Subclinical Atherosclerosis, Cardiac and Kidney Function, Heart Failure, and Dementia in the Very Elderly

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Background—Heart failure (HF) and dementia are major causes of disability and death among older individuals. Risk factors and biomarkers of HF may be determinants of dementia in the elderly. We evaluated the relationship between biomarkers of cardiovascular disease and HF and risk of dementia and death. Three hypotheses were tested: (1) higher levels of high-sensitivity cardiac troponin T, N-terminal of prohormone brain natriuretic peptide, and cystatin C predict risk of death, cardiovascular disease, HF, and dementia; (2) higher levels of cardiovascular disease biomarkers are associated with increased risk of HF and then secondary increased risk of dementia; and (3) risk of dementia is lower among participants with a combination of lower coronary artery calcium, atherosclerosis, and lower high-sensitivity cardiac troponin T (myocardial injury).

Methods and Results—The Cardiovascular Health Study Cognition Study was a continuation of the Cardiovascular Health Study limited to the Pittsburgh, PA, center from 1998–1999 to 2014. In 1992–1994, 924 participants underwent magnetic resonance imaging of the brain. There were 199 deaths and 116 developed dementia before 1998–1999. Of the 609 participants eligible for the Pittsburgh Cardiovascular Health Study Cognition Study, 87.5% (n=532) were included in the study. There were 120 incident HF cases and 72% had dementia. In 80 of 87, dementia preceded HF. A combination of low coronary artery calcium score and low high-sensitivity cardiac troponin T was significantly associated with reduced risk of dementia and HF.

Conclusions—Most participants with HF had dementia but with onset before HF. Lower high-sensitivity cardiac troponin T and coronary artery calcium was associated with low risk of dementia based on a small number of events.

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Key Words: coronary artery calcium • dementia • epidemiology • heart failure • risk factors

Individuals older than 80 years are the fastest growing segment of the US population. The high incidence of dementia, especially in very old age groups is well documented. The majority of individuals aged 80 years and older have dementia (65%) and practically all have either clinical or subclinical cardiovascular disease (CVD).1–3 Most dementia in individuals 80 years and older is caused by a combination of Alzheimer’s disease, neurodegeneration, and vascular pathology. In 2005, we reported that 44% of incident dementia cases in individuals aged 65 years and older had vascular disease, either as the sole cause of dementia or as a contributory factor, usually also with Alzheimer’s disease. Results from pathology studies demonstrated a linear increase in small vessel disease in the brain with increasing age.4

Two characteristics determine the risk of dementia at older ages: (1) determinants of survival to older age; and (2) given survival, the factors associated with dementia-free survival. The extent of clinical and subclinical CVD is a major determinant of survival to very old age.5–7 The prevention
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pressure has its primary effects on the smaller blood vessels. Smoking, and diabetes mellitus. Increased blood pressure, as primarily related to long-term effects of elevated blood pressure, smoking, and diabetes mellitus. Increased blood pressure has its primary effects on the smaller blood vessels in the brain and in the kidney. Elevated blood pressure in midlife and increase in blood pressure over time have been identified as risk factors for dementia. There is, however, no consistent clinical trial evidence that treatment of hypertension in older individuals reduces the risk of dementia, although at least one trial has reported a reduction in dementia with hypertension treatment.

Coronary artery disease in the elderly may also be risk factors for dementia. Risk of dementia is increased among patients with congestive heart failure (HF), atrial fibrillation, stroke, and possibly myocardial infarction.

Recent studies have suggested that the risk of dementia may be substantially increased among individuals with HF possibly secondary to decreased cerebral blood flow or brain oxygen supply. In the Rotterdam Study, better diastolic function was associated with a lower risk of both stroke and dementia. Low cardiac index was also a risk factor for dementia in the Framingham Heart Study.

The diagnosis of dementia is likely underestimated in the older population, especially in those with HF, because: (1) the diagnosis of dementia depends on repeat cognitive evaluations over time to measure changes in cognition and function (this may not be available for the attending physician); (2) dementia may be misclassified as depression; (3) symptoms related to HF or to drug therapies for HF may impair cognitive evaluation; (4) the higher case fatality rate following HF diagnosis may result in missed antimortem diagnosis of dementia unless there are frequent short-term evaluations; and (5) the time of onset of dementia may be misinterpreted, leading to the spurious observation that the HF was present before the dementia diagnosis.

There is growing evidence of similarities between brain and heart pathologies with aging, including increased prevalence of amyloid deposition in the heart secondary to transthyretin protein, abnormalities of protein folding, and increasing fibrosis and collagen deposition with HF in the elderly. The aging processes may be similar in the heart and brain. Abnormalities of protein folding or chaperones to assist in metabolism of misfolded proteins, including amyloid in the brain and heart, may be a common pathogenesis for both HF and Alzheimer’s dementia.

Subclinical atherosclerosis may also be a risk factor for dementia. Low coronary artery calcium (CAC) was associated with reduced risk of dementia in the Multi-Ethnic Study of Atherosclerosis. A pathology study, however, reported no association of coronary artery disease and dementia but a strong association of cerebral atherosclerosis and dementia. The autopsy study from the US National Alzheimer’s Coordinating Center reported a strong association of cerebral atherosclerosis and neuritic plaques, a marker of Alzheimer’s disease, but did not measure coronary atherosclerosis.

Higher levels of NT-proBNP (N-terminal of prohormone brain natriuretic peptide; a measure of left ventricular dysfunction) and high-sensitivity cardiac troponin (hs-cTnT; a measure of myocardial ischemic injury), and cystatin C (a measure of renal function and, in part, hypertensive small vessel disease) were predictors of coronary heart disease (CHD), HF, stroke, sudden death, and measures of cardiac structure and total mortality in CHS (Cardiovascular Health Study). Decreased kidney function, as measured by cystatin C, was associated with a faster decline over time in the Modified Mini-Mental State examination and Digit Symbol Substitution Test. Cystatin C levels were directly related to the prevalence of subclinical brain infarction in CHS. CHS, the ARIC (Atherosclerosis Risk in Communities) study, and the Dallas Heart Study together reported that levels of hs-cTnT just above the level of sensitivity, ie, 3 to 4.99 ng/mL, were associated with increased risk of HF, total mortality, and cardiovascular deaths compared with levels <3 ng/mL.

Many other studies have documented the association between higher levels of NT-proBNP, hs-cTnT, cystatin C, CVD, and total mortality. A report from Group Health suggested an association between decreased renal function and risk of dementia.

In the ARIC study, high hs-cTnT levels (a marker of myocardial injury) were associated with lower scores on the
Digit Symbol Substitution Test and word fluency test. In the Reasons for Geographic and Racial Differences in Stroke study, high hs-cTnT was associated with incident cognitive impairment as measured by scoring below the 6th percentile on 2 of 3 cognitive tests over a 3.5-year follow-up.

In the Rotterdam Study, high NT-proBNP was associated with increased risk of dementia even after excluding patients with CVD. Similarly, in the Age, Gene/Environment Susceptibility-Reykjavik Study, NT-proBNP was associated with poorer scores on cognitive tests and lower gray and white matter brain volumes. In another recent report from the AGES-Reykjavik Study, both higher NT-proBNP (a marker of left ventricular dysfunction) and greater carotid intima-media thickness were associated with increased risk of brain parenchymal loss as measured by serial magnetic resonance imaging. The association of cardiac biomarkers, HF, and risk of dementia has recently been published.

