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Risk of Dementia and Death in the Long Term Follow Up of the Pittsburgh CHS Cognition Study

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Abstract

INTRODUCTION—Increasing life expectancy has resulted in a larger population of older individuals at risk of dementia.

METHODS—The Cardiovascular Health Study–Cognition Study (CHS-CS) followed 532 participants from 1998–99 (mean age 79) to 2013 (mean age 93) for death and dementia.

RESULTS—Risk of death was determined by extent of coronary artery calcium, high-sensitivity cardiac troponin, and brain natriuretic peptide, and white matter grade. Significant predictors of dementia were age, apolipoprotein-E4, vocabulary raw score, hippocampal volume, ventricular size, cognitive performance, and number of blocks walked. By 2013, 160 of 532 were alive, including 19 cognitively normal. Those with normal cognition had higher grade education, better cognition test scores, greater hippocampal volume, faster gait speed, and number of blocks walked as compared to survivors who were demented.

DISCUSSION—Few survived free of dementia and disability. Prevention and delay of cognitive decline for this older population is an imperative.

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Keywords

dementia; epidemiology; aging; MRI; cognition

1. Introduction

This report focuses on the Cardiovascular Health Study (CHS) Cognition Study (CHS-CS) of 532 participants at the Pittsburgh CHS Field Center from 1998–99 to 2013, mean age 79 to 93, and describes the interrelationship of risk factors, MRI findings, apolipoprotein E (ApoE), and cognitive evaluations and incidence of dementia and death. Very few longitudinal studies have been able to follow a large cohort to close to extinction, e.g. death, dementia, at old age. The Pittsburgh CHS-CS determined the probability of survival with or without dementia over 20+ years to mid-90+ years of age. Surviving to this older age is obviously necessary to be at risk of older age dementia. Therefore, we first evaluated the determinants of survival to older ages. Second, we determined the risk factors for incident dementia, primarily Alzheimer's disease (AD). Third, we did a very detailed evaluation at the end of the study in 2013 to better characterize the survivors to 2013 who were either normal, mild cognitive impairment (MCI) or dementia. The survivors free of dementia to this older age, median age 92, are a very unique sample and may provide important information about approaches to prevention of incident dementia at 80–85+ years of age.

The incidence of dementia doubles every 10 years after age 65. There is relatively little difference in incidence and prevalence of dementia, AD among older individuals 75+ between men and women [1]. The majority of dementia cases in the United States are over the age of 75 at the time of diagnosis and probably at least 1/3 are over the age of 85 [2].

Risk factors for dementia and AD have been evaluated in numerous cross-sectional and longitudinal studies [3]. A Consensus Conference in 2010 concluded that there was insufficient evidence for modifiable risk factors for AD [4].

Vascular disease in the brain is prevalent at older ages and may contribute to increased risk of dementia. Vascular disease in the brain, atherosclerosis and arteriosclerosis, are primarily related to long term effects of elevated blood pressure (BP), smoking and diabetes mellitus. Increased BP has its primary effects on the smaller blood vessels in the brain and in the kidney [5]. Midlife elevated BP and increase in BP over time have been identified as risk factors for dementia. There is no consistent clinical trial evidence that treatment of hypertension in older individuals reduced risk of dementia, although at least one trial has reported a reduction in dementia with hypertension treatment [6].

Coronary artery disease (CAD) and carotid atherosclerosis in the elderly may also be risk factors for dementia. Risk of dementia is increased among patients with congestive heart failure (CHF), atrial fibrillation (AF), stroke and possibly myocardial infarction (MI) [7].

Early age cognitive development and brain size contribute to the subsequent risk of dementia [8,9]. There is a long incubation period to incidence of dementia. Subtle cognitive declines can be identified years before the onset of either mild cognitive impairment (MCI)

or dementia [10,11]. The cognitive reserve hypothesis may explain why individuals with higher IQ and better education had lower risk of developing dementia and AD.

ApoE is the major genetic determinant of dementia with onset after 65 years of age. ApoE4 is also a determinant of the risk of cardiovascular disease (CVD) and susceptibility to infectious diseases [12,13].

2. Methods (See Technical Appendix for Expanded Methods)

The CHS has previously been described in many publications and was a population-based study of risk factors for CVD in age 65 and older participants recruited from random samples of Medicare Part A eligible lists in 4 communities: Sacramento County, CA, Washington County, MD, Forsythe County, NC, and Allegheny County, PA. The original cohort was 5,201 participants enrolled in 1989–90. A second cohort of 687 predominantly African Americans was enrolled 3 years later, totaling 5,888 individuals. Fifty-seven percent were women and 15.7% were African American, average age 72.8 years [14]. Cognitive function was measured annually using the Modified MMSE (3MSE) and the Digit Symbol Substitution Test (DSST) [15]. Depression was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) 10-item questionnaire, data on physical functioning including activities of daily living (ADLs) and instrumental ADLs (IADLs) were also collected annually [15,16]. From baseline in 1989–90 until 1998–99, participants completed up to 10 annual clinic visits.

In 1998–99, the CHS conducted the CHS-CS to identify incidence and prevalence of dementia during the 1992–1999 period in 3,608 participants who had an MRI of the brain in 1992–94; 2,865 white and 492 African American. The MRI scans of the brain were repeated in 1998–99 [15,17]. A neuropsychological battery, including measures of IQ, memory, language, visuospatial, attention/concentration, and executive function tests [18], was administered in 1998–99 [16,17]. The battery was also the baseline evaluation for the Pittsburgh CHS-CS [16,17]. (See Table in Technical Appendix)

Based on all available information, an adjudication committee classified 707 participants as demented, 227 as having prevalent dementia onset prior to the first MRI in 1992–94 and 480 as incident dementia between 1992–94 (first MRI) and 1998–99 evaluation [18]. Results of the study to 1998–99 have been published [17,19–22].

Further cross-sectional and longitudinal analyses have been based on both first (1992–94) and second MRI in 1998–99 [23–29].

2.1 Methods for Pittsburgh CHS-CS, 1998–99 to 2013

The continuation of the CHS-CS was restricted to the Pittsburgh Field Center. In 1992–94, 924 (62%) participants in Pittsburgh, PA had MRI of the brain [30–32]. (Figure 1) In 1998–99, 532 of the 924 (58%) participants were included in the Pittsburgh CHS-CS (1998–99 through 2013) [18]. The inclusion criteria were being alive and not demented in 1998–99, having either a second MRI in 1998–99 and/or a detailed cognitive evaluation in 1998–99 [18].

At 1998–99, 199 (22%) of 924 participants were deceased, 58 demented prior to death and 116 (16%) were demented by 1998–99. A second MRI was available for 455 of 609 (75%) alive participants, of whom 449 were included in the study. There were 154 who did not have a 2nd MRI, of whom 83 (54%) were included in the follow up CHS-CS. The detailed CHS-CS therefore included 83 who had only 1 MRI but a detailed cognitive evaluation and 449 with a second MRI, of whom 63 had no second detailed cognitive evaluation in 1997–99, total 532, 396 normal and 136 MCI in 1998–99. (Figure 1) Mean age at 1992–94 was 75. There were 345 (65%) women and 116 (22%) blacks among the 532 participants. Mean age was 79 in 1998–99, including 65 age 70–74 (12%), 262 (49%) age 75–79, 139 (26%) age 80–84 and 66 (12%) age 85+. (Figure 1)

There were 77 participants not included in the follow up (Figure 1), 39 were classified as cognitively normal and 38 as MCI in 1998–99. Thirty-two (84%) of the 38 MCI and 29 (74%) of the 39 cognitively normal participants had died by 2012. Of the 61 deceased, 22 were classified as cognitively normal prior to death, 18 MCI and 21 dementia based on review of records from the CHS and of those who were still alive as of 2013 (n=5), 3 were classified as cognitively normal and 2 as MCI as of 2008. There were also 23 participants out of the original total 924 who refused any further evaluation, 14 had been included in the detailed CHS-CS and as of 2010, 8 of these 14 were deceased.

