CHS-CS (n = 422 [79%] of 532 Deaths)

	Deceased-Normal*	Deceased-MCI*	Deceased-Demented*	Total
No cause of death	0 (0)	1 (1.4)	1 (0.4)	2
Atherosclerotic CHD	22 (28.2)	19 (26.0)	65 (24.0)	106
Cerebrovascular disease	3 (3.9)	4 (5.5)	17 (6.3)	24
Other atherosclerotic disease	2 (2.6)	2 (2.7)	6 (1.9)	9
Other CVD	3 (3.9)	4 (5.5)	6 (2.2)	13
Noncardiovascular	48 (61.5)	43 (58.9)	177 (65.3)	268
Dementia	0 (0)	1 (1.4)	66 (24.4)	67
Parkinson disease	0 (0)	0 (0)	13 (4.8)	13
Pneumonia	2 (2.6)	2 (2.7)	11 (4.1)	15
Sepsis	0 (0)	1 (1.4)	12 (4.4)	13
Cancer	34 (43.6)	22 (30.1)	38 (14.0)	94
Other	12 (15.4)	17 (23.3)	36 (13.3)	66
Total	78 (18)	73 (17)	271 (64)	422

Values are n (%). *Status before death.
CHD = coronary heart disease; MCI = mild cognitive impairment; other abbreviations as in Table 1.

2070A (Toshiba America Medical Systems, Tustin, CA) ultrasound instrument (36,37). Analysis was restricted to 311 (72%) of the 433 subjects free of clinical CAD in 1998/1999 (**Table 1**, Online Figure 1).

STATISTICAL ANALYSES. Descriptive statistics characterized the study population. Categorical variables were presented as frequency and percentage, and continuous variables as mean ± standard deviation or median and interquartile ranges if the distribution was skewed. Age-adjusted rates and their 95% confidence intervals (CIs) were calculated using the direct method. To quantify hazard ratios (HRs) and 95% CIs for the outcome, we used Cox proportional hazard models adjusted for potential confounders. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina). All models were 2-sided at alpha = 0.05. Cognitive status was adjudicated to 2013, and death to 2011 centrally and locally at Pittsburgh to 2014. The adjudicators of CVD did not have access to CHS-CS dementia evaluations. Person-years (PY) of follow-up for most analyses began at the time of entry to the Pittsburgh CHS-CS in 1998/1999 because participants had to be alive and free of dementia on the basis of 1998/1999 evaluations. Participants were censored for PY at either the time of incident diagnosis of dementia or death. Competing risk survival models were used to quantify HRs for dementia and CHD, where those who died without dementia or CHD were treated as having competing events. The average time between the dementia diagnosis and death was 5 years. All deaths were evaluated for a diagnosis of dementia before death. Because follow-up in the CHS was every 6 months and yearly for dementia evaluation, detailed information about cognitive performance before death was almost always available.

RESULTS

The analysis was restricted to 311 (72%) of the 433 participants free of clinical CAD in 1998/1999 (**Table 1**). There were 157 white women, 45 African-American (AA) women, 77 white men, 29 AA men, and 3 others. AAs have lower CAC Agatston scores than whites, and men have higher CAC Agatston scores than women (39). The association of CAC and risk factors at baseline is shown in **Table 1**.

TOTAL MORTALITY. The median age of death for 73 cognitively normal participants before death was 86 years, for 67 subjects with MCI it was 89 years, and for 269 subjects with a diagnosis of dementia before death it was 90 years of age. The median year of death was approximately 9 years after the beginning of study and CAC measurements in 1998/1999.

Only 106 of 422 deaths (25%) were adjudicated by the CHS as caused by CHD and 24 (6%) by stroke (**Table 2**). Dementia was the cause of death in 67 (16%). Approximately 64% of deaths (n = 271) had a prior diagnosis of dementia on the basis of adjudication in the CHS-CS.

CAC scores were significantly related to total mortality for white men and black women, and showed a nonsignificant trend (p = 0.11) for white women (**Table 3**, Online Table 1).

In a Cox regression model, CAC scores >400 versus <10 were an independent significant predictor of total mortality for the entire sample (HR: 1.73; 95% CI: 1.18 to 2.54). Other predictors were age and the extent of white matter grade in the brain. Traditional CVD risk factors and measures of physical activity were not independent predictors of mortality (Online Table 2). Smoking, lower cognitive scores, diabetes, and higher interleukin-6 were also predictors with wide confidence limits (Online Table 2).