In this article, we have further evaluated the relationship between subclinical markers of myocardial damage (hs-cTnT), left ventricular dysfunction (NT-proBNP), renal function (cystatin C), CAC, and risk of dementia and CVD including HF in participants 80 years and older in CHS-CS (CHS Cognition Study) (n=517) from 1998–1999 to 2013–2014. We evaluated 3 hypotheses: (1) higher levels of hs-cTnT, NT-proBNP, and cystatin C predict the risk of death, CVD, and dementia; (2) higher levels of these cardiovascular markers are associated with increased risk of CHD and HF, which results secondarily in an increased risk of dementia; and (3) risk of dementia is lower among mostly white women with a combination of lower CAC and lower hs-cTnT, NT-proBNP, and cystatin C.

CHS began in 1989–1990 and recruited 5201 participants 65 years and older from Medicare Part A lists in 4 field centers. In 1992–1993, an additional 687 black participants were recruited. A detailed cognition follow-up study in Pittsburgh, PA, one of the 4 CHS centers (CHS-CS) included repeat cognitive evaluations (1998–1999 through 2013) in 532 participants. We previously reported that among 924 participants without dementia by 1998–1999, 136 (26%) participants were initially classified as having mild cognitive impairment and 396 (74%) were classified as cognitively normal. This study was approved by the institutional review board of the University of Pittsburgh, and informed consent was obtained from all participants in the study.

Fifteen participants among the 532 subsequently refused follow-up, leaving a sample of 517. The focus of the study is on incident CVD and dementia among participants free of CVD in 1998–1999 (n=369). There were 334 cases of incident dementia in 2013. Further evaluation of the 334 participants, including cognitive evaluations, interviews with family after 1998–1999, and review of other records, established that for 104 of the 334 participants, the onset of dementia was before 1998–1999, including 72 of 369 with no CVD in 1998–1999, and have been excluded from the evaluation of the incidence of dementia after 1998–1999 (Figure 1).

The definition of cardiovascular events and methods of ascertainment have been described in detail. Incident cardiac events were evaluated every 6 months by phone call or clinic visit followed by a review of medical records and informant interviews. Diagnoses were adjudicated by a committee. CHD was defined as angina pectoris, myocardial infarction, coronary bypass surgery, or angioplasty. The diagnosis of HF was based on a consensus of experts using prespecified and validated criteria, including having a new clinical diagnosis of HF made by a physician and being actively on prescription medications for HF, including both a diuretic and either a digitalis preparation or vasodilator. Participants who had an assessment of left ventricular ejection fraction following the diagnosis of HF were divided into 2 categories: HF with preserved ejection fraction if left ventricular ejection fraction was ≥50%, and HF with reduced ejection fraction if left ventricular ejection fraction was <45%. CVD included CHD, stroke, transient ischemic attack, revascularization procedures, peripheral vascular disease, HF, and angina pectoris.

CAC was measured from 1997 to 2000 by an electron beam tomography scanner and quantified measures were available in 434 (82%) CHS-CS participants; 311 (72%) were free of clinical coronary artery disease in 1998–1999.

### Methods

CHS-CS was a continuation of the original CHS limited to the Pittsburgh site and has been discussed in detail. In 1992–1994, 924 participants underwent magnetic resonance imaging of the brain and in 1998–1999, 532 of the 924 were included in CHS-CS (1998–1999 through 2014). Participants were included if they were alive and did not have dementia in 1998–1999 and had either a second magnetic resonance image and/or a detailed cognitive evaluation in 1998–1999. There were 117 deaths between 1992–1994 and 1998–1999, and of the 725 alive participants, 116 developed dementia by 1998–1999, leaving 609 participants alive and without dementia by 1998–1999 and 532 participants (87%) in the follow-up study (1998–2014), with a mean age of 79 years. In 1998–1999, 136 (26%) participants were initially classified as having mild cognitive impairment and 396 (74%) were classified as cognitively normal. This study was approved by the institutional review board of the University of Pittsburgh, and informed consent was obtained from all participants in the study.

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CAC was measured from 1997 to 2000 by an electron beam tomography scanner and quantified measures were available in 434 (82%) CHS-CS participants; 311 (72%) were free of clinical coronary artery disease in 1998–1999.
In-person neuropsychological examination was completed in 1998–1999, which included the American version of the National Reading Test, Raven’s Colored Progressive Matrices, California Verbal Learning Test, Rey-Osterrieth figure test, immediate and delayed recall, modified Boston Naming Test, verbal fluency test, block design test, Stroop Neuropsychological Screening Test, Trail Making Test, Digit Span test, and the Baddeley and Papagno Divided Attention Task. This examination was repeated yearly from 2002 to 2013.

For participants who refused or were unable to come into the clinic for evaluation or were deceased, dementia was assessed using prospectively collected information from the annual clinic examinations supplemented with data from medical records, physician questionnaires, and informant-proxy interviews. Telephone information was collected by the telephone interview for cognitive status. Information from informants was collected from the Informant Questionnaire on Cognitive Decline in the Elderly and the Dementia Questionnaire. Longitudinal data included the Modified Mini-Mental State examination, the Digit Symbol Substitution Test, Center for Epidemiologic Studies Depression Scale, instrumental activities of daily living and activities of daily living, and hearing and vision evaluations. Hospitalizations and medication use were also reviewed.

The definition of dementia was based on a progressive or static cognitive decline of sufficient severity to affect the patients’ activities of daily living and history of normal intellectual function before the onset of cognitive abnormalities. Participants were also required to have impairments in at least 2 cognitive domains, which did not necessarily include memory. Individuals who did not meet dementia criteria but who were failing cognitively were classified with mild cognitive impairment. Patients with mild cognitive impairment presented with memory deficits, defined as performance more than 1.5 SDs below that of individuals of comparable age and education; deterioration in other cognitive domains such as language, executive function, and visuconstructional abilities; and one abnormal test result in at least 2 cognitive domains, without sufficiently severe cognitive impairment or loss of instrumental activities of daily living to constitute dementia.

Dementia was further classified according to type (Alzheimer’s disease, vascular dementia, Parkinson’s disease–related dementia using standard criteria) and magnetic resonance imaging findings.

### Laboratory Measurements

Detailed descriptions of the laboratory methods have been previously published by CHS. hs-cTnT was measured with hs-cTnT reagents on an Elecsys 2010 system analyzer (Roche Diagnostics). NT-proBNP was measured in serum on the Elecsys 2010 system (Roche Diagnostics). Cystatin C was measured in serum using a BNII Nephelometer (Dade-Behring) with a latex-enhanced immunonephelometric assay.
The above measures were available for most participants in 1992–1994. hs-cTnT was available for 493 (88%), NT-proBNP for 499 (88%), and cystatin C for 514 (99%) of 517 participants. Measurement of hs-cTnT, NT-proBNP, and cystatin C were highly correlated over time in CHS. For example, Pearson correlation for hs-cTnT between 1989–1990 and 1992–1994 was 0.81 (P=0.0001) and between 1992–1994 and 1996–1997 (n=87) was 0.87 (P=0.0001).