MRI acquisition and measurements have been described. MRI scanning was completed using a 1.5 Tesla scanner [31,32]. (See Technical Appendix for details)

2.2 Cognitive Tests

The cognitive tests in 1998–99 (see Technical Appendix Table) were considered baseline for the CHS-CS follow up to 2013 in the CHS-CS in Pittsburgh, PA. The same neuropsychological battery as in 1998–99 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 visit or using the telephone interview for cognitive TICS [33]. Information on cognition was also obtained from proxies using the Dementia Questionnaire (DQ) [17]. Symptoms of depression were measured annually with the modified CES-D.

Neurological examinations were done in 1998–99 and annually from 2002–03 through 2013 and included a brief mental status evaluation, as well as evaluation of cranial nerves, gait and postural stability, etc. also completed a semi-structured examination for Parkinsonism and for cerebrovascular disease. (Figure 2)

2.3 Adjudication of Cognitive Status, 1998–99 through 2013

The criteria for evaluating the cognitive status of participants have also been published [18,22]. A test response was considered abnormal if it was >1.5 SD below individuals of comparable age and education level. If >2 tests of the same domain were abnormal then the domain was considered abnormal.

Diagnosis of dementia was based on a deficit in performance in two or more cognitive domains of sufficient severity to affect IADLs [34] with a history of normal intellectual

function before the onset of cognitive abnormalities. A memory deficit was not required for the diagnosis of dementia [22].

The MCI amnesic type included subjects with impairments (defined as performance >1.5 SD below age/education appropriate means) in delayed recall of verbal or nonverbal material (or both) and with cognitive deficits that represented a decline from a previous level of functioning. MCI-multiple cognitive deficits required impairments in at least 1 cognitive domain other than memory (i.e., results of 2 or more tests were abnormal), or else 1 normal test result (which could be a memory test result) in at least 2 separate domains, without sufficient severity or loss of IADLs to constitute dementia [18].

At the last 2013 examination, there were 68 eligible participants who were alive and not demented. Information was available for 66 participants, 1 was lost to follow up and 1 refused all evaluations. Of the 66, 21 had clinic visits: 13 cognitively normal and 8 MCI; 23 TICS only by telephone, 8 cognitively normal and 15 MCI; 15 home visits, 9 cognitively normal and 6 MCI; and 7 who were deceased had only DQ from family members, 2 of these cognitively normal and 5 had MCI. Twelve of the 23 with TICS only resided outside of the area. In prior years, staff traveled to Florida for home visits for many of these participants. Almost all of the participants who had a home visit were severely disabled and were unable to attend a clinic visit. At the 2013 evaluation, 10 of 66 were classified as incident dementia. Participants who were classified as demented were not evaluated in the detailed CHS-CS at subsequent follow up visits but continued to be followed within the overall CHS.

2.4 Statistical Methods

Univariate association between dementia status, demographic and medical characteristics were assessed by Chi-square tests and analyses of variance. Age adjusted dementia and mortality rates as well as their 95% confidence intervals were estimated using direct methods. Cox models were conducted to study the longitudinal association between the outcomes (mortality, dementia) and risk factors at baseline and during the follow up. All analyses were completed using SAS 9.4 (SAS Institute, Cary NC) and significant finding was defined by a p-value <0.05 .

Person-years (PYs) of follow up for most analyses began at the time of entry to the Pittsburgh CHS-CS in 1998–99 since participants had to be alive and free of dementia based on 1998–99 evaluations. Since participants had to be alive and free of dementia based on the 1998–99 evaluations and, therefore, were essentially immortal between 1992–94 and 1998–99. In some analysis, the follow up included the entire 924 in the Pittsburgh CHS evaluations in 1992–94, in which case PYs were acquired from 1992–94 onward. Participants were censored for PYs at either the time of incident diagnosis of dementia or death. As noted, 63% of the deaths had a dementia diagnosis prior to death and the average time between the dementia diagnosis and death was 5 years. All deaths were evaluated for a diagnosis of dementia prior to death. Since follow up in the CHS was every 6 months and yearly for dementia evaluation, detailed information about cognitive performance prior to death was almost always available.

Most of the follow up is limited to 2011 or 2012. The CHS mortality file was limited to 2011 at the time of the analysis. The 2013 evaluation (at the end of the CHS-CS) was a special evaluation. There were very few (only 47) still alive and free of dementia, limiting the sample size for many of the longitudinal evaluations. However, there were only 12 new dementia cases between 12/19/2012 and 2013 and many of them were incident before 2012. It makes little difference in the analysis whether we used 2012 or 2013.

Missing variables (few) were excluded from the analyses. ApoE was only available for a subset that agreed to genetic analysis. As noted, the 1991–92 cognitive measures were not used for classifying dementia status. The 1998–99 cognitive measures were used for classifying dementia but most were different tests than 1991–92 and learning effects should be small.

3. Results

This paper focused on the participants in the detailed CHS–CS ($n=532$) from 1998–99 to 2013. (Figure 1) By 2012, 324 (62.5%) were demented, including 102 (77.3%) of 132 with MCI and 222 (57.7%) of the cognitively normal participants in 1998–99. Also, 119 of 204 (58%) men and 205 of 314 (65%) women were demented by 2012. (Table 1)

There were 324 of 532 (61%) participants classified as dementia based on the NINCDS-ADRDA classification through 2011, 321 classified as dementia based on DSM-IV and 287 (89.4%) were classified as AD. The ADDTC criteria classified 10 as probable vascular dementia and 46 as possible pure vascular dementia. There were no frontal temporal dementias, 3 classified as probable Lewy Body, 14 as Parkinson's-related dementia, and 3 as other causes.

After detailed review of the records, including information from family and participants after 1998–99, 102 of the 324 (32%) incident dementia cases initially identified after 1998–99 had probable onset prior to 1998–99, including 12 in 1995, 15 in 1997, 30 in 1998 and 55 in 1999. These participants had originally been classified as cognitively normal or MCI in 1998–99 at the beginning of the follow up. The time of onset could be more accurately measured as new information was collected from participants and family regarding prior history of cognitive changes. Measurement of incidence of dementia from 1998–99 was restricted to the 222 that were incident after 1998–99. Incident dementia was diagnosed a median of 6 years (mean 6.9 ± 3.0) after 1998–99. The mean age of onset of dementia for the 222 incident cases was 83 years, 19 (8%) <80 at onset, 95 (43%) 80–84, 80 (36%) 85–89, 24 (11%) 90–94 and 4 (2%) >95. All incident dementia cases with onset prior to 1998–99 were included in the study but were not at risk for dementia in analysis that was based on variables collected in 1998–99, including the second MRI and clinical evaluations.

There were 335 (65%) deaths among the 518 (excluding 14 refusals) through 2011; 211 (63%) were demented, 68 (20%) were cognitively normal and 56 (16%) were MCI prior to death. (Table 1) There were 92 deaths <85 years of age and 39% were demented prior to death, 131 deaths age 85–90 and 68% were demented prior to death, and 112 deaths at age >90 and 77% were demented prior to death. Mean age at death for deceased but not demented prior to death was 85 ± 5 years ($n=124$) and for deceased and demented, 89 ± 4.6

years (n=211). Mean time from incidence of dementia to death was 5.2 ± 3.3 years. The length of survival following incident dementia diagnosis was inversely related to age at diagnosis of dementia, 6 years for diagnosis less than age 80 to 2.3 years for onset 95 years of age.

3.1 Mortality

Risk factors for total mortality measured either in 1998–99 or at 1992–94 were primarily related to clinical and subclinical CVD and measures of myocardial injury and cardiac function, higher Agatston CAC scores, a measure of coronary atherosclerosis and aging, maximum wall thickness of both the common and internal carotid arteries and the percent maximal stenosis, lower ankle brachial index, increased WMG at baseline, history of clinical CVD in 1998–99 and baseline levels of high-sensitivity cardiac troponin (hs-TnT) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP). (Table 2)

3.2 Prevalence and Incidence Dementia

The point prevalence of dementia at 2013 among alive participants (n=160) was 113 of 160 (71%) demented including 47% age 85–89, 69% age 90–94, 87% age 95–99 to 100% for 3 participants over age 100.