DEMENTIA. The age-specific incidence of dementia was similar for men and women (41). Among white women, the incidence of dementia with a CAC score of 0 was approximately one-third the rate for women with CAC scores >400 (p = 0.04) (**Table 3**, **Central Illustration**). There were no significant trends of CAC and risk of dementia for white men (**Table 3**), or for AA men and women (Online Table 1). The analysis was limited by the small number of participants, especially for subjects with low CAC scores.

Time to dementia from the initial CAC measurement was 7.1 ± 1.6 years for those with CAC scores of 0 ± versus 5.2 ± 3.3 years for those with CAC scores

TABLE 3 Death and Dementia Rates* to 2011 and CAC Agatston Score Among CHS-CS Participants, White Participants Only, Alive, Not Demented, and No CVD at 1998/1999 by Sex

	Death						Dementia					
	Women (n = 148)			Men (n = 74)			Women (n = 121)			Men (n = 67)		
CAC Agatston Score	Population	Death	Age-Adjusted Rate/1,000 PY†	Population	Death	Age-Adjusted Rate/1,000 PY†	Population	Dementia	Age-Adjusted Rate/1,000 PY†	Population	Dementia	Age-Adjusted Rate/1,000 PY†
0	14	7	49 (24–103)	4	0	0	14	4	31 (12–83)	4	3	77 (25–239)
1–10	11	5	40 (17–96)	1	0	0	9	4	52 (20–138)	1	0	0
11–100	32	19	56 (25–134)	11	8	78 (39–157)	28	16	74 (31–193)	10	7	111 (53–233)
101–400	41	29	76 (41–142)	18	8	70 (20–280)	33	18	84 (37–194)	17	6	28 (13–63)
>400	50	33	67 (37–121)	40	30	82 (44–157)	37	23	102 (51–205)	35	18	81 (38–188)
	Trend p = 0.110			Trend p = 0.01			Trend p = 0.044			Trend p = 0.432		

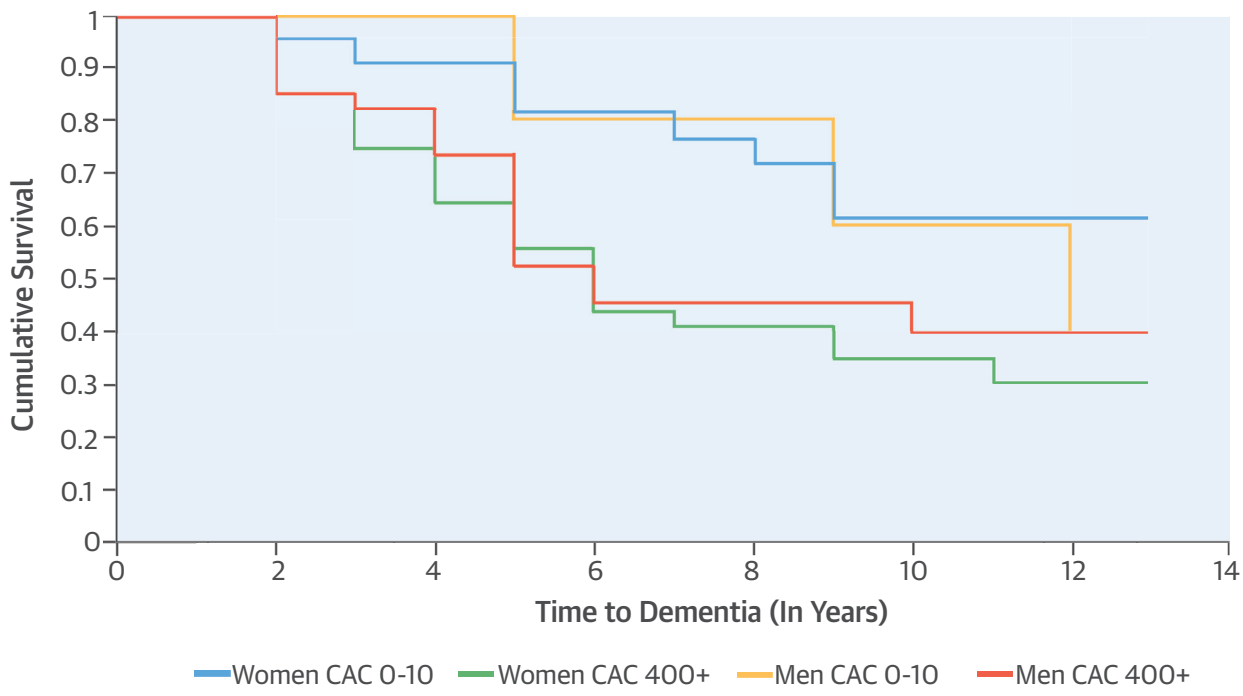
Values are n unless otherwise indicated. *Dementia rates restricted to participants without incident dementia before 1998/1999. †95% confidence limits.
PY = person-years; other abbreviations as in Table 1.