Statistical Analysis

Descriptive statistics characterized the study population. Categorical variables were presented as frequency (percentage) and continuous variables as mean (±SD) or median (interquartiles) if the distribution was skewed. Age-adjusted rates and their 95% CIs were calculated using 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). All models were tested with a 2-sided α=0.05. Cognitive status was adjudicated through 2013 and death to 2014–2015. 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. Participants were censored for PY at either the time of the diagnosis of dementia or at death. All deaths were evaluated for a diagnosis of dementia before death and 63% of patients who died (271 of 432) had a dementia diagnosis before death. Because follow-up in CHS was every 6 months and yearly for dementia evaluation, detailed information about cognitive performance before death was almost always available.

The measurements of hs-cTnT, NT-proBNP, and cystatin C were performed in 1992–1994 and follow-up began in 1998–1999. PY at risk began at 1998–1999. Participants who died or developed dementia before 1998–1999 were excluded from the study. We previously reported that these variables (hs-cTnT, NT-proBNP, cystatin C) as measured in 1992–1994 were significantly related to the risk of HF, CHD, CVD, and death in CHS.26–28 The relationship of higher levels of these markers with death in 1992–1998 likely underestimates the effect of these biomarkers on subsequent outcome between 1998–1999 and 2014.

The measurement of dementia was different between 1992 and 1998–1999 and 1998–1999 and 2013–2014. The incubation period from normal cognition to dementia is likely many years. Therefore, follow-up beginning 5 or more years after the measurement of the attributes (hs-cTnT, NT-proBNP, cystatin C) is likely to be a better measure of potential risk of dementia than measuring these variables within the first years after the diagnosis of dementia. As we have previously reported, the short-term determinants of dementia are the presence of existing cognitive dysfunction; brain atrophy, eg, size of the ventricle; apolipoprotein E4; white matter abnormalities; age; and education. In a sensitivity analysis, we determined whether there was any relationship between the 3 above biomarkers and dementia between 1992–1994 and 1998–1999 within the cohort. There was no relationship in this cohort of these 3 measures and the risk of dementia between 1992–1994 and 1998–1999.

There were few missing variables for the analysis. These missing variables were excluded from the analysis. Apolipoprotein E was collected in only a subsample of the participants who agreed to have their genetic information available for further analysis within CHS. There was also no loss to follow-up with regards to survivorship and in only a few participants, information regarding CVD and other diseases was obtained only from review of hospital records.

Results

Determinants of Levels of Subclinical CVD Risk Factors

Descriptive baseline characteristics of the participants in 1998–1999 are shown in Table 1. Of note, by 2013, 154 (64%) white women, 52 (72%) black women, 94 (58%) white men, and 28 (67%) black men had dementia (Table 1). Time to dementia from 1998–1999 to 2012–2014 was a mean of 4.5 (SD 3.2) years and median of 4.0 years; time to HF was a mean of 8.1 (SD 4.3) years and median of 8.0 years; and to death was a mean of 8.7 (SD 4.0) years and median of 9.0 years. The average time between dementia diagnosis and death was a mean of 5.9 (SD 3.3) years and median of 6.0 years (Table S1).

Characteristics of hs-cTnT and NT-proBNP are shown in Table S2. hs-cTnT and NT-proBNP levels were significantly correlated with NT-proBNP and cystatin C for both men and women. Cystatin C was also significantly correlated with NT-proBNP (Table S3). Levels of hs-cTnT and NT-proBNP increased with age. hs-cTnT was higher in patients with prior CVD (Table 2). hs-cTnT was significantly correlated with NT-proBNP and cystatin C for both men and women. Cystatin C was also significantly correlated with NT-proBNP and cystatin C (not shown).

Risk Factors (hs-cTnT, NT-proBNP, Cystatin C) and Outcomes

Death and dementia

Levels of hs-cTnT, NT-proBNP, and cystatin C levels were directly related to total mortality, as previously reported in CHS (Figure 2). Risk of CVD, CHD, and HF was directly related...
to hs-cTnT and NT-proBNP for the total sample free of CVD in 1998–1999 (Table 2), consistent with previous CHS analysis.

The incidence of dementia was not significantly related to levels of cystatin C, hs-cTnT, and NT-proBNP for both white men and women (Figures 3 through 5). The biggest differences were at the extreme lowest versus highest quartiles. For example, for white women with hs-cTnT < 3 pg/mL, the age-adjusted incidence rates of dementia were 66/1000 PY (95% CI, 38–118) (n = 83, 39 dementia) as compared with 94/1000 PY (95% CI, 42–209) for those with hs-cTnT between 8.17 and 12.93 pg/mL and 160/1000 PY (95% CI, 60–426) for those with hs-cTnT > 12.93 pg/mL, but only 6 individuals and 4 dementia were included in the analysis (Figures 3 and 4, Table S4).

**CVD and HF**

Among the 369 patients with no CVD in 1998–1999, 120 (33%) had incident HF, including 53 (44%) with normal or borderline ejection fraction, 29 (24%) with reduced ejection fraction <45%; and 41 (33%) with no ejection fraction available in the medical records at the time of the diagnosis of