Incidence of dementia after 1998–99 to 2011 increased with age. There was little difference in the incidence of dementia between men and women. Age-adjusted incidence rates of dementia were similar for blacks and whites, 94.4 (56–160)/1000 PYs (n=44) as compared to whites, n=176, 81.1 (62–102)/1000 PYs, not significant. Incidence of dementia was higher for MCI versus cognitively normal but number of MCI cases in 1998–99 was very small. The prevalence of ApoE4 in 1998–99 among whites, declined with age in 1998–99, 23% <75 years of age, 21% age 76–80, 18% age 81–85 and only 6% age 85+. There was little difference in the incidence of dementia by ApoE4 status with the greatest difference in the 76–80 age group where the incidence of dementia was 70 (CL: 55.8–88.9) for those without ApoE4 versus 100 with ApoE4. (Table 3, Figure 3 & 4) Results were similar when analysis was restricted to whites only.

3.3 Risk Factors for Dementia

Risk factors for dementia based on 1992–94 measurements for the entire 924 participants in the CHS-CS Pittsburgh, PA cohort are shown in Table 5. Higher ventricular grade 5 on MRI but not white matter grade 3 were predictors of dementia. These results were similar when ventricular or white matter grade were treated as continuous variables (not shown). ApoE4 was also a significant predictor of dementia.

There was an inverse association between number of blocks walked in 1992–94 and risk of dementia between 1998–99 and 2011 but not with blocks walked measured in 1998–99. Blocks walked were greater in 1998–99 than in 1992–94 for the same participants measured at both time points, as approximately 20% of 399 participants in 1998–99 reported walking 50 blocks per week in 1998–99 as compared to only 7% in 1992–94. There were few participants involved in other specific physical activities. Total Kcalories of physical activity (not shown) were not related to risk of dementia. (Table 5)

The CES-D 10-item questionnaire was used to evaluate depression symptoms [35]. There was no significant difference in the CES-D scores between normal and dementia in 1998–99 to 2011 either based on the baseline (mean 3.92 for nondemented versus 4.09 for demented) or at 1998–99 (mean 5.11 for nondemented versus 5.19 for demented participants). There were very small changes in the CES-D between baseline to 1998–99 and also not related to risk of dementia, 1.19 for nondemented versus 1.09 for those who became demented.

Hippocampal volume was only measured in 1998–99 in a sample of MRIs. There was an inverse relationship between hippocampal volume and risk of dementia for both men and women [22]. (Figure 4)

3.4 Cognitive Performance and Risk of Dementia

An ancillary study [36] administered a cognitive battery in 1990–91 prior to their first MRI. The results of the cognitive testing were not available to the investigators evaluating dementia status. Among those cognitively normal in 1998–99, 105 were not demented and 148 demented to 2011 and had available cognitive testing in 1990–91.

Measures for the Wechsler Memory Scale-Revised (WMS-R) evaluated verbal memory, visual memory and general memory (a composite of verbal and visual memory). Visual memory but not verbal memory scores were higher for cognitively normal participants as compared to dementia. General memory was higher for those cognitively normal than for dementia.

Delayed recall from the WMS-R was lower for the dementia than the cognitively normal participants. Trails A and B are measures of psychomotor speed and working memory were much longer for the dementia versus the cognitively normal participants. After adjusting for both age and Vocabulary Raw Score, Trail B was significantly longer for incident dementia cases, DSST ($p=.06$), attention/concentration ($p=.08$) and general memory scores ($p=.10$) were borderline significant given the small sample sizes. (Table 6) The cognitive battery from 1998–99 onward was used in the evaluation of the diagnosis of dementia and, therefore, would likely be biased when comparing dementia versus cognitively normal. This battery was not the same as in 1990–91 nor administered by the same individuals and therefore evaluation of changes in specific cognitive tests between 1991 and 1998 was not feasible.

3.5 Characteristics of Long Term Survivors

We did a further detailed evaluation of 19 cognitively normal, 28 MCI and 113 dementia participants who were alive at 2013, the last evaluation in the study. There were only 5 cognitively normal surviving black participants.

CHS medical records were reviewed and interviews with participants and their families were conducted to obtain further information about prior history of disease and disability. Among the 19 cognitively normal participants, 11 (58%) were women, 14 (74%) were white. Mean and median age in 2013 was 92, minimum age was 86 and maximum was 98. Among 28 MCI: 17 (61%) women, 22 (79%) white, mean age was 92 ± 2.1 , median age 92, minimum 87.6 and maximum was 95.4. (Appendix Figures 1 and 2)

Among the 113 dementia survivors, age at onset of dementia was <80 in 29 (26%), 40 (35%) age 80–84, 33 (29%) age 85–89 and 11 (10%) age >90. Many of these participants were demented for many years, 51 (45%) had onset of dementia between 1997 to 2003, approximately 10 years before 2013 and only 10 incident dementia between 2010 and 2012.

Level of education, i.e. greater than college degree, was very high, greatest for normal versus dementia. (Table 7) Approximately 89% normal versus 44% dementia ($p=.001$) had greater than college degree. Other variables that significantly discriminated surviving normals from dementia included higher 3MSE scores and DSST scores in 1992–94, greater hippocampal volume among cognitively normal participants and faster gait speed in 1992–94 and 1998–99. Number of blocks walked in 1992–94 was significantly greater for those cognitively normal. Neither extent of CAC, hs-TnT, NT-proBNP nor 6 minute walking distance were different between cognitively normal and dementia, although cognitively normal participants generally had better scores than demented participants. Also, 8 of 17 (47%) alive and normal cognition had CAC <10 compared to only 27 of 357 (10%) who had died by 2013. Only 1 of 16 (6.2%) cognitively normal participants had a ventricular grade 5 versus 10% of demented. The measurement of white matter abnormalities in CHS in 1992–94 and 1998–99 was less sensitive to vascular pathology compared with newer methods, such as diffusion tensor imaging. Cognitive tests scores from 1990–91 were available for 12 cognitively normal and 64 dementia alive in 2013. Vocabulary raw score was much greater for cognitively normal versus dementia ($p=.0005$). Most other cognitive tests were also better for cognitively normal as compared to dementia. After adjustment for the vocabulary raw score and age, delayed recalls ($p=.05$) and Trails B ($p=.08$) measured in 1991–92 were significantly different between cognitively normal and dementia.

We further evaluated the determinants of survival free of dementia in Cox survival models to 2013 for the participants alive and without dementia at 1992–94. The sample size was reduced to 667 because some participants had refused ApoE4 measurement ($n=99$) and others had onset of dementia prior to 1992–94 ($n=46$) or had missing data ($n=112$). In the stepwise prediction model, age, ventricular grade 5, number of blocks walked, ApoE4, measures of subclinical CVD in 1992–94, and gait speed were predictors of death or dementia. White matter grade 3, HR 1.21 (0.99–1.49), diabetes HR 1.19 (0.92–1.53), current cigarette smoking HR 1.24 (0.92–1.65) were also determinants but not included in the stepwise model. Hippocampal volume, coronary artery calcium, hs-cTnT, NT-proBNP, and detailed cognition performance measures were not included in Cox models because they were not part of the 1992–94 evaluations.

4. Discussion

The incidence and prevalence of dementia in this study of older age participants was very high, consistent with other studies [1,37–40]. The high incidence and prevalence of dementia is also consistent with extensive brain pathology, e.g. AD, plaques and neurofibrillary tangles, vascular disease and neurodegeneration documented by pathology and, more recently, in neuroimaging studies in older age groups [41–44] Very few of the participants survived to age 90+ free of dementia. This study is consistent with other recent studies of very elderly [45–48]. Only 19 (2%) of the 865 free of dementia in 1992–94 or

3.5% of 532 included in the 1998–99 sample were alive and had normal cognition at the end of the study in 2013. Only 47 (29%) of 160 alive in 2013 were not demented. The 113 participants with dementia met the criteria for dementia based on standard diagnostic criteria (see Methods section) and had both cognitive changes from baseline and disability related to their cognitive changes. They also differed from the normals on brain MRI, especially hippocampal volume and ventricular size [49].

Lower hippocampal volume and higher ventricular grade, a marker of brain ‘atrophy’, were determinants of dementia in the CHS-CS [49]. We have previously reported that specific volumetric brain loss evaluated by Voxel-based morphometry was associated with time to both MCI and dementia in the CHS-CS [50].

Extent of white matter hyperintensities, e.g. white matter grade, was a risk factor for dementia at younger ages in the CHS-CS but not in this older age cohort [21]. White matter grade abnormalities were a determinant of mortality in the CHS and correlated with extent of CVD. Therefore, it is possible that individuals with high white matter grade may have either died or become demented prior to the beginning of the follow up study in 1998–99.