>400. The mean age at dementia onset (83 years) was unrelated to CAC levels (Central Illustration).

Brain MRI abnormalities, including ventricular and white matter grade, markers of brain infarct, were directly related to CAC score, but did not modulate any relationship of CAC and risk of dementia. There was no significant association between hippocampal volume or ApoE4 and CAC for white men or women (not shown).

For white women, lower ankle brachial index was significantly related to an increased incidence of dementia, and for white men, maximal percent stenosis (inversely) was significant related to the risk of dementia (Table 4). Risk of dementia increased with

CENTRAL ILLUSTRATION Coronary Artery Calcium and Risk of Dementia: Cumulative Incidence of Dementia, 1998/1999 to 2013 for White Women and Men by CAC Score 0 to 10 and 400+



Kuller, L.H. et al. J Am Coll Cardiol. 2016; 67(9):1013–22.

The incidence of dementia is similar in men and women. Men with low CAC scores from 0 to 10 have a low cumulative incidence of dementia. CAC = coronary artery calcium.

TABLE 4 Age-Adjusted Incidence of CHD (Excluding Participants With CVD [CHD, CHF, Stroke, MI] at 1998/1999) and Dementia by Carotid Artery Measures and ABI by Sex Among CHS-CS Participants, White Participants Only

	CHD at 2014				Dementia at 2012*			
	Women (n = 170)		Men (n = 87)		Women (n = 137)		Men (n = 76)	
1998/1999 Variables	Population	Age-Adjusted Rate/1,000 PY†	Population	Age-Adjusted Rate/1,000 PY†	Population	Age-Adjusted Rate/1,000 PY†	Population	Age-Adjusted Rate/1,000 PY†
Wall max-common, mm								
≤0.95	55	25 (10-59)	20	30 (10-86)	44	73 (36-149)	18	132 (41-453)
0.951-1.06	44	26 (11-70)	20	62 (22-181)	36	85 (39-184)	20	85 (30-252)
1.061-1.24	43	46 (21-103)	22	95 (26-457)	34	99 (47-209)	19	44 (19-124)
>1.24	26	32 (14-76)	25	71 (29-217)	23	81 (36-180)	19	71 (29-173)
p for trend		0.074		0.190		0.747		0.998
Wall max-internal, mm		(n = 166)		(n = 87)		(n = 136)		(n = 76)
<1.01	37	26 (9-78)	24	40 (15-129)	31	68 (29-165)	21	93 (38-246)
1.011-1.45	42	25 (10-67)	22	75 (26-218)	32	81 (35-188)	21	83 (33-231)
1.451-2.15	54	37 (17-82)	18	55 (20-155)	46	84 (44-165)	16	67 (20-286)
>2.15	33	53 (23-125)	23	85 (34-218)	27	116 (54-254)	18	51 (15-198)
p for trend		0.028		0.290		0.221		0.214
Maximum % stenosis		(n = 167)		(n = 86)		(n = 137)		(n = 75)
Normal	42	23 (8-67)	26	34 (12-115)	34	67 (29-155)	24	120 (57-278)
1-24	77	36 (19-67)	36	63 (27-150)	60	80 (45-144)	30	55 (21-156)
25-49	40	38 (16-95)	20	88 (34-239)	35	105 (51-221)	17	56 (19-168)
≥50	8	34 (11-106)	4	59 (15-235)	8	88 (37-211)	4	80 (20-320)
p for trend		0.290		0.073		0.355		0.047
ABI		(n = 168)		(n = 89)	(n = 137)			(n = 78)
<0.9	33	34 (12-98)	12	70 (31-155)	28	125 (58-274)	9	43 (14-135)
≥0.9	135	31 (19-53)	77	57 (32-102)	109	74 (46-119)	69	75 (43-136)
p for trend		0.621		0.834		0.020		0.487

Values are n unless otherwise indicated. *Restricted to participants without incident dementia before 1998/1999. †95% confidence limits.
CHF = congestive heart failure; MI = myocardial infarction; other abbreviations as in Tables 1 to 3.

greater carotid artery wall maximal IMT, especially for white women, but not significantly.