### Table 1. Descriptive Characteristics of Participants in CHS-CS by Race and Sex*

| Characteristic                        | White Women | Black Women | White Men | Black Men |
|--------------------------------------|-------------|-------------|-----------|-----------|
|                                      | (n=190), No. (%) | (n=53), No. (%) | (n=93), No. (%) | (n=32), No. (%) |
| Education ≥ high school              | 105 (55.3) | 25 (47.2) | 69 (74.2) | 9 (28.1) |
| Subclinical CVD (1992–1993)          | 111 (59.4) | 29 (56.9) | 64 (69.6) | 20 (64.5) |
| Hypertension (1998–1999)             | 79 (43.9) | 36 (69.2) | 35 (37.6) | 9 (30.0) |
| Diabetes mellitus (1998–1999)        | 10 (5.6) | 9 (18.0) | 6 (6.5) | 8 (26.7) |
| No. of blocks walked per w (1998–1999) |           |            |           |           |
| ≤5                                   | 49 (26.9) | 19 (36.6) | 18 (19.8) | 12 (41.4) |
| 6–12                                 | 41 (22.5) | 6 (12.5) | 15 (16.5) | 3 (10.3) |
| >12                                  | 92 (50.6) | 23 (47.9) | 58 (63.7) | 14 (48.3) |
| BMI (1998–1999)                      |            |            |           |           |
| ≤25                                  | 79 (43.7) | 10 (19.6) | 33 (35.5) | 8 (25.8) |
| 25–28                                | 44 (24.3) | 10 (19.6) | 32 (34.4) | 5 (16.1) |
| 28.1–30                              | 23 (12.7) | 14 (27.5) | 17 (18.3) | 10 (32.3) |
| >30                                  | 35 (19.3) | 17 (33.3) | 11 (11.8) | 8 (25.8) |
| MMSE score (1998–1999)               |            |            |           |           |
| ≤90                                  | 30 (16.9) | 15 (30.0) | 12 (12.9) | 11 (36.7) |
| 91–97                                | 64 (36.0) | 26 (52.0) | 36 (38.7) | 11 (36.7) |
| >97                                  | 84 (47.2) | 9 (18.0) | 45 (48.4) | 8 (26.7) |
| DSST score (1998–1999)               |            |            |           |           |
| ≤34                                  | 26 (14.9) | 18 (36.0) | 12 (13.0) | 18 (60.0) |
| 35–47                                | 65 (37.4) | 16 (32.0) | 34 (37.0) | 8 (26.7) |
| >47                                  | 83 (47.7) | 16 (32.0) | 46 (50.0) | 4 (13.3) |
| Gait speed >5 s (1998–1999)           | 57 (31.8) | 28 (56.0) | 21 (23.1) | 10 (34.5) |
| Ventricular grade ≥5 (1998–1999)      | 36 (22.4) | 4 (8.9) | 17 (21.0) | 6 (23.1) |
| White matter grade ≥3 (1998–1999)     | 65 (40.4) | 6 (11.3) | 24 (29.3) | 8 (30.8) |
| Lipid-lowering medication (1998–1999) | 38 (20.0) | 6 (11.3) | 10 (10.8) | 4 (12.9) |
| Hypertension medication (1998–1999)   | 93 (49.0) | 35 (66.0) | 47 (50.5) | 11 (35.5) |
| ADL ≥2 (2011)                        | 74 (53.6) | 15 (34.1) | 13 (23.6) | 7 (35.0) |
| IADL ≥2 (2011)                       | 91 (65.9) | 23 (53.5) | 19 (34.6) | 9 (45.0) |
| Deceased (2013)                      | 158 (83.2) | 31 (58.5) | 75 (80.7) | 24 (75.0) |
| Dementia (2013)                      | 119 (62.6) | 41 (77.4) | 51 (54.8) | 22 (68.8) |

ADL indicates activities of daily living; BMI, body mass index; CHS-CS, Cardiovascular Health Study Cognition Study; DSST, Digit Symbol Substitution Test; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

*Excluding participants with cardiovascular disease (CVD) at 1998–1999.
The mean age of participants with incident HF was 88 years for those with normal ejection fraction and 87 years for those with low ejection fraction or with no information available (Table S5).

The prevalence of dementia was high among participants with HF (Table 3), as 72.5% of all patients with incident HF had a diagnosis of dementia. In 80 of 87 patients, the onset of dementia occurred before the first hospitalization for HF, with an average of about 5 years from the diagnosis of dementia to the first hospitalization for HF. The prevalence of dementia was similar for the 3 HF groups: 39 (74%) of the 53 patients with normal baseline ejection fraction had dementia.

Table 2. Cox Models for Predictors of CVD, CHD, and HF, 1998–1999 Through 2014 for Participants in CHS-CS With No CVD in 1998–1999

|                | CVD                        | CHD                        | HF                         |
|----------------|----------------------------|----------------------------|----------------------------|
|                | HR (95% CI)                | P Value                    | HR (95% CI)                | P Value                    | HR (95% CI)                | P Value                    |
| Age            | 1.09 (1.04–1.14)           | <0.0001                    | 1.07 (1.02–1.12)*          | 0.005                      | 1.08 (1.03–1.14)           | 0.002                      |
| hs-cTnT, pg/mL |                            |                            |                            |                           |                            |                            |
| 3.0–5.3        | 0.97 (0.63–1.49)           |                            | 0.91 (0.52–1.57)*          |                            | 1.34 (0.79–2.26)           |                            |
| 5.4–10.5       | 1.17 (0.78–1.76)           |                            | 1.40 (0.86–2.29)           |                            | 1.22 (0.72–2.07)           |                            |
| >10.5          | 1.79 (1.16–2.77)           | 0.048                      | 2.53 (1.54–4.14)           | 0.001                      | 2.10 (1.23–3.59)           | 0.059                      |
| NT-proBNP, pg/mL |                           |                            |                            |                           |                            |                            |
| 54.4–102.2     | 0.74 (0.51–1.10)           |                            | 0.70 (0.45–1.11)           |                            | 0.86 (0.51–1.46)           |                            |
| 102.3–192.8    | 0.86 (0.59–1.26)           |                            | 0.57 (0.35–0.92)           |                            | 1.28 (0.78–2.08)           |                            |
| >192.8         | 1.43 (0.93–2.18)           | 0.031                      | 1.34 (0.81–2.21)           | 0.010                      | 1.84 (1.06–3.22)           | 0.049                      |
| Cystatin C, nmol/L |                          |                            |                            |                           |                            |                            |
| 0.96–1.1       | 1.07 (0.77–1.48)           |                            | 1.13 (0.75–1.70)           |                            | 1.08 (0.69–1.68)           |                            |
| 1.11–1.3       | 1.02 (0.68–1.52)           |                            | 1.21 (0.75–1.95)           |                            | 1.48 (0.92–2.38)           |                            |
| >1.3           | 1.05 (0.62–1.78)           | 0.984                      | 1.37 (0.74–2.55)           | 0.741                      | 1.40 (0.71–2.73)           | 0.388                      |

CHD indicates coronary heart disease; CHS-CS, Cardiovascular Health Study Cognition Study; CVD, cardiovascular disease; HF, heart failure; HR, hazards ratio; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal of prohormone brain natriuretic peptide.

Figure 2. Age-adjusted mortality 1998–1999 to 2014 in white men and women only in the Cardiovascular Health Study Cognition Study by levels of high-sensitivity cardiac troponin (hs-cTnT), NT-proBNP (N-terminal of prohormone brain natriuretic peptide), and cystatin C (excluding cardiovascular disease in 1998–1999). hs-cTnT, NT-proBNP, and cystatin C were directly related to total mortality. PY indicates person-years.

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fraction, 19 (61%) of the 29 patients with low ejection fraction, and 32 (78%) of the 41 patients with ejection fraction not available. HF diagnosis occurred after the time of diagnosis of dementia and therefore measurement of dementia incidence after HF could not be evaluated. In addition, 61% of participants with no history of HF had a diagnosis of dementia before death.

The association of CHD and dementia was similar to that for HF. Of the 123 participants with incident HF, 79 (64%) also had CHD. Of the 82 who had both dementia and CHD, dementia preceded the diagnosis of CHD in 68 patients (83%).

**Subclinical cardiovascular variables, CAC, and risk of dementia**

There was a substantial overlap among participants for the combination of low CAC <10 (n=48) and low hs-cTnT, NT-proBNP, or cystatin C. Therefore, we limited the further analysis to the low hs-cTnT, low CAC subgroup.

**Figure 3.** Age-adjusted incidence of dementia in 1998–1999 to 2014 in white women only in the Cardiovascular Health Study Cognition Study by levels of high-sensitivity cardiac troponin (hs-cTnT), NT-proBNP (N-terminal of prohormone brain natriuretic peptide), and cystatin C (excluding cardiovascular disease in 1998–1999). There was only a weak nonsignificant relationship between hs-cTnT, NT-proBNP, cystatin C, and risk of dementia for women. PY indicates person-years.