Measurement of both subclinical and clinical CHD and other vascular disease are determinants of mortality in this older age group. There were very few participants with low Agatston CAC scores, a measure of atherosclerosis [51]. Older participants with lower prevalence of atherosclerosis have lower mortality and risk of clinical CVD and greater longevity and may be candidates for evaluation of therapies, i.e. clinical trials, to reduce risk of dementia because they will have lower risk of competing events, MI, stroke, CHF, and greater longevity and follow up but higher risk of dementia because of greater longevity.

One hypothesis is that the lower prevalence of peripheral atherosclerosis, probably secondary to lower long term levels of CV risk factors, may be associated with better brain reserve as well as decreased brain vascular disease and reduced risk of dementia. Clinical trials of lipid lowering therapy, statin therapy have not documented a reduction in dementia or AD [52]. These trials, however, did not focus specifically on measures of dementia or specific types of dementia based on neuropathology, MRI, or PET imaging. Treatment of hypertension to date has also not been consistently shown in clinical trials to reduce risk of dementia, nor treatment of type 2 diabetes.

A second hypothesis is that dementia in the very old is a result of brain amyloid disease with a long incubation period, secondary neurodegeneration [53–55]. In the GEMS, we recently reported that amyloid deposition, vascular disease as well as neurodegeneration as measured by decreased volumes in the hippocampus were risk factors for AD [41]. A recent report, however, from the Mayo Clinic, a cross-sectional study, suggested that vascular disease or other factors associated with cognitive decline may precede amyloid deposition [56].

A third hypothesis is that dementia in the very old, age 85+, is a component of “normal aging”. Age remained an important predictor of dementia in this study even including many possible risk factors for dementia in Cox models. If incident dementia occurring at older ages is “normal brain aging”, then the next critical question is whether brain aging and peripheral nonbrain aging are correlated within the same individual, in which case

prevention or slowing of the aging process would be the primary therapies for decreasing the incidence and prevalence of dementia in this older population, i.e. exercise, specific dietary factors, cognitive training, etc. Brain aging and peripheral aging may be discordant, slowing of brain aging would not necessarily impact on peripheral disability and frailty [57–63]. A new Institute of Medicine report on cognitive aging has attempted to separate cognitive aging from AD and other specific causes of dementia, assuming that age-related cognitive decline is ‘normal’ and independent of specific neuropathology other than neurodegeneration [64]. The environmental and genetic determinants of brain aging may be different than the traditional risk factors evaluated in most epidemiological and clinical dementia studies [65].

There are, unfortunately, few very good markers of aging independent of “disease” and especially brain aging that could discriminate brain aging from long incubation period diseases, e.g. CHD, lung cancer, osteoporosis, prion diseases of the brain [66–69]. It is difficult to separate aging from distinct pathology except by long term longitudinal studies that would include brain imaging, both MRI and PET, cognition, and independent measures of aging. Studies of dementia among older individuals should include measures of both brain and peripheral aging.

Fitness declines with age and is determined in part from cardiac, pulmonary and muscle function, blood oxygen transport, i.e. hemoglobin, and genetic attributes. Poorer fitness may be an important determinant of risk of dementia. We did not observe a strong association of the 6-minute corridor walk with either dementia or disability in this older cohort. However, the 6-minute walk, as has been done in the CHS included a fairly large number of incomplete or no testing done, may not be an adequate test of the fitness hypothesis although it did predict CVD in the CHS[70]. We did find an association with number of blocks walked, especially >50 blocks per week, which is almost certainly a measure of fitness and risk of dementia and also with gait speed which may also be a function of fitness [71–74]

The study of brain aging should not be done in isolation but should also include measures of peripheral aging. The long incubation period both to clinical disease and extensive pathobiological changes in the brain strongly suggest that future longitudinal epidemiology studies will have to start at early age (probably 65 years of age) and long follow up, perhaps 10 or more years, including detailed cognitive measures, imaging, genetics, evaluation of new possible risk factors, and markers of aging [75–80]. Such studies will need to focus first on intermediate endpoints, especially changes in brain structure and pathology, e.g. hippocampal volume, amyloid and tau, vascular disease, gray matter volume, etc. and relation to cognitive changes over time. Risk factors that modulate the slope of change in brain gray matter loss in key regions beginning at earlier ages are more likely to impact on dementia risk [81–85]. Such studies will require repetitive detailed cognitive testing and effects on physical and social functioning.

At least five intervention trials need to be considered, for the prevention of incident dementia in the older age group besides current anti-amyloid drug therapy trials. First, can modification of risk factors in the general population, such as diabetes, hypertension, smoking, obesity, less physical activity, delay cognitive decline and dementia either by

modifying the development of brain amyloid, less neurodegeneration, and brain reserve [85–88]? A recent report from the Alzheimer's Association stated there was strong evidence from a population perspective that regular physical activity and management of cardiovascular risk factors reduced the risk of cognitive decline and may also reduce the risk of dementia. [89] Second, would more intensive prevention of peripheral atherosclerotic disease, such as maintaining 0 or near 0 CAC score which has recently been reported in CHS to be associated with very low incidence of dementia [90], reduce the risk of dementia? This intervention would require aggressive lipid lowering and antihypertensive drug therapy, nonsmoking, and tight control of diabetes. Such trials would probably have to be restricted to women since the prevalence atherosclerosis among men in these older age groups is very high. Third, would improved fitness by more intensive exercise programs in older age groups reduce the risk of dementia most likely by modifying the progression of neurodegeneration? Fourth, dementia in the very elderly may be approached as a 'chronic disease'. Even if the underlying pathophysiology is not treatable, would prevention of brain injury due to CHF, hypoperfusion of brain, atrial fibrillation, stroke, brain trauma, or exposure to toxic environmental factors, slow or delay progression of cognitive decline and disability to clinical dementia? Fifth, is it possible that dietary modifications, such as vegan diet, very high omega-3 fatty acids, or Mediterranean diet, as recently reported [91], reduce incidence of dementia? Such diet trials probably need to be done among populations that consume such diets from early age rather than modification of diet at very old age.

Finally, a null hypothesis is that it the primary determinants of dementia, especially in these older age groups have not yet been identified and most currently proposed interventions will fail until we successfully identify the lifestyle or environmental agents that interact in genetically susceptible hosts as determinants of the risk of dementia.

3. Conclusion

Very few older individuals live into their 90s free of dementia and disability. Cognition test scores even 20 years before onset of dementia, greater ventricular volume, a measure of brain atrophy, smaller hippocampal volume ApoE4, education, and 'intelligence' are key determinants of dementia. Vascular disease is the primary determinant of mortality. Most important, given the very high incidence and prevalence of dementia, research to identify environmental and genetic determinants of brain pathology, dementia and aging must have a very high priority as well as new clinical trials that will evaluate alternative hypotheses other than the amyloid cascade in the very elderly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CAC	Coronary artery calcium
CAD	coronary artery disease
CVD	cardiovascular disease
CHS-CS	Cardiovascular Health Study – Cognition Study
CHF	congestive heart failure
CRP	C-reactive protein
Hs-cTnT	high-sensitivity cardiac troponin
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
IL-6	interleukin-6

References

1. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest old: The 90+ study. *Ann Neurol*. 2010; 67:114–121. [PubMed: 20186856]
2. Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, et al. Trends in the incidence and prevalence of alzheimer's disease, dementia, and cognitive impairment in the united states. *Alzheimers Dement*. 2011; 7:80–93. [PubMed: 21255746]
3. Plassman BL, Williams JW Jr, Burke JR, Holsinger T, Benjamin S. Systematic review: Factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med*. 2010; 153:182–193. [PubMed: 20547887]
4. Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly ES Jr, Cox NJ, et al. National institutes of health state-of-the-science conference statement: Preventing Alzheimer disease and cognitive decline. *Ann Intern Med*. 2010; 153:176–181. [PubMed: 20547888]
5. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011; 42:2672–2713. [PubMed: 21778438]
6. Mackey RH, Kuller LH. Blood pressure and cognitive decline. *Curr Cardio Risk Rep*. 2010; 4:369–375.
7. Kuller LH. Preventing dementia in older cardiovascular patients. *Curr Cardio Risk Rep*. 2014;8.
8. Royle NA, Booth T, Valdes Hernandez MC, Penke L, Murray C, Gow AJ, et al. Estimated maximal and current brain volume predict cognitive ability in old age. *Neurobiol Aging*. 2013; 34:2726–2733. [PubMed: 23850342]
9. Lindenberger U. Human cognitive aging: Corriger la fortune? *Science*. 2014; 346:572–578. [PubMed: 25359964]
10. Reisberg B, Shulman MB, Torossian C, Leng L, Zhu W. Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimers Dement*. 2010; 6:11–24. [PubMed: 20129317]