CHD, CVD INCIDENCE. There were 146 incident CHD, mean age 85.0 ± 5.3 years (Online Figures 2 and 3). There were 61 CHD events among white women, 44 CHD events among white men, 17 CHD events for AA women, and 11 CHD events for AA men. Median time for the 133 incident CHD events from 1998/1999 was approximately 6 years. There was little difference in the time to clinical incident events by race and sex.

The age-specific incidence of dementia was greater than for CHD at all ages for women and at older ages for men (**Table 5**). There were too few events among participants age 85+ years in 1998/1999 to be included in the analysis (**Table 5**). Incidence of CHD, but not dementia, was higher in men than women. Risk factors for CHD are shown in Online Table 3 and were previously published in the CHS (37).

CHD incidence was directly related to extent of CAC for white men and for both white and black women (**Figures 1 and 2**). Results were similar when restricted to only MI. Among 14 white women with CAC scores of 0, there were no MIs, as compared with 11 of 58 (19%) in subjects with CAC scores >400, an age-adjusted incidence rate of 17 per 1,000 PY. Among black women, only 1 of 11 MIs had a 0 CAC score, as compared with 2 of 5 (40%) among the small number with CAC >400. In a Cox competing risk model (Online Table 2) comparing CAC scores <10 with those >400, the HR for CHD was 1.54 (95% CI: 0.83 to 2.86). Diabetes mellitus and subclinical CVD were significant predictors of CHD (47).

We also evaluated the relationship between the number of coronary artery calcifications and risk of dementia and CHD for white men and women (Online Table 4). The CAC Agatston score and number of calcifications was highly correlated, 0.817 (p = 0.0001). The incidence of CHD was significantly related to the number of calcifications for both white men and women: for whites, p = 0.003; for white women, p = 0.215; and for white men, p = 0.041.

The age-adjusted incidence of dementia was very low for white women with very few calcifications (e.g., 0, 1, or 2 [p = 0.19]) (Online Table 4). There was an approximately 2-fold difference in the dementia rates from the very low to very high number of calcifications for white women, but no association for white men.

TABLE 5 Comparison of Incidence of Dementia and CHD by Age, Race, and Sex in 1998/1999 Among CHS-CS Participants With CAC Measurement Only

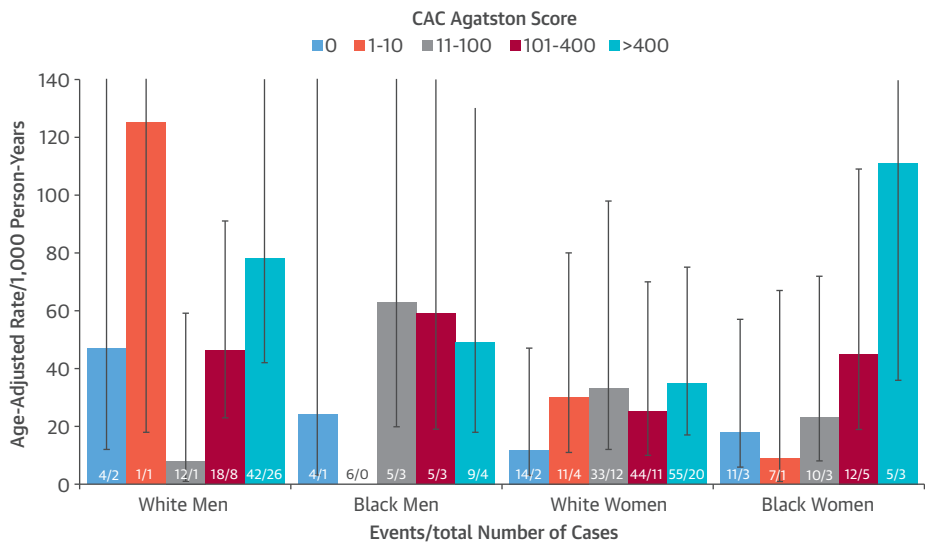
		Dementia at 2011–2012			CHD at 2013–2014		
	Age (Yrs) in 1998/1999	N	Demented	Age-Specific Rate/1,000 PY*	N	CHD	Age-Specific Rate/1,000 PY*
Women							
White	≤75	49	27	67 (46-98)	45	12	22 (13-40)
	76-80	79	45	78 (58-104)	77	22	24 (16-37)
	81-85	30	19	126 (80-197)	30	12	52 (30-92)
Black	≤75	24	10	48 (26-90)	24	6	19 (8-42)
	76-80	14	10	98 (53-182)	16	7	43 (21-91)
	81-85	4	4	129 (48-344)	4	1	18 (3-129)
Men							
White	≤75	20	7	41 (19-85)	16	7	44 (21-93)
	76-80	69	36	76 (55-106)	48	24	56 (38-84)
	81-85	15	9	92 (48-177)	11	6	85 (38-188)
Black	≤75	10	4	57 (21-152)	11	4	32 (12-85)
	76-80	9	6	90 (40-199)	13	6	44 (20-98)
	81-85	7	4	129 (48-344)	4	1	33 (5-237)