**Figure 4.** Age-adjusted incidence of dementia in 1998–1999 to 2014 in white men only in the Cardiovascular Health Study Cognition Study by levels of high-sensitivity cardiac troponin (hs-cTnT), NT-proBNP (N-terminal of prohormone brain natriuretic peptide), and cystatin C (excluding cardiovascular disease at 1998–1999). There was only a weak nonsignificant relationship between hs-cTnT, NT-proBNP, cystatin C, and risk of dementia for men. PY indicates person-years.
The incidence of dementia for cognitively normal participants in 1998–1999 (n = 215) was significantly lower (P < 0.01) for those with hs-cTnT < 3 and CAC 0 to 10 for all 4 race and sex groups combined (Table S6). The lowest incidence of dementia by 2013 was for participants with both low CAC and hs-cTnT based on a small number of cases. For white women, combination of low CAC and low levels of hs-cTnT were associated with low incidence of HF, CHD, dementia, and death (Table 4).

Time to dementia was significantly longer for white women with low risk, eg, CAC <10 Agatston units and hs-cTnT <3 pg/mL (Figure 6). White women at low risk were younger and had less subclinical peripheral vascular disease compared with white women with CAC >100 Agatston units and hs-cTnT >5.3 pg/mL in 1992–1994 (Table S7). They were also better educated and had significantly lower age-adjusted prevalence of dementia.

Table 3. Relationship of Dementia and Incident HF Among Participants in CHS-CS, Excluding Those With CVD at 1998–1999 (n=369)

|                       | No. (%) |
|-----------------------|---------|
| No HF, no dementia    | 99 (26.8) |
| No HF, dementia       | 150 (40.7) |
| HF, no dementia       | 33 (8.9) |
| Dementia then having HF | 80 (21.7) |
| Having HF then dementia | 7 (1.9) |

A total of 120 participants with heart failure (HF)—72.5% had dementia; 249 with no HF—61.0% had dementia; 237 with dementia—36.7% had HF; 132 with no dementia—25.0% had HF. Average time to HF after dementia: 5 years. CHS-CS indicates Cardiovascular Health Study Cognition Study; CVD, cardiovascular disease.

In a Cox model for predictors of dementia (n=200, 106 with dementia) using predictors of dementia on previous analysis in CHS-CS and hs-cTnT, NT-proBNP, and cystatin C, ventricular grade (HR, 1.63), apolipoprotein E4 (HR, 1.47), number of blocks walked (HR, 2.14), the Digit Symbol Substitution Test (HR, 1.59), and Modified Mini-Mental State score (HR, 1.60) were predictors of dementia. High CAC Agatston score (HR, 1.83) was a significant predictor but hs-cTnT (HR, 1.18) and NT-proBNP (HR, 1.27) were much weaker predictors of dementia (Table 5). Apolipoprotein E was excluded from the Cox model, increasing the number of participants to 217 (115 with dementia). The results were similar to those in Table 5. The sample of black women was small (n=53), and they were younger than white women in 1998–1999, with a mean age of 76 years versus 79 years. Of the 29 black women with no CVD in 1998–1999 and measures of both CAC and hs-cTnT, 8 had both low CAC <10 Agatston units and hs-cTnT <3 pg/mL and about half (14 of 29) had low CAC. The incidence of congestive HF (1 of 8) was 8.9/1000 PY and dementia (3 of 7) was 39.5/1000 PY, which was lower than for blacks with higher CAC levels based on small numbers but consistent with observations in white women.

Only 95 of 517 (18%) participants in CHS-CS were still alive as of 2014, with 17% (n=16) having normal cognition, 22% (n=21) having mild cognitive impairment, and 61% (n=58) having dementia. The mean age at the end of follow-up in 2014 was 93 years. Among the 16 cognitively normal participants still alive at 2014, 10 (67%) had neither CHD nor HF, 3 had CHD only, and 3 had HF only. Therefore, only 10 (2%) of 532 of the original participants in CHS-CS survived to a mean age of 93 years at 2014 free of dementia and CHD and CVD (Table 6).
Table 4. Incidence of HF, Death, and Dementia in 2014 by hs-cTnT and First CAC Score in 1998–1999 Among White Women Participants in CHS-CS Who Were Cognitively Normal and Had No CVD in 1998–1999

| CAC Score | hs-cTnT | Total, No. | HF No. (%) | Rate/1000 PY | Death No. (%) | Rate/1000 PY | Dementia No. (%) | Rate/1000 PY |
|-----------|---------|------------|------------|--------------|---------------|--------------|-----------------|--------------|
| 0–10      | <3      | 14         | 2 (14)     | 11.9 (3.0–47.6) | 6 (43)        | 33.3 (15.0–74.2) | 4 (29)         | 28.6 (10.7–76.1) |
|           | ≥3      | 8          | 2 (25)     | 20.8 (5.2–83.3) | 4 (50)        | 39.2 (14.7–104.5) | 3 (43)         | 60.0 (19.4–186.0) |
| 11–300    | <3      | 28         | 9 (32)     | 30.4 (11.2–99.7) | 22 (79)       | 65.0 (31.8–136.3) | 17 (61)        | 90.4 (40.9–205.3) |
|           | ≥3      | 24         | 6 (25)     | 23.9 (6.1–101.6) | 17 (71)       | 59.6 (26.7–141.4) | 16 (70)        | 144.7 (65.4–332.0) |
| >300      | <3      | 33         | 11 (33)    | 28.1 (9.7–85.5) | 19 (58)       | 47.7 (21.4–108.2) | 17 (61)        | 104.2 (44.2–269.8) |
|           | ≥3      | 19         | 7 (37)     | 40.4 (11.3–146.7) | 13 (68)       | 53.4 (19.9–153.1) | 13 (68)        | 117.6 (44.2–323.5) |

CAC indicates coronary artery calcium, CHS-CS, Cardiovascular Health Study Cognition Study; CVD, cardiovascular disease; HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; PY, person-years.

Discussion

There are 2 important observations. First, levels of hs-cTnT, NT-proBNP, and cystatin C were more strongly related to the risk of total mortality and incident CVD than to incident dementia (hypothesis 1). Participants, mostly white women, with low levels of hs-cTnT in combination with low CAC score had a low risk of dementia (hypothesis 3) but with a small sample size.

Second, at older ages, beginning at 80 to 85+ years, the incidence and prevalence of dementia and CVD, especially HF, were high. There were 120 patients with incident HF and 72% had a history of dementia. Surprisingly, most of the dementia predated the onset of clinically hospitalized HF. Therefore, we could not determine the relationship between incident HF and risk of dementia (hypothesis 2). The mean age at onset of HF was ≈86 years.

Survival to very old age requires avoidance of clinical CVD, including HF, and lower prevalence of subclinical CVD.

Whether a lower extent of subclinical vascular disease also reduces long-term risk of dementia in the very old (older than 80 years) is still unresolved, suggested by the results of this study but limited by small sample size. Replication of these results of low subclinical cardiac disease, eg, CAC, hs-cTnT, NT-proBNP, and risk of dementia in the very old is needed, especially with good measures of dementia incidence and time to onset of dementia.