11. Jorm AF, Masaki KH, Petrovitch H, Ross GW, White LR. Cognitive deficits 3 to 6 years before dementia onset in a population sample: The Honolulu-Asia aging study. *J Am Geriatr Soc.* 2005; 53:452–455. [PubMed: 15743288]
12. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer's disease. A meta-analysis. *JAMA.* 1997; 278:1349–1356. [PubMed: 9343467]
13. Mahley RW, Rall SC Jr. Apolipoprotein E: Far more than a lipid lowering transport protein. *Ann Rev Genomics Hum Genet.* 2000; 1:507–537. [PubMed: 11701639]
14. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The cardiovascular health study: Design and rationale. *Ann Epidemiol.* 1991; 1:263–276. [PubMed: 1669507]
15. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, et al. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology.* 2003; 22:13–22. [PubMed: 12566949]
16. Lopez OL, Becker JT, Jagust WJ, Fitzpatrick A, Carlson MC, DeKosky ST, et al. Neuropsychological characteristics of mild cognitive impairment subgroups. *J Neurol Neurosurg Psychiatry.* 2006; 77:159–165. [PubMed: 16103044]
17. Fitzpatrick AL, Kuller LH, Ives DG, Lopez OL, Jagust W, Breitner JC, et al. Incidence and prevalence of dementia in the cardiovascular health study. *J Am Geriatr Soc.* 2004; 52:195–204. [PubMed: 14728627]
18. Lopez OL, Becker JT, Chang YF, Sweet RA, DeKosky ST, Gach MH, et al. Incidence of mild cognitive impairment in the Pittsburgh Cardiovascular Health Study-Cognition Study. *Neurology.* 2012; 79:1599–1606. [PubMed: 23019262]
19. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: The late-life dementia risk index. *Neurology.* 2009; 73:173–179. [PubMed: 19439724]
20. Kuller LH, Lopez OL, Jagust WJ, Becker JT, DeKosky ST, Lyketsos C, et al. Determinants of vascular dementia in the Cardiovascular Health Cognition Study. *Neurology.* 2005; 64:1548–1552. [PubMed: 15883315]
21. Kuller LH, Chang Y, Becker JT, Lopez O. Does Alzheimer's disease over 80 years old have a different etiology? *Alzheimers Dement.* 2011; 7:S596–S597.
22. Rosano C, Aizenstein HJ, Wu M, Newman AB, Becker JT, Lopez OL, et al. Focal atrophy and cerebrovascular disease increase dementia risk among cognitively normal older adults. *J Neuroimaging.* 2007; 17:148–155. [PubMed: 17441836]
23. Raji CA, Lopez OL, Kuller LH, Carmichael OT, Longstreth WT Jr, Gach HM, et al. White matter lesions and brain gray matter volume in cognitively normal elders. *Neurobiol Aging.* 2012; 33:834, e837–e816. [PubMed: 21943959]
24. Braskie MN, Boyle CP, Rajagopalan P, Gutman BA, Toga AW, Raji CA, et al. Physical activity, inflammation, and volume of the aging brain. *Neuroscience.* 2014; 273:199–209. [PubMed: 24836855]
25. Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, et al. The effects of physical activity, education, and body mass index on the aging brain. *Hum Brain Mapp.* 2011; 32:1371–1382. [PubMed: 20715081]
26. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr, et al. Midlife and late-life obesity and the risk of dementia: Cardiovascular Health Study. *Arch Neurol.* 2009; 66:336–342. [PubMed: 19273752]
27. Carmichael OT, Kuller LH, Lopez OL, Thompson PM, Dutton RA, Lu A, et al. Cerebral ventricular changes associated with transitions between normal cognitive function, mild cognitive impairment, and dementia. *Alzheimer Dis Assoc Disord.* 2007; 21:14–24. [PubMed: 17334268]
28. Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB, et al. Physical activity predicts gray matter volume in late adulthood: The Cardiovascular Health Study. *Neurology.* 2010; 75:1415–1422. [PubMed: 20944075]
29. Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, et al. Physical activity, apoe genotype, and dementia risk: Findings from the Cardiovascular Health Cognition Study. *Am J Epidemiol.* 2005; 161:639–651. [PubMed: 15781953]

30. Bryan RN, Wells SW, Miller TJ, Elster AD, Jungreis CA, Poirier VC, 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. [PubMed: 8988191]
31. Yue NC, Arnold AM, Longstreth WT Jr, Elster AD, Jungreis CA, O'Leary DH, et al. Sulcal, ventricular, and white matter changes at MR imaging in the aging brain: Data from the Cardiovascular Health Study. *Radiology*. 1997; 202:33–39. [PubMed: 8988189]
32. Bryan RN, Manolio TA, Schertz LD, Jungreis C, Poirier VC, Elster AD, et al. A method for using MR to evaluate the effects of cardiovascular disease on the brain: The Cardiovascular Health Study. *Am J Neuroradiol*. 1994; 15:1625–1633. [PubMed: 7847205]
33. Arnold AM, Newman AB, Dermond N, Haan M, Fitzpatrick A. Using telephone and informant assessments to estimate missing modified mini-mental state exam scores and rates of cognitive decline. The Cardiovascular Health Study. *Neuroepidemiology*. 2009; 33:55–65. [PubMed: 19407461]
34. Satariano, WA. *Epidemiology of Aging*. Sudbury, MA: Jones and Bartlett Publishers; 2006. Physical functioning and activities of everyday life; p. 125-169.
35. Luppá M, Luck T, Ritschel F, Angermeyer MC, Villringer A, Riedel-Heller SG. Depression and incident dementia. An 8-year population-based prospective study. *PLoS One*. 2013; 8:e59246. [PubMed: 23527147]
36. Saxton J, Ratcliff G, Newman A, Belle S, Fried L, Yee J, et al. Cognitive test performance and presence of subclinical cardiovascular disease in the Cardiovascular Health Study. *Neuroepidemiology*. 2000; 19:312–319. [PubMed: 11060505]
37. Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Llibre Rodriguez JJ, Salas A, Sosa AL, Williams JD, Dewey ME, Acosta I, Jotheeswaran AT, Liu Z. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: A 10/66 dementia research group population-based cohort study. *Lancet*. 2012; 380:50–58. [PubMed: 22626851]
38. Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology*. 2012; 78:1456–1463. [PubMed: 22551732]
39. Jorm AF, Jolley D. The incidence of dementia: A meta-analysis. *Neurology*. 1998; 51:728–733. [PubMed: 9748017]
40. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: A meta-analysis. *Arch General Psychiatry*. 1998; 55:809–815.
41. Lopez OL, Klunk WE, Mathis C, Coleman RL, Price J, Becker JT, Aizenstein HJ, Snitz B, Cohen A, Ikonomic M, McDade E, DeKosky ST, Weissfeld L, Kuller LH. Amyloid, neurodegeneration, and small vessel disease as predictors of dementia in the oldest-old. *Neurology*. 2014; 83:1804–1811. [PubMed: 25305156]
42. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010; 9:119–128. [PubMed: 20083042]
43. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol*. 2009; 66:200–208. [PubMed: 19743450]
44. Balasubramanian AB, Kawas CH, Peltz CB, Brookmeyer R, Corrada MM. Alzheimer disease pathology and longitudinal cognitive performance in the oldest-old with no dementia. *Neurology*. 2012; 79:915–921. [PubMed: 22895581]
45. Christensen K, Thinggaard M, Oksuzyan A, Steenstrup T, Andersen-Ranberg K, Jeune B, McGue M, Vaupel JW. Physical and cognitive functioning of people older than 90 years: A comparison of two Danish cohorts born 10 years apart. *Lancet*. 2013; 382:1507–1513. [PubMed: 23849796]
46. Andersen-Ranberg K, Schroll M, Jeune B. Healthy centenarians do not exist, but autonomous centenarians do: A population-based study of morbidity among Danish centenarians. *J Am Geriatr Soc*. 2001; 49:900–908. [PubMed: 11527481]
47. Gondo Y, Hirose N, Arai Y, Inagaki H, Masui Y, Yamamura K, Shimizu K, Takayama M, Ebihara Y, Nakazawa S, Kitagawa K. Functional status of centenarians in Tokyo, Japan: Developing better