Values are n unless otherwise indicated. *95% confidence limits.
Abbreviations as in Tables 1 to 3.

Maximum wall thickness in both the internal and common carotid artery was related to the risk of CHD for white women, and maximal stenosis was related to the risk of CHD for white men (Table 4). There was a nonsignificant trend of increased incidence of CHD for both common and internal carotid artery wall thickness for white men (Table 4).

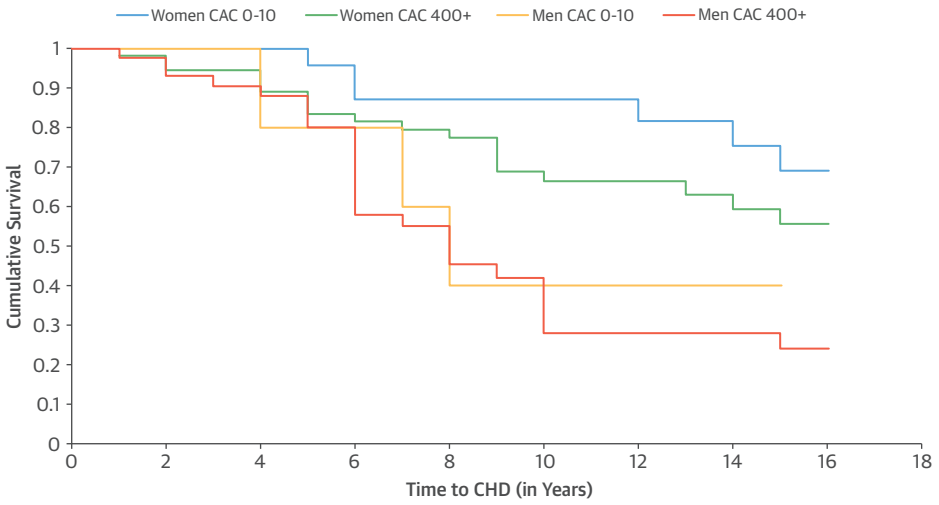
Among 412 participants free of dementia as of 1998/1999, a total of 90 (22%) had a clinical diagnosis of CHD before 1998/1999: 73 white, 15 AA, and 2 other. By 2014, 56% had become demented, as compared with 55% of those without CHD in 1998/1999. The risk of dementia increased from 6% per year in those 65 to 74 years of age in 1998/1999 to 15% per year in those who were 80+ years of age in 1998/1999. Among white women, history of CHD was associated with greater risk of dementia than no history of CHD from 65 to 74 years of age, 66 per 1,000 PY versus 146 per

FIGURE 1 CAC Scores in 1998/1999 in Relation to Age-Adjusted Incident CHD Through 2014 by Race and Sex



CHD incidence, even in the very old, is higher in men than in women and positively related to CAC score, especially low rates (0 CAC).
CAC = coronary artery calcium; CHD = coronary heart disease.

FIGURE 2 Cumulative Incidence of CHD, 1998/1999 to 2013 for White Women and Men by CAC Scores 0 to 10 and 400+



Cumulative incidence of CHD is higher in men than women. Both white men and women with lower CAC scores have reduced risk of CHD. Abbreviations as in Figure 1.

1,000 PY; from 75 to 80 years of age, 72 per 1,000 versus 130 per 1,000; and >80 years of age, 113 per 1,000 versus 146 per 1,000 (Online Table 5). Results were in the same direction for white men, but limited by the small sample size.