An alternative view is that dementia at older ages may be independent of both clinical and subclinical CVD, including HF, primarily a function of aging, or increased amyloid or tau deposition attributable to an as-yet unmeasured risk factor. Prevention or better treatment of HF or CHD in the elderly will increase life expectancy, reduce the risk of HF and stroke, but not dementia, and therefore will result in a growing population of very elderly individuals with a high prevalence of dementia.

CHS-CS provides some support for both of these views, eg, causal or noncausal association of subclinical cardiac disease and HF and risk of dementia. First, there was a weak relationship between dementia and the measures of subclinical myocardial disease, such as hs-cTnT and NT-proBNP, and dementia. Similarly CAC, as previously reported, was more strongly related to CHD and death than to risk of dementia in the elderly. Such evidence would support an independent relationship between CVD in the elderly and dementia.

On the other hand, a small number of older participants, mostly white women, with low levels of CAC and hs-cTnT had reduced incidence of dementia. The number of such individuals was small and further evaluation of these observations in longitudinal studies with good measures of incident dementia and vascular disease will be important. Prevention of subclinical atherosclerosis, myocardial injury, and left ventricular dysfunction leading to HF even in the elderly is feasible and could reduce the burden of dementia.

Figure 6. Kaplan–Meier curve for dementia in 2013–2014 among white women in the Cardiovascular Health Study Cognition Study. Low coronary artery calcium (CAC) and high-sensitivity cardiac troponin (hs-cTnT) were associated with significantly low risk of dementia for white women.
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Table 5. Cox Model for Predictors of Dementia in 1998–1999 Through 2011–2012 for Participants in CHS-CS With No CVD and No Dementia in 1998–1999 (n=191, 101 Dementia)∗

| Variable                                      | No. | HR (95% CI) | P Value |
|-----------------------------------------------|-----|-------------|---------|
| Age                                           |     | 1.07 (1.00–1.15) | 0.043   |
| Ventricular grade ≥5 (1998–1999)              | 19  | 1.63 (0.82–3.23) | 0.163   |
| White matter grade ≥3 (1998–1999)             | 24  | 0.82 (0.44–1.52) | 0.525   |
| No. of blocks walked per w                    |     |             |         |
| 6–12                                          | 98  | 1.39 (0.86–2.24) |         |
| ≤5                                            | 73  | 2.15 (1.15–4.00) | 0.056   |
| DSST ≤34                                      | 19  | 1.59 (0.79–3.17) |         |
| 35–47                                         | 114 | 1.18 (0.74–1.86) | 0.413   |
| MMSE <90                                      | 21  | 1.63 (0.85–3.12) |         |
| 90–95                                         | 111 | 1.00 (0.63–1.59) | 0.276   |
| Apolipoprotein E4                              | 51  | 1.47 (0.96–2.25) | 0.075   |
| hs-cTnT >2.99 pg/mL                            | 100 | 1.18 (0.77–1.81) | 0.443   |
| NT-proBNP >54.3 pg/mL                         | 144 | 1.27 (0.79–2.03) | 0.322   |
| Cystatin C >0.95 nmol/L                       | 110 | 0.79 (0.53–1.17) | 0.234   |
| CAC >10 Agatston score                         | 160 | 1.83 (1.05–3.18) | 0.032   |

CHS-CS indicates Cardiovascular Health Study Cognition Study; DSST, Digit Symbol Substitution Test; HR, hazard ratio; MMSE, Mini-Mental State Examination.

Table 6. Survival and Dementia Status and CHD and HF in 2014 Among Participants in CHS-CS With No CVD in 1998–1999 (n=369)

|                  | Deceased and No Dementia (n=101, 27%) | Deceased and Dementia (n=187, 51%) | Alive and Dementia (n=47, 13%) | Alive and Cognitively Normal (n=15, 4%) | Alive and MCI (n=19, 5%) |
|------------------|----------------------------------------|----------------------------------|-----------------------------|------------------------------------------|-------------------------|
| CHD              |                                        |                                  |                             |                                          |                         |
| No               | 59 (58)                                | 113 (60)                         | 40 (85)                     | 10 (67)                                  | 14 (74)                 |
| Yes              | 42 (42)                                | 74 (40)                          | 7 (15)                      | 5 (33)                                   | 5 (33)                  |
| HF               |                                        |                                  |                             |                                          |                         |
| No               | 68 (67)                                | 108 (58)                         | 40 (85)                     | 13 (87)                                  | 13 (87)                 |
| Yes              | 33 (33)                                | 79 (42)                          | 7 (15)                      | 2 (13)                                   | 2 (13)                  |

CHD indicates coronary heart disease; CHS-CS, Cardiovascular Health Study Cognition Study; CVD, cardiovascular disease; HF, heart failure; MCI, mild cognitive impairment.

CHS-CS focused on older individuals, primarily 78 years and older, in 1998–1999 and followed to 2012–2014. A major problem in this study is selected survival and survival free of clinical and subclinical CVD. By 2014, only 16 (3%) patients in this cohort of ≈532 were still alive and cognitively normal. Therefore, the small sample size of individuals who have survived to this older age free of dementia and clinical CVD is a major restraint on the analysis, especially for men. No other longitudinal studies of dementia have provided similar analysis of measurements of CAC, the above biomarkers, HF, and dementia.

The timing of the onset of dementia in the elderly requires frequent cognitive evaluations over relatively short periods, from 6 months to a year. Otherwise, there is a substantial potential for misclassification of time of onset of dementia in relation to HF as well as missing many cases of dementia that occur before death and are missed by infrequent examinations. The time of onset of HF in this study could not be determined except by time of first hospitalization. Cardiovascular pathology leading to HF may have been present for a long time before hospitalization for clinical HF. This likely resulted in a misclassification of time of onset of HF. Similarly, there is substantial progression of CAC and atherosclerosis among older individuals, and measures of CAC in the distant past, eg, at younger ages, may not reflect the relationship of continued low CAC scores to risk of dementia in the elderly. The high prevalence of dementia among older patients with incident HF (72% had history of dementia) strongly suggests the need for both evaluation of dementia among patients with HF and that dementia may both impact treatment of HF and, most important, disability associated with HF in older individuals. Clinical trials of drugs and other therapies for HF should include as outcomes the incidence of dementia.64–70

A limitation of the study is that the independent variables were measured at different times. There was, however, a high
correlation between hs-cTnT levels measured in a small sample in 1998–1999 and in 1992–1994 (0.87, \(P=0.001\)). In addition, in sensitivity analysis, risk of dementia was evaluated from 1992–1994 through 2012, including a competing risk model. Results were similar to those from 1998–1999 through the 2014 analysis (not shown).

**Conclusion**

There is a very high prevalence of individuals with HF. The dementia occurred prior to diagnosis of HF. A very low CAC and low hs-cTnT was associated with decreased incidence of dementia.

**Author Contributions**

Kuller and Lopez conceptualized and designed the study. All authors were responsible for analysis or interpretation of data and for critical revision of the manuscript. Chang had full access to all of the data in the study and for critical revision of the manuscript. Chang was responsible for the statistical analysis, and Kuller and Lopez conceptualized and designed the study. All authors obtained funding and provided administrative and technical support. Study supervision was conducted by Kuller and Lopez.