- phenotypes of exceptional longevity. *J Gerontol A Biol Sci Med Sci*. 2006; 61:305–310. [PubMed: 16567382]
48. Ganguli M, Lee CW, Snitz BE, Hughes TE, McDade E, Chang CHC. Rates and risk factors for progression to incident dementia vary by age in a population cohort. *Neurology*. 2015; 84:72–80. [PubMed: 25471390]
 49. Zeifman L, Eddy W, Lopez O, Kuller LH, Raji CA, Becker JT. Whole brain, voxel level analysis of grey matter volume and time to incident mild cognitive impairment or Alzheimer's disease (Abstract). *Neurology*. 2014; 82(Suppl):p4.020.
 50. Zeifman LE, Eddy WF, Lopez OL, Kuller LH, Raji CA, Thompson PM, Becker JT. Voxel level survival analysis of grey matter volume and incident mild cognitive impairment or Alzheimer's disease. *J Alzheimers Disease*. 2015 Feb 26. Epub ahead of print.
 51. Newman AB, Naydeck BL, Sutton-Tyrrell K, Edmundowicz D, O'Leary D, Kronmal R, Burke GL, Kuller LH. Relationship between coronary artery calcification and other measures of subclinical cardiovascular disease in older adults. *Arterioscler Thromb Vasc Biol*. 2002; 22:1674–1679. [PubMed: 12377748]
 52. Kuller LH. Statins and dementia. *Curr Atheroscler Rep*. 2007; 9:154–161. [PubMed: 17877925]
 53. Lim YY, Maruff P, Pietrzak RH, Ellis KA, Darby D, Ames D, Harrington K, Martins RN, Masters CL, Szoek C, Savage G, Villemagne VL, Rowe CC. for the AIBL Research Group. A β and cognitive change: Examining the preclinical and prodromal stages of Alzheimer's disease. *Alzheimers Dement*. 2014; 10:743–751. [PubMed: 24589436]
 54. Mormino EC, Betensky RA, Hedden T, Schultz AP, Ward A, Huijbers W, et al. Amyloid and APOE ϵ 4 interact to influence short-term decline in preclinical Alzheimer disease. *Neurology*. 2014; 82:1760–1767. [PubMed: 24748674]
 55. Vos SJB, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, Cairns NJ, Morris JC, Holtzman DM, Fagan AM. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. *Lancet Neurol*. 2013; 12:957–65. [PubMed: 24012374]
 56. Jack CR Jr, Wiste HJ, Weigand SD, Knopman DS, Vemuri P, Mielke MM, Lowe V, Senjem ML, Gunter JL, Machulda MM, Gregg BE, Pankratz VS, Rocca WA, Petersen RC. Age, sex, and APOE ϵ 4 effects on memory, brain structure, and β -amyloid across the adult life span. *JAMA Neurol*. 2015 Mar 16. [Epub ahead of print]. 10.1001/jamaneurol.2014.4821
 57. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *JAMA*. 1996; 275:528–532. [PubMed: 8606473]
 58. Spiro A 3rd, Brady CB. Integrating health into cognitive aging: Toward a preventive cognitive neuroscience of aging. *J Gerontol B Psychol Sciences Soc Sci*. 2011; 66 (Suppl 1):i17–25.
 59. Ritchie K, Kildea D. Is senile dementia "age-related" or "ageing-related"?--evidence from meta-analysis of dementia prevalence in the oldest old. *Lancet*. 1995; 346:931–934. [PubMed: 7564727]
 60. Desai AK, Grossberg GT, Chibnall JT. Healthy brain aging: A road map. *Clin Geriatr Med*. 2010; 26:1–16. [PubMed: 20176289]
 61. Raji CA, Lopez OL, Kuller LH, Carmichael OT, Becker JT. Age, Alzheimer disease, and brain structure. *Neurology*. 2009; 73:1899–1905. [PubMed: 19846828]
 62. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol*. 2004; 3:343–353. [PubMed: 15157849]
 63. Brayne C. The elephant in the room - healthy brains in later life, epidemiology and public health. *Nat Rev Neurosci*. 2007; 8:233–239. [PubMed: 17299455]
 64. Blazer, DG.; Yafee, K.; Liverman, CT., editors. Progress in understanding and opportunities. Washington, DC: National Academies Press; 2015. Cognitive aging.
 65. Kuller LH, Lopez OL. Dementia and Alzheimer's disease: A new direction. The 2010 Jay L. Foster Memorial Lecture *Alzheimers Dement*. 2011; 7:540–550. [PubMed: 21889117]
 66. King KS, Kozlitina J, Rosenberg RN, Peshock RM, McColl RW, Garcia CK. Effect of leukocyte telomere length on total and regional brain volumes in a large population-based cohort. *JAMA Neurol*. 2014; 71:1247–1254. [PubMed: 25090243]

67. McClearn GE, Johansson B, Berg S, Pedersen NL, Ahern F, Petrill SA, Plomin R. Substantial genetic influence on cognitive abilities in twins 80 or more years old. *Science*. 1997; 276:1560–1563. [PubMed: 9171059]
68. Olive M, Harten I, Mitchell R, Beers JK, Djabali K, Cao K, Erdos MR, Blair C, Funke B, Smoot L, Gerhard-Herman M, Machan JT, Kutys R, Virmani R, Collins FS, Wight TN, Nabel EG, Gordon LB. Cardiovascular pathology in Hutchinson-Gilford progeria: Correlation with the vascular pathology of aging. *Arterioscler Thromb Vascular Biol*. 2010; 30:2301–2309.
69. McClintock D, Ratner D, Lokuge M, Owens DM, Gordon LB, Collins FS, Djabali K. The mutant form of lamin a that causes Hutchinson-Gilford progeria is a biomarker of cellular aging in human skin. *PloS One*. 2007; 2:e1269. [PubMed: 18060063]
70. Yazdanyar A, Aziz MM, Enright PL, Edmundowicz D, Boudreau R, Sutton-Tyrell K, Kuller L, Newman AB. Association between 6-minute walk test and all-cause mortality, coronary heart disease-specific mortality, and incident coronary heart disease. *J Aging Health*. 2014; 26:583–599. [PubMed: 24695552]
71. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol Sci*. 2003; 14:125–130. [PubMed: 12661673]
72. Artero EG, Jackson AS, Sui X, Lee DC, O'Connor DP, Lavie CJ, Church TS, Blair SN. Longitudinal algorithms to estimate cardiorespiratory fitness: Associations with nonfatal cardiovascular disease and disease-specific mortality. *J Am Coll Cardiol*. 2014; 63:2289–2296. [PubMed: 24703924]
73. Newman AB, Simonsick EM, Naydeck BL, Boudreau RM, Kritchevsky SB, Nevitt MC, Pahor M, Satterfield S, Brach JS, Studenski SA, Harris TB. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA*. 2006; 295:2018–2026. [PubMed: 16670410]
74. Enright PL. The six-minute walk test. *Respir Care*. 2003; 48:783–785. [PubMed: 12890299]
75. Tilvis RS, Kahonen-Vare MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. *J Gerontol A Biol Sci Med Sci*. 2004; 59:268–274.
76. Ganguli M, Ratcliff G, Huff FJ, Belle S, Kancel MJ, Fischer L, Seaberg EC, Kuller LH. Effects of age, gender, and education on cognitive tests in a rural elderly community sample: Norms from the Monongahela valley independent elders survey. *Neuroepidemiology*. 1991; 10:42–52. [PubMed: 2062416]
77. Bernard C, Helmer C, Dilharreguy B, Amieva H, Auriacombe S, Dartigues JF, Allard M, Catheline G. Time course of brain volume changes in the preclinical phase of Alzheimer's disease. *Alzheimers Dement*. 2014; 10:143–151. e141. [PubMed: 24418054]
78. van Harten AC, Smits LL, Teunissen CE, Visser PJ, Koene T, Blankenstein MA, Scheltens P, van der Flier WM. Preclinical ad predicts decline in memory and executive functions in subjective complaints. *Neurology*. 2013; 81:1409–1416. [PubMed: 24049134]
79. Donohue MC, Sperling RA, Salmon DP, Rentz DM, Raman R, Thomas RG, Weiner M, Aisen PS. Australian Imaging B, Lifestyle Flagship Study of A, Alzheimer's Disease Neuroimaging I, Alzheimer's Disease Cooperative S. The preclinical Alzheimer cognitive composite: Measuring amyloid-related decline. *JAMA Neurol*. 2014; 71:961–970. [PubMed: 24886908]
80. van Rossum IA, Vos SJ, Burns L, Knol DL, Scheltens P, Soininen H, Wahlund LO, Hampel H, Tsolaki M, Minthon L, L'Italien G, van der Flier WM, Teunissen CE, Blennow K, Barkhof F, Rueckert D, Wolz R, Verhey F, Visser PJ. Injury markers predict time to dementia in subjects with MCI and amyloid pathology. *Neurology*. 2012; 79:1809–1816. [PubMed: 23019259]
81. Brickman AM, Khan UA, Provenzano FA, Yeung LK, Suzuki W, Schroeter H, Wall M, Sloan RP, Small SA. Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults. *Nature Neurosci*. 2014; 17:1798–1803. [PubMed: 25344629]
82. Elwood P, Galante J, Pickering J, Palmer S, Bayer A, Ben-Shlomo Y, Longley M, Gallacher J. Healthy lifestyles reduce the incidence of chronic diseases and dementia: Evidence from the Caerphilly Cohort Study. *PloS One*. 2013; 8:e81877. [PubMed: 24349147]
83. Kryscio RJ. Secondary prevention trials in Alzheimer disease: The challenge of identifying a meaningful end point. *JAMA Neurol*. 2014; 71:947–949. [PubMed: 24886838]