At the end of the study in 2013, only 47 (9%) of survivors were free of dementia, for example normal (n = 19) and MCI (n = 28), mean age 92 years among 517 participants in 1998/1999, including 33 survivors free of dementia who had CAC measured in 1998/2000 (Online Table 6). CAC and ankle brachial index were significantly lower, especially for alive versus dead, but did not differentiate dementia versus no dementia for either alive or dead participants. Cigarette smoking was significantly less for the alive, nondemented participants. There was also a lower prevalence of hypertension and greater number of blocks walked among those who were alive and nondemented (Online Table 6). Results were similar when CAC analysis was restricted to participants without CVD in 1998/1999.

DISCUSSION

The incidence of dementia in participants 80+ years of age is greater than for CHD, especially for women. Only about one-fourth of the deaths in this older-age population, 80+ years of age, were attributed to CAD and 16% caused by dementia. Almost two-thirds of those who died had been diagnosed with dementia, on an average of 5 years before death. Previous studies underestimated the incidence of dementia in older-age groups because of the use of insensitive instruments and infrequent cognitive evaluations (20).

Zero or very low CAC scores among white women was associated with a very low risk of dementia, CHD, MI, and total mortality on the basis of a small number of white women with 0 or very low CAC scores. These results are consistent with other studies (48). A recent abstract from the Multi-Ethnic Study of Atherosclerosis noted, solely on the basis of hospital records, much lower rates of many diseases, including dementia, for participants 45 to 84 years of age with low CAC scores followed for 8 years (49).

We previously reported in the Healthy Women Study that premenopausal risk factors measured at ~48 years of age were predictors of post-menopausal CAC, even to approximately 80+ years of age. Approximately 57% of women had CAC scores of 0 at age 62, a total of 12 years post-menopausal (50). Women converted from 0 CAC to some CAC at about 6% per year over the next 12 years; for example, 27% at 0 CAC at age 72, and only 13% of the women at 80+ years of age had CAC scores of 0 in the CHS. Low CAC Agatston scores are a measure of risk factors many years before the CAC measurements.

These results suggest several scenarios. First, the prevalence of dementia in older populations will likely increase with continued improvement in prevention and treatment of CHD and increasing longevity of the population, assuming that no new therapies either prevent or delay the onset of incident

dementia. As age at first heart attack continues to rise, dementia will be an important comorbidity and will affect treatment decisions and outcomes.

Second, a 0 or very low CAC Agatston score was associated with lower incidence of dementia among women.

Third, cardiovascular risk factors, such as elevated blood pressure, diabetes, cigarette smoking, physical inactivity, and abnormal lipoprotein metabolism, are determinants of progression of atherosclerosis to CHD, and could also affect progression of brain pathology, such as amyloid, tau, or neurodegeneration and risk of dementia in the elderly (21,22,28,51). Clinical trials that have evaluated treatment of some of these risk factors, such as blood glucose and lipid lowering, antihypertensive therapy, and recently increasing physical activity, have not consistently demonstrated a reduced risk of dementia. A broad-based cardiovascular risk reduction study also showed improved cognitive function (41).

If delay or prevention of peripheral atherosclerosis resulted in the reduction or slowing of progression of brain neuropathology and subsequent incidence of dementia, then there is the potential for a very substantial impact on reducing most dementia in very old ages (e.g., 80+ years of age). There is a need to test such hypotheses by substantially modifying risk factors, slowing the progression of atherosclerosis, and determining whether such an effect will substantially reduce the incidence of dementia and specific neuropathology among older patients.

STUDY LIMITATIONS. The sample size is small because few women and practically no men in this older age group have 0 CAC scores. The results, on the basis of a small sample size, need replication in other studies of the elderly, with frequent sensitive measures of dementia and CAC.

CONCLUSIONS

A very important unanswered question is whether 0 or very low CAC scores or other measures of lower extent of atherosclerosis or arteriosclerosis are associated with reduced risk of incident dementia. Interventions to modify known risk factors to prevent the progression of atherosclerosis and arteriosclerosis could result in a decreased older-age incidence of CHD, CVD, and dementia. The alternative could be an unfortunate outcome: that successful control of risk factors and treatment of CHD results in an increasing epidemic of dementia among older people.

ACKNOWLEDGMENTS A full list of principal Cardiovascular Health Study investigators and institutions can be found at CHS-NHLBI.org.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Lewis H. Kuller, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 North Bellefield Avenue, Room 550, Pittsburgh, Pennsylvania 15261. E-mail: kullerl@edc.pitt.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In subjects 80 years of age and older, the incidence of dementia exceeds that of coronary heart disease, but coronary artery calcification, a marker of atherosclerosis, is a determinant of mortality and the risk of myocardial infarction in this elderly population.