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**Disclosures**

None.

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SUPPLEMENTAL MATERIAL
Table S1. Distribution of Follow Up Times and Age at Diagnosis of Dementia, Death, and CVD for Participants in the CHS-CS

| Description                                               | n   | Mean | SD  | Median |
|-----------------------------------------------------------|-----|------|-----|--------|
| FU years in dementia analysis                             | 458 | 6.1  | 4.5 | 5.0    |
| (from 1998-2013)                                          |     |      |     |        |
| FU years in death analysis                                | 517 | 11.2 | 4.7 | 12.0   |
| (1998-99 to 2014)                                         |     |      |     |        |
| FU years in HF analysis                                   | 485 | 10.1 | 4.9 | 10.0   |
| (1998-99 to 2014)                                         |     |      |     |        |
| Time to dementia from 1998-99                            | 281 | 4.5  | 3.2 | 4.0    |
| (among those demented)                                   |     |      |     |        |
| Time to death from 1998-99                               | 341 | 8.7  | 4.0 | 9.0    |
| (among those deceased)                                   |     |      |     |        |
| Time to HF from 1998-99                                  | 120 | 8.1  | 4.3 | 8.0    |
| (among those with HF)                                    |     |      |     |        |
| Time from dementia to death                               | 183 | 5.9  | 3.1 | 6.0    |
| Age at CHD                                                | 133 | 86.4 | 4.8 | 86.0   |
| Age at HF                                                 | 120 | 87.6 | 4.8 | 88.0   |

Abbreviations: CHS-CS indicates Cardiovascular Health Study Cognition Study; CVD, cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; FU, follow up
Table S2. Relationship of Median hs-cTnT, NT-proBNP, and Cystatin-C Levels at 1992-94 and Selected Variables for Participants in the CHS-CS*

|                          | N  | hs-cTnT, pg/ml | NT-proBNP, pg/ml | Cystatin-C, nmol/L |
|--------------------------|----|----------------|------------------|-------------------|
| CVD at 1998-99           | 153| 5.9            | 98.8             | 1.1               |
| No CVD at 1998-99        | 361| 3.2            | 82.4             | 1.0               |
| White men, age at 1992-94|    |                |                  |                   |
| <70                      | 38 | 6.0            | 77.7             | 1.1               |
| 71-75                    | 127| 7.5            | 89.8             | 1.1               |
| >75                      | 135| 10.8           | 136.9            | 1.1               |
| White women, age at 1992-94|   |                |                  |                   |
| <70                      | 65 | 3.0            | 72.1             | 1.0               |
| 71-75                    | 171| 3.0            | 109.2            | 1.0               |
| >75                      | 140| 6.2            | 161.0            | 1.1               |
| White men                | 159| 6.5            | 83.9*            | 1.1               |
| White women              | 241| 3.0            | 109.1            | 1.0               |
| Black men                | 42 | 5.6            | 64.4             | 0.9               |
| Black women              | 71 | 3.2            | 72.3             | 0.9               |

Abbreviations: CHS-CS indicates Cardiovascular Health Study Cognition Study; CVD, cardiovascular disease; hs-cTnT indicates high sensitivity cardiac troponin; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide

*Significant comparisons p<.05: hs-cTnT: White men vs. white women age <70; white men vs. white
Table S2. Cont’d

women age 71-75; white men vs. white women age >75; white men vs. white women; black men vs. black women. NT-proBNP: white women vs. black women. Cystatin C: white men vs. white women age <70; white men vs. white women; white men vs. black men; white women vs. black women
Table S3. Partial Spearman Correlation (Age-adjusted) Between Variables by Sex for Participants in the CHS-CS

|               | Women |          |          | Men  |          |          |
|---------------|-------|----------|----------|------|----------|----------|
|               | NT-proBNP | Cystatin-C | NT-proBNP | Cystatin-C |          |          |
|               | N  | Corr p- | N  | Corr p- | N  | Corr p- | N  | Corr p- |
| Hs-cTnT       | 286 | 0.16    | 0.008 | 286 | 0.22    | 0.000 | 167 | 0.18    | 0.020 | 166 | 0.38    | <.0001 | 191 | 0.32    | <.0001 |
| NT-proBNP     | 306 | 0.23    | <.0001 | 191 | 0.32    | <.0001 |      |          |        |      |          |        |

Abbreviations: CHS-CS indicates Cardiovascular Health Study Cognition Study; Corr, correlation; hs-cTnT, high sensitivity cardiac troponin; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.
Table S4. Dementia Status at 2013-2014 for Participants in the CHS-CS by Baseline Variables, Excluding Those With CVD and Dementia at 1998-99

| Participants | Baseline Variable | N  | # Dementia | % Dementia | Age Adjusted Rate/1000 PY (95% CI) |
|--------------|-------------------|----|------------|------------|-----------------------------------|
| White women  | Hs-cTnT, pg/ml    |    |            |            |                                   |
|              | <3                | 83 | 39         | 46.99      | 66.52 (37.77-118.43)              |
|              | 3.01-5.43         | 33 | 19         | 57.58      | 76.70 (35.22-167.68)              |
|              | 5.44-8.16         | 11 | 9          | 81.82      | 214.30 (111.49-411.85)            |
|              | 8.17-12.93        | 10 | 6          | 60.00      | 93.75 (42.12-208.67)              |
|              | >12.93            | 6  | 4          | 66.67      | 160.00 (60.05-426.31)             |
|              | NT-proBNP, pg/ml  |    |            |            |                                   |
|              | ≤54.3             | 36 | 17         | 47.22      | 81.81 (33.71-200.67)              |
|              | 54.4-102.2        | 40 | 23         | 57.50      | 88.80 (43.73-182.23)              |
|              | 102.3-192.8       | 46 | 26         | 56.52      | 79.33 (40.70-154.81)              |
|              | >192.8            | 30 | 16         | 53.33      | 91.73 (36.29-254.28)              |
|              | Cystatin-C, nmol/l|    |            |            |                                   |
|              | ≤0.95             | 58 | 36         | 62.07      | 87.79 (49.85-154.58)              |
|              | 0.96-1.1          | 57 | 28         | 49.12      | 70.42 (37.30-133.49)              |
|              | 1.11-1.3          | 19 | 7          | 36.84      | 59.18 (16.79-229.34)              |
|              | >1.3              | 20 | 12         | 60.00      | 202.85 (73.88-575.67)             |
| Abbreviations: CHS-CS indicates Cardiovascular Health Study Cognition Study; CI, confidence interval; CVD, cardiovascular disease; hs-cTnT, high sensitivity cardiac troponin; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; PY, person-years |