84. Owen AM, Hampshire A, Grahn JA, Stenton R, Dajani S, Burns AS, Howard RJ, Ballard CG. Putting brain training to the test. *Nature*. 2010; 465:775–778. [PubMed: 20407435]
85. Solomon A, Levalahti E, Soininen H, Tuomilehto J, Lindstrom J, Lehtisalo J, Peltonen M, Kivipelto M, Antikainen R, Paajanen T, Ngandu T, Laatikainen T, Strandberg TE, Hanninen T. A multidomain, two-year, randomized controlled trial to prevent cognitive impairment: The FINGER Study. *Alzheimers Dement*. 2014; 10:P137.
86. Haan MN, Wallace R. Can dementia be prevented? Brain aging in a population-based context. *Annu Rev Public Health*. 2004; 25:1–24. [PubMed: 15015910]
87. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014; 13:788–94. [PubMed: 25030513]
88. Gregory MA, Gill DP, Petrella RJ. Brain health and exercise in older adults. *Curr Sports Med Rep*. 2013; 12:256–271. [PubMed: 23851414]
89. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement*. 2015; 11:718–726. [PubMed: 26045020]
90. Kuller LH, Lopez OL, Mackey RH, Rosano C, Edmundowicz D, Becker JT, et al. Incident dementia, subclinical and clinical coronary heart disease in older individuals: The CHS Cognition Study [abstract]. *Alzheimers Dement*. 2015 in press.
91. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martinez-Gonzalez MA, et al. Mediterranean diet and age-related cognitive decline. A randomized clinical trial. *JAMA Intern Med*. 2015; 175:1094–1103. [PubMed: 25961184]

Research in Context

1. Systematic Review

We used Medline and PubMed searches and the recent Institute of Medicine report on cognitive aging to identify longitudinal studies of aging and dementia. Few studies included brain imaging, risk factors for dementia, and long term follow up.

2. Interpretation

We determined that: a) measures of cardiovascular disease are the determinants of longevity; b) incidence of dementia was very high; c) few individuals survived to age 90+ with normal cognition; d) determinants of successful aging, free of dementia were higher education and IQ, greater hippocampal volume, greater number of blocks walked, and faster gait speed.

3. Future Directions

Further studies: a) determine the relationship between brain and peripheral aging; b) whether older individuals with little atherosclerosis have lower risk of dementia; c) whether better cardiovascular fitness reduces risk of dementia; d) can effects of brain aging be discriminated from long incubation pathologies; e) can better treatment of chronic diseases slow progression of dementia?

Figure 1.
Selection of Participants of the CHS-CS

Figure 2.
Procedures Over Time for the CHS-CS

Figure 3.
Kaplan-Meier Cumulative Survival Curve Free of Dementia by Age and Time from 1998–99

Figure 4.
Kaplan-Meier Cumulative Survival Curve Free of Dementia by ApoE4 Status, 1992–2013

Figure 5.
Incidence of Dementia 1998–99 to 2012 by Hippocampal Volume Measured in 1998–99

Table 1

Survival Status: Normal, MCI or Dementia, 1998–99 to 2012 in the CHS-CS

	Alive						Deceased						Total						Total
	Normal			MCI			Dementia			Normal			MCI			Dementia			
	N	%		N	%		N	%		N	%		N	%		N	%		
Men	16	08	10	05	37	18	36	18	23	11	82	40	52	25	33	16	119	58	204
Women	19	06	25	08	76	24	32	10	33	11	129	41	51	16	58	18	205	65	314
Total	35	07	35	07	113	22	68	13	56	11	211	41	103	20	91	18	324	62	518

141 of 204 (69%) men deceased
194 of 314 (62%) women deceased
76 of 120 (63%) women alive, demented
37 of 63 (59%) men alive, demented
211 of 335 (63%) of deceased, demented prior to death
Excludes 14 refusals

Table 2

Cox Regression Model in Detailed CHS-CS (Outcome Variable: Death at 2011, Method: All the predicting variables were entered into the model. No. of Observations: 306 (189 deaths)

	HR (95% CI)
Age	1.08 (1.03, 1.13)
White matter grade 3	1.42 (1.01, 1.99)
MMSE <90	1.68 (1.01, 2.80)
NT-proBNP >192.8 pg/ml	2.07 (1.27, 3.37)
CAC score >400 Agatston units	1.50 (1.01, 2.23)
Troponin 12 pg/ml	1.67 (1.04–2.68)

Predicting variables: age, gender, race, education, diabetes, hypertension, sub clinical disease, HDL, LDL, ventricular grade, white matter grade, smoking, timed walked, blocks walked, DSST, MMSE, IL6, CRP, BNP, Cystat C, 1st CAC. (using 1998–99 data if available).

Table 3

Incidence of Dementia 1998–99 to 2011 By Age, Race, Sex and ApoE4 and Normal, MCI*

	Age in 1998–99	N	N Demented	Age-specific rate/1000 PYs
Women	70–75	82	43	64.7 (48–87)
	76–80	109	63	79.9(62–102)
	81–85	45	28	113.4 (78–164)
	>85	14	7	150.0 (67–334)
Men	70–75	34	11	40.1 (22–72)
	76–80	93	47	75.7 (57–101)
	81–85	32	20	122.6 (78–192)
	>85	6	2	105.3 (26–421)
ApoE4 – No	70–75	86	39	56.3 (41–77)
	76–80	141	72	70.4 (56–89)
	81–85	59	38	120.9 (88–167)
	>85	16	8	155.5 (74–326)
ApoE4 – Yes	70–75	23	12	63.8 (36–112)
	76–80	42	27	99.6 (68–145)
	81–85	13	8	131.2 (66–262)
	>85	1	1	166.7 (23–1183)
White	70–75	78	38	59.7 (43–82)
	76–80	174	91	74.7 (61–92)
	81–85	63	38	112.8 (82–156)
	>85	19	9	153.8 (77–308)
Black	70–75	37	15	51.0 (31–85)
	76–80	28	19	99.0 (63–155)
	81–85	14	10	135.1 (73–251)
	>85	1	0	0.0
	White Only			
Normal 1997–98	70–75	73	34	55.7 (40–78)
	76–80	148	78	72.0 (58–90)
	81–85	50	30	111.1 (78–159)
	>85	15	8	170.7 (81–358)
MCI 1997–98	70–75	5	4	148.2 (56–395)
	76–80	26	13	95.6 (56–165)
	81–85	13	8	120.7 (58–253)
	>85	4	1	90.9 (13–645)