TRANSLATIONAL OUTLOOK: Despite its multiple etiologies in the elderly, further research is needed to determine whether the incidence of dementia can be reduced through modification of vascular risk factors or other variables associated with aging.

REFERENCES

1. Fleg JL, Forman DE, Berra K, et al. Secondary prevention of atherosclerotic cardiovascular disease in older adults: a scientific statement from the American Heart Association. Circulation 2013;128:2422–46.

2. Gerber Y, Weston SA, Jiang R, et al. The changing epidemiology of myocardial infarction in the population, 1995-2012 (abstr). Circulation 2014;130:A15807.

3. Go AS, Mozaffarian D, Roger VL, et al., for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2014 update: a report from the American Heart Association. Circulation 2014;129:e28–292.

4. Gudmundsson EF, Gudnason V, Sigurdsson S, et al. Coronary artery calcium distributions in older persons in the AGES-Reykjavik study. Eur J Epidemiol 2012;27:673–87.

5. Rosamond WD, Chambless LE, Heiss G, et al. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987-2008. Circulation 2012;125:1848–57.

6. Kuller LH, Edmundowicz D. Imaging of the coronary arteries aid in prevention of atherosclerosis and clinical coronary heart disease. Open Epidemiol J 2011;4:152–64.

7. Leening MJ, Ferket BS, Kavousi M, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: an evidence gap in preventive cardiology (abstr). Circulation 2014;130:A12068.

8. Bucholz EM, Normand SL, Wang Y, et al. Life expectancy and years of potential life lost after acute myocardial infarction by sex and race: a cohort-based study of Medicare beneficiaries. J Am Coll Cardiol 2015;66:645–55.

9. Kälsch H, Lehmann N, Möhlenkamp S, et al. Association of coronary artery calcium and congestive heart failure in the general population: results of the Heinz Nixdorf Recall study. Clin Res Cardiol 2010;99:175–82.

10. Madhavan MV, Tarigopula M, Mintz GS, et al. Coronary artery calcification: pathogenesis and

prognostic implications. J Am Coll Cardiol 2014;63:1703–14.

11. Criqui MH, Denenberg JO, Ix JH, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA 2014;311:271–8.

12. Tota-Maharaj R, Blaha MJ, McEvoy JW, et al. Coronary artery calcium for the prediction of mortality in young adults <45 years old and elderly adults >75 years old. Eur Heart J 2012;33:2955–62.

13. Blaha MJ, Feldman DI, Nasir K. Coronary artery calcium and physical fitness: the two best predictors of long-term survival. Atherosclerosis 2014;234:93–4.

14. Valenti V, ó Hartaigh B, Heo R, et al. A 15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-up of 9,715 individuals. J Am Coll Cardiol Img 2015;8:900–9.

15. Hebert LE, Weuve J, Scherr PA, et al. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 2013;80:1778–83.

16. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology 2007;29:125–32.

17. Matthews FE, Arthur A, Barnes LE, et al., Medical Research Council Cognitive Function and Ageing Collaboration. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet 2013;382:1405–12.

18. Fratiglioni L, Viitanen M, von Strauss E, et al. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. Neurology 1997;48:132–8.

19. Skoog I, Nilsson L, Palmertz B, et al. A population-based study of dementia in 85-year-olds. N Engl J Med 1993;328:153–8.

20. Corrada MM, Brookmeyer R, Paganini-Hill A, et al. Dementia incidence continues to increase with age in the oldest old: the 90+ study. Ann Neurol 2010;67:114–21.

21. Kawas CH, Kim RC, Sonnen JA, et al. Multiple pathologies are common and related to dementia in the oldest-old: The 90+ Study. Neurology 2015;85:535–42.

22. Vemuri P, Lesnick TG, Przybelski SA, et al. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. Brain 2015;138:761–71.

23. Friedman JI, Tang CY, de Haas HJ, et al. Brain imaging changes associated with risk factors for cardiovascular and cerebrovascular disease in asymptomatic patients. J Am Coll Cardiol Img 2014;7:1039–53.

24. Roher AE, Tyas SL, Maarouf CL, et al. Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. Alzheimers Dement 2011;7:436–44.

25. Kovacic JC, Fuster V. Atherosclerotic risk factors, vascular cognitive impairment, and Alzheimer disease. Mt Sinai J Med 2012;79:664–73.