|                            | Hs-cTnT, pg/ml | NT-proBNP, pg/ml | Cystatin-C, nmol/l |
|-----------------------------|---------------|------------------|-------------------|
| **White Men**               |               |                  |                   |
| **Hs-cTnT, pg/ml**          |               |                  |                   |
| <3                          | 16            | 5                | 31.25 (14.25-82.28) |
| 3.01-5.43                   | 13            | 9                | 69.23 (80.74-298.23) |
| 5.44-8.16                   | 12            | 8                | 66.67 (62.51-249.95) |
| 8.17-12.93                  | 13            | 5                | 38.46 (22.87-132.01) |
| >12.93                      | 16            | 7                | 43.75 (27.35-120.36) |
| **NT-proBNP, pg/ml**        |               |                  |                   |
| ≤54.3                       | 29            | 15               | 51.72 (28.06-211.42) |
| 54.4-102.2                  | 19            | 8                | 42.11 (26.80-192.13) |
| 102.3-192.8                 | 19            | 10               | 52.63 (30.05-249.22) |
| >192.8                      | 8             | 4                | 133.33 (50.04-355.26) |
| **Cystatin-C, nmol/l**      |               |                  |                   |
| ≤0.95                       | 23            | 12               | 52.17 (33.78-250.10) |
| 0.96-1.1                    | 34            | 16               | 47.06 (33.88-175.92) |
| 1.11-1.3                    | 21            | 9                | 42.86 (22.78-197.50) |
| >1.3                        | 4             | 3                | 75.00 (80.63-775.15) |
| \( \text{White Women} \) | \( \text{Black Women} \) | \( \text{White Men} \) | \( \text{Black Men} \) |
|---------------------|---------------------|---------------------|---------------------|
| \( n \)             | \( \text{Mean (SD) Age} \) | \( n \)             | \( \text{Mean (SD) Age} \) | \( n \)             | \( \text{Mean (SD) Age} \) | \( n \)             | \( \text{Mean (SD) Age} \) |
| CHD                 | 61 87.6 (4.9)         | 17 85.4 (5.0)       | 44 85.5 (4.7)       | 11 85.1 (3.5)       |
| HF                  | 59 88.8 (4.7)         | 15 84.9 (4.9)       | 38 86.8 (4.3)       | 8 87.4 (4.7)        |
| MI                  | 35 88.2 (4.9)         | 5 86.8 (3.5)        | 31 85.6 (4.6)       | 6 86.0 (2.6)        |
| Stroke              | 34 88.2 (5.5)         | 7 81.9 (4.6)        | 8 87.1 (4.4)        | 5 86.8 (5.6)        |

Abbreviations: CHS-CS indicates Cardiovascular Health Study Cognition Study; CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; hs-cTnT, high sensitivity cardiac troponin; MI, myocardial infarction; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.
Table S6. Dementia Status by 2013 by hs-cTnT and CAC Score as Measured in 1998-99 Among Cognitively Normal Participants in the CHS-CS Without CVD and Dementia at 1998-99 for all 4 Race and Sex Groups (n=215)*

| Hs-cTnT | 1st CAC: 0 - 10 | 1st CAC: 10.1 - 300 | 1st CAC: > 300 |
|---------|----------------|---------------------|----------------|
|         | Age-Adjusted   | Age-Adjusted        | Age-Adjusted   |
| N       | Dementia       | Rate/1000 PY (95% CI)| N       | Dementia       | Rate/1000 PY (95% CI)| N       | Dementia       | Rate/1000 PY (95% CI)|
| <3      | 26             | 10 (39)             | 42             | 25             | 89.8 (45.9-177.8)    | 38             | 19             | 87.7 (37.5-216.1)    |
|         | 37.6 (14.9-98.7)|                      | 89.8 (45.9-177.8)|                      | 87.7 (37.5-216.1)    |
| ≥3      | 16             | 10 (63)             | 46             | 28             | 119.2 (62.5-231.7)   | 47             | 30             | 104.6 (55.5-200.9)   |
|         | 67.8 (22.6-207.4)|                      | 119.2 (62.5-231.7)|                      | 104.6 (55.5-200.9)   |

Abbreviations: CHS-CS indicates Cardiovascular Health Study Cognition Study; CI, confidence interval; CAC, coronary artery calcium; CVD, cardiovascular disease; hs-cTnT, high sensitivity cardiac troponin; PY, person-years

*Excludes 43 participants with MCI and 35 prevalent dementia in 1998-99, including 6 with CAC <10 Agatston units

P<.01
### Table S7. Comparison of White Women (Without CVD at 1998-99) in the CHS-CS With Low CAC and hs-cTnT to Higher CAC and hs-cTnT

| Variable                        | CAC 0-10 (n=14) | CAC >100 (n=20) | Age-Adjusted P-value |
|--------------------------------|-----------------|-----------------|---------------------|
| Hs-cTnT <3, pg/mL              | N (%)           | N (%)           |                     |
| Median age at 1998-99          | 75.5            | 80.5            | 0.0002              |
| Subclinical CVD at 1992-93     | 4 (28.6)        | 16 (80.0)       | 0.050               |
| Hypertension at 1998-99        | 3 (21.4)        | 11 (55.0)       | 0.595               |
| Diabetes at 1998-99            | 1 (7.1)         | 0               | 0.981               |
| Number of blocks walked/week 1998-99 |               |                 |                     |
| ≤5                             | 3 (21.4)        | 5 (25.0)        | 0.845               |
| 6-12                           | 3 (21.4)        | 5 (25.0)        |                     |
| >12                            | 8 (57.1)        | 10 (50.0)       |                     |
| MMSE score at 1998-99          |                 |                 |                     |
| ≤90                            | 0               | 5 (25.0)        |                     |
| 91-97                          | 3 (21.4)        | 10 (50.0)       |                     |
| >97                            | 11 (78.6)       | 5 (25.0)        | 0.138               |
| DSST score at 1998-99          |                 |                 |                     |
| ≤34                            | 1 (7.1)         | 6 (30.0)        |                     |
| 35-47                          | 4 (28.6)        | 8 (40.0)        |                     |
| >47                            | 9 (64.3)        | 6 (30.0)        | 0.319               |
| Ventricular grade ≥ 5 at 1998-99 | 3 (23.1)        | 5 (31.3)        | 0.517               |
| White matter grade ≥3 at 1998-99 | 4 (30.8)        | 9 (56.3)        | 0.892               |
| Education >19 years            | 7 (50.0)        | 6 (30.0)        | 0.149               |
| Lipid lowering medication at 1998-99 | 2 (14.3)        | 4 (20.0)        | 0.322               |
| Hypertension medication at 1998-99 | 3 (21.4)        | 12 (60.0)       | 0.198               |
| BMI at 1998-99, kg/m² |  |  |
|----------------------|---|---|
| ≤25                  | 4 (28.6) | 8 (42.1) |
| 25-28                | 4 (28.6) | 4 (21.1) |
| 28.1-30              | 2 (14.3) | 4 (21.1) |
| >30                  | 4 (28.6) | 3 (15.8) | 0.760 |

| Deceased at 2013 | 9 (64.3) | 18 (90.0) | 0.658 |
| Demented at 2013 | 4 (28.6) | 17 (85.0) | 0.013 |

Abbreviations: BMI indicates body mass index, DSST, Digit Symbol Substitution Test, CHS-CS indicates Cardiovascular Health Study Cognition Study; CVD, cardiovascular disease; hs-cTnT, high sensitivity cardiac troponin; MMSE, Mini-Mental State Examination