* Excludes 102 participants with incident dementia prior to 1998–99

Table 4

Cox Regression Model for Predictors of Dementia by Baseline Variables (1992–94) Age <80 at 1992–94, Follow Up 1992–2011 (77 Not in Detailed CHS-CS Censored at 1998–99)

Baseline variable (1992–94)		HR (95% CI)	P value
Age		1.08 (1.04–1.13)	0.0001
Race	Black	0.90 (0.63–1.30)	0.580
Gender	Female	1.43 (1.04–1.95)	0.026
Ventricular grade 1992–93	5	1.73 (1.14–2.61)	0.010
White matter grade 1992–93	3	1.23 (0.87–1.74)	0.237
Number of blocks walked/week	5 6–12	1.73 (1.19–2.53) 1.22 (0.87–1.74)	0.015
DSST	34 35–47	2.47 (1.58–3.85) 1.43 (1.03–1.98)	0.0004
MMSE	<90 90–95	1.92 (1.23–2.98) 1.27 (0.91–1.76)	0.015
Hypertension	Yes	0.95 (0.70–1.28)	0.723
Diabetes	Yes	1.06 (0.67–1.66)	0.818
Subclinical CVD	Yes	1.07 (0.81–1.42)	0.625
Smoking	Current Past	0.69 (0.42–1.11) 1.05 (0.79–1.40)	0.225
BMI kg/m ²	25–28 28.1–30 >30	0.86 (0.62–1.20) 0.63 (0.41–0.98) 1.05 (0.71–1.56)	0.134
Gait speed 15' ft	>5 sec	0.92 (0.68–1.25)	0.608
ApoE4	Yes	1.53 (1.13–2.06)	0.005

Comparison group: number of blocks walked >12, DSST >47, 3MSE >95, ApoE4 status no, BMI 25

Table 5

Blocks Walked Per Week in 1992–94 and 1998–99 and Incidence of dementia in 1998–99 through 2011 (Same Individuals)

	Blocks Walked at 1998–99				Blocks Walked at 1992–93*			
	N	# Demented (%)	Age-adjusted Dementia Rate/1000 PYs (CL) in 2011	N	# Demented (%)	Age-adjusted Dementia Rate/1000 PYs (CL) in 2011		
<= 5	108	55 (50.9)	84.6 (54–133)	72	38 (52.8)	90.1 (50–164)		
5.1–12	72	38 (52.8)	84.4 (48–151)	190	113 (59.5)	95.7 (69–133)		
12.1–20	23	16 (69.6)	117.7 (46–337)	85	38 (44.7)	62.9 (35–116)		
21–35	75	38 (50.7)	86.3 (49–156)	17	7 (41.2)	59.2 (16–286)		
36–50	42	24 (57.1)	82.3 (38–195)	9	6 (66.7)	115.4 (52–257)		
> 50	79	40 (50.6)	86.8 (46–169)	27	9 (33.3)	43.9 (13–170)		
Total	399	211 (52.9)		400	211 (52.8)			

* p<.05

1990–91 Neuropsychological Assessment by Dementia Status at 2011 (Normal at 1998–99)

Table 6

Variable	Not demented at 2011 (n=105)				Demented by 2011 (n=148)				p-value*	p-value**
	Mean	SD	median		Mean	SD	median			
Vocabulary raw score	54.0	9.8	56.0		50.6	11.8	52.0		0.03	-
Block design raw score	23.7	7.9	23.0		22.0	8.2	22.0		0.11	0.79
Digit symbol	52.2	10.6	52.0		47.8	11.0	49.5		0.00	0.06
Fluency fruit score	14.2	3.4	14.0		13.9	3.2	14.0		0.46	0.81
Trails A time	39.7	15.7	37.0		41.8	12.1	39.0		0.06	0.54
Trails B time	86.4	35.8	80.0		103.5	46.7	91.0		0.00	0.05
Visual memory score	50.3	8.0	51.0		48.5	7.3	48.0		0.06	0.32
Verbal memory score	70.7	14.1	70.0		66.0	14.8	66.0		0.01	0.13
Attention/concentration	67.1	10.9	67.0		63.1	11.4	64.0		0.01	0.08
Delayed recall score	69.6	14.9	71.0		65.4	14.1	66.0		0.02	0.34
General memory score	121.1	18.2	121.0		114.4	18.6	114.0		0.01	0.10
Boston naming total score	54.4	4.2	55.0		53.6	4.7	54.0		0.17	0.99
P fluency	14.9	3.8	14.0		14.6	5.1	14.0		0.52	0.70
S fluency	14.9	4.2	15.0		14.3	5.0	14.5		0.33	0.93
Fluency total score	29.8	7.1	29.0		28.9	9.2	29.0		0.38	0.87

* Adjusted for age

** Adjusted for age and vocabulary raw score

Table 7

Comparison of Normal and Demented Survivors Through 2013

Alive & Normal (n=19)								Alive and Demented (n=113)		
			n	col %	n	col %	p-value			
Gender	Women		11	57.89	76	67.26	0.426			
Education	Post college		17	89.5	50	44.3	0.001			
Vocabulary raw score mean 1991–92			12	59	64	47.0	0.005			
ApoE4	Yes		2	11.1	27	25.0	0.252			
Hippocampus L	>5276 mm ³		8	72.7	16	29.6	0.016			
IADL	2		4	21.1	55	49.1	0.023			
ADL	2		2	10.5	35	31.3	0.064			
Ventricular grade 1998–99	5		1	6.3	16	16.2	0.46			
MMSE 1992–94	>95		17	89.5	48	42.5	0.001			
DSST 1992–94	>47		15	79.0	44	38.9	0.005			
Gait speed, 15 ft 1992–94	>5 sec		0	0.0	34	30.1	0.003			
Gait speed, 15 ft 1998–99	>5 sec		2	10.5	33	30.6	0.072			
Smoking	Never		9	47.4	55	50.9	0.387			
Diabetes	no		18	94.7	95	88.0	0.692			
HTN 1998–99	no		9	57.9	55	50.0	0.525			
SBP	>140 mmHg		3	15.8	29	26.6	0.187			
DBP	>74 mmHg		3	15.8	36	33.0	0.021			
Smoking	never		9	47.4	55	50.9	0.387			
HDL-C 1998–99	>56 mg%		7	43.8	36	36.4	0.375			
LDL-C 1998–99	>133 mg%		3	18.8	39	40.2	0.110			
CAC 1998–99	<=10		8	47.1	30	28.9	0.416			
Troponin 1992–94	<2.10 pg/ml		11	61.1	52	52.5	0.591			
NT-proBNP 1992–94	>192.80 pg/ml		1	5.6	8	7.3	0.297			
Number of blocks walked 1992–94	>12		13	68.4	27	25.2	0.0004			
6-min walk distance 1998–99	> 365 m		7	36.8	32	28.3	0.596			

Table 8

Cox Models, Stepwise Selection on Predicting Variables for Dementia or Death As Compared To Alive and Not Demented Participants in 2013 (n=47)

Variables Measured in 1992–94	HR (95% CI)	P value
Age	1.07 (1.05–1.09)	<0.0001
Ventricular grade 5	1.30 (1.04–1.61)	0.019
Number of blocks walked	1.32 (1.07–1.63)	0.0003
ApoE4 – yes	1.21 (1.01–1.46)	0.040
DSST 34	1.84 (1.48–2.28)	<0.0001
Any subclinical CVD	1.20 (1.00–1.44)	0.050
Gait speed 15 ft >5 sec	1.33 (1.12–1.58)	0.001

Predicting baseline variables: Age, race, gender, ApoE4, education, hypertension, diabetes, large infarct, ventricular grade, white matter grade, number of blocks walked, cholesterol, HDL, LDL, triglycerides, DSST, 3MSE, general health, any subclinical CVD, smoking, BMI, gait speed, cystatin-C, CESD

Note: 257 participants were not included in the analyses, including 25 refusals, 46 demented at or before 1992, 11 died in 2013. 175 had missing data, including 99 ApoE measurement refusal and 47 missing blocks walked.