26. Debette S, Beiser A, DeCarli C, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. Stroke 2010;41:600–6.

27. Beach TG, Wilson JR, Sue LI, et al. Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta Neuropathol 2007;113:13–21.

28. Snyder HM, Corriveau RA, Craft S, et al. Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. Alzheimers Dement 2015;11:710–7.

29. Gaita F, Corsinovi L, Anselmino M, et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. J Am Coll Cardiol 2013;62:1990–7.

30. Vogels RL, Scheltens P, Schroeder-Tanka JM, et al. Cognitive impairment in heart failure: a systematic review of the literature. Eur J Heart Fail 2007;9:440–9.

31. van Oijen M, de Jong FJ, Witteman JC, et al. Atherosclerosis and risk for dementia. Ann Neurol 2007;61:403–10.

32. Bos D, Vernooij MW, Elias-Smale SE, et al. Atherosclerotic calcification relates to cognitive function and to brain changes on magnetic resonance imaging. Alzheimers Dement 2012;8 5 Suppl:S104–11.

33. Bos D, Vernooij MW, de Bruijn RF, et al. Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline. Alzheimers Dement 2015;11:639–47.e1.

34. Vidal JS, Sigurdsson S, Jonsdottir MK, et al. Coronary artery calcium, brain function and structure: the AGES-Reykjavik Study. Stroke 2010;41:891–7.

35. Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. J Am Geriatr Soc 2005;53:1101–7.

36. Newman AB, Naydeck BL, Sutton-Tyrrell K, et al. Relationship between coronary artery calcification and other measures of subclinical cardiovascular disease in older adults. Arterioscler Thromb Vasc Biol 2002;22:1674–9.

37. Newman AB, Naydeck BL, Ives DG, et al. Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcomes in adults 70 to 99 years old. Am J Cardiol 2008;101:186–92.

38. Rosano C, Naydeck B, Kuller LH, et al. Coronary artery calcium: associations with brain magnetic resonance imaging abnormalities and cognitive status. J Am Geriatr Soc 2005;53:609–15.

39. Newman AB, Naydeck BL, Whittle J, et al. Racial differences in coronary artery calcification in older adults. Arterioscler Thromb Vasc Biol 2002;22:424–30.

40. Lopez OL, Kuller LH, Becker JT, et al. Incidence of dementia in mild cognitive impairment in the Cardiovascular Health Study Cognition Study. Arch Neurol 2007;64:416–20.

41. Kuller LH, Lopez OL, Becker JT, Chang Y, Newman AB. Risk of dementia and death in the long-term follow-up of the Pittsburgh Cardiovascular Health Study-Cognition Study. Alzheimers Dement 2016;12:170–83.

42. Yue NC, Arnold AM, Longstreth WT Jr., et al. Sulcal, ventricular, and white matter changes at MR imaging in the aging brain: data from the cardiovascular health study. Radiology 1997;202:33–9.

43. Bryan RN, Wells SW, Miller TJ, et al. Infarctlike lesions in the brain: prevalence and anatomic characteristics at MR imaging of the elderly. Data from the Cardiovascular Health Study. Radiology 1997;202:47–54.

44. Rosano C, Aizenstein HJ, Wu M, et al. Focal atrophy and cerebrovascular disease increase dementia risk among cognitively normal older adults. J Neuroimaging 2007;17:148–55.

45. Psaty BM, Delaney JA, Arnold AM, et al. The study of cardiovascular health outcomes in the era of claims data: the Cardiovascular Health Study. Circulation 2016;133:156–64.

46. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol 1995;5:278–85.

47. Kuller LH, Shemanski L, Psaty BM, et al. Subclinical disease as an independent risk factor for cardiovascular disease. Circulation 1995;92:720–6.

48. Elias-Smale SE, Proença RV, Koller MT, et al. Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J Am Coll Cardiol 2010;56:1407–14.

49. Handy CE, Desai CS, Dardari ZA, et al. The association of coronary artery calcium with age-related non-cardiovascular diseases: the importance of "biological aging" from the Multi-Ethnic Study of Atherosclerosis (MESA) (abstr). Circulation 2014;130:A12288.

50. Kuller LH, Matthews KA, Edmundowicz D, et al. Incident coronary artery calcium among postmenopausal women. Atherosclerosis 2008;200:278–85.

51. Xu W, Tan L, Wang HF, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry 2015;86:1299–306.

KEY WORDS aging, ankle brachial index, carotid intimal medial thickness, coronary artery calcium, mortality

APPENDIX For supplemental tables and figures, please see the online version of this